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COMMENTARY

GROWTH HORMONE, LYMPHOCYTES AND MACROPHAGES*

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Recombinant human growth hormone (somatotropin) was approved for human use in October, 1985, and is now being used extensively to treat a large number of children born with a growth hormone deficiency. The synthesis of human growth hormone by recombinant methods has certainly been an important advance for all growth hormone-deficient children who can now be safely treated by pediatric endocrinologists to achieve an augmentation in growth rate. Other potential clinical uses of growth hormone have generated much excitement, and concern, by medical scientists. Growth hormone may be useful for controlling obesity in middle-aged humans, reversing some aspects of the aging process, improving wound healing in burn patients, augmenting the physical abilities of athletes, reversing some aspects of the aging process and improving growth rate and reducing carcass fat in domestic food animals. Unfortunately, however, it is unclear how growth hormone affects human and animal health.

Polymorphonuclear and mononuclear myeloid cells and lymphocytes are absolutely essential for protection of the host against infectious diseases. Macrophages are critical to the induction and expression of most immune responses. Macrophages can be triggered to produce reactive oxygen intermediates, such as hydroxyl radicals, singlet oxygen molecules, hydrogen peroxide and superoxide anion (O_2^-), which nonspecifically kill ingested bacteria. Activated macrophages also process and present bacterial antigens to T cells, show enhanced expression of Class II genes of the major histocompatibility complex, kill tumor cells and secrete a number of monokines, such as IL-1 and tumor necrosis factor-α. The thymus gland attracts progenitor T lymphocytes from the bone marrow and serves as an organ that permits differentiation into mature, functional T cells by generating rearranged T cell receptor genes. T lymphocytes perform a variety of functions in the immune system. A subset of these cells, known as CD 4 cells (helper/inducer), can secrete a number of lymphokines that affect T cell (e.g. IL-2, IL-4), B cell (e.g. IL-4, IL-5, IL-6, IL-7) and macrophage function (e.g. interferon-γ). Although it is somewhat bewildering, it is now widely recognized that all of these lymphokines share pleiotropic properties on a variety of cell types and that different cell types can synthesize these molecules. Given the recent finding that a single cytokine is responsible for multiple biologic activities on a single cell, it certainly seems possible that other hormones produced in the body possess activities in addition to the one that led to their discovery.

Growth hormone is a protein, consisting of 191 amino acids, that is synthesized by the adenohypophysis. It has long been suggested to be involved in immunoregulation, and several recent reports support the conclusion that growth hormone possesses a number of important immunomodulatory activities. As outlined in Table 1, this commentary will highlight the immunoregulatory properties of growth hormone by focusing on immunodeficiencies in growth hormone-deficient animals and describing the effects of growth hormone on the thymus gland and lymphoid, phagocytic and hemopoietic cells.

GROWTH HORMONE DEFICIENCIES AND IMMUNOREGULATION

The concept that growth hormone affects cells of the immune system was initially established by two major findings: (a) mice injected with antiserum to either the pituitary gland [1] or to growth hormone [2] develop thymic atrophy and wasting disease and (b) growth hormone-deficient mice [3, 4, 6] and dogs [7] have smaller thymus glands and spleens. Weimaraner dwarf dogs are particularly susceptible to a wide variety of infectious organisms that often lead to premature death. Similarly, hypopituitary Snell–Bagg dwarf mice, which are deficient in at least growth hormone and thyroxin, have a reduced ability to synthesize antibodies to particulate antigens [8–11] and a significant delay in rejecting allogeneic skin grafts [5, 10]. Contact sensitivity reactions to oxazolone are also reduced slightly when tested *in vivo* [12], even though *in vitro* mitogenic responses of thymocytes and splenocytes are normal [13]. However, the wasting disease that develops in hypopituitary mice is apparently a function of the environment. If pathogenic organisms are present in the mouse colony, Snell–Bagg dwarf mice but not littermate controls develop wasting disease and die, presumably of infectious disease. If a sanitary environment is maintained in the colony, Snell–Bagg dwarf mice survive well [12] and have normal proportions of splenocyte [5] and thymocyte [13]

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Table 1. Regulation by growth hormone of the activities of cells of the immune system

Item	Refs.
Growth hormone deficiencies and immunoregulation:	
Thymic atrophy and wasting in mice and dogs	1–7
Reduced antibody synthesis in mice	8–11
Delayed skin graft rejection in mice	5, 10
Normal lymphoid cell subsets and thymic histology with reduction in peripheral T and B cells	5, 12, 13
Pituitary hypoplasia and thymic atrophy in humans	14
X-linked growth hormone deficiency and complete inability to synthesize antibodies	15
Reduction in activity of natural killer cells in humans	16
Defective allogeneic mixed lymphocyte reaction	17, 18
Reduction in plasma thymulin in humans and mice	19, 20
Normal immunoglobulin concentrations and lymphoid cell subsets in humans	16, 21, 22
Decreased insulin-induced growth hormone response in patients with telangiectasis and bowel disease	23, 25
Growth hormone and the thymus gland:	
Increases thymic size and DNA synthesis in young rodents	4, 8–10, 26–30
Improves thymic size and morphology in aged animals	31, 32
Increases plasma thymulin in humans and dogs	20, 33
Growth hormone and lymphoid cells:	
Lymphocytes have receptors for growth hormone	34–39
Augments antibody synthesis and reduces skin graft survival *in vivo*	5, 9, 10, 40–44
Increases lectin-induced T cell proliferation and IL-2 synthesis *in vivo*	21, 22, 31, 45, 46
Stimulates proliferation of human lymphoblastoid cells	46–48
Augments basal lymphocyte proliferation *in vitro*	22, 49, 50
Increases activity of cytotoxic T lymphocytes *in vitro*	51
Augments activity of natural killer cells *in vivo*	45, 52, 53
Synthesized by lymphoid cells	54, 55
Growth hormone and phagocytic cells:	
Primes macrophages for superoxide anion release *in vitro* and *in vivo*	56
Augments respiratory burst in neutrophils from growth hormone-deficient patients *in vivo*	57
Increases basal respiratory burst of human neutrophils and inhibits activated burst *in vitro*	58
Growth hormone and hemopoiesis:	
Augments neutrophil differentiation *in vitro*	59
Augments erythropoiesis	60, 61

subpopulations. These mice do continue to show a reduced number of peripheral leukocytes [5] and T and B lymphocytes [13].

In contrast to rodents, growth hormone-deficient humans do not present with an abnormal number of infectious diseases and are not generally considered to be immunodeficient. Humans with panhypopituitarism certainly have endocrine abnormalities other than growth hormone deficiency, which confounds the ascription of any potential immunological derangement to a single pituitary hormone. Growth hormone-deficient humans generally have normal levels of circulating immunoglobulins [16, 21, 22], the proportion of B cells and T cell subsets do not show profound alterations [16, 18, 21, 22], and mitogenic and autologous mixed lymphocyte proliferative responses are not defective [21, 22].

Although a number of immune events are normal in growth-hormone deficient patients, several alterations in the immune system of these patients have been described. These changes include thymic hypoplasia [14], inability to synthesize antibodies to clinically-important antigens [15], defective antibody- and cell-mediated immunity as assessed *in vivo* [17], reduced activity of natural killer cells [16], inability of lymphoid cells to respond or stimulate cells in an allogeneic mixed lymphocyte reaction [18] and reduced plasma levels of thymulin [20]. Furthermore, substantial data indicate that there are alterations in the regulation of growth hormone secretion in a number of diseases, including ataxia-telangiectasia [23], inflammatory bowel disease [24, 25], a variety of cancers [62], and allergy patients with either asthma or hay fever [63]. It is not known whether these changes in growth hormone secretion are causal or simply a result of these diseases. Also, since growth hormone is now known to be released in a periodic pattern, complete kinetic studies reporting both spikes and troughs of growth hormone in these patients should be investigated.

At least five possibilities could explain the discrepancy between growth hormone-deficient rodents and humans in their susceptibility to wasting disease and infectious organisms: (a) It can be argued that growth hormone does not affect any immunological cell type that is needed in the protection of humans

against disease. In view of the evidence that growth hormone affects a variety of immune events (Table 1), this possibility is considered unlikely. (b) It may be that there is a classic environment–disease interaction in growth hormone-deficient rodents. If sanitation is not adequate, wasting disease and death appear in rodents, whereas no extreme susceptibility to infectious diseases appears in growth hormone-deficient rodents that are raised under clean housing conditions. If growth hormone-deficient children are well cared for and properly treated at the earliest sign of an infectious disease, unusual susceptibility to disease might not be noticed. (c) Many growth hormone-deficient children are not completely deficient in growth hormone. Perhaps only small amounts of the hormone are needed by the immune system. This possibility would be more likely if small amounts of growth hormone were sufficient to initiate synthesis of somatomedin C in lymphoid or surrounding parenchymal tissue, which in turn was responsible for the action of growth hormone. (d) It has been reported recently that human lymphoid cells can synthesize growth hormone (*vide infra*, [54, 55]). Perhaps peripheral concentrations of growth hormone are less important than the local synthesis of growth hormone in regional lymphatic tissues where active immune responses normally occur. (e) A growth hormone- and prolactin-deficient patient has not been described, so perhaps prolactin mimics many of the immunomodulating properties of growth hormone. This effect would be particularly strong in humans. Prolactin, which consists of 199 amino acids, is a pituitary hormone that is closely related to growth hormone. Both growth hormone and prolactin share between 20 and 85% amino acid homologies [64], depending on the species compared, with the human proteins showing the closest homology. Indeed, human growth hormone shares the lactogenic properties of prolactin. Genes for both hormones evolved by duplication around 380 million years ago [65]. In addition to the growth hormone receptor [66], the rat prolactin receptor has also been cloned recently [67]. Growth hormone and prolactin receptors share about 30% overall homology, and these receptors also appear to be derived from a common primordial gene. Human growth hormone, bovine growth hormone and ovine prolactin bind the recombinant rabbit growth hormone receptor, and ovine prolactin, rat prolactin, human prolactin and human growth hormone bind the recombinant rat prolactin receptor. These findings explain why growth hormone and prolactin share a variety of biological effects [68], including immunomodulatory properties.

THE THYMUS GLAND AND GROWTH HORMONE

The idea that pituitary factors exist which might affect thymic function could have important implications in understanding the age-associated involution of the thymus gland. Growth hormone secretion is highest around puberty and then declines with age in both humans [69, 70] and rats [71, 72]. Although basal levels of growth hormone do not show dramatic changes, the age-associated reduction in amplitude of secretory spikes of growth hormone is large, with differences exceeding 200 ng/ml of plasma in pulsatile releases of growth hormone between old and young rats [73]. As might be expected, the concentration of somatomedin C also declines with age [74].

Pandian and Talwar [29] clearly showed that growth hormone increases DNA and RNA synthesis in the thymus and spleen, but not the liver, in both normal and hypophysectomized rats *in vivo*, and that these effects could be reversed with antiserum to growth hormone. These studies suggested that lymphoid tissue is an important target for the action of growth hormone. Yet, it has generally been considered that involution of the thymus gland which occurs with aging is an irreversible process. Since both growth hormone [4, 8–10, 26–30] and prolactin [75] augment thymic size in young animals, we implanted GH_3 pituitary adenoma cells, which secrete high quantities of rat growth hormone and prolactin, into aged female Wistar–Furth rats [32]. Two months later, thymus glands were detected in the GH_3-implanted rats that were grossly and histologically comparable to thymus glands of young rats. However, only remnants of thymic tissue could be detected in the aged, control females. These data provided some of the first evidence that thymic involution which occurs during aging is not an irreversible process, which is similar to conclusions made by our laboratory [76] and others [77]. It is as yet unknown whether the thymic growth that is caused by GH_3 cells is due to growth hormone, prolactin or other unknown molecules.

Pandian and Talwar [29] were also the first to suggest that growth hormone affects epithelial cells in the thymus gland. Their results led us to postulate that the reconstituted thymus glands in GH_3-implanted rats were capable of processing progenitor stem cells from the bone marrow into functional T lymphocytes and synthesizing thymic hormones. Since our report, Goff *et al.* [33] demonstrated that growth hormone reverses thymic aging in old dogs and augments synthesis of a thymic hormone known as thymulin. Furthermore, the thymus gland is atrophied in immunodeficient dwarf Weimaraner dogs, and exogenous growth hormone treatment dramatically improves thymic size and cellularity as well as the clinical condition of these dogs [7]. Thymulin is reduced in the plasma of dwarf mice [19] and growth hormone-deficient children [20], and exogenous growth hormone is able to reverse this defect in children. Mice that are transgenic for the rat metallothionein-growth hormone gene also have significantly more thymic epithelial cells than their littermates [45], and these cells are an important source of thymulin. Therefore, it seems clear that growth hormone augments the synthesis of thymulin. This conclusion permits an alternative interpretation of earlier findings by Arrenbrecht and Sorkin [78] who suggested that growth hormone was capable of inducing differentiation of thymocyte precursors into T helper cells in the periphery. Since our work showed that neither growth hormone nor prolactin could induce the differentiation of functional T cells in nude rats [45], perhaps the effects reported by Arrenbrecht and Sorkin were mediated by growth

hormone increasing the synthesis of thymic hormones in recipient animals, and these thymic hormones may have induced terminal differentiation of T cells in secondary lymphoid tissue.

GROWTH HORMONE AND LYMPHOCYTES

A number of authors have shown that normal thymic and lymphoid cells, as well as the transformed human lymphoid cell line IM-9, have binding sites for both growth hormone [34–39] and prolactin [79–81]. Therefore, a natural mechanism exists for transducing information from the binding of growth hormone on the surface membrane to the cytoplasm of lymphoid cells. Human lymphoid cells appear to have only high-affinity receptors with around 7000 binding sites per cell and an affinity constant of $2 \times 10^9\ M^{-1}$. Since human peripheral blood mononuclear cells consist of T lymphocytes, B lymphocytes, NK cells, monocytes and a small but detectable proportion of granulocytes, potential differences in receptor numbers on various cell types is unknown.

Growth hormone consistently augments a number of immune responses when injected into hypopituitary animals, including antibody synthesis and skin graft rejection [5, 9, 10, 40–44]. It can even reverse leukopenia, the suppression in antibody synthesis and delayed skin graft survival caused by stress or glucocorticoids [44, 82–84]. We demonstrated that high levels of growth hormone injected *in vivo* double both basal and lectin-induced proliferative responses from splenocytes of aged rats [45]. Similarly, lectin-induced proliferative responses of mice that are transgenic for the rat growth hormone gene are elevated [45]. Even though mitogenic responses of lymphocytes from growth hormone-deficient children are not suppressed [21, 22, 85], these responses can be augmented by administration of growth hormone *in vivo* [21, 22]. Although one report showed that administration of native human growth hormone to patients actually reduced proliferative responses to phytohemagglutinin [86], this effect has not been reported in patients treated with recombinant growth hormone that is known to be free of slow viruses.

Only limited reports have appeared on the effect of growth hormone on immune events *in vitro*. Proliferative responses of both transformed [46–48] and normal [22, 46, 49, 50] lymphoid cells are generally greater when treated with growth hormone *in vitro*. However, growth hormone has been reported to increase [46, 50], decrease [49] or cause no change [22, 87] in lectin-induced mitogenesis. The reason for this discrepancy is not at all clear, but it is important that none of these studies used recombinant growth hormone, complete dose–response curves were not reported, and in most cases appropriate antibody blocking experiments were not conducted. Furthermore, most of the *in vitro* incubation media utilized some type of serum, which often contains significant quantities of growth hormone and prolactin and their binding proteins that may not be destroyed by heat inactivation at 56°. Finally, perhaps the difference between *in vivo* and *in vitro* results can be explained by secondary mediators, such as somatomedin C, that may be induced by growth hormone *in vivo* but not *in vitro*.

Growth hormone affects the functional activity of cytolytic cells, including both cytolytic T lymphocytes (CTL) and NK cells. Growth hormone, at nanogram concentrations, was necessary for T lymphocytes to develop cytolytic activity against an allogeneic stimulus when cultured in a serum-free system [51]. This finding could be particularly important if confirmed *in vivo* because CTL are well known to mediate class I restricted killing of virus-infected cells. The cytolytic activity of another type of non-T, non-B lymphoid cell, known as NK cells, is reduced by hypophysectomy, and this effect can be partially reversed by administration of growth hormone *in vivo* [52]. There is also a decline in the activity of NK cells with age [88], and this decline can be at least partially prevented in aged mice [45] and women [53] by injection of growth hormone. Activity of NK cells is reduced in growth hormone-deficient children [16], but this defect cannot be reversed *in vivo* with short-term administration of either growth hormone or growth hormone-releasing hormone (GHRH). There may be an intrinsic defect in NK cells in growth hormone-deficient children for two reasons: (a) there is no reduction in the actual number of NK cells in growth hormone-deficient children and (b) incubation with human interferon-α *in vitro* can augment NK activity in healthy control children but not in growth hormone-deficient children.

GROWTH HORMONE AND ACTIVITY OF PHAGOCYTIC CELLS

Macrophages can be activated by a number of cytokines to display increased biochemical and metabolic activities as well as enhanced resistance to bacterial pathogens. The classic macrophage activating factor in both *in vitro* and *in vivo* systems is interferon-γ, which has been shown to augment macrophage killing of a number of parasites, including a variety of species of bacteria, protozoa, fungi and helminths.

Similar to the observations of Astaldi *et al.* [50], we noticed that macrophages in the liver (Kupffer cells) possessed morphologic characteristics of activated macrophages after overnight incubation with growth hormone [56]. We then measured the production of O_2^- in both blood-derived monocytes and alveolar porcine macrophages incubated *in vitro* with various concentrations of recombinant porcine growth hormone. Growth hormone, at concentrations as low as 50 ng/ml, augmented the production of O_2^- by zymosan-stimulated macrophages, and this effect could be blocked by a specific antibody to growth hormone. When hypophysectomized rats were injected with concentrations of rat or porcine growth hormone that were effective in augmenting growth rate, resident peritoneal macrophages from these rats could also be primed to produce augmented quantities of O_2^-. The amount of O_2^- produced by macrophages from growth hormone-treated hypophysectomized rats was identical to the amount of O_2^- produced by macrophages from rats treated with the classic macrophage activating factor, recombinant rat interferon-γ. Subsequent work in our laboratory demonstrated that neither interferon-

γ nor growth hormone affects the respiratory burst of resident macrophages that are not stimulated with opsonized-zymosan. Therefore, the release of reactive oxygen intermediates from macrophages primed with growth hormone does not occur unless the macrophage has been stimulated by an activating signal to initiate the respiratory burst. These data established that growth hormone is a newly defined macrophage activating factor, as assessed by the production of O_2^-, in both *in vitro* and *in vivo* assays. Since reactive oxygen metabolites are the most important products which are used by macrophages to kill ingested bacteria, these findings could be very important for growth hormone-deficient children who are treated with exogenous recombinant human growth hormone to stimulate growth. Similarly, the closely-related hormone, prolactin, has been shown recently to be needed for the synthesis of interferon-γ and the subsequent generation of tumoricidal macrophages [89].

Growth hormone also affects the activity of polymorphonuclear phagocytes. Both the resting and the starch-stimulated production of reactive oxygen intermediates of granulocytes from growth hormone-deficient children are augmented after administration of human growth hormone [57]. Furthermore, granulocytes from patients with acromegaly have significantly higher resting and starch-elicited metabolic burst activity. Injections of growth hormone also increase the activities of two key enzymes in granulocytes: myeloperoxidase and lysozyme [58]. Myeloperoxidase is found in the granules of neutrophils and is important for generating hypohalides in the presence of hydrogen peroxide, which then decompose spontaneously into highly toxic molecules. When growth hormone is added to human granulocytes *in vitro*, an increase in metabolic burst activity is observed, which is similar to the effects of growth hormone when administered *in vivo*. However, growth hormone causes a significant inhibition in the respiratory burst if granulocytes are stimulated with opsonized-zymosan, which contrasts with the *in vivo* effects of growth hormone. Again, perhaps this difference can be explained by growth hormone stimulating the release of other mediators (e.g. somatomedin C) *in vivo* that are not present in the *in vitro* system.

HEMOPOIESIS AND GROWTH HORMONE

Growth hormone is involved in the normal differentiation of stem cells into erythrocytes and granulocytes. Blood cells arise from pluripotent stem cells that differentiate along defined maturation pathways. Granulocyte/macrophage colony-stimulating factor (GM-CSF) promotes the differentiation of myeloid progenitors into colonies of granulocytes, macrophages/monocytes and mixed colonies of these two types of cells. Growth hormone cannot induce the appearance of these colonies in the absence of GM-CSF. However, in the presence of recombinant GM-CSF, both recombinant human growth hormone and somatomedin C double the number of granulocyte colonies [59]. This enhancement caused by either somatomedin C or growth hormone is totally blocked by the addition of a monoclonal antibody to the somatomedin C receptor.

These very provocative findings show that growth hormone augments human granulopoiesis *in vitro* and suggests that human bone marrow adherent cells respond to growth hormone by synthesizing somatomedin C, which is in turn directly responsible for the enhanced maturation of granulocytic precursor cells. This suggestion is in accord with a recent report which found that activated macrophages express mRNA transcripts for somatomedin C [90]. Thus, the effect of growth hormone on myeloid cell differentiation may be mediated exactly in a paracrine fashion as it is in other target tissues (e.g. liver, fibroblasts, skeletal muscle): by induction of somatomedin C synthesis. These kinds of experiments clearly need to be conducted on other types of myeloid/lymphoid cell populations that are responsive to growth hormone. If successful, these experiments may lead to alternative strategies for enhancing myeloid cell differentiation in neutropenic and leukemia patients.

Growth hormone is also important for erythropoiesis. Physiologic concentrations of growth hormone augment the number of erythroid colonies that develop from bone marrow cells incubated with erythropoietin [60]. Similarly, low concentrations of either growth hormone or prolactin augment the proliferation of virus-infected erythroleukemia cells *in vitro* [61]. Growth hormone also increases bone marrow lymphocytosis and erythropoiesis in human hypopituitary dwarfs [91].

PHYSIOLOGICAL ROLE FOR GROWTH HORMONE IN IMMUNOREGULATION

The potential physiological role for growth hormone in immunoregulation has been best demonstrated by studies in which growth hormone induces an increase in body growth and at the same time alters some immunologic event (e.g. Ref. 56). Three other lines of evidence also argue for a physiologic role for growth hormone in immunoregulation. First, growth hormone has been shown recently to be synthesized by lymphoid cells [54, 55], and the same may be true for prolactin [92]. Therefore, growth hormone may be synthesized locally in regional lymph nodes, and its effect upon the immune response may bear no relationship to the quantity of growth hormone in serum. Both growth hormone and prolactin are known to exist in multiple forms, and a single gene encodes two different forms of the growth hormone receptor [66]. The potential for multimeric forms of growth hormone, prolactin or their receptors, as well as the newly-recognized growth hormone binding protein that is the extracellular binding domain of the receptor [66, 93], to regulate immune events has not been explored. Second, growth hormone stimulates growth of the thymus gland and the synthesis of some thymic hormones, and it has been demonstrated recently that thymosin fraction 5 stimulates the release of both growth hormone and prolactin from pituitary adenoma cells [94] and normal anterior pituitary cells [95]. It thus appears that both thymic size and secretion of thymulin are augmented by growth hormone, and products from the thymus gland feed-

back to affect the hypophysis. Third, endotoxin is a potent stimulus of growth hormone [96] and an inhibitor of prolactin secretion [97]. It is well known that endotoxin stimulates the release of IL-1 and tumor necrosis factor-α by mononuclear phagocytes, and IL-1 also causes the release of growth hormone *in vivo* [98] and inhibits prolactin release *in vitro* [99]. These findings suggest that a macrophage-derived product alters the release of pituitary hormones and that the ratio of growth hormone to prolactin after macrophage activation may have important functional implications in immunoregulation. It is as yet unknown whether either of these two hormones affect the secretion of macrophage-derived IL-1 or tumor necrosis factor-α. Growth hormone injections reduce body fat, increase muscle mass, and augment the activity of NK cells in women [53]. Since growth hormone is a well-known lipolytic agent, and tumor necrosis factor-α inhibits several lipogenic enzymes [100], the possibility that growth hormone reduces body fat by augmenting the synthesis of tumor necrosis factor-α is an interesting hypothesis that should be explored further.

CONCLUDING REMARKS

Growth hormone is currently being used in human medicine to stimulate growth in deficient patients. Recombinant human growth hormone is free of slow viruses that cause Creutzfeldt–Jakob disease and is quite efficacious in permitting children to attain a normal growth curve. Its development and application, therefore, have been significant advances in human medicine. In the future, growth hormone may be used clinically for a wide variety of other applications, such as aiding wound healing, repartitioning fat into muscle, reversing certain aspects of aging and immunopotentiation in conjunction with vaccines. It is therefore imperative to understand all of the biologic effects of growth hormone other than just animal growth.

Even though the fears may be unjustified, there is evidence that growth hormone promotes the proliferation of certain types of transformed cells [46–48, 61]. Furthermore, immunoreactive growth hormone can be found in prostatic tumors [101], and growth hormone can be elevated in human cancer patients [62, 102]. Similarly, although the secretion of reactive oxygen intermediates is important in intracellular killing of parasites by macrophages, high levels of these compounds can directly induce damage to adjacent cells. Other health concerns about the use of growth hormone have been raised, ranging from diabetes to hypertension [103]. Although the use of growth hormone appears to be safe and is actually improving the quality of life for some patients, its use must be monitored to learn whether it causes any significant long-term side-effects.

Research published in the past 2 years has added a totally different dimension to our appreciation of the role of growth hormone in immunoregulation. Growth hormone can regenerate thymic tissue in aged subjects and augment secretion of the thymic hormone thymulin. Growth hormone is as potent as interferon-γ in priming macrophages for the production of O_2^-. Growth hormone augments granulopoiesis in humans, and this effect on bone marrow cells is mediated by somatomedin C. Growth hormone is synthesized by lymphoid cells. In the future, experiments such as these will reveal even more insights into the role of growth hormone in communication networks among lymphoid cells, macrophages and the neuroendocrine system, as well as its potential role in human and animal health and disease.

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