Growth Hormone Exerts Hematopoietic Growth-Promoting Effects In Vivo and Partially Counteracts the Myelosuppressive Effects of Azidothymidine

By William J. Murphy, Galia Tsarfaty, and Dan L. Longo

Recombinant human growth hormone (rhGH) was administered to mice to determine its effect on hematopoiesis. BALB/c mice and mice with severe combined immune deficiency (SCID), which lack T cells and B cells, were administered intraperitoneal injections of rhGH for 7 days. Upon analysis, both strains of mice exhibited an increase in splenic and bone marrow hematopoietic progenitor cell content and cellularity, indicating that rhGH can act as a hematopoietic growth factor. C57BL/6 mice were then placed on azidothymidine (AZT). AZT is a reverse transcriptase inhibitor currently used as a treatment for acquired immune deficiency syndrome (AIDS), but which also produces significant myelotoxic effects. Treatment of mice with rhGH partially counteracted the myelosuppressive properties of AZT. Bone marrow cellularity, hematocrit values, white blood cell counts, and splenic hematopoietic progenitor cell content were all significantly increased if rhGH (20 μg injected intraperitoneally every other day) was concurrently administered with AZT. Administration of ovine GH (ovGH), which, unlike rhGH, has no effect on murine prolactin receptors, also prevented the erythroid-suppressive effects of AZT in mice, but had no significant effect on granulocyte counts. Thus, the effects of GH are mediated at least in part through GH receptors in vivo. Additionally, when mice were initially myelosuppressed by several weeks of AZT treatment, the subsequent administration of ovGH resulted in an increase in splenic hematopoietic progenitor cells. No significant pathologic effects were observed in mice receiving either repeated rhGH or ovGH injections. Thus, GH exerts significant direct hematopoietic growth-promoting effects in vivo and may be of potential clinical use to promote hematopoiesis in the face of myelotoxic therapy.

GROWTH HORMONE (GH) exerts a variety of growth promoting effects on the body. GH has also been implicated in immune development and function.[1] There is also evidence, primarily through in vitro analysis, that GH can influence hematopoiesis.[2,3] GH has been shown to directly enhance erythropoiesis in vitro,[2] and GH-deficient dwarf mice have been reported to exhibit suppressed splenic hematopoietic progenitor cell content.[4] Additionally, GH has been shown to indirectly stimulate granulopoiesis in vitro through the release of secondary mediators such as insulin-like growth factor-1 (IGF-1).[3]

Azidothymidine (AZT) is a reverse transcriptase inhibitor currently used as a treatment for acquired immune deficiency syndrome (AIDS). One of the significant dose-limiting toxicities of AZT involves an anemia and neutropenia arising from its myelotoxic effects on the marrow.[5] We examined whether recombinant human GH (rhGH) would be an effective hematopoietic stimulating agent when administered in vivo and whether it would counteract the myelosuppressive properties of AZT. We report here that human GH exerts significant hematopoietic growth-promoting effects in vivo, partially reverses the myelosuppression by AZT, and may be of use clinically to promote hematopoiesis in the face of AZT or other myelotoxic therapy.

MATERIALS AND METHODS

Mice. C57BL/6 (B6), BALB/c, and CB17 *scid/scid* (SCID) mice were obtained from the Animal Production Facility (NCI-FCRDC, Frederick, MD) and were not used until 8 weeks of age. SCID mice were housed under specific pathogen-free conditions at all times.

Hematopoietic analysis. Blood was collected from mice via the lateral tail vein, using EDTA as an anticoagulant. Complete blood counts were performed with a Coulter counter (Coulter, Hialeah, FL) and differential cell counts were performed by microscopic examination of Wright's stained peripheral blood smears (MetPath, Inc, Rockville, MD). Samples were run through a Coulter STKS (Coulter) and a manual differential count was performed. Statistics were performed comparing different values using parametric analysis with the Student's *t*-test. All experiments had at least three mice per group and were performed at least three times.

Assay for in vitro hematopoiesis. Spleen cells (SC) or bone marrow cells (BMC) from mice were washed and resuspended in Iscove's modified Dulbecco's medium with 10% fetal bovine serum, 1% L-glutamine, and antibiotics (complete Iscove's modified Dulbecco's medium). Nucleated cells were counted on a Coulter counter (Coulter). The cells were then plated in 0.3% bactoagar (Difco Laboratories, Detroit, MI) in 35-mm Lux petri dishes (Miles Laboratories, Inc, Naperville, IL) at a concentration of 1×10^5 BMC or 5×10^5 spleen cells per plate. Colony formation was stimulated in some instances with predetermined optimal doses of growth-promoting cytokines such as recombinant murine granulocyte-macrophage colony-stimulating factor (GM-CSF) at 10 ng/mL (Amgen Corporation, Thousand Oaks, CA) and purified murine interleukin-3 (IL-3; 10 ng/mL) supplied by the Biological Response Modifiers Program Repository (Frederick, MD). Plates were incubated at 37°C for 7 days in 100% humidity, 5% CO_2 atmosphere. All experiments had at least three mice per group and were performed two to four times, with a representative experiment being shown. A Student's *t*-test was performed to determine if the values differed significantly ($P < .001$).

Treatment with GH. Mice in some groups received either 20 μg rhGH (provided by Genentech, San Francisco, CA) or 20 μg of ovine GH (ovGH; provided by the National Institute of Diabetes and Digestive and Kidney Diseases, the Center for Population Research of the National Institute of Child Health and Human Development, and the Agricultural Research Service of the US Department of Agriculture, as well as University of Maryland School of Medicine, Baltimore, MD) resuspended in 0.2 mL

From the Biological Response Modifiers Program, Division of Cancer Treatment, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD.

Submitted February 11, 1992; accepted May 19, 1992.

Address reprint requests to William J. Murphy, PhD, Biological Response Modifiers Program, NCI-Frederick Cancer Research and Development Center, Bldg 567, Rm 141, Frederick, MD 21702-1201.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" *in accordance with 18 U.S.C. section 1734 solely to indicate this fact.*

0006-4971/92/8006-0008$0.00/0

phosphate-buffered saline (PBS) and injected intraperitoneally (IP) every other day until the mice were assayed. Mice not receiving GH received daily IP injections of PBS.

Treatment with AZT. Mice received AZT (provided by Division of AIDS, NIAID, Bethesda, MD) in their drinking water (1 mg/mL). Mice were then assayed weekly.

RESULTS

Administration of rhGH in vivo results in an increase in hematopoietic progenitor cells. To determine if rhGH could exert hematopoietic growth promoting properties in vivo, BALB/c mice and mice with severe combined immune deficiency (SCID) were administered injections of 20 μg of rhGH every other day for 7 days (a total of three injections). A soft agar colony assay was then performed to determine hematopoietic progenitor cell content of BMC and SC. SCID mice were used because they lack T cells and B cells due to an inability to productively rearrange their immune receptor genes.[6] These mice allowed us to determine if the hematopoietic effects of rhGH were due to the production of cytokines by T cells because GH has been shown to stimulate T cells.[1] The results showed that the administration of rhGH resulted in significant ($P < .001$) increases in splenic and BMC colony-forming unit granulocyte-macrophage (CFU-GM) colonies in both BALB/c and SCID recipients (Table 1). Splenic cellularity was also increased after rhGH treatment (Table 2). However, no significant effects were detected on BMC cellularity or on peripheral blood differential counts in the normal recipients, even when 100-μg doses of rhGH were administered (data not shown). Additionally, no significant increases in body weight were noted in the recipients receiving 20-μg injections of rhGH (data not shown). Therefore, rhGH appears to exert significant hematopoietic growth-promoting effects after in vivo administration. Because rhGH treatment also increased the splenic hematopoietic progenitor cell content in SCID mice, these results also suggest that rhGH is not exerting its hematopoietic effects indirectly by inducing colony-stimulating factor production by T cells.

rhGH treatment prevents the myelosuppressive properties of AZT. Because one of the dose-limiting toxicities of AZT is anemia and neutropenia resulting from its myelotoxic properties, we then examined whether concurrent treatment of mice with rhGH and AZT would result in an improvement in their hematologic parameters. B6 mice were placed on AZT (1 mg/mL in drinking water) for several weeks. Upon analysis, these mice exhibited significantly lower ($P < .001$) BMC cellularity (Table 3), splenic hematopoietic progenitor cell content (Table 4), hematocrit (HCT) (Fig 1), and white blood cell (WBC) counts (Fig 2) than control mice. These effects became more pronounced the longer the mice were placed on AZT, with most hematologic values approaching half the control values. If mice were concurrently treated with 20-μg injections of rhGH administered every other day, all of these hematologic parameters improved significantly ($P < .001$). The absolute number of segmented cells also increased in response to rhGH treatment, increasing from 445 ± 85/mm^3 to 840 ± 26/mm^3 with mice placed on AZT and examined at day 21 after concurrent rhGH treatment. Similar results were obtained after 28 days (absolute granulocyte count was 889 ± 110/mm^3 on AZT alone compared with 1,485 ± 33/mm^3 in mice on AZT plus GH). However, the hematologic parameters failed to attain control values, even when higher doses (100 μg) of rhGH

Table 1. Effect of rhGH Treatment on Hematopoietic Progenitor Cell Content

Strain (organ)	Treatment	Colonies	
		Cytokines*	Media
BALB/c (spleen)	—	2.5 ± 1.9	0 ± 0
BALB/c (spleen)	rhGH†	9.3 ± 2.5‡	0 ± 0
BALB/c (BMC)	—	6.5 ± 1.8	0 ± 0
BALB/c (BMC)	rhGH†	52.3 ± 12.4‡	0 ± 0
SCID (spleen)	—	26.0 ± 5.4	0 ± 0
SCID (spleen)	rhGH†	87.0 ± 3.7‡	0 ± 0
SCID (BMC)	—	3.0 ± 0.0	0 ± 0
SCID (BMC)	rhGH†	13.3 ± 1.7‡	0 ± 0

*BMC or SC placed in soft agar with IL-3 and GM-CSF as described in Materials and Methods.

†Mice received 20 μg rhGH IP every other day for 7 days.

‡Values significantly ($P < .001$) greater than mice not receiving rhGH.

Table 2. Effect of rhGH on Splenic and BMC Cellularity

Strain (organ)	Treatment	No. of Cells (×10^6)
BALB/c (spleen)	—	61.9 ± 5.2
BALB/c (spleen)	rhGH*	93.1 ± 5.6†
BALB/c (BMC)	—	31.8 ± 3.3
BALB/c (BMC)	rhGH*	33.0 ± 2.7
SCID (spleen)	—	17.5 ± 2.0
SCID (spleen)	rhGH*	29.5 ± 1.6†
SCID (BMC)	—	21.1 ± 1.8
SCID (BMC)	rhGH*	27.8 ± 0.7†

*Mice received 20 μg rhGH IP every other day for 7 days with cellularity determined after 7 days. Values are representative of three experiments containing three to four mice per group.

†Values significantly ($P < .001$) greater than mice not receiving rhGH.

Table 3. Effect of rhGH on Splenic or BMC Cellularity During AZT Treatment

Strain (organ)	Treatment	No. of Cells (×10^6)
B6 (spleen)	—	101.8 ± 8.7
B6 (spleen)	AZT*	72.0 ± 4.2†
B6 (spleen)	AZT, rhGH‡	100.3 ± 1.2§
B6 (BMC)	—	45.3 ± 2.9
B6 (BMC)	AZT*	18.2 ± 2.4†
B6 (BMC)	AZT, rhGH‡	32.2 ± 3.7§

Values are representative of three to four experiments with three mice per group.

*Mice were placed on AZT (1 mg/mL) in drinking water for 21 days before assay.

†Values significantly lower ($P < .001$) than control mice that did not receive AZT.

‡Mice were placed on AZT (1 mg/mL) in drinking water and rhGH (20 μg) IP injections every other day for 21 days before assay.

§Values significantly higher ($P < .001$) than mice receiving AZT but no rhGH.

Table 4. Effect of rhGH on Hematopoietic Progenitor Cell Content in Mice Placed on AZT

Strain (organ)	Treatment	Colonies	
		Cytokines*	Media
B6 (spleen)	—	274.3 ± 18.7	0 ± 0
B6 (spleen)	AZT†	16.0 ± 7.1‡	0 ± 0
B6 (spleen)	AZT, rhGH§	43.5 ± 1.7‖	0 ± 0
B6 (BMC)	—	135.3 ± 19.7	0 ± 0
B6 (BMC)	AZT	56.4 ± 4.7‡	0 ± 0
B6 (BMC)	AZT, rhGH	120.0 ± 20.3‖	0 ± 0

Values are representative of three to four experiments with three mice per group.

*BMC or SC placed with IL-3 and GM-CSF as described in Materials and Methods.

†Mice were placed on AZT (1 mg/mL) in drinking water for 21 days.

‡Values significantly ($P < .001$) less than group not receiving AZT.

§Mice also received 20 μg rhGH IP every other day while on AZT.

‖Values significantly greater ($P < .001$) than mice receiving AZT only.

were administered (data not shown). Additionally, the mice exhibited no apparent pathologic effects from repeated rhGH administration. The mice appeared to be in good health throughout the study. They maintained a constant weight and mice killed at the end of the study showed no gross pathologic abnormality. Thus, treatment of mice with rhGH partially ameliorates the anemia and neutropenia arising from AZT treatment.

ovGH prevents and reverses the myelosuppression induced by AZT treatment. Because hGH has been reported to be capable of binding the prolactin receptor,[7] it is possible that rhGH can mediate its hematopoietic effects via the prolactin receptor pathway. To address this question, mice were treated with 20-μg injections of ovGH every other day to determine if ovGH would also counteract the myelosuppression caused by AZT treatment. ovGH does not bind to the murine prolactin receptor and any hematopoietic effects it exerts would be due to binding the GH receptor.[7] The

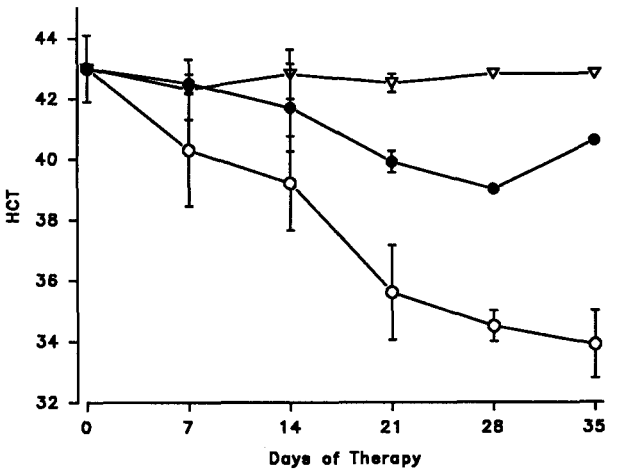

Fig 1. HCT levels (vol %) in mice receiving AZT (○) 1 mg/mL in drinking H_2O. In some groups, mice also received 20-μg injections of rhGH administered every other day (●). The points that appear to lack error bars actually have standard errors that are smaller than the size of the symbol and were thus omitted by the graphics program. (▽) Control.

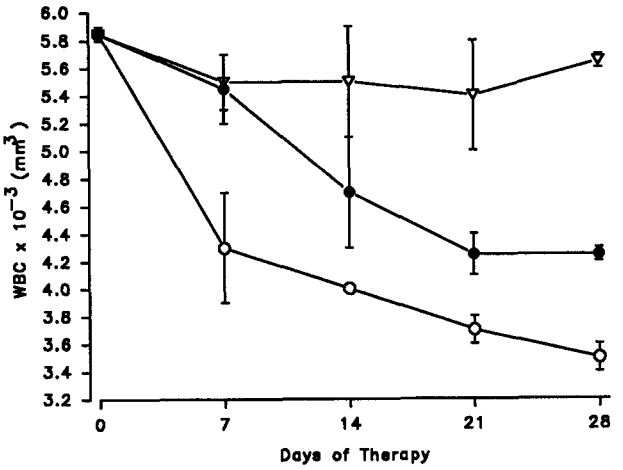

Fig 2. WBC counts (10^{-3}/mm³) in mice receiving AZT (○) 1 mg/mL in drinking H_2O. In some groups, mice also received 20-μg injections of rhGH administered every other day (●). The points that appear to lack error bars actually have standard errors that are smaller than the size of the symbol and were thus omitted by the graphics program. (▽) Control.

results show that administration of ovGH can also counteract the myelosuppressive effects of AZT as determined by HCT (Fig 3) and splenic hematopoietic progenitor cell content (Table 5, experiment A). However, no significant increases in WBC counts were obtained after ovGH treatment (data not shown).

Later ovGH treatment partially reverses the myelosuppression induced by AZT. It was then of interest to determine if the administration of ovGH after myelosuppression was already induced by AZT would improve hematologic parameters. Mice were administered AZT and after 3 weeks were analyzed to confirm that they were myelosuppressed. They then received 20-μg injections of ovGH administered every other day for 7 and 14 days. Upon analysis of both time points, significant improvement of splenic hematopoietic progenitor cell content was noted in the ovGH-treated

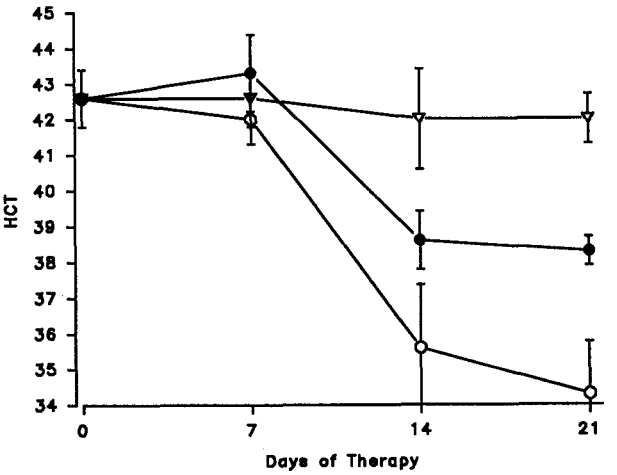

Fig 3. HCT levels (vol %) in mice receiving AZT (○) 1 mg/mL in drinking H_2O. In some groups, mice also received 20-μg injections of ovGH administered every other day (●). (▽) Control.

Table 5. Effect of ovGH on Splenic Hematopoietic Progenitor Cell Content in Mice Placed on AZT

Experiment*	Day of Analysis†	Treatment	Colonies	
			Cytokines‡	Media
A	14	AZT	47 ± 12	0 ± 0
		AZT + ovGH§	76 ± 7	0 ± 0
	21	AZT	30 ± 0	0 ± 0
		AZT + ovGH§	62 ± 8‖	0 ± 0
B	28	AZT	13 ± 7	0 ± 0
		AZT + ovGH¶	36 ± 9‖	0 ± 0
	35	AZT	55 ± 15	0 ± 0
		AZT + ovGH¶	116 ± 15‖	0 ± 0

*Representative of two to three experiments with three mice per group.

†Number of days after mice were placed on AZT (1 mg/mL) in drinking water.

‡SC placed with IL-3 and GM-CSF as described in Materials and Methods.

§Mice placed on AZT and received 20 μg of ovGH IP administered every other day starting at day 0.

‖Values significantly ($P < .001$) greater than mice receiving AZT only.

¶Mice were placed on AZT only for 21 days and were then treated with 20 μg of ovGH every other day starting at day 21. Mice were assayed later on day 28 (3 total injections of ovGH) and on day 35 (6 total injections of ovGH).

recipients (Table 5, experiment B), indicating that later ovGH administration also results in the partial reversal of myelosuppression induced by AZT. Similar results were obtained with rhGH (data not shown).

DISCUSSION

GH has a variety of biologic effects in vivo and has been suggested to exert effects on immune system development.[1] We report here that rhGH also enhances hematopoiesis when administered in vivo and can prevent or reverse the myelosuppression induced by AZT. Both the anemia and neutropenia resulting from AZT treatment were improved by the administration of rhGH. It is important to note that the hematopoietic growth-promoting effects of GH administration occurred at a dose regimen that did not result in significant body weight gain. Thus, the doses required for the manifestation of the hematopoietic effects of GH are not so high that undesirable side effects (such as growth) or significant pathology were noted.

The hematopoietic effects of rhGH could be due to both direct and indirect mechanisms. The data using SCID mice show that rhGH does not require T cells to produce its hematopoietic effects. While GH has been shown to exert hematopoietic growth-promoting effects in vitro,[2,3] little is known about its effects in vivo. It has been shown that GH can directly enhance erythropoiesis in vitro[2] and these properties may explain the increase in HCT levels in mice treated with both AZT and GH. Additionally, many of the growth-promoting effects of GH are mediated by IGF-I, which is produced in the liver in response to GH.[8] GH has also been shown to enhance granulopoiesis in vitro through the induction of IGF-I release by adherent cells in the BM.[3] Furthermore, BM stromal cells have been recently reported to secrete IGF-I.[9] Because the data presented here show that rhGH administration to mice placed on AZT resulted in the improvement of both WBC counts and HCTs, part of the hematopoietic effects of GH administration may be due to the induction of IGF-I release. However, the lack of effect of ovGH on WBC counts suggests that rhGH may mediate some of its granulopoietic effects via its ability to stimulate prolactin receptors.[7] We have found that dwarf mice, which lack GH and other neuroendocrine mediators, such as IGF-I and prolactin,[4] also display suppressed hematologic parameters, and treatment of the mice with rhGH resulted in an improvement of hematologic parameters involving both myeloid and erythroid lineages.[10] Preliminary results also indicate that treatment of mice with IGF-I produces significant hematopoietic growth-promoting effects (manuscript in preparation).

Human GH has also been shown to be capable of binding the prolactin receptor,[7] and some of the in vivo effects of rhGH may be due to this binding capability. Indeed, we have preliminary results indicating that prolactin exerts significant hematopoietic growth-promoting properties when administered in vivo and can also counteract the myelosuppression caused by AZT treatment (manuscript in preparation). However, the data obtained using ovGH, which does not bind the murine prolactin receptor,[7] indicate that at least some of the hematopoietic effects of rhGH are due to GH receptor binding activity because ovGH administration also yielded significant hematopoietic growth-promoting effects, particularly in the erythroid series.

The minimal toxicities associated with rhGH administration make it an attractive therapeutic agent in patients with AIDS undergoing AZT therapy.[11] In contrast, many cytokines (GM-CSF and IL-1) currently used to augment hematopoiesis clinically have significant dose-limiting toxicities[12] or affect only the neutropenia resulting from AZT treatment.[13] The use of rhGH resulted in increases in both erythroid- and myeloid-lineage cells and this may be more efficacious, less toxic, and less expensive than administering various myeloid-lineage–specific cytokines with or without erythropoietin or transfusions. Whereas rhGH has been shown to increase viral replication in human immunodeficiency virus (HIV)-infected T cells in vitro, coculture with AZT abolished this activity, suggesting that rhGH does not interfere with AZT's reverse transcriptase-inhibiting functions.[14] Because GH has also been suggested to improve T-cell function[1] and can result in increased body mass in patients with AIDS,[15] the use of rhGH in AIDS may offer other benefits in addition to the hematopoietic growth-promoting effects it may exert. HIV-infected individuals have also been shown to have defects in neutrophil respiratory burst and defects in the microbicidal capability of their neutrophils and monocytes.[16] GH has been recently shown to prime neutrophils for superoxide anion secretion[17] and has also been shown to exert similar effects on macrophages.[18] This suggests that rhGH may be of significant therapeutic use in AIDS for a variety of hematologic and immunologic reasons. However, while these results suggest that GH administration can improve hematologic parame-

ters after AZT treatment, it must be acknowledged that not all the peripheral cytopenias seen in AIDS patients are related to AZT toxicity alone. HIV infection may also impair hematopoiesis. Because rhGH does not appear to exert antiviral effects, it may have no effect on retroviral-mediated suppression of hematopoiesis in HIV infection. More work needs to be performed concerning the effects of GH in situations where both AZT treatment and active HIV infection occurs.

The use of rhGH may also improve hematopoietic engraftment after BM transplantation (BMT) or improve hematologic parameters in patients undergoing chemotherapy or radiation therapy. Preliminary results indicate both GH and prolactin administration resulted in greater hematopoietic engraftment in mice after syngeneic BMT (manuscript in preparation). Thus, rhGH exerts significant hematopoietic effects in vivo and may be of considerable clinical use to augment hematopoiesis in humans.

ACKNOWLEDGMENT

The authors thank Terry Phillips for outstanding secretarial services, Christie Harrison for superb technical assistance, Dr Ron Hornung for critically reviewing the manuscript, and Dr Scott Durum for helpful and stimulating discussions. The authors also gratefully acknowledge the assistance of Drs Ron Hornung and Ilan Tsarfaty with the statistical analysis and figures.

REFERENCES

1. Weigent DA, Blalock JE: Growth hormone and the immune system. Prog Neuroendocrinimmunol 3:231, 1990

2. Golde DW, Bersch N, Li CH: Growth hormone: Species-specific stimulation of erythropoiesis in vitro. Science 196:1112, 1976

3. Merchav S, Tatarsky I, Hochberg Z: Enhancement of human granulopoiesis in vitro by biosynthetic insulin-like growth factor I/somatomedin C and human growth hormone. J Clin Invest 81:791, 1988

4. Duquesnoy RJ, Pedersen GM: Immunologic and hematologic deficiencies of the hypopituitary dwarf mouse, in Gershwin ME, Merchant B (eds): Immunologic Defects in Laboratory Animals, vol 1. New York, NY, Plenum, 1981, p 309

5. Richman DD, Fischl MA, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, Hirsch MS, Jackson GG, Durack DT, Nusinoff-Lehrman S, the AZT Collaborative Working Group: The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 317:192, 1987

6. Schuler W, Weiler IJ, Schuler A, Phillips RA, Rosenberg N, Mak TW, Kearney JF, Perry RP, Bosma MJ: Rearrangement of antigen receptor genes is defective in mice with severe combined immune deficiency. Cell 46:963, 1986

7. Cunningham BC, Ultsch M, DeVos AM, Mulkerrin MG, Clauser KR, Wells JA: Dimerization of the extracellular domain of the human growth hormone receptor by a single hormone molecule. Science 254:821, 1991

8. D'Ercole AJ, Stiles AD, Underwood LE: Tissue concentrations of somatomedin C: Further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc Natl Acad Sci USA 81:935, 1984

9. Abboud SL, Bethel CR, Aron DC: Secretion of insulinlike growth factor I and insulinlike growth factor-binding proteins by murine bone marrow stromal cells. J Clin Invest 88:470, 1991

10. Murphy WJ, Durum SK, Anver MR, Longo DL: Immunologic and hematologic effects of neuroendocrine hormones: Studies on DW/J dwarf mice. J Immunol 148:3799, 1992

11. Salomon F, Cuneo RC, Hesp R, Sonksen PH: The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797, 1989

12. Smith JW II, Urba WJ, Curti BD, Elwood L, Steis RG, Janik JE, Sharfman WH, Miller L, Fenton RG, Conlon KC, Sznol M, Creekmore SP, Wells N, Ruscetti FW, Keller JW, Hestdal K, Shimizu M, Rossio J, Alvord WG, Oppenheim JJ, Longo DL: The toxic and hematologic effects of interleukin-1 alpha administered in a phase I trial to patients with advanced malignancies. J Clin Oncol (in press)

13. Levine JD, Allan JD, Tessitore JH, Falcone N, Galasso F, Israel RJ, Groopman JE: Recombinant human granulocyte-macrophage colony-stimulating factor ameliorates zidovudine-induced neutropenia in patients with acquired immunodeficiency syndrome (AIDS)/AIDS-related complex. Blood 78:3148, 1991

14. Laurence J, Grimison B, Gonenne A: Effect of recombinant human growth hormone on acute and chronic human immunodeficiency virus infection in vitro. Blood 79:467, 1992

15. Krentz AJ, Koster FT, Crist D, Finn K, Boyle PJ, Schade DS: Beneficial anthropometric effects of human growth hormone in the treatment of AIDS. Clin Res 39:220A, 1991 (abstr)

16. Smith PD, Ohura K, Masur H, Lane HC, Fauci AS, Wahl SM: Monocyte function in the acquired immune deficiency syndrome: Defective chemotaxis. J Clin Invest 74:2121, 1984

17. Fu Y-K, Arkins S, Shang Wang B, Kelley KW: A novel role of growth hormone and insulin-like growth factor-I. Priming neutrophils for superoxide anion secretion. J Immunol 146:1602, 1991

18. Edwards CK III, Ghiasuddin SM, Schepper JM, Yunger LM, Kelley KW: A newly defined property of somatotropin: Priming of macrophages for production of superoxide anion. Science 239:769, 1988