

INCREASED MORTALITY ASSOCIATED WITH GROWTH HORMONE TREATMENT IN CRITICALLY ILL ADULTS

JUKKA TAKALA, M.D., PH.D., ESKO RUOKONEN, M.D., PH.D., NIGEL R. WEBSTER, M.D., MICHAEL S. NIELSEN, M.D., DURK F. ZANDSTRA, M.D., GUY VUNDELINCKX, M.D., AND CHARLES J. HINDS, M.D.*

ABSTRACT

Background The administration of growth hormone can attenuate the catabolic response to injury, surgery, and sepsis. However, the effect of high doses of growth hormone on the length of stay in intensive care and in the hospital, the duration of mechanical ventilation, and the outcome in critically ill adults who are hospitalized for long periods is not known.

Methods We carried out two prospective, multicenter, double-blind, randomized, placebo-controlled trials in parallel involving 247 Finnish patients and 285 patients in other European countries who had been in an intensive care unit for 5 to 7 days and who were expected to require intensive care for at least 10 days. The patients had had cardiac surgery, abdominal surgery, multiple trauma, or acute respiratory failure. The patients received either growth hormone (mean [\pm SD] daily dose, 0.10 ± 0.02 mg per kilogram of body weight) or placebo until discharge from intensive care or for a maximum of 21 days.

Results The in-hospital mortality rate was higher in the patients who received growth hormone than in those who did not ($P < 0.001$ for both studies). In the Finnish study, the mortality rate was 39 percent in the growth hormone group, as compared with 20 percent in the placebo group. The respective rates in the multinational study were 44 percent and 18 percent. The relative risk of death for patients receiving growth hormone was 1.9 (95 percent confidence interval, 1.3 to 2.9) in the Finnish study and 2.4 (95 percent confidence interval, 1.6 to 3.5) in the multinational study. Among the survivors, the length of stay in intensive care and in the hospital and the duration of mechanical ventilation were prolonged in the growth hormone group.

Conclusions In patients with prolonged critical illness, high doses of growth hormone are associated with increased morbidity and mortality. (N Engl J Med 1999;341:785-92.)

©1999, Massachusetts Medical Society.

INCREASED protein turnover and negative nitrogen balance are characteristic features of critical illness.^{1,2} As a consequence, the structure and function of essential organs are compromised, most obviously in skeletal muscle, leading to respiratory-muscle weakness, a prolonged need for mechanical ventilation, and delayed mobility. Tissue repair, wound healing, and immune function may also be compromised.

The negative nitrogen balance in critically ill patients is partly attributable to resistance to growth hor-

mone and the decreased production and action of insulin-like growth factor I (IGF-I).³⁻⁵ Studies have shown that the administration of high doses of recombinant human growth hormone (5 to 20 times the dose needed for replacement therapy in growth hormone-deficient adults) improves nitrogen balance in normal subjects receiving hypocaloric parenteral nutrition,⁶ patients with severe burns,⁷ patients with trauma receiving parenteral nutrition,⁸ patients with gastrointestinal diseases receiving parenteral nutrition,⁹ patients who have undergone surgery,¹⁰ patients in the early phase of sepsis,¹¹ and other critically ill patients.¹² There is, however, only limited evidence that this improvement in nitrogen balance results in a shorter duration of mechanical ventilation, a shorter stay in the intensive care unit or in the hospital, or an improved outcome. In children with burns, growth hormone treatment reduced the hospital stay and shortened the time required for the sites from which the grafts were taken to heal.¹³ In surgical patients, treatment with growth hormone preserved muscle glutamine levels¹⁴ and hand-grip strength,¹⁵ improved the ability to cough, and facilitated weaning from mechanical ventilation.^{15,16} A three-week course of growth hormone treatment increased the maximal inspiratory pressure in patients with chronic obstructive pulmonary disease.¹⁷ However, a much shorter course was ineffective in similar patients in another study,¹⁸ and in a small, controlled study of patients undergoing mechanical ventilation, treatment with growth hormone was not associated with the preservation of muscle strength or a shortened period of weaning from mechanical ventilation, despite marked nitrogen retention.¹⁹

We evaluated the effect of treatment with high doses of growth hormone on clinical outcome variables in critically ill adults receiving prolonged intensive care.

METHODS

We conducted two independent, prospective, multicenter, double-blind, randomized, placebo-controlled trials in parallel, using similar, but not identical, protocols. One study involved 247 pa-

From the Critical Care Research Program, Department of Anesthesiology and Intensive Care, Kuopio University Hospital, Kuopio, Finland (J.T., E.R.); and the Intensive Care Units at Aberdeen Royal Infirmary, Aberdeen, United Kingdom (N.R.W.); Southampton General Hospital, Southampton, United Kingdom (M.S.N.); Onze Lieve Vrouwe Gasthuis, Amsterdam (D.F.Z.); St. Jans Hospital, Genk, Belgium (G.V.); and St. Bartholomew's Hospital, West Smithfield, London (C.J.H.). Address reprint requests to Dr. Takala at the Department of Anesthesiology and Intensive Care, Kuopio University Hospital, FIN-70210 Kuopio, Finland.

*Other participating investigators are listed in the Appendix.

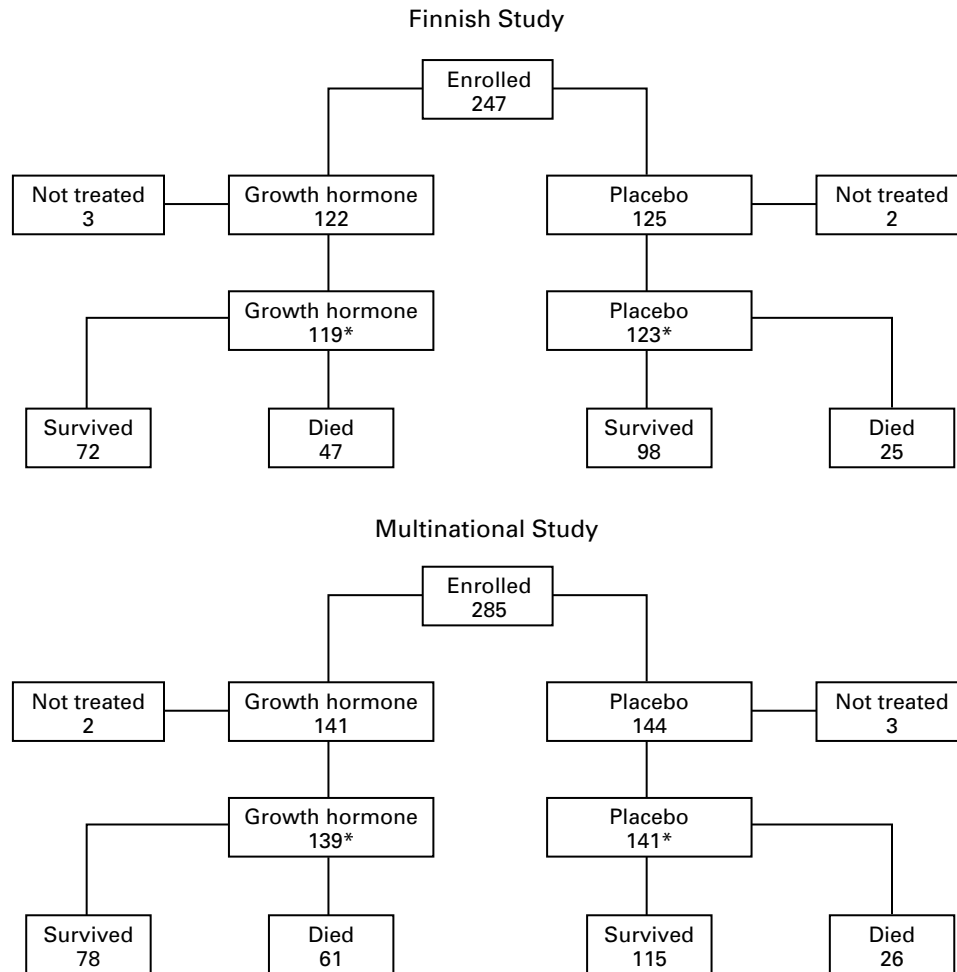


Figure 1. Numbers of Critically Ill Patients Assigned to Receive Growth Hormone or Placebo and Numbers of Patients Who Survived in the Finnish and Multinational Studies. The asterisks denote patients who received at least one dose of the study drug and who were therefore included in the intention-to-treat analysis. The analysis specified in the protocol was not performed, because of the high mortality rates in the growth hormone groups.

tients in 6 hospitals in Finland and was conducted from February 1994 to the end of June 1997, and the other involved 285 patients in 12 hospitals in the United Kingdom, the Netherlands, Belgium, and Sweden and was conducted from June 1994 to the end of June 1997 (Fig. 1). The randomization scheme was balanced and stratified according to both the reason for admission and the center in the Finnish study and according to the center in the multinational study.

Both studies were approved by the local ethics committees and were performed in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient or the next of kin. Overall mortality and adverse events were monitored continuously throughout the studies.

Patients 18 to 80 years old who had been in an intensive care unit for 5 to 7 days and were expected to need intensive care for a total of at least 10 days were eligible for enrollment. The patients belonged to one of four diagnostic groups, which were defined on the basis of the primary cause of admission to the intensive care unit: cardiac surgery, abdominal surgery, multiple trauma, or acute respiratory failure. Patients were excluded if they had cancer,

type 1 diabetes mellitus, chronic renal failure, burns, organ transplants, acute central nervous system damage, liver dysfunction, or septic shock at enrollment or if they were receiving glucocorticoid therapy.

The patients enrolled in the study received subcutaneous injections of recombinant growth hormone (Genotropin, 3 units per milligram, Pharmacia and Upjohn, Stockholm, Sweden) or placebo (saline) once daily in the morning. Patients weighing less than 60 kg received a dose of 5.3 mg of growth hormone, and those weighing 60 kg or more received 8.0 mg. The dose ranged from 0.07 to 0.13 mg per kilogram of body weight per day for patients weighing between 40 and 120 kg (1 mg of growth hormone is equivalent to 3 IU). In the Finnish study, the dose was increased from one quarter of the final dose initially to the full amount over a period of three days, whereas in the multinational study, the full dose was given from the time of enrollment. Treatment was administered for as long as the patient remained in the intensive care unit, but not for more than 21 days, except that in the multinational study, treatment could be continued after discharge from the intensive care unit, for a maximum of 21 days. Energy

intake was intended to be equivalent to 80 to 120 percent of the measured energy expenditure (in the Finnish study) or was based on clinical evaluation (in the multinational study). For nitrogen intake, the intention was to provide 1.5 g of protein per kilogram per day (in the Finnish study) or 0.7 to 1.5 g per kilogram per day (in the multinational study).

The primary efficacy variable was the duration of the stay in the intensive care unit. The secondary efficacy variables were use of intensive care resources (assessed on the basis of the Therapeutic Intervention Scoring System [TISS]²⁰), duration of mechanical ventilation, duration of hospital stay, hand-grip strength (determined with a dynamometer), level of general fatigue (assessed according to the fatigue scale of Christensen et al.²¹), exercise tolerance (assessed according to the ability to stand or walk, classified in six categories), incidence and clinical course of organ failures (assessed according to a scoring system based on the method of Ruokonen et al.²² [in the Finnish study] or Coakley et al.²³ [in the multinational study]), nitrogen balance (in the Finnish study), and in-hospital mortality. Survival at six months was determined when possible. The cause of death was determined from the patients' medical records independently by two clinicians who were unaware of the treatment assignments; if there was a disagreement, the cause was determined by consensus.

The severity of illness was assessed during the first 24 hours of intensive care and on entry into the trial with the use of the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system.²⁴ Adverse events, medications, and vital signs were recorded daily. Routine hematologic and biochemical tests were performed regularly. Serum IGF-I and IGF-binding proteins 1 and 3 were measured at base line and on days 4, 7, 14, and 21.

The calculations of sample size for each study were based on the numbers of patients receiving prolonged intensive care and the length of stay and mortality rate among such patients during a period of three consecutive years at Kuopio University Hospital in Kuopio, Finland. Originally, both studies were designed as group sequential trials, with the first analysis to be performed when 150 patients had received growth hormone or placebo for at least three days and had survived for at least two days after discharge from the intensive care unit and with subsequent analyses after each group of 40 additional patients had completed the study, up to a maximum of 436 patients. Because of slow recruitment due to the unexpectedly high incidence of exclusion criteria, the design was changed before the first interim analysis. The revised design was a fixed-sample analysis of 170 and 190 patients in the Finnish and multinational studies, respectively, who could be evaluated.

Data on mortality were analyzed with the use of the chi-square test. Demographic and safety data were analyzed with the use of frequency tables and Wilcoxon rank-sum tests for between-group comparisons. All patients who received at least one dose of placebo or growth hormone were included in the analyses.

RESULTS

In order to obtain 170 patients who could be evaluated (see the Methods section) in the Finnish study, 247 patients were enrolled, of whom 242 received growth hormone or placebo. In order to obtain 190 patients who could be evaluated in the multinational study, 285 patients were enrolled, of whom 280 received growth hormone or placebo (Fig. 1).

In both studies, the base-line characteristics of the patients, including APACHE II scores, TISS scores, and the number and nature of organ failures, were similar in the growth hormone and placebo groups (Table 1). The distribution of patients in the growth hormone and placebo groups between the four diagnostic categories was also similar in the two studies (Table 1). The mean (\pm SD) daily dose of growth

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	FINNISH STUDY		MULTINATIONAL STUDY	
	GROWTH HORMONE (N=119)	PLACEBO (N=123)	GROWTH HORMONE (N=139)	PLACEBO (N=141)
Male sex (% of patients)	76	73	68	64
Age (yr)	60 \pm 13	57 \pm 15	61 \pm 15	61 \pm 15
Body weight (kg)	81 \pm 16	81 \pm 19	76 \pm 17	74 \pm 15
Height (cm)	170 \pm 8	170 \pm 9	170 \pm 9	170 \pm 11
Diagnostic group (% of patients)				
Cardiac surgery	20	20	29	33
Abdominal surgery	28	29	18	18
Trauma	6	7	14	18
Acute respiratory failure	46	44	39	31
APACHE II score				
During first 24 hr	18 \pm 7	17 \pm 9	17 \pm 8	18 \pm 8
At enrollment	14 \pm 6	13 \pm 5	15 \pm 6	15 \pm 6
Organ failure at enrollment (% of patients)				
Cardiovascular	28	31	62	51
Respiratory	97	96	93	91
Gastrointestinal	50	41	17	21
Central nervous system	2	2	2	1
Renal	18	10	40	38
Hepatic	9	7	15	17
Coagulation	3	0	1	1
TISS score at enrollment†	39 \pm 8	40 \pm 9	37 \pm 11	35 \pm 9

*Plus-minus values are means \pm SD. P>0.05 for all comparisons between the treatment groups in each study. APACHE denotes Acute Physiology and Chronic Health Evaluation.

†In the Therapeutic Intervention Scoring System (TISS), each therapeutic intervention is assigned 1 to 4 points. An increasing score represents increasing intensity of treatment. The sum of the points is calculated daily for each patient.

hormone was 0.10 \pm 0.02 mg per kilogram for both survivors and nonsurvivors in the two studies.

In both studies, in-hospital mortality was significantly higher in the growth hormone group (39 percent in the Finnish study and 44 percent in the multinational study) than in the placebo group (20 percent in the Finnish study and 18 percent in the multinational study) (P<0.001 for the comparison of treatment groups in both studies). The relative risk of death for patients receiving growth hormone, as compared with those receiving placebo, was 1.9 (95 percent confidence interval, 1.3 to 2.9) in the Finnish study and 2.4 (95 percent confidence interval, 1.6 to 3.5) in the multinational study. The difference in mortality persisted at six months (43 percent in the growth hormone group and 23 percent in the placebo group in the Finnish study; 52 percent in the growth hormone group and 25 percent in the placebo group in the multinational study). The excess mortality associated with growth hormone treatment persisted when the data were analyzed according to diagnostic group, APACHE II score, and age (Table 2). Mortality rates were similar in men and women. In the multinational study, most of the excess deaths

TABLE 2. IN-HOSPITAL DEATHS AND CAUSES OF DEATH DURING INTENSIVE CARE.*

DEATHS AND CAUSES	FINNISH STUDY			MULTINATIONAL STUDY		
	GROWTH HORMONE (N=119)	PLACEBO (N=123)	P VALUE	GROWTH HORMONE (N=139)	PLACEBO (N=141)	P VALUE
Deaths						
Total — no. of patients (%)	47 (39)	25 (20)	<0.001	61 (44)	26 (18)	<0.001
Relative risk of death (95% CI)	1.9 (1.3–2.9)			2.4 (1.6–3.5)		
Diagnostic group — no. of patients/total no. (%)						
Cardiac surgery	10/24 (42)	6/25 (24)		21/40 (52)	8/47 (17)	
Abdominal surgery	17/33 (52)	11/36 (31)		12/25 (48)	10/25 (40)	
Trauma	2/7 (29)	1/8 (12)		4/20 (20)	1/25 (4)	
Acute respiratory failure	18/55 (33)	7/54 (13)		24/54 (44)	7/44 (16)	
APACHE II score during first 24 hr — no. of patients/total no. (%)						
≤20	30/79 (38)	12/83 (14)		42/100 (42)	13/92 (14)	
>20	17/40 (42)	13/40 (32)		19/39 (49)	13/49 (27)	
APACHE II score at enrollment — no. of patients/total no. (%)						
≤20	34/97 (35)	22/110 (20)		43/115 (37)	16/115 (14)	
>20	13/22 (59)	3/13 (23)		18/24 (75)	10/26 (38)	
Age — no. of patients/total no. (%)						
<55 yr	9/36 (25)	7/47 (15)		8/34 (24)	0/35	
55–70 yr	17/45 (38)	7/44 (16)		28/61 (46)	14/61 (23)	
>70 yr	21/38 (55)	11/32 (34)		25/44 (57)	12/45 (27)	
Causes of death during intensive care — no. of patients			0.66			0.71
Multiple-organ failure	12	6		22	11	
Septic shock or uncontrolled infection	15	4		16	4	
Cardiovascular cause	3	2		9	2	
Refractory respiratory failure	2	1		4	1	
Other	4	4		3	2	

*P values are for comparisons between the treatment groups in each study. CI denotes confidence interval, and APACHE Acute Physiology and Chronic Health Evaluation.

occurred during the first 10 days of treatment, whereas in the Finnish study, half the excess deaths occurred during the first 10 days of treatment and the remainder occurred more than 3 weeks after enrollment — that is, after growth hormone treatment had been stopped (Fig. 2). Because of the significant difference in mortality between the growth hormone and placebo groups, the planned analysis of the primary and secondary efficacy variables was considered inappropriate, and the results presented below are mainly confined to a descriptive analysis of potential explanatory variables.

Multiple-organ failure and septic shock or uncontrolled infection were the main causes of death in both treatment groups. The predominance of these causes of death was particularly marked in the patients treated with growth hormone (Table 2). Among the patients who were ultimately discharged from the hospital, those treated with growth hormone tended to have longer periods of mechanical ventilation, intensive care, and hospitalization and higher cumulative TISS scores than those who received placebo (Table 3). Grip strength and fatigue scores were similar among survivors in the two treatment groups. In the multinational study, the survivors who were treated

with growth hormone had worse exercise tolerance than those who received placebo (P=0.008).

The daily energy and nitrogen intakes were the same in the growth hormone and placebo groups, but nitrogen intake was somewhat lower in the multinational study than in the Finnish study. Patients who received growth hormone required more insulin and had higher blood glucose concentrations than those who received placebo (Table 4), but among patients given growth hormone, the mean daily dose of insulin in the survivors and nonsurvivors was similar. Although base-line serum concentrations of IGF-I, IGF-binding protein 1, and IGF-binding protein 3 were similar in the growth hormone and placebo groups in the multinational study, in the Finnish study the base-line serum IGF-I and IGF-binding protein 3 concentrations were lower, and the serum IGF-binding protein 1 concentration was higher in the growth hormone group (Table 4). At the last assessment, serum IGF-I concentrations had increased to a greater extent in the growth hormone group than in the placebo group in both studies. In both studies, serum IGF-I concentrations increased in response to growth hormone more frequently in the survivors than in the nonsurvivors. The nitrogen balance (as-

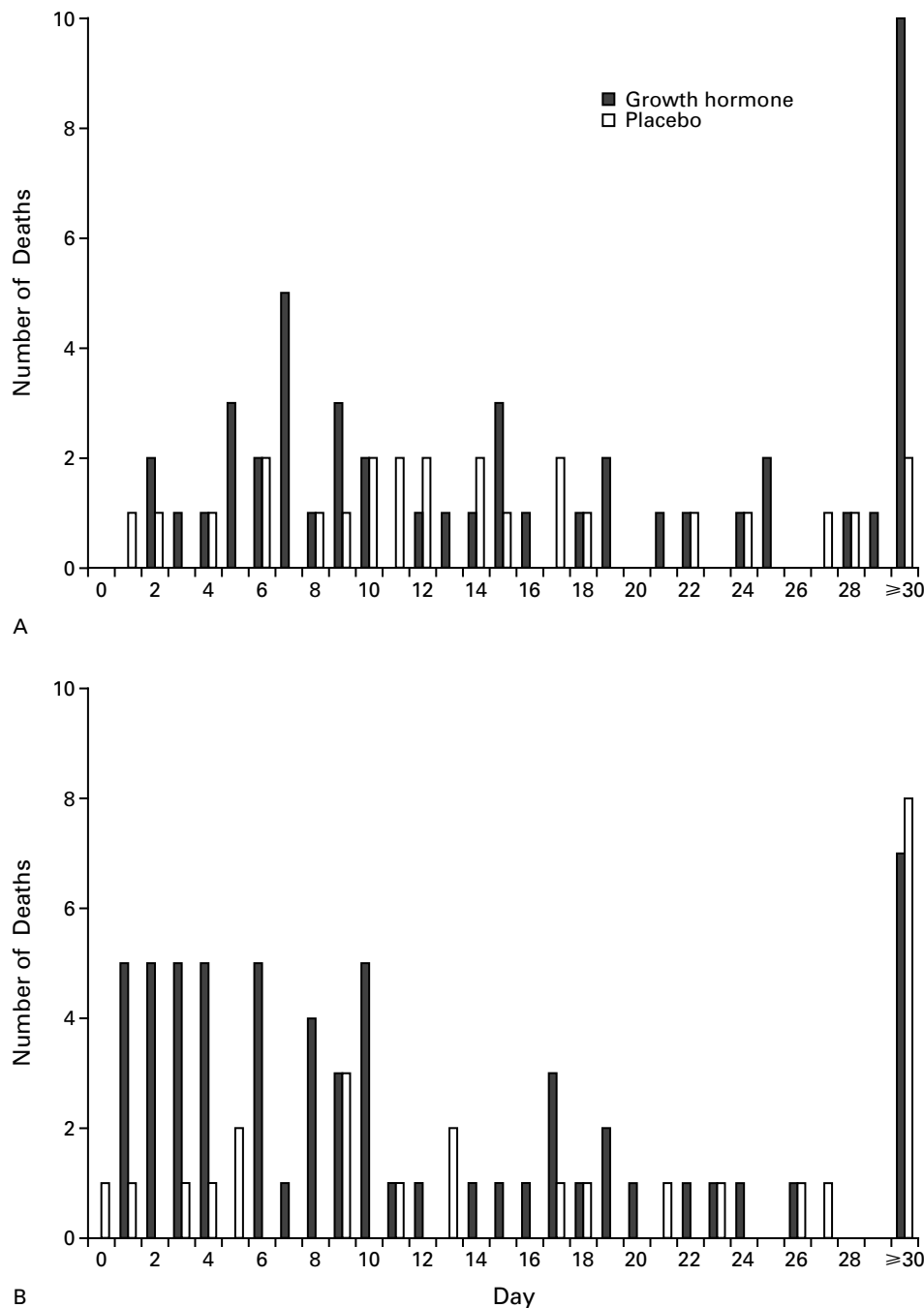


Figure 2. Numbers of Deaths in the Finnish Study (Panel A) and the Multinational Study (Panel B) According to the Treatment Assignment and Day of Treatment.

essed in the Finnish study only) was better in the growth hormone group than in the placebo group ($P=0.002$, $P=0.003$, and $P=0.21$ on days 7, 14, and 21, respectively; data not shown).

There were no significant differences in the overall frequency of adverse events in the treatment and placebo groups in either study. However, metabolic or

nutritional adverse events (mainly hyperglycemia) were reported more often in the growth hormone groups (in 71 percent of the patients in the Finnish study and 58 percent of those in the multinational study) than in the placebo groups (60 percent and 36 percent, respectively). Sepsis was also reported more frequently in the growth hormone groups (in

TABLE 3. RECOVERY AND USE OF RESOURCES AMONG THE SURVIVORS.*

VARIABLE	FINNISH STUDY			MULTINATIONAL STUDY		
	GROWTH HORMONE (N=72)	PLACEBO (N=98)	P VALUE	GROWTH HORMONE (N=78)	PLACEBO (N=115)	P VALUE
	median (interquartile range)			median (interquartile range)		
Duration of mechanical ventilation — days	14 (4–22)	9 (4–19)	0.18	12 (7–21)	8 (4–14)	<0.001
Duration of intensive care — days	16 (5–30)	10 (5–20)	0.10	15 (9–28)	11 (6–17)	0.001
Duration of hospital stay — days	35 (18–57)	28 (15–44)	0.20	30 (20–36)	24 (18–32)	0.18
Cumulative TISS score	577 (183–782)	351 (185–671)	0.18	443 (250–690)	298 (170–491)	0.001
Grip strength — first measurement (kg)	14 (8–21)	13 (6–24)	0.92	10 (6–19)	13 (7–22)	0.27
Fatigue score†	7 (5–9)	7 (5–8)	0.57	8 (6–9)	7 (6–9)	0.57
	no. of patients			no. of patients		
Exercise tolerance at discharge			0.49			0.008
Able to walk upstairs	20	22		11	15	
Able to walk without limitation	9	17		11	10	
Able to walk without aid	2	6		8	13	
Able to walk with aid	16	15		9	32	
Able to stand without aid	0	0		0	2	
Able to stand with aid	5	9		15	7	

*All periods refer to time after starting the study. P values refer to the differences between the treatment groups in each study. TISS denotes Therapeutic Intervention Scoring System.

†Fatigue was scored on a scale of 1 to 10, with higher scores indicating more fatigue.

TABLE 4. ENERGY AND NITROGEN INTAKE, INSULIN REQUIREMENTS, BLOOD GLUCOSE CONCENTRATIONS, AND SERUM CONCENTRATIONS OF IGF-I AND IGF-BINDING PROTEINS 1 AND 3.*

VALUE	FINNISH STUDY			MULTINATIONAL STUDY		
	GROWTH HORMONE	PLACEBO	P VALUE	GROWTH HORMONE	PLACEBO	P VALUE
Energy intake — kcal/day	1736±373	1722±363	0.78	1556±510	1510±557	0.47
Energy intake — kcal/kg/day	22±5	21±6	0.90	22±9	21±9	0.79
Nitrogen intake — g/day	15±3	15±4	0.34	9±3	9±3	0.38
Nitrogen intake — g/kg/day	0.2±0.0	0.2±0.0	0.37	0.1±0.1	0.1±0.0	0.49
Daily insulin						
No. of patients	83	57	<0.001	94	50	<0.001
Dose — IU	128±59	59±55	<0.001	90±78	38±27	<0.001
	median (interquartile range)			median (interquartile range)		
Blood glucose — mg/dl†	166 (139–196)	148 (124–173)	<0.001	178 (144–225)	133 (115–153)	<0.001
Serum IGF-I — ng/ml‡						
At enrollment	46 (32–79)	64 (42–91)	0.003	69 (45–109)	72 (47–114)	0.69
At last assessment	190 (120–384)	86 (52–114)	<0.001	346 (205–586)	115 (62–163)	<0.001
Serum IGF-binding protein 1 — µg/ml						
At enrollment	6 (2–18)	4 (2–9)	0.04	10 (3–32)	7 (2–26)	0.24
At last assessment	3 (1–13)	3 (1–7)	<0.001	3 (1–45)	5 (2–12)	<0.001
Serum IGF-binding protein 3 — µg/ml						
At enrollment	1.0 (0.6–1.4)	1.2 (0.7–1.7)	0.03	1.5 (1.0–1.9)	1.4 (1.0–2.1)	0.96
At last assessment	2.3 (1.4–3.1)	1.4 (0.9–1.8)	<0.001	3.6 (2.5–4.7)	1.9 (1.2–2.4)	<0.001

*Plus-minus values are means ±SD. P values refer to the differences between the treatment groups in each study.

†To convert the values for blood glucose to millimoles per liter, multiply by 0.056.

‡The normal ranges for serum IGF-I, according to age, are as follows: 16 to 24 years, 182 to 780 ng per milliliter; 25 to 39 years, 114 to 492 ng per milliliter; 40 to 54 years, 90 to 360 ng per milliliter; ≥55 years, 71 to 290 ng per milliliter.

13 percent of the patients in the Finnish study and 18 percent of those in the multinational study) than in the placebo groups (8 percent and 10 percent, respectively). Except for the more frequent need for insulin in the growth hormone-treated patients, there was no apparent difference in the need for medications between the two treatment groups.

DISCUSSION

Our two parallel studies provide strong evidence that the administration of high doses of growth hormone to critically ill adults receiving prolonged intensive care is associated with an increase in mortality. Moreover, among the patients in our studies who survived, the duration of mechanical ventilation, intensive care, and hospitalization was prolonged by growth hormone treatment. Despite significant improvements in nitrogen balance and increases in serum IGF-I concentrations, grip strength and fatigue were unaffected by treatment with growth hormone. The difference in the timing of the excess deaths between the two studies is difficult to explain, but the escalation of the dose of growth hormone over the course of three days may have contributed. In both studies, the mortality rate in the placebo group was lower than had been anticipated for patients with such severe illness, possibly because we excluded some categories of patients whose prognosis was particularly poor, such as those with cancer.

The reason for the increased morbidity and mortality associated with growth hormone administration in these studies is unclear, but the preponderance of multiple-organ failure and septic shock or uncontrolled infection as causes of death in the growth hormone group suggests that a modulation of immune function may be involved. Depending on the experimental conditions, growth hormone can either augment^{25,26} or inhibit^{27,28} the production of reactive oxygen species and proinflammatory cytokines, and it can either reduce²⁹ or increase³⁰ the susceptibility to endotoxin or bacterial challenge in animals. These findings suggest that, depending on the underlying clinical condition, the effects of growth hormone administration on immune function in patients in a catabolic state can be either beneficial or detrimental. In surgical patients, treatment with growth hormone has been associated with improved cell-mediated immunity and a reduced incidence of postoperative wound infections.³¹ However, growth hormone treatment did not reduce the number of episodes of sepsis in a study of children with burns¹³ and did not affect the sepsis score or the outcome in a study of patients with sepsis.³²

Fluid retention is a well-recognized side effect of growth hormone administration, but it is usually identified and treated rapidly in an intensive care unit and was rarely reported as an adverse event in our study. Moreover, in critically ill surgical patients, treatment

with growth hormone attenuated abnormal fluid distribution.³³ In our studies, blood glucose concentrations and insulin requirements were higher in the growth hormone groups, but there were no differences between the survivors and nonsurvivors in these groups. Hyperglycemia has, however, been associated with an increased risk of sepsis, and we cannot exclude the possibility that the insulin resistance induced by growth hormone treatment deprived cells of glucose. Another possible explanation for the poorer outcome associated with the administration of growth hormone is that it prevents the mobilization of glutamine from muscle and that, as a result, less glutamine is available for rapidly dividing cells, such as leukocytes and enterocytes, and for hepatic production of glutathione.³⁴ Other possible explanations include stimulation of lipolysis³⁵ and interference with thyroid or adrenocortical function.³⁶ The deleterious effects of growth hormone in critically ill patients are probably multifactorial, complex, interlinked, and dependent on the timing of treatment, the patient's condition, and the dose of growth hormone.

Because patients in a catabolic state have a resistance to the anabolic effects of growth hormone, most previous investigators^{6-14,16,19,37-39} have given such patients high doses of growth hormone, similar to those given in this study. In a previous study, the threshold dose for improving nitrogen balance in postoperative patients was 0.06 mg of growth hormone per kilogram per day, and there was a dose-related increase in the serum concentration of IGF-I of 0.03 to 0.12 mg per kilogram per day.⁴⁰ In studies of critically ill patients, those with severe injuries, and those with sepsis, the administration of such high doses of growth hormone improved nitrogen balance.^{8,11,12,19,38} In these relatively small studies, the administration of growth hormone was not associated with an increase in morbidity or mortality,^{11,12,37,38} and indeed, several studies have indicated that such treatment may be beneficial. However, many of these studies involved patients who were less severely ill than those in our studies, such as postoperative patients^{10,14,15} and those receiving parenteral nutrition.^{6,9} Treatment with growth hormone in a dose of 0.10 to 0.20 mg per kilogram per day has also been reported to be effective in children with burns,¹³ and in one retrospective study, it was associated with increased survival among adults with severe burns.³⁹ Children and patients with burns were excluded from our studies. Several studies have indicated that treatment with growth hormone is safe in patients with sepsis^{31,32,37,38} and in those with severe sepsis,¹¹ as well as in critically ill patients without sepsis.¹² In seriously ill postoperative patients with respiratory failure, the mortality rate was lower than predicted.¹⁶

In conclusion, the two studies reported here clearly indicate that the administration of high doses of growth hormone to critically ill patients receiving pro-

longed intensive care is associated with increased morbidity and mortality.

Supported by research contracts with Pharmacia and Upjohn, Stockholm, Sweden.

We are indebted to Johan Szamosi, M.Sc., for statistical analysis and advice; to Dr. I. Parviainen for an independent review of the causes of death; and to Dr. B. Pettersson for helpful advice and support.

APPENDIX

The other participating centers and investigators were as follows: Finnish study — E. Lopenon, Central Hospital of Mikkeli, Mikkeli; V. Rauhala, Central Hospital of Central Finland, Jyväskylä; S. Hovilehto, Central Hospital of South Carelia, Lappeenranta; S. Karlsson, Central Hospital of North Carelia, Joensuu; and P. Kairi, Vaasa Central Hospital, Vaasa. Multicenter study — M.C. Bellamy, St. James University Hospital, Leeds, United Kingdom; J.M. Sepers, Alkmaar Medical Center, Alkmaar, the Netherlands; M. Reynaert, St. Luc University Hospital, Brussels, Belgium; A.M. Dive, Mont Godinne University Hospital, Namur, Belgium; T. Dugernier, St. Pierre Hospital, Ottignies, Belgium; A. Rydvall, Norrlands University Hospital, Umeå, Sweden; and E. Vernerson, University Hospital, Malmö, Sweden. Research fellows: F. Gibson and C. Botfield, St. Bartholomew's Hospital, London.

REFERENCES

- Rennie MJ. Muscle protein turnover and the wasting due to injury and disease. *Br Med Bull* 1985;41:257-64.
- Arnold J, Campbell IT, Samuels TA, et al. Increased whole body protein breakdown predominates over increased whole body protein synthesis in multiple organ failure. *Clin Sci (Colch)* 1993;84:655-61. [Erratum, *Clin Sci (Colch)* 1993;85:xxv.]
- Ross R, Miell J, Freeman E, et al. Critically ill patients have high basal growth hormone levels with attenuated oscillatory activity associated with low levels of insulin-like growth factor-I. *Clin Endocrinol (Oxf)* 1991;35:47-54.
- Van den Berghe G, De Zegher F, Veldhuis JD, et al. The somatotrophic axis in critical illness: effect of continuous growth hormone (GH)-releasing hormone and GH-releasing peptide-2 infusion. *J Clin Endocrinol Metab* 1997;82:590-9.
- Timmins AC, Cotterill AM, Hughes SC, et al. Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins, and induction of an insulin-like growth factor binding protein 3 protease. *Crit Care Med* 1996;24:1460-6.
- Manson JM, Smith RJ, Wilmore DW. Growth hormone stimulates protein synthesis during hypocaloric parenteral nutrition: role of hormonal-substrate environment. *Ann Surg* 1988;208:136-42.
- Gore DC, Honeycutt D, Jahoor F, Wolfe RR, Herndon DN. Effect of exogenous growth hormone on whole-body and isolated-limb protein kinetics in burned patients. *Arch Surg* 1991;126:38-43.
- Jeevanandam M, Ali MR, Holaday NJ, Petersen SR. Adjuvant recombinant human growth hormone normalizes plasma amino acids in parenterally fed trauma patients. *J Parenter Enteral Nutr* 1995;19:137-44.
- Ziegler TR, Rombeau JL, Young LS, et al. Recombinant human growth hormone enhances the metabolic efficacy of parenteral nutrition: a double-blind, randomized controlled study. *J Clin Endocrinol Metab* 1992;74:865-73.
- Ponting GA, Halliday D, Teale JD, Sim AJW. Postoperative positive nitrogen balance with intravenous hyponutrition and growth hormone. *Lancet* 1988;1:438-40.
- Voerman HJ, van Schijndel RJM, Groeneveld ABJ, et al. Effects of recombinant human growth hormone in patients with severe sepsis. *Ann Surg* 1992;216:648-55.
- Voerman BJ, Strack van Schijndel RJM, Groeneveld AB, de Boer H, Nauta JP, Thijs LG. Effects of human growth hormone in critically ill non-septic patients: results from a prospective, randomized, placebo-controlled trial. *Crit Care Med* 1995;23:665-73.
- Herndon DN, Barrow RE, Kunkel KR, Brocmeel L, Rutan RL. Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990;212:424-9.
- Hammarqvist E, Stromberg C, von der Decken A, Vinnars E, Wernerman J. Biosynthetic human growth hormone preserves both muscle protein synthesis and the decrease in muscle-free glutamine, and improves whole-body nitrogen economy after operation. *Ann Surg* 1992;216:184-91.
- Jiang Z-M, He G-Z, Zhang S-Y, et al. Low-dose growth hormone and hypocaloric nutrition attenuate the protein-catabolic response after major operation. *Ann Surg* 1989;210:513-25.
- Knox JB, Wilmore DW, Demling RH, Sarraf P, Santos AA. Use of growth hormone for postoperative respiratory failure. *Am J Surg* 1996;171:576-80.
- Pape GS, Friedman M, Underwood LE, Clemmons DR. The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. *Chest* 1991;99:1495-500.
- Suchner U, Rothkopf MM, Stanislaus G, Elwyn DH, Kvetan V, Askanazi J. Growth hormone and pulmonary disease: metabolic effects in patients receiving parenteral nutrition. *Arch Intern Med* 1990;150:1225-30.
- Pichard C, Kyle U, Chevrolet J-C, et al. Lack of effects of recombinant growth hormone on muscle function in patients requiring prolonged mechanical ventilation: a prospective, randomized, controlled study. *Crit Care Med* 1996;24:403-13.
- Malstam J, Lind L. Therapeutic Intervention Scoring System (TISS) — a method for measuring workload and calculating costs in the ICU. *Acta Anaesthesiol Scand* 1992;36:758-63.
- Christensen T, Bendix T, Kehlet H. Fatigue and cardiorespiratory function following abdominal surgery. *Br J Surg* 1982;69:417-9.
- Ruokonen E, Takala J, Kari A, Alhava E. Septic shock and multiple organ failure. *Crit Care Med* 1991;19:1146-51.
- Coakley JH, Nagendran K, Honavar M, Hinds CJ. Preliminary observations on the neuromuscular abnormalities in patients with organ failure and sepsis. *Intensive Care Med* 1993;19:323-8.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
- Warwick-Davies J, Lowrie DB, Cole PJ. Growth hormone is a human macrophage activating factor: priming of human monocytes for enhanced release of H₂O₂. *J Immunol* 1995;154:1909-18.
- Edwards CK III, Lorence RM, Dunham DM, et al. Hypophysectomy inhibits the synthesis of tumor necrosis factor α by rat macrophages: partial restoration by exogenous growth hormone or interferon γ . *Endocrinology* 1991;128:989-96.
- Kappel M, Hansen MB, Diamant M, Pedersen BK. In vitro effects of human growth hormone on the proliferative responses and cytokine production of blood mononuclear cells. *Horm Metab Res* 1994;26:612-4.
- Elsasser TH, Fayer R, Rumsey TS, Hartnell GE. Recombinant bovine somatotropin blunts plasma tumour necrosis factor- α , cortisol, and thromboxane-B2 responses to endotoxin in vivo. *Endocrinology* 1994;134:1082-8.
- Inoue T, Saito H, Fukushima R, et al. Growth hormone and insulin-like growth factor I enhance host defense in a murine sepsis model. *Arch Surg* 1995;130:1115-22.
- Liao W, Rudling M, Angelin B. Growth hormone potentiates the in vivo biological activities of endotoxin in the rat. *Eur J Clin Invest* 1996;26:254-8.
- Vara-Thorbeck R, Guerrero JA, Rosell J, Ruiz-Requena E, Capitan JM. Exogenous growth hormone: effects on the catabolic response to surgically produced acute stress and on postoperative immune function. *World J Surg* 1993;17:530-8.
- Gottardis M, Benzer A, Koller W, Luger TJ, Puhlinger F, Hackl J. Improvement of septic syndrome after administration of recombinant human growth hormone (rhGH)? *J Trauma* 1991;31:81-6.
- Gatzen C, Scheltinga MR, Kimbrough TD, Jacobs DO, Wilmore DW. Growth hormone attenuates the abnormal distribution of body water in critically ill surgical patients. *Surgery* 1992;112:181-7.
- Biolo G, Iscra F, Toigo G, et al. Effects of growth hormone administration on skeletal muscle glutamine metabolism in severely traumatized patients: preliminary report. *Clin Nutr* 1997;16:89-91.
- Jeevanandam M, Petersen SR. Altered lipid kinetics in adjuvant recombinant human growth hormone-treated multiple-trauma patients. *Am J Physiol* 1994;267:E560-E565.
- Gelding SV, Taylor NF, Wood PJ, et al. The effect of growth hormone replacement therapy on cortisol-cortisone interconversion in hypopituitary adults: evidence for growth hormone modulation of extrarenal 11β -hydroxysteroid dehydrogenase activity. *Clin Endocrinol (Oxf)* 1998;48:153-62.
- Koea JB, Breier BH, Douglas RG, Gluckman PD, Shaw JHE. Anabolic and cardiovascular effects of recombinant human growth hormone in surgical patients with sepsis. *Br J Surg* 1996;83:196-202.
- Voerman BJ, Strack van Schijndel RJ, de Boer H, et al. Effects of human growth hormone on fuel utilization and mineral balance in critically ill patients on full intravenous nutritional support. *J Crit Care* 1994;9:143-50.
- Knox J, Demling R, Wilmore D, Sarraf P, Santos A. Increased survival after major thermal injury: the effect of growth hormone therapy in adults. *J Trauma* 1995;39:526-30.
- Tacke J, Bolder U, Lohlein D. Improved cumulated nitrogen balance after administration of recombinant human growth hormone in patients undergoing gastrointestinal surgery. *Infusionsther Transfusionsmed* 1994;21:24-9.