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REVIEW

Does the GH–IGF axis play a role in cancer pathogenesis?

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Summary Recent case-controlled studies have found increases in the serum levels of insulin-like growth factor-I (IGF-I) in subjects who had, or who eventually developed, prostate or premenopausal breast cancers. Since growth hormone (GH) increases IGF-I levels, concern has been raised regarding its potential role as a cancer initiation factor. The epidemiological studies, which indicate an association between serum IGF-I levels and cancer risk, have not established causality. In fact, several alternative explanations for the elevated serum IGF-I levels in cancer patients may be proposed based on human and animal models. First, an effect of IGF-I causing symptomatic benign tissue hyperplasia may result in an ascertainment bias leading to an initiation of procedures resulting in the diagnosis of asymptomatic cancers. Second, elevated serum IGF-I in cancer patients may originate within the tumor (as suggested by some animal studies). Thirdly, serum IGF-I may actually be a surrogate marker of tissue IGF-I levels or of nutritional factors, which are not under GH control and may be involved in cancer initiation. The role of GH in cancer initiation is further negated by the fact that in acromegaly, the incidence of cancer, other than possibly colonic neoplasia does not appear to be significantly increased. Furthermore, GH transgenic mice, with high IGF-I levels, do not develop breast, prostate, or colonic malignancies. It is known that IGFBP-3 can inhibit IGF action on cancer cells *in vitro* and also can induce apoptosis via an IGF-independent mechanism. Importantly, in addition to increasing IGF-I levels, GH also increases the serum levels of IGFBP-3 and serum IGFBP-3 levels have been shown to be negatively correlated with the risk of cancer in the above mentioned epidemiological studies and in a similar study on colon cancer. These studies suggest that cancer risk is increased in individuals in whom both high IGF-I levels and low IGFBP-3 levels are present. In subjects treated with GH, IGF-I and IGFBP-3 levels both rise together and are not within the elevated cancer-risk range, based on published studies. Long-term studies are needed to assess the potential risks, including the long-term cancer risk associated with GH therapy. These should take into account several factors, including the duration of exposure, the risk magnitude associated with the degree of serum IGF-I elevation, and the adjusted risk based on a concomitant increase in IGFBP-3 levels. Since GH treated patients often have sub-normal IGF-I serum levels, which normalize on therapy, one might predict that their cancer risk on GH therapy should not increase above the normal population. Until further research in the area dictates otherwise, on-going cancer surveillance and routine monitoring of serum IGF-I and IGFBP-3 levels in GH-recipients should be the standard of care. At present, the data that are available do not warrant a change in our current management of approved indications for GH therapy.

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EPIDEMIOLOGY OF THE GH–IGF–IGFBP-3 AXIS AND CANCER IN HUMANS

Recently, several epidemiological studies have been published suggesting an association between serum IGF-I levels and the incidence of malignancies. While some of these papers indicated higher IGF-I levels in subjects at

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the time of diagnosis of prostate cancer[1,2], and lung cancer[3], others utilized the Harvard Physicians and Nurses Health Studies (PHS and NHS), which are prospective epidemiological studies. The latter reports suggested that serum IGF-I levels could serve as a prognostic risk factor for the development of cancer. Chan *et al* found a 2.4 higher risk of developing prostate cancer in men in the highest quartile of serum IGF-I, versus men with the lowest quartile, 7 years before the cancers were clinically evident[4]. Hankinson *et al* found a similar risk of developing premenopausal breast cancer in women 2 years prior to diagnosis[5]. Other studies, however, failed to observe such a relationship between IGF-I and prostate cancer[6,7]. Furthermore, the association of IGF-I with breast cancer risk has not been validated in a second prospective cohort analysed in the Rancho Bernardo Study[8]. This may indicate that the observed association could represent a type II error in the NHS. The fact that some studies failed to find an association between IGF-I levels and cancer risk and the well known pitfalls in the performance of IGF assays[9], have raised concerns regarding the possible artifactual explanations of some of these findings. In the studies analysing the PHS and NHS, serum IGFBP-3 levels were also measured and they suggested a lower risk in subjects with higher IGFBP-3 concentrations. Conversely, the risk of cancer calculated in those studies was increased for patients with low IGFBP-3 evels. In a report on children with leukemia, it was found that IGF-I was not a risk factor, although low IGFBP-3 levels were found to be associated with an increased risk and high IGFBP-3 levels were associated with a decreased leukemia risk[10]. In a paper analysing the risk of colon cancer in PHS participants, Ma *et al* showed that IGF-I was not found to be statistically associated with cancer risk, however, the combination of high IGF-I and low IGFBP-3 was shown to be related to an increased risk [11]. In that paper the population studied was further divided into nine groups (Table 1). These groups were divided according to the low, middle and high tertiles of IGF-I and IGFBP-3. Only the group with the highest IGF-I and lowest IGFBP-3 was found to be associated with an increased colon cancer risk.

Overall, the series of papers described here raises the possibility that IGF-I and IGFBP-3 may be somehow related to the risk of cancer. There are, however, alternatives that have been suggested to explain these findings.

Table 1

	IGF-I lowest tertile	IGF-I middle tertile	IGF-I upper tertile
IGFBP-3 upper tertile	–	–	–
IGFBP-3 middle tertile	–	–	–
IGFBP-3 lowest tertile	–	–	4-fold increased risk

Nevertheless, while additional studies are being conducted to verify or disprove the association between serum IGF-I and cancer risk, the role of growth hormone (GH) in this potential phenomenon should be carefully examined. As discussed below, while cancer risk has been suggested to be directly related to serum IGF-I and inversely related to serum IGFBP-3, GH positively influences both parameters in parallel. This casts doubt on its role as a driving force in the IGF-cancer equation. In addition, GH, through its receptor-linked signal transduction mechanism, stimulates the expression of several genes whose significance in the development of cancer is unknown. Unlike IGF-I, the significance of GH receptor activation in experimental animal models of tumorigenesis has been minimally evaluated. Therefore, it is impossible at present to make hypotheses regarding GH receptor linked signal transduction pathways that are distinct from the pathways activated by the IGF-I receptor and tumor formation or growth.

Additional epidemiological data of note involve the risk of malignancy associated with acromegaly. A number of studies have been published which claimed to identify an association between acromegaly and overall cancer risk[12-14], while others did not find significant association[15,16]. The interpretation of these studies is made difficult due to their small size, their uncontrolled retrospective nature, and multiple possible sources of bias. The largest study, however, incorporating several smaller British data sets published previously and considered by many to be the definitive study in the field, by Orme *et al*, indicated that overall cancer incidence is not increased in acromegaly[17]. Specifically, prostate, breast, and lung cancer were not increased in acromegalics. The overall incidence of colon cancer was also not shown to be increased in that study, although mortality from colon cancer was higher in this population, suggesting perhaps an effect of GH or IGF-I on established tumors[18]. Elevated mortality and/or incidence of colon cancer has been the most commonly observed finding in some (but not all) of the smaller cohorts mentioned above. Conflicting reports on colonic neoplasia in acromegaly have made this an unresolved issue, with the possibility of an association between colon cancer and acromegaly not fully ruled out. A recent prospective analysis of colon cancer and colonic polyps in acromegalics using controlled colonoscopies, however, did not observe an association between these two diseases when using either autopsy series or prospective colonoscopy screening series for the control population[19]. Interestingly, a single prospective study looking at the relation of serum growth hormone levels in healthy men without acromegaly, suggested a relationship between cancer mortality and GH levels[20]. It is

notable that acromegaly is associated with a dramatic increase in the incidence of benign hyperplasia of several organs, including colonic polyps[21], and benign prostatic hyperplasia[22]. In addition, primate studies suggested that treatment with high dose GH resulted in hyperplasia of the mammary gland in aging females[23]. These findings raise the possibility that the GH–IGF axis may lead to symptomatic benign proliferative disease, which could be associated with frequent urination or breast discomfort that would then lead to a potential detection bias. This ascertainment bias for cancer diagnosis needs to be considered as a possible explanation for the published data.

THE IGF AXIS IN *IN VITRO* MODELS OF CANCER

In normal tissues, growth and differentiation are controlled by multiple growth factors including those belonging to the IGF axis[24]. Changes at all levels of the IGF axis have been reported in a variety of cancers[25,26]. As noted previously, similar data are not available for assessing non-IGF-I dependent effects of GH receptor activation. Among the changes in IGF system physiology are the enhanced autocrine production of IGF-I and IGF-II[27–31]. The effects of IGFs on normal and cancer cells are mediated via the type 1 IGF receptor (IGF-1R)[32]. IGF-1R abnormalities may participate in the tumor development process as autocrine stimuli of survival and growth dysregulation. Additional regulators of tissue growth are the IGFBPs and the IGFBP proteases, which modulate IGF action[33]. Local IGFBP-3 levels may be important in the pathogenesis of cancer. IGFBP-3 is reduced in some types of neoplastic cells compared to normal cells by immunostaining[34]. *In vitro* studies of benign and malignant tissues and cell lines have demonstrated that IGFBP-3 has inhibitory effects on cancer cell growth[35]. Recent reports have shown that IGFBP-3 dose-dependently induces apoptosis though an IGF/IGF receptor independent pathway in prostate and breast cancer cells *in vitro*, suggesting a role for reduced IGFBP-3 mediated apoptosis in tumors. IGFPB-3 has been shown to directly induce apoptosis by binding to cell surface associated proteins in addition to blocking IGF interactions with the IGF-1R receptor[36].

IGFBP alterations have also been linked to changes in their proteases[37]. PSA is an IGFBP-3 protease, capable of acting as a co-mitogen with IGFs in the presence of IGFBP-3 *in vitro*[38]. IGFBP-3 proteolysis by PSA[39] and cathepsin D[40], within the breast and the prostate or their metastatic foci, could potentially contribute to the local propagation of neoplasia or metastasis. Elevation in serum PSA level has been correlated with decreased intact IGFBP-3 as well as to the stage of prostate cancer[41,42].

Of note is the fact that GH-independent regulation of IGF system components has been well characterized. In the prostate, the expression of the tissue IGF-related molecules is under potent control of androgens, which induce IGF-I and IGF receptors and suppress IGFBPs[43]. In the breast, estrogen regulates local IGF system components[44].

Thus, when cancer cells are studied *in vitro*, it appears that IGF, IGFBP and IGFBP protease perturbations play an important role in tumor cell propagation. GH is not thought to be an active participant in these cellular events, *in vitro*, and its non-IGF dependent effects *in vivo* have not been determined.

THE GH–IGF SYSTEM IN ANIMAL MODELS OF CANCER

Several rodent models have shed light on the GH–IGF-cancer issue. Key among these are the GH transgenic mice[45]. A central component of this model is the effect of various forms of GH on the prolactin receptor. An early publication using human growth hormone (hGH) transgenic mice demonstrated the development of mammary tumors[46]. A later publication using bovine GH as the transgene and contrasting it with prolactin transgenesis, demonstrated that prolactin is capable of inducing breast cancer[47]. Human growth hormone can activate the murine prolactin receptor and can thus cause mammary tumors in mice. The bovine GH transgenic mouse model showed that activation of the GH receptor alone, does not result in breast tumors, even though IGF-I levels were dramatically elevated and the mice displayed features of acromegaly over their lifetime. Animal models of tumor bearing animals, in which the GH–IGF axis has been manipulated, suggest that this system does affect the growth of established tumors. In GH deficient mice, breast cancer xenografts grow more slowly [48]. Similarly a GHRH antagonist or somatostatin analogues can inhibit cancer xenograft progression in SCID mice [49,50]. IGF-I infusion can promote tumor growth *in vivo*[51]. Other studies, however, did not find an effect of IGF-I infusion on rhabdomyosarcoma xenograft models[52] and one study showed that tumor-bearing animals actually benefited from IGF-I therapy through preservation of host lean tissue mass and reduction in cancer cachexia[53]. Conversely, IGFBP-3 infusion inhibits the growth of cancer xenografts in nude mice[54]. These models indicate that existing active tumors should constitute a contraindication to GH therapy as is currently stated in GH product labels. These studies, however, do not suggest a role of GH in *de novo* carcinogenesis in humans. On the other hand, treatment of cancer xenograft-bearing animals serving as models of tumor cachexia indicate that GH therapy might be favorable to the host survival and anabolism, while having no growth promoting effects on the tumor[55,56]. In fact some models reported a shrinking

of tumor growth in response to such therapy[57] and to a decrease in metastasis[58].

Other animal models that shed light on the controversy of the role of the GH-IGF axis in cancer include mice that are transgenic for IGF-I in the prostate and develop prostate tumors[59]. These mice clearly show that autocrine-paracrine IGF-I production (not under GH control) leads to the development of adenocarcinomas in aging transgenic mice. As noted below, factors in addition to GH control IGF-I expression. A prostate cancer model, which has been instrumental to our understanding of this issue, is the TRAMP mouse. These animals, transgenic for the SV40 T-antigen, driven by the prostate-specific probasin promotor, develop prostate cancer. This process is preceded by increased expression of IGF-I in the prostate. Strikingly, even though these mice have a completely normal GH-IGF endocrine axis, they display elevated serum IGF-I levels when carcinoma *in situ* was present, prior to the development of large tumors [60]. This is particularly relevant to the paper by Chan *et al*[4] where a similar elevation of IGF-I proceeded the diagnosis of clinically evident prostate cancer, and suggest those early, small tumors may be secreting IGF-I into the circulation.

REGULATION OF SERUM IGF-I AND IGFBP-3

The major hormonal determinant of plasma IGF-I concentrations is GH. The liver is the primary source of plasma IGF-I, but there are multiple tissues where GH stimulates IGF-I synthesis. Expression of IGF-I mRNA has been shown to be low in GH deficient animals, and it increases after administration of GH. Deletion of IGF-I gene expression in the liver in mice results in a 70% decrease in plasma IGF-I concentrations and poorer responsiveness of plasma IGF-I to GH, suggesting that much of the plasma IGF-I under normal circumstances is derived from stimulation of its synthesis in the liver by GH[61]. Nutrition is a major regulator of serum IGF-I in the liver, independently of GH[62]. In addition to the liver, IGF-I synthesis does occur in peripheral tissues, and peripheral tissue synthesis can be stimulated by GH as well as by other, less well-defined factors. Connective tissue, kidney, and skeletal muscle synthesis of IGF-I could be increased by GH administration to GH deficient animals[63]. The effects of GH on IGF-I production in prostate, breast, and colon are not known. In general, the major rate-limiting factor for controlling the response of nonhepatic tissue to GH administration with regard to IGF-I synthesis is GH receptor number. When GH receptor number is adequate, peripheral tissue responsiveness to GH can usually be demonstrated. Cartilage has been shown to respond to GH, with increased IGF-I synthesis[64]. This has been elegantly demonstrated in animal models, wherein direct injection of GH into perichondrial tissue results in increased synthesis of IGF-I locally, independently of changes in plasma GH. Thus, given adequate GH receptor numbers and an adequate increase in the local concentration of GH, IGF-I synthesis will be stimulated. It is not clear, however, that tissues that develop malignancies, which may be related to IGF-I, do so under GH control.

Changes in plasma IGF-I mirror changes in GH secretion that occur throughout the lifespan[65]. Specifically, IGF-I levels are low in early childhood, when GH secretion is low, and increase in tandem with GH, reaching a maximum level at puberty and then declining during adulthood in proportion to the decrease in GH secretion that occurs with aging. Serum IGF-I levels are low in children with GH deficiency (GHD) and increase appropriately with GH replacement therapy[66]. In adulthood, GHD is generally accompanied by low IGF-I concentrations, although approximately 30% of GHD adults have IGF-I levels that are in the low–normal range, but not below the fifth percentile. In states of GH excess, there is also a correlation between the change in IGF-I concentration and the degree of hypersecretion of GH[67].

The lack of a perfect correlation between plasma IGF-I concentrations and GH exposure is partially explained by the fact that IGF-I circulates bound to IGFBPs[68]. Although six IGFBPs are found in serum, the great majority of IGF-I is bound to a stable ternary complex that consists of IGF binding protein-3 (IGFBP-3) and a third protein called acid labile subunit (ALS). Both ALS and IGFBP-3 synthesis and secretion are also stimulated by GH, and therefore the increase in all three factors results in the formation of a stable, high molecular weight complex that has a half life of 16 h in serum[69]. In contrast, the other binding proteins that bind to IGF-I in serum, with the exception of IGFBP-5, do not form complexes with ALS, and therefore their concentrations have a shorter half-life. Furthermore, the secretion of these proteins is not necessarily increased in response to GH, and therefore major changes in their plasma concentrations by non-GH dependent variables may result in changes in plasma IGF-I that do not correlate with changes in GH secretion. This probably accounts for a part of the discrepancies that have been observed between GH secretion and plasma IGF-I concentrations[70]. Hormones other than GH can also influence the synthesis of IGFBP-3. Gonadal steroids and thyroxine have been shown to alter plasma IGFBP-3 concentrations, and insulin potentiates the effect of GH on IGFBP-3 synthesis[71,72]. Finally, IGFBP-3 in serum is partially controlled by proteolytic cleavage. A protease that is particularly abundant in the plasma of pregnant women cleaves IGFBP-3 to lower molecular weight fragments[73].

In addition to GH, nutrition is an important regulator of plasma IGF-I. Starvation in humans for 10 days results

in a 70% decrease in plasma IGF-I[74]. This decrease is dependent upon both protein and total energy intake, and at energy intakes below 20 kcal/day or protein intakes below 0.6 kg/day substantial decreases in IGF-I occur[75]. Catabolic conditions result in major decreases in IGF-I, but it is difficult in these states, such as hepatic failure, inflammatory bowel disease and renal failure, to discern the portion of change that occurs as a consequence of changes in nutritional intake, compared to the underlying inflammatory process itself, and concomitant tissue breakdown. Poorly controlled diabetes mellitus is associated with low plasma IGF-I concentrations that rise into the normal range with appropriate insulin substitution therapy[76].

Serum concentrations of IGF-I are also genetically determined and are related to polymorphisms of the IGF-I gene. Such a polymorphism, located near the P2 promotor is associated with varying serum IGF-I levels and with a different risk of developing osteoporosis. Analysis of this microsatellite repeat, which is approximately 1 kb upstream from the IGF-I gene transcription start site, shows a higher prevalence of the 192/192 genotype of this polymorphism among men with idiopathic osteoporosis compared to controls[77] and also predicted certain other bony conditions[78]. This polymorphism was also related to obesity and fat mass[79], two independent predictors of cancer; however, it was not related to serum GH and the differences in serum IGF-I among men with different genotypes and different serum IGF-I were not associated with differences in plasma GH. A study of cancer incidence in twins indicated that prostate, colon and breast malignancies, the three cancers linked to serum IGF-I have a strong genetic component, which was not seen in other types of cancer [80].

Thus, elevations of serum IGF-I, which are associated with cancer, may be related to non-GH sources and could represent a genetically determined marker of other cancer risk factors.

PHARMACO-VIGILANCE DATA ON GH RECIPIENTS AND CANCER

In a number of reported studies, no increased incidence of cancer was found in GH recipients among adults who were treated for GH deficiency [81]. Furthermore, careful follow-up of pediatric patients indicated no increased risk of solid tumor recurrence or development of leukemia[82]. Clearly, these reports represent imperfect, uncontrolled studies, but the experience gained through them, particularly in the pediatric population is extremely vast and demonstrates that, in the absence of other risk factors, GH therapy is not associated with tumor recurrence, leukemia, or other *de novo* tumors[83–86]. These findings indicate that GH therapy in GH deficient individuals does not increase the incidence of cancer, even though the IGF-I levels are normalized.

HYPOTHESES REGARDING GH–IGF-I AND CANCER

Table 2 summarizes the potential explanations for the observed association between IGF-I and cancer seen in some studies. It is possible that there is no true association and that an ascertainment bias or a methodological error contributed to the observation. It is possible that other cancer-controlling factors, such as nutrition, modulate IGF-I and thus IGF-I is actually a marker, rather than a cause of cancer. It is also possible that tumors secrete IGF-I, which then serves as a "tumor marker". It is also possible that autocrine IGF-I is involved in the pathogenesis of some tumors, but the opposing role of IGFBP-3 also needs to be considered. Finally it is possible that the GH-IGF axis is involved in the growth of some established cancers. Given the evidence available at this time it is prudent to continue to monitor patients receiving GH for tumor development.

The results could have arisen through diagnostic bias, in that IGF-1 might have caused benign symptoms, which led to diagnosis of malignancy, or have caused growth of preclinical cancers, leading to their more rapid diagnosis. This is specifically a concern for prostatic cancer because of the high prevalence of latent, asymptomatic prostatic cancers in elderly men[87], such that more intensive scrutiny can often detect tumors that might have remained undiagnosed or been diagnosed later without deliberate investigation. This scrutiny and detection of asymptomatic cancers could occur if raised IGF-1 causes benign prostatic hypertrophy, because the latter will lead to PSA measurements, prostate biopsies and prostatectomy and pathological examination of the removed tissue.

Raised IGF-I levels might be caused by the cancer (for instance, because the cancer may secrete IGF-I) rather than being the cause of it. This is supported by some

Table 2 Hypotheses regarding IGF-I and cancer

The "null (laboratory or statistical errors)" hypothesis—relating to the possibility of chance or error
The "ascertainment bias" hypothesis
The "IGF-I as a marker" hypothesis
The "nutrition" hypothesis—relating to the possibility of confounding effects
The "tumor as a source" hypothesis—relating to the possibility of reverse causation
The "IGF-I causes, and IGFBP-3 prevents, cancer (and GH is neutral)" hypothesis
The "GH causes cancer through IGF-I" hypothesis

animal models as noted above. This is of particular concern regarding the premenopausal breast cancer patients who were diagnosed only 2 years after the blood sample was obtained as it is likely that they had a small undiagnosed tumour already.

The association between IGF levels and cancer might be due to confounding by other etiological factors for cancer, for instance, nutritional factors. Although the nested case-control studies adjusted for some confounding variables, many of the major etiological factors, particularly for prostatic and colon cancers, are not clearly known and could not be adjusted for, and hence remain as potential confounders. Since nutrition is a well-recognized regulator of IGF-I levels (in a GH-independent fashion) this is particularly important.

GH SAFETY

The theoretical risks associated with an elevated serum IGF-I level in a GH recipient need to be considered in the context of several factors. Firstly, the co-elevations in IGFBP-3 discussed earlier which counteract the effects of IGF-I on cells. Secondly, the degree of serum IGF-I elevation induced by GH, which is often small, and in therapeutic situations leads to normalization of the serum IGF-I levels into the range of age matched controls. Finally, the length of time involved in therapy is also important, since any risk imposed by IGF-I is over a lifetime. The treatment over a single decade is, therefore, diluted by a factor of six and may become close to negligible[88].

Thus, the evidence is overwhelming for GH safety in replacement indications, short-term use, and in pediatric recipient. Long-term, placebo controlled trials of GH in the elderly are being conducted by the National Institute of Aging, and their results should be available within the next few years. These trials are assessing functional improvement in exercise tolerance, endurance, gait stability, and maintenance of muscle strength. Risk factors of concern, such as change in prostate specific antigen levels and prostate volumes, are also being monitored. These data should be extremely helpful in answering the question of the risk/benefit ratio of administering GH to elderly patients. In the meantime, this use should be considered experimental, and any elderly patient started on GH should be monitored carefully for changes in PSA, IGF-I and IGFBP-3 levels as well as for assessment of hematocrit, blood in the stool, or breast masses.

The use of IGF-I and IGFBP-3 in the monitoring of GH recipients, both adult and pediatric, has been recommended and endorsed by the GRS[89]. Until the issue of cancer risk in GH therapy is fully resolved, the most prudent approach appears to be regular monitoring of both IGF-I and IGFBP-3 and modulation of the GH dose to insure that the theoretical risk profile induced by GH therapy is favourable. This can be done by avoiding the unlikely situation where a GH treated patient will have an IGF-I level at the upper tertile and an IGFBP-3 level at the lower tertile of the population. In the 21st century, many GH deficient patients will receive a lifetime of GH replacement. In that setting, it is especially important that we monitor serum IGF-I and IGFBP-3 on a regular basis.

Overall, this review summarized the controversies around the issue of IGF-I and cancer risk and highlighted the issues specifically concerning the safety of GH therapy. It is, in general, quite compelling to believe that the currently approved indications for GH therapy including GH deficiency in children and adults and Turner's syndrome and renal failure in children, do not represent cases of concern regarding future cancer risk. While additional research in the models discussed here and other ones currently being developed, coupled with stringent pharmaco-vigilance, is clearly warranted to answer these interesting theoretical questions, the state of the clinical field mandates that patients, parents and practicing physicians be assured of the vast body of evidence regarding the safety of GH in this regard.

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