Metabolic Effects of Recombinant Human Growth Hormone in Patients Receiving Parenteral Nutrition

THOMAS R. ZIEGLER, M.D., LORRAINE S. YOUNG, R.D., M.S., JAMES McK. MANSON, F.R.C.S., and DOUGLAS W. WILMORE, M.D.

Recombinant human methionyl growth hormone (Protropin®) (Genetech, Inc., San Francisco, CA) administered to normal volunteers receiving hypocaloric parenteral nutrition minimized weight loss and induced positive nitrogen balance. To evaluate whether growth hormone (GH) can promote anabolism in surgical patients, 11 stable malnourished individuals were studied. In the initial trial, subjects received a constant parenteral infusion of a hypocaloric diet that provided approximately 1100 kcal/24 hr and 1.3 g protein/kg/24 hr for at least 2 weeks. During 1 week, GH 10 mg was given subcutaneously daily, whereas the other week served as the control. Daily balance studies demonstrated that administration of GH resulted in significant retention of nitrogen (+3.4 g/24 h) and phosphorus (+218 mg/24 h), despite provision of only 60% of caloric requirements. With GH, serum blood urea nitrogen (BUN) and potassium fell, whereas glucose and insulin tended to rise, and levels of insulin-like growth factor 1 increased three to fourfold. Weight gain occurred with GH and was associated with positive mineral and water balance. Six patients received GH (10 mg subcutaneously daily) for 13–25 consecutive days after an initial control week. Significant nitrogen and phosphorus retention occurred over the entire period of GH administration, and no significant side effects were observed. In these depleted patients, GH caused significant and sustained nitrogen retention over a wide range of nutritional support. GH appears to enhance the efficacy of parenteral nutrition in stable individuals requiring repletion of body protein.

NEGATIVE NITROGEN BALANCE and erosion of the lean body mass are characteristic responses that occur after operation, injury, and infection.[1-3] The accelerated net breakdown of protein is at-

tenuated by the administration of adequate quantities of energy, protein, and other essential nutrients; in the critically ill patient, this administration of nutrients is usually accomplished by the intravenous infusion of a hypertonic nutrient solution *via* a central venous catheter.

Central venous parenteral nutrition has greatly improved the care of the severely ill patient. Because body weight is usually stabilized and nitrogen balance estimates frequently approach equilibrium, it is commonly assumed that the erosion of the lean body mass—the functional and structural components of the body—is prevented by such nutritional support. However, a variety of investigators using newer assessment methodologies have studied hospitalized patients receiving "optimal" parenteral nutrition, and their reports have failed to substantiate the optimism often expressed at the patient's bedside.[4] Serial body composition analysis suggests that stabilization or gain of body weight can be accounted for by increases in total body water and, to a lesser extent, gain in adipose tissue.[4-6] Of greater concern is the inability to increase body protein with almost all forms of nutritional support. The infusion of large quantities of amino acids (2.0–3.0 g/kg/day) has become a popular method of attempting to reverse this process. However, critical assessment of the available data[7] and stable isotope studies that determine maximal rates of protein synthesis[8] fail to support the concept that more is better.

Loss of moderate amounts of body protein would be of little concern if this alteration were unrelated to morbidity. However, fatigue is one of the most common patient complaints during convalescence,[9] and skeletal muscle weakness and altered muscle function are com-

monly observed in malnourished hospitalized patients.[10] Despite their having "adequate" nutritional support, trauma/septic patients demonstrate protracted rates of wound closure, have repeated episodes of infection, and develop multiorgan system failure,[11] events that are interrelated to the metabolic state of the individual and the support provided. In addition to these problems, parenteral nutrition has been causally related to hepatic dysfunction,[12] pulmonary compromise,[13-14] and increased rates of septicemia.[15]

Several years ago, we studied a group of normal volunteers who received intravenous feedings and human growth hormone, made available for the first time in large quantities by newly developed genetic engineering techniques.[16] The purpose of our investigation was to determine the relationship between dietary energy, growth hormone administration, and nitrogen balance. Caloric intake was provided at three levels: 100%, 50%, and 30% of energy requirements. Adequate protein and other essential nutrients were also administered. During control studies, reduction in energy intake was associated with negative nitrogen balance; nitrogen equilibrium occurred only with adequate (100%) calorie intake. With growth hormone (GH) administration, positive nitrogen balance of approximately 2 g/day occurred at *all levels of caloric intake,* even when only 30% of the energy requirements (approximately 150 g of glucose) were provided.[16]

The ability to feed patients a hypocaloric diet and simultaneously achieve positive nitrogen balance is appealing. Body fat, which is usually readily available, is utilized as a major energy source, thereby minimizing the problems and complications associated with infusion of hypertonic glucose solutions. In addition, the hormonal environment created by GH stimulates marked protein synthesis, and therefore a significant quantity of protein-rich tissue is generated.[17]

The purpose of this study was to evaluate this approach in stable patients who required protein repletion. After controlled observations in a short-term study, longer periods of GH administration were carried out to determine if these alterations were merely transient in nature. In all studies, GH administration was associated with minimal side effects and marked positive nitrogen balance.

Materials and Methods

All subjects were studied in the Clinical Research Center of Brigham and Women's Hospital. The protocol was approved by the Committee for the Protection of Human Subjects from Research Risks, Brigham and Women's Hospital, Boston, Massachusetts, and informed consent was obtained from all subjects.

Short-term Study

Patients. Nine patients requiring parenteral nutrition for at least 2 weeks were studied initially (Table 1). Eight subjects were studied after gastrointestinal tract operations, and seven of these had enterocutaneous fistulas. One subject was studied while receiving nutritional support in preparation for an operation. All subjects were clinically stable, without evidence of uncontrolled infection or acute nongastrointestinal organ dysfunction. With the exception of one patient with chronic renal insufficiency (Pt 7, creatinine ≈ 2.5 mg/dl), all were free of significant renal, hepatic, cardiopulmonary, endocrine, or central nervous system disease. None of the patients had cancer at the time of study, although Patients 2 and 9 had undergone a recent resection for Duke's Stage BII adenocarcinoma of the colon, and Patient 6 had a history of Stage BI carcinoma of the cervix treated by partial hysterectomy and pelvic radiation 7 years before the study. Recent laparotomy revealed no evidence of cancer at the time of this hospitalization. Two subjects received daily steroid therapy in constant doses throughout their study (Patient 2 received 20 mg of oral prednisone every 24 hours for Crohn's disease and Patient 9 received 30 mg of hydrocortisone intravenously every 24 hours for rheumatoid arthritis). Patient 9 also received gold injections every other week.

Study design. Each short-term study consisted of two consecutive 7-day periods (control and treatment) in which the nutrient mix was kept constant for the entire 14 days. A double-blind, randomized, crossover study design was employed for the first five subjects. At the time of entry into the study, the order of treatment (control week followed by treatment week or treatment week followed by control) was determined by sequential entry on a random order list. During their control period, a daily subcutaneous injection of saline (placebo) was given at 8:30 A.M. The exception to this administration schedule was Patient 1, who received nutrient infusions in the evening and the daily saline or GH injections at 8:30 P.M. During the treatment week, 10 mg of recombinant human methionyl growth hormone (m-hGH, Protropin, Genentech, Inc., San Francisco, CA) was given subcutaneously daily at 8:30 A.M. The syringes were filled by the research pharmacist, and the contents were not specified to the nursing and physician staff. The periods were otherwise identical.

Three subjects (2, 3, and 5) entered the control week first followed by the GH week, whereas two subjects (1 and 4) received GH the first week and saline injections the second week. Patient 3 was also studied during a control week after the GH week. Thus, three subjects had a control period of study following completion of m-hGH therapy. After this initial phase, the code was

TABLE 1. Clinical Characteristics of Patients in the Short-Term Trial

Patient	Age	Sex	Weight (KG)	% IBW	BSA	Diagnosis	Medications	Days After Operation	Week Control	Week m-hGH
1	46	F	81	129	1.98	Gastrocutaneous fistula (following gastric bypass)	Ranitidine	121	2	1
2	35	M	63	96	1.76	Ileocolocutaneous fistula (following small bowel resection for Crohn's disease)	Prednisone, antibiotics	66	1	2
3	78	F	68	123	1.74	Ileocolocutaneous fistula (following hemicolectomy for colonic carcinoma)	Warfarin	106	1 + 3	2
4	23	F	60	97	1.72	Short-bowel syndrome (following trauma)	Cimetidine	34	2	1
5	53	M	61	100	1.68	Multiple enterocutaneous fistulas (following lysis of adhesions)	None	25	1	2
6	48	F	77	132	1.82	Jejunal-cutaneous fistula (following drainage of appendicial abscess)	Ranitidine	17	1	2
7	69	M	56	88	1.66	Enterocutaneous fistula (following lysis of adhesions and bowel resection)	Ranitidine	23	1	2
8	50	F	55	85	1.66	Postvagotomy gastric stasis	Ranitidine	Before Operation	1	2
9	65	F	47	98	1.42	Ileocolcutaneous fistula (following hemicolectomy for colonic carcinoma)	Hydrocortisone, estrogen, ranitidine, gold	29	1	2
Mean	52		63	105	1.72			53		
Range	23–78		47–81	85–132	1.42–1.98			17–121		

broken and the study was performed in an unblinded manner in the last four subjects. These four patients entered the control period initially and did not receive saline placebo injections during this period. All other aspects of the protocol were similar. Thus, seven of nine patients in the short-term study entered a control period first, and two entered the GH period before the control period.

Nutritional prescription. Basal energy requirements were estimated from standard tables based on height, weight, age, and sex.[3] An additional 5–10% of the basal energy requirement was added to the basal requirement to account for the stress of the underlying disease. An additional 25% of this adjusted energy requirement was then added to account for energy expenditure associated with activity. All subjects were encouraged to ambulate ad lib on the ward as indicated.

The daily energy requirement was divided by 150 to determine daily nitrogen requirements. The nine subjects received this level of nitrogen intake ($\approx$1.3 grams protein/kg/24 hr). However, only 60% of the energy requirements as determined above were provided as exogenous nutrients. After determining the energy intake (metabolic requirements as defined above $\times$ 0.6), the calories provided as amino acids were then subtracted from the 60% energy level to determine the nonprotein energy needs. This was provided as dextrose (assuming

3.4 kcal/g of hydrated dextrose), and this quantity ($\approx$200 g of dextrose) was added to the nutrient solution.

Fluid requirements for each subject were based on body size, urine output, nasogastric and/or fistula losses, and clinical signs. This total volume was provided in a 3-liter bag, which contained the parenteral nutrients added in the form of stock nutrient solutions and sterile water. When indicated, additional sterile water was added to the nutrient solution to maintain hydration, but fluid intake usually remained constant throughout each individual study.

Nutrient solutions were prepared from commercially available amino acid solutions (10% Travasol,™ Travenol Laboratories, Inc., Deerfield, IL) and 70% dextrose solution, using an Automix High Speed Compounder (Travenol Laboratories, Inc., Deerfield, IL) in the hospital pharmacy during the afternoon before infusion. Adequate quantities of vitamins (MVI-12, Lyphomed, Melrose Park, IL) and trace elements (Multitrace Concentrate, Armour Pharmaceuticals, Kankakee, IL) were added in constant amounts daily to the 3-liter infusion bags. All subjects received 10 mg of Vitamin K weekly (AquaMephyton, Merck, Sharp, and Dohme, West Point, PA), except for the one subject receiving warfarin therapy. Electrolytes were added daily in appropriate amounts to maintain serum concentrations within the normal range.

The nutrients were infused through a central line dedicated solely to the administration of the parenteral nutrients over a 24-hour period, from 6 A.M. to 6 A.M. of the following day. (The one exception to this protocol was Patient 1, who received nutrient infusions over 14 hours at night.) The intravenous tubing was changed every 48 hours, and the catheter care and dressing change was performed 3 times weekly by a nutrition support service nurse. No dextrose-containing fluids other than the nutrient solution were administered.

Collections. Urine, stool, emesis, fistula, and tube drainage were collected for each 24-hour period that coincided with the 24-hour infusion of each bag of nutrient solution. The losses were immediately refrigerated after collection. Urine was collected separately every 24 hours, and stool, fistula, and tube drainage were combined in 7-day pools that coincided with the study weeks.

Measurements. The subjects were weighed daily at 6 A.M. Blood pressure, pulse, respiratory rate, and oral temperature were measured at least every 8 hours, or as clinically indicated, throughout the study.

Each 24 hour urine sample was analyzed for total nitrogen, urea, creatinine, potassium, inorganic phosphorus, sodium, glucose, β-hydroxybutyrate, and acetoacetate. The aliquots of stool, fistula, and tube drainage were analyzed for total nitrogen concentration. The nutrient bag was taken down at 6 A.M. each morning, and the residual volume was measured daily. An aliquot of the nutrient solution was saved from each 7-day period for nitrogen determination.

Venous blood was obtained in the morning between 7:30–8:30 A.M., prior to the GH or saline injections. On the first day (and weekly thereafter), blood was obtained for determination of glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, magnesium, total protein, albumin, globulin, alkaline phosphatase, lactate dehydrogenase (LDH), alanine-aminotransferase (SGPT), aspartate-aminotransferase (SGOT), indirect and direct bilirubin, cholesterol, triglyceride, hemoglobin, hematocrit, white blood cell count, and differential. On days 3 and 5 of each 7-day period, glucose, BUN, creatinine, sodium, potassium, chloride, and carbon dioxide were obtained. Blood was also obtained on days 1, 3, and 5 of each 7-day period of study for GH, insulin, insulin-like growth factor 1 (IGF 1), and free fatty acid (FFA) determinations. Blood was also obtained once during each 7-day period for analysis for antihuman GH antibodies.

Standard analytic techniques were used to determine concentrations of blood and urine metabolites as previously described.[18] Radioimmunoassay techniques were used for determination of insulin and GH,[19] IGF-1

concentration,[20] and presence of anti-hGH antibodies.[20] Nitrogen concentration in urine, TPN solution, stool, and other fluids was determined by the macro-Kjeldahl and chemiluminesence (Antek Instruments, Inc., Houston, TX) techniques.

Metabolic balances. Daily balances of nitrogen, potassium, sodium, phosphorus, and fluid were calculated for the control and treatment weeks of each subject. The volume of the residual nutrition solution was subtracted from the initial bag volume to determine actual administered volume. Fluid balance was then calculated as the difference between fluid intake and the measured volume of urine, stool, fistula, and tube drainage output. Daily balances of nitrogen and electrolytes were similarly determined.

Calculations. The first 24 hours of each 7-day period were considered an equilibration day, and data obtained from this initial 24-hour period were not included in the daily averages comparing the control and treatment periods. Nitrogen and urea excretion values were corrected as previously described[3] for change in the serum BUN concentration in Patient 7, whose level fell from 76 mg/dl to 19 mg/dl during the study period. For each individual subject, the daily balances of nitrogen, potassium, phosphorus, sodium, and fluid from day 2 to 7 were averaged for the control and treatment periods, and these values were used to determine overall group means for each study period.

The daily measurements of pulse, respiration, blood pressure, and temperature were averaged for each subject, and these values averaged for the group of subjects for each study period. Blood tests obtained on the first day of an individual's study were not included in the data analysis. Results obtained after the first day (including laboratory data obtained by the patient's physicians for clinical care) were averaged to determine the mean value for each individual during a particular study period. The daily weights obtained during each study period were plotted against time to determine the best fit linear regression. The slope of each line was used to calculate the weight change during each 7-day period of study for an individual patient, and this value was used to determine overall group means for weight change. (This method utilizes all daily measurements and thus does not rely solely on the difference between the two measurements taken at the beginning and end of a study period.)

Long-term Study

Patients. Six individuals were studied for more than 2 weeks and received 13–25 days of GH, given daily at the same dose. Patients 6, 7, 8, and 9 continued to receive GH daily after completion of the treatment week of their short-term study. Patients 10 and 11 had an initial con-

trol week prior to receiving GH during their treatment period. Thus, all six patients in this long-term trial entered an initial control week followed by the GH period. Patients 8 and 10 underwent gastrointestinal operations during this period; with Patient 7, the nitrogen content of the TPN solution was increased, and later, additional calories were given as fat emulsion. All six subjects were studied while enteral diets were started, and parenteral feedings decreased before hospital discharge.

Patient 10 (a 29-year-old woman) had an 8-year history of Crohn's disease and was hospitalized for preoperative feeding before elective repair of a colonic stricture and an internal fistula. She weighed 41 kg on admission (77% of ideal body weight) and had sustained an 18% body weight loss over the previous 6 months. Her medications included metronidazole, iron sulfate, and an oral contraceptive agent (ethynodiol diacetate/ethinyl estradiol). Her maintenence requirements were provided by intravenous feedings. One-half of the nonprotein calories were given as dextrose, and the remainder as lipid emulsion (20% Intralipid, KabiVitrum Inc., Alameda, CA). An additional 1000 calories were taken daily orally.

Patient 1 (a 34-year-old woman) had a 15-year history of Crohn's disease and a 12-year history of colocutaneous and duodenal-colonic fistulas. She was hospitalized for initiation of parenteral nutrition that was intended to supplement her oral intake at home. On admission, she weighed 39 kg (74% of ideal body weight) and had sustained a 13% body weight loss over the previous 6 months. Her medications included prednisone (20 mg/24 hr), ranitidine, and iron dextran. She was fed adequate nitrogen and 700 kcals above her maintenence energy requirements intravenously ($\approx$2200 calories and 16.9 g nitrogen/24 hr). The nutrient solution was cycled over 14 hours daily. During weeks 3 and 4, she received fat emulsion intravenously to provide essential fatty acids.

As in the short-term trial, the first 24 hours of the control and first GH week were not included in data analysis; however, data obtained during all 7 days of subsequent complete treatment weeks (weeks 2–3 of GH) were utilized. Mineral balances were not performed during periods of oral food intake, due to lack of precision in determining mineral intake from mixed food sources. However, nitrogen and calorie content of the enteral feedings were estimated using standard techniques, and these values were added to the intravenous intake for calculation of nitrogen and total caloric intake for each study week. Details of GH dosage and administration, parenteral nutrition preparation, collections, clinical/metabolic measurements and balances, calculations, and analytical techniques were otherwise identical to those of the short-term trial.

Statistics. Statistical calculations were performed on an IBM 4341 computer utilizing MINITAB (Pennsylvania State University, State College, PA, 1981) and a Macintosh™ Plus (Apple Computer, Inc., Cupertino, CA) with a standard statistical software package (Statview 512+™ Brainpower, Inc., Calabasas, CA) to apply paired t-testing, linear regression, and nonparametric techniques where appropriate. The Bonferroni adjustment was used when three or more group means were compared by paired t-tests. Results are expressed as mean ±SEM. A p value <0.05 between means was accepted as significant.

Results

Short-term Study: Clinical Observations

All patients received all prescribed injections during the 14-day study. One patient complained of pain at the subcutaneous injection site; no allergic reactions or other untoward response related to the drug delivery occurred.

The nine patients were relatively stable throughout the study period. Patient 2 had a low-grade fever (<39 C) on days 2 and 3 of the control week, and again on the last two days of the treatment week. He received antibiotics for these febrile episodes and underwent laparotomy and small bowel resection 5 days after study completion. Ileus developed in patients 5 and 7, requiring nasogastric decompression associated with low-grade fever (<39 C) during GH treatment. Patients 4 and 7 required additional intravenous fluid for several days to maintain fluid balance during the GH and control periods, respectively. The central venous catheter of Patient 8 became unattached briefly without significant sequelae; otherwise no complications associated with the intravenous solution administration or the indwelling catheters occurred.

The mean daily pulse rate rose slightly during the GH period as compared with control (93 ± 5 bpm with GH *vs.* 84 ± 3, p < 0.01). There were no significant differences in respiratory rate (control 19 ± 1 breaths/min, *vs.* 19 ± 1), systolic blood pressure (control 112 ± 3 mmHg, *vs.* 113 ± 4), diastolic blood pressure (control 71 ± 2 mmHg, *vs.* 71 ± 2), oral temperature (control 36.9 ± 0.1 C *vs.* 36.9 ± 0.1), or maximal temperature (control 37.3 ± 0.2 C, *vs.* 37.2 ± 0.2) between the two study periods.

Fluid intake remained constant during the two study weeks (control 2368 ± 123 ml/24 hr *vs.* GH 2363 ± 143, NS). However, daily urine excretion decreased significantly during the GH period (GH 1217 ± 90 ml/24 hr *vs.* 1543 ± 101, p < 0.01). As a result, fluid balance became more positive during the GH period than the control period (GH 841 ± 132 ml/24 hr *vs.* 582 ± 122, p < 0.05). During the control week, the patients lost a

TABLE 2. *Blood Values: Short-term Study (Mean ± SEM)*

	At Entry (Day 1)	Control (Days 2–7)	GH (Days 2–7)
Blood urea N (mg/dl)	19 ± 2	22 ± 4	16 ± 2*
Glucose (mg/dl)	115 ± 10	113 ± 7	133 ± 13
Insulin (μU/ml)	26 ± 8	21 ± 4	60 ± 22
Phosphorus (mg/dl)	3.8 ± 0.3	4.0 ± 0.2	4.0 ± 0.2
Potassium (mEq/l)	4.2 ± 0.2	4.4 ± 0.1	4.0 ± 0.1*
Sodium (mEq/l)	138 ± 1	137 ± 0.7	138 ± 0.5
Total bilirubin (mg/dl)	0.6 ± 0.2	0.5 ± 0.1	0.4 ± 0.1
Alkaline phosphatase (U/L)	218 ± 47	183 ± 29	160 ± 24
Free fatty acids (μEq/l)	685 ± 41	829 ± 58	792 ± 72
Growth hormone (ng/ml)	4.7 ± 1	4.6 ± 1.0	9.0 ± 3.2
IGF–1 (U/ml)	1.0 ± 0.2	1.5 ± 0.4	5.8 ± 1.2†

* p < 0.05. †p < 0.01 as determined by paired t-tests control vs. GH

TABLE 3. *Urinary Excretion: Short-Term Study (Mean ± SEM)*

	Control (Days 2–7)	GH (Days 2–7)
Volume (cc/24 hr)	1543 ± 101	1217 ± 90†
Nitrogen (g/24 hr)	12.3 ± 0.8	9.6 ± 0.9†
Urea (g/24 hr)	10.3 ± 0.7	7.2 ± 0.6‡
Phosphorus (mg/24 hr)	547 ± 53	401 ± 65*
Potassium (mEq/24 hr)	60 ± 6	48 ± 5*
Sodium (mEq/24 hr)	93 ± 19	57 ± 14†
Glucose (mg/24 hr)	219 ± 19	723 ± 511
Creatinine (g/24 hr)	0.84 ± 0.05	0.86 ± 0.07
B-OH (mM/24 hr)	0.03 ± 0.01	0.06 ± 0.01
AcAc (mM/24 hr)	0.04 ± 0.01	0.04 ± 0.01

* p < 0.05, †p < 0.01, ‡p < 0.001 as determined by paired t-tests

mean of 1.0 ± 0.6 kg compared with the GH week, in which a mean weight gain of 1.3 ± 0.4 kg occurred (p < 0.01).

Blood Values

On entry into the study, the patient's serum concentrations of BUN, glucose, electrolytes, total bilirubin, alkaline phosphatase, GH, insulin, and IGF-1 were within normal limits except in patient 7, whose BUN was 76 mg/dl. These values did not change significantly during the control period (Table 2). The exception was serum FFA, which rose from 685 ± 41 μEq/l on the entry day to 829 ± 58 during the control period (p < 0.05). With GH administration, BUN fell significantly (control 22 ± 4 mg/dl vs. GH 16 ± 2, p < 0.05), serum glucose tended to rise (113 ± 7 mg/dl vs. 133 ± 13, NS), and insulin concentration also tended to

increase (21 ± 4 μU/ml vs. 60 ± 22, NS). Potassium concentration fell slightly but significantly with GH administration (p < 0.05), whereas concentrations of serum phosphorus, sodium, total bilirubin, alkaline phosphatase, and free fatty acids did not change.

Serum GH concentration tended to rise during the GH administration (4.6 ± 1.0 ng/ml vs. 9.0 ± 3.2, NS). Levels of IGF-1 increased nearly fourfold with GH therapy (1.5 ± 0.4 U/ml vs. 5.8 ± 1.2, p < 0.01). Antibodies against human GH were not detected in any of the patients.

Urinary Excretion

Urinary excretion of nitrogen, urea, phosphorus, potassium, and sodium decreased significantly during GH administration (Table 3). The urinary excretion of glucose, creatinine, beta-hydroxybuterate and acetoacetate were similar during the two study weeks. Beta-hydroxybuterate excretion tended to rise during GH (0.03 ± 0.01 mM/24 hr vs. 0.06 ± 0.01, NS).

TABLE 4. *Nutrient Intake and Balances: Short-Term Study*

	Control								Growth Hormone							
	Kcal (per/24 hr)	Fluid (cc/24 hr)	Nitrogen (g/24 hr)		Potassium (mEq/ 24 hr)		Phosphorus (mg/24 hr)		Kcal (per/24 hr)	Fluid (cc/24 hr)	Nitrogen (g/24 hr)		Potassium (mEq/ 24 hr)		Phosphorus (mg/24 hr)	
Pt.	In	In	In	Bal	In	Bal	In	Bal	In	In	In	Bal	In	Bal	In	Bal
1	1090	2058	16.6	+4.9	62	+23	575	+98	1091	2137	16.4	+5.4	51	+17	623	+150
2	1233	2614	17.6	+1.4	91	+49	677	−78	1164	2176	17.6	+4.9	87	+39	675	+136
3	1088	2198	13.8	+3.0	88	+9	679	−10	1058	2128	13.4	+4.9	85	+34	660	+229
4	1017	2785	15.5	+0.4	83	+25	428	+13	1129	2880	17.1	+3.9	94	+45	1057	+382
5	1117	2961	12.4	−1.6	89	−4	459	−85	1087	2884	12.1	+2.3	82	+24	447	+171
6	995	1961	13.1	+0.2	72	+24	305	+51	1012	2035	13.2	+2.5	69	+21	258	+179
7	1016	2571	8.0	−4.3	43	−4	371	−135	1052	3020	8.3	+1.3	44	+19	358	+213
8	1146	2177	11.8	+0.1	56	−12	829	+122	1103	1962	11.3	+2.7	60	−3	897	+369
9	908	1990	9.8	+0.5	73	−3	605	+24	906	2049	9.7	+2.5	73	+6	603	+135
Mean	1068	2368	13.2	+0.5	73	+12	548	0	1067	2363	13.2	+3.4*	72	+22	620	+218*
SEM	±32	±123	±1.0	±0.9	±6	±7	±56	±29	±25	±143	±1.1	±0.5	±6	±5	±84	±32

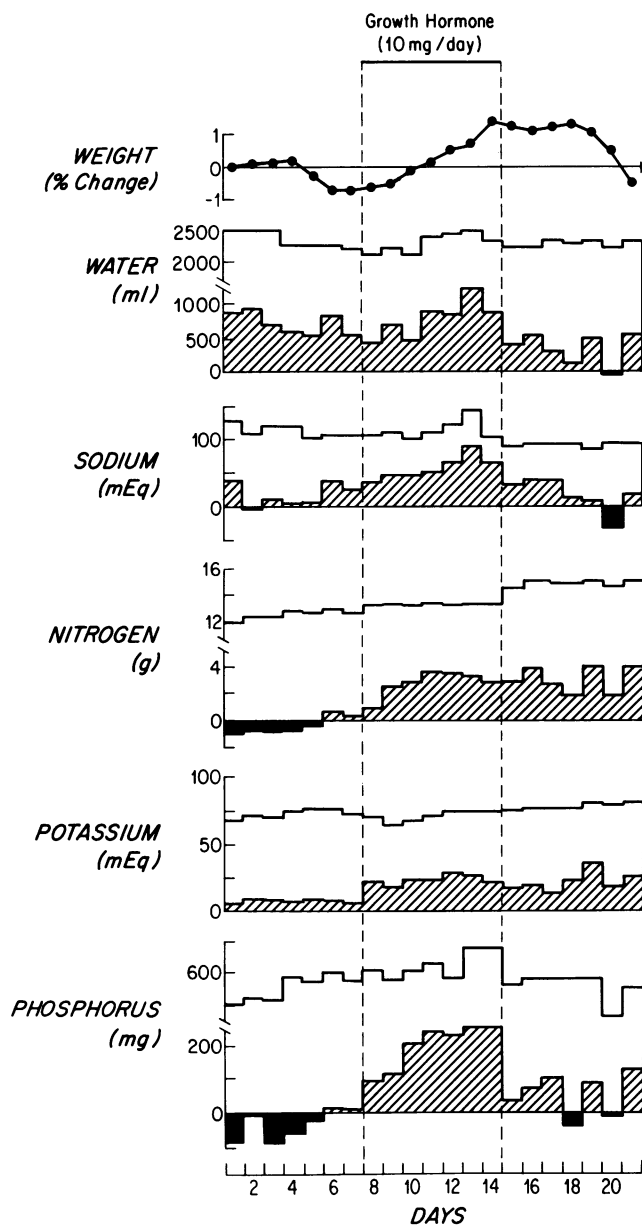* p < 0.001 paired t-test

In = Intake
Bal = Balance

FIG. 1. During the first week of hypocaloric nutrition in these nine depleted patients, body weight fell and balances for nitrogen, potassium, and phosphorus were negative or neutral. With GH administration, there was marked positive balance of nitrogen and phosphorus. In addition to mineral retention, body weight gain was associated with retention of additional water and sodium. Following administration of GH, body weight and balances returned to pretreatment values. The upper line represents the quantity of a substance infused, while the black areas demonstrate negative balance and the shaded areas, positive balance.

Nutrient Balance

The intake of fluid, calories, nitrogen, phosphorus, and potassium were similar during the two study periods (Table 4). Sodium intake was 106 ± 22 mEq/24 hr during control versus 115 ± 20 during GH (NS). During the control period, excretion of nitrogen, phosphorus, and

potassium was similar to intake; hence, the subjects were near balance. During the 7 days of GH administration, the excretion of nitrogen and phosphorus was significantly less than during the control period, and therefore the subjects had a positive balance of these substances (Table 4). Nitrogen balance rose from $+0.5 \pm 0.9$ g/24 hr during control to $+3.4 \pm 0.5$ with GH, whereas phosphorus balance rose from 0 ± 29 mg/24 hr to $+218 \pm 32$ (p < 0.001) Potassium balance also rose, and approached but did not achieve significance (p < 0.06). GH administration was also associated with positive sodium balance (control 13 ± 11 mEq/24 hr vs. 58 ± 19 with GH p < 0.05).

When the data from the individual weeks were examined, it appeared that the nitrogen-retaining effect of GH persisted into the third week of study (Fig. 1). Nitrogen balance from the third week (post-GH control week) was statistically indistinguishable from the week of GH therapy using rank order analysis. In contrast, phosphorus balance rapidly returned to prestudy levels. In the week after GH administration, fluid balance was maintained for several days, but this was followed by increased urinary volume and sodium excretion, resulting in negative balance of water and sodium. Body weight returned to baseline values (Fig. 1).

Long-term Study Observations

All six patients in the long-term trial received their prescribed injections without untoward effects, and remained relatively stable throughout their individual studies. During their studies, all patients remained afebrile with stable vital signs. Daily pulse rate tended to rise with GH therapy (control 84 ± 4 bpm, GH Week 1 92 ± 5, GH Week 2 94 ± 5, GH Week 3 92 ± 6, NS). The mean weight change during the control week was $+0.3 \pm 0.6$ kg, compared with the mean weight change during GH Week 1 of $+1.9 \pm 0.4$ kg (p < 0.05). However, after the first week of GH, body weight tended to stabilize (GH Week 2 was $+0.5 \pm 0.6$ kg, NS from control). All six patients were successfully weaned from parenteral nutrition and were taking enteral diets before discharge 1-2 days after completion of the study.

The nitrogen and mineral balances in these long-term studies were similar to those during the 7 days of GH administration. Mean nitrogen balance during the control week was $+0.4 \pm 1.1$ g/24 hr, and rose to $+3.2 \pm 0.7$ during GH Week 1, $+3.7 \pm 1.0$ during GH Week 2, and $+3.4 \pm 1.0$ during GH Week 3 (see Table 5 for individual patient data). Positive nitrogen balance persisted into Weeks 2 and 3 of GH therapy in all patients except Patient 8, who underwent laparotomy during the second GH week (Fig. 2). A second patient receiving hypercaloric nutrition and GH underwent laparotomy but

TABLE 5. *Nutrient Intake and Balances: Long-Term Study*

Pt.*	Week of Study*	Route of Feeding	Caloric Intake (Kcal/24 hr)	Nitrogen		Potassium		Phosphorus	
				Intake	Balance	Intake	Balance	Intake	Balance
				(g/24 hr)		(mEq/24 hr)		(mg/24 hr)	
6	2	I.V./Enteral	1410	14.0	+7.2	68	+21.0	262	+281
7	2	I.V.	1155	12.5	+3.5	68	+19.0	705	+429
	3	I.V.	1573	11.9	+2.9	50	+3.3	732	+235
8	2†	I.V.	1138	11.5	−0.5	77	−3.0	912	+250
	3	I.V./Enteral	1465	13.1	+2.1	81	−7.0	913	+263
9	2	I.V.	936	10.0	+2.8	75	+5.0	620	+155
10	C	I.V./Enteral	2488	15.2	+4.4	—	—	—	—
	1	I.V./Enteral	2389	14.6	+6.4	—	—	—	—
	2‡	I.V.	2428	16.5	+5.1	—	—	—	—
11	C	I.V.	2114	16.8	+1.6	—	—	618	+142
	1	I.V.	2118	16.7	+4.0	89	+9.8	616	+304
	2	I.V.	2232	16.5	+3.9	88	+26.5	640	+337
	3	I.V./Enteral	2408	17.8	+5.3	87	+24.0	—	—

* C = Control week, numbers represent consecutive weeks of GH therapy. Data for C and Week 1 for patients 6–9 are included on Table 4.

† Laparotomy on Day 2 of this week.
‡ Laparotomy on Day 2 of this week.

maintained positive nitrogen balance throughout her perioperative course (Fig. 3). Patient 7 had chronic renal insufficiency and maintained positive nitrogen balance while receiving hypocaloric feedings and GH over 3 weeks (Fig. 4). Positive mineral balance, when determined, also tended to remain positive during the long-term study (Table 5). The blood values for the long-term patients tended to reflect the changes observed with the short-term trial (Table 6).

Discussion

Our observations in this controlled trial suggest that GH enhances the efficacy of parenteral nutrition in clinically stable, hospitalized adults. Patients achieved positive nitrogen balance while receiving hypocaloric feedings, and this balance was maintained for as long as
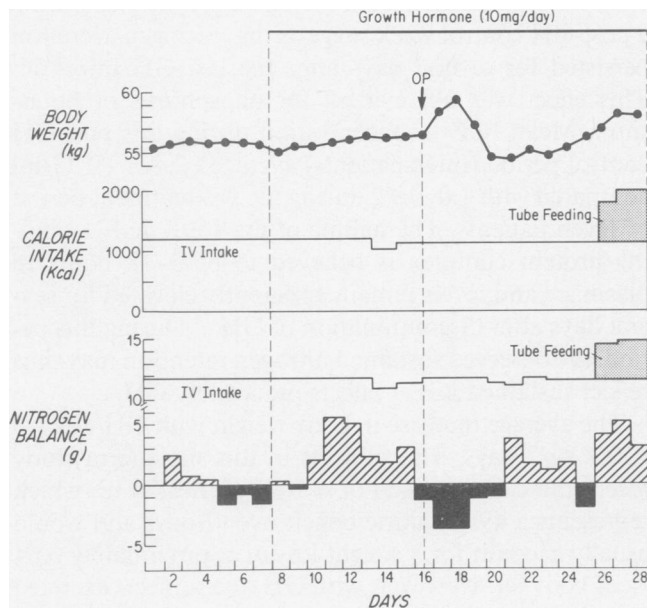

FIG. 2. This 50-year-old woman (Patient 8) with gastric stasis and a 26% weight loss received a fixed intravenous hypocaloric intake for over 3 weeks. At the end of 8 days of GH administration, she underwent a laparotomy, gastrojejunostomy, and placement of a feeding jejunostomy. Her postoperative loss of nitrogen and other minerals was minimal (see also Table 5), and she remained anabolic with the institution of tube feedings.
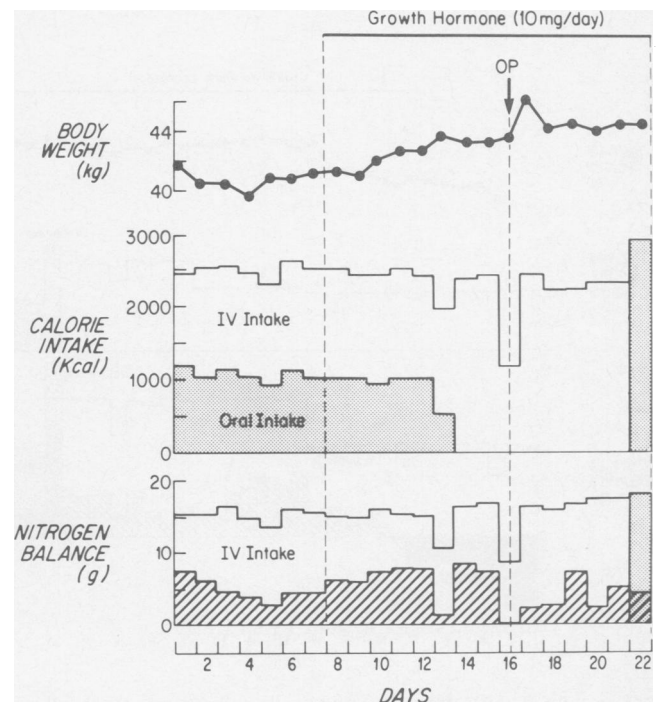

FIG. 3. Weight gain and positive nitrogen balance occurred in this 29-year-old woman (Patient 10) with Crohn's disease, who weighed 41 kg on admission and received hypercaloric nutrition and GH. Anabolism was maintained despite laparotomy, colectomy, and small bowel resection.

TABLE 6. Blood Values Long-Term Study (Mean ± SEM)

	Control Week (n)	GH Week 1 (n)	GH Week 2 (n)	GH Week 3 (n)
Blood urea N (mg/dl)	24 ± 5 (6)	18 ± 2 (6)	18 ± 4 (6)	23 ± 8 (3)
Glucose (mg/dl)	104 ± 9 (6)	135 ± 18 (6)	130 ± 10 (6)	120 ± 15 (3)
Insulin (μU/ml)	30 ± 8 (6)	62 ± 31 (6)	65 ± 23 (6)	29 ± 13 (3)
Phosphorus (mg/dl)	3.7 ± 0.2 (6)	3.8 ± 0.2 (6)	4.3 ± 0.1 (6)	4.8 ± 0.4 (2)
Potassium (mEq/l)	4.5 ± 0.1 (6)	4.1 ± 0.2 (6)	4.2 ± 0.1 (6)	4.2 ± 0.3 (3)
Triglyceride (mg/dl)	118 ± 14 (5)	187 ± 23 (4)	149 ± 20 (5)	150 ± 14 (2)
Free Fatty Acids (μEq/l)	638 ± 137 (6)	709 ± 96 (6)	762 ± 67 (6)	785 ± 135 (3)
Growth Hormone (ng/ml)	5 ± 1 (6)	16 ± 8 (6)	14 ± 6 (6)	11 ± 4 (3)
IGF-1 (U/ml)	1.0 ± 0.2 (5)	4.4 ± 1.9 (5)	5.4 ± 2.2 (5)	2.3 ± 0.4 (3)

3 weeks. No significant untoward effects were noted during the several weeks of GH administration.

During the short-term trial, *cumulative* nitrogen balance rose from 3.1 ± 5.2 g/6 days during control (not different from zero) to 20.3 ± 2.3 g/6 days during GH (p < 0.001) in association with parenteral feeding supplying ≈1.3 g protein/kg/24 hr but only 60% of caloric requirements. Retention of phosphorus was signifi-
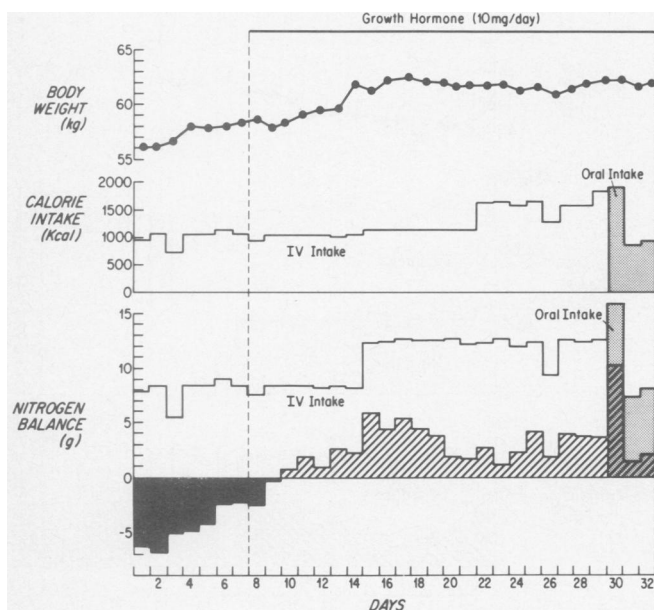

FIG. 4. This 65-year-old man (Patient 7) with chronic renal failure achieved positive nitrogen balance, while BUN fell from 76 mg/dl to 19 mg/dl with hypocaloric parenteral nutrition and GH. On Day 15, additional amino acid nitrogen was infused and nitrogen balance improved. On Day 22, fat emulsion (500 kcal/day) was added to the nutrient infusion, and additional calories exerted minimal effects on nitrogen and mineral balance (see also Table 5). Oral intake was started on Day 30.

cantly enhanced, and a strong trend toward potassium retention was observed with GH. The anabolic effect of this hormone was evident 1–2 days after administration, as excretion of nitrogen and minerals decreased and nutrient balance improved.

The retention ratio (calculated as the difference in mean balance between control and GH weeks) for nitrogen, potassium, and phosphorus was 1:3.4:75, respectively. This ratio is similar to the reported intracellular ratio of these constituents in skeletal muscle; for every gram of nitrogen retained as skeletal muscle, approximately 3 mEq of potassium and 66 mg of phosphorus are also retained.[21-22]

The net positive balance of these substances occurred in association with decreased excretion of urea, nitrogen, potassium, and phosphorus during constant intake in each study week. The drop in BUN reflected a decrease in urea production due to GH. Despite a significantly decreased urinary excretion, blood levels of potassium dropped and phosphorus remained stable, suggesting efficient retention of these minerals with nitrogen as new protoplasm.

Although GH has potent lipolytic effects, we did not observe a significant rise in serum FFA or urinary ketone excretion during the short-term study. Continued lipolysis during GH was suggested by the trend toward increased urinary excretion of beta-hydroxybuterate and the lack of a fall in serum FFA levels in the face of hyperinsulinemia.

The measurements from three patients studied during a post-GH control week suggests that nitrogen accretion persisted for several days after the last GH injection. This effect was not evident for phosphorus or potassium. Mean IGF-1 concentration during this post-GH control period (three patients) averaged 2.4 ± 1.1 U/ml compared with 1.0 ± 0.2 during the pretreatment period of seven patients. The halflife of the 150K IGF-1-binding protein complex is believed to be 3–18 hours in plasma,[23] and levels remain apparently elevated for several days after discontinuation of GH.[24] During this period, the observed sustained nitrogen retention may thus reflect sustained IGF-1 effects induced by GH.

The average increase in body weight with GH was 1.3 ± 0.4 kg/7 days. The subjects in this short-term study received a caloric deficit of ≈700 calories/24 hr, which represents a 4900 calorie deficit over 7 days and would usually account for a weight loss of approximately 0.64 kg of body fat. However, with GH, the subjects excreted less urine volume. Assuming that insensible water loss was the same during control and GH weeks, the difference in fluid balance of ≈260 ml/24 h would account for a gain of approximately 1.82 kg/week (260 × 7 = 1820 ml). The observed change in body weight (+1.3 kg) reflects the difference between the gain in fluid (≈1.8 kg) and the loss of body fat (≈0.6 kg).

Since daily nitrogen balance during the GH period was +3.4 g/24 h ($\approx$150 g protein/week), this accounts for 0.6 kg hydrated tissue. Thus, about one third of the water retained during GH was associated with protein-rich tissues, whereas the remainder was in other body compartments. At no time was fluid retention clinically evident as pulmonary or significant peripheral edema. Glycogen synthesis might also have contributed to a portion of the fluid retention and weight gain, but the influence of GH on glycogen stores was not evaluated in this study. Additional factors that could have contributed to water and sodium retention include a direct effect of GH on sodium reabsorption by the kidney,[25] and the effect of hyperinsulinemia which may have decreased renal excretion of sodium.[26] During the post-GH week, body weight returned to prestudy values in association with a naturesis and diuresis.

The long-term study demonstrates that GH can be safely administered to stable patients for several weeks. No significant problems occurred necessitating drug withdrawal during the study. Two patients (Patients 6 and 11) had mild, transient ankle edema, which resolved after limiting fluid intake by $\approx$500 ml/day. During the control week Patient 6 had a serum glucose that ranged between 102–119 mg/dl. With GH, her blood glucose rose to range between 180–275 mg/dl. During GH Week 2, she started oral feedings and was weaned from parenteral nutrition; during this transition her glucose values averaged $\approx$150 mg/dl. No patients received insulin during this study. Two patients underwent operative procedures without complication while receiving GH, and in general, all patients remained stable during this long-term trial.

The anabolic effect of GH was sustained in these patients, as evidenced by the cumulative nitrogen balance in each study week; cumulative balance improved from 2.5 $\pm$ 6.9 gN/6 days during the control week (not different from zero) to 19.4 $\pm$ 4.3, 22 $\pm$ 6.3, 20.6 $\pm$ 5.8 during GH treatment weeks 1, 2, and 3, respectively. Retention of phosphorus was also evident throughout GH administration. Blood studies suggested a sustained anabolic environment during GH with increased blood levels of insulin, GH, and IGF-1. The rate of weight gain noted during the first GH week did not persist during the long-term study, suggesting decreased fluid retention with time and/or a gradual alteration in body composition. Patients in the short-term study received a mean of $\approx$17 kcal/kg/day and $\approx$1.3 g protein/kg/day. GH was administered in a mean dose of $\approx$0.16 mg/kg/day. Patients in this study retained 3.4 gN/24 h ($\approx$ +21 g protein/24 h) during the first week of GH therapy, and in the long-term study, this marked accretion persisted throughout several weeks of GH administration. Most of our study patients had sustained postoperative complications and lost an average of 13.6% of their preoper-ative body weight. Because of their protracted catabolic course, they probably demonstrated increased avidity for dietary protein.

In another recent study, obese postoperative patients achieved nitrogen equilibrium *after* 24 $\pm$ 9.7 days while receiving hypocaloric (881 nonprotein kcal/24 h), high protein (2.1 g protein/kg IBW/24 h) parenteral nutrition.[27] In contrast, our patients achieved N equilibrium during the control week, while receiving similar calories and much less nitrogen than in the previous study. However, GH clearly favored a more efficient utilization of the administered nitrogen, as we observed marked retention within the first week, which was sustained throughout GH administration. Our patients received enough glucose ($\approx$200 g/24 h) to meet obligatory requirements, and the remaining energy was derived from body fat. Similar protein-sparing effects of GH have been observed in obese subjects consuming low energy diets.[28]

IGF-1 increased markedly with GH administration. This protein, made by liver (and probably many other tissues), is predominantly regulated by GH and may be responsible for many of the GH anabolic effects.[29-30] IGF-1 production and/or function is attenuated with hepatic and renal dysfunction and severe protein-calorie malnutrition.[31-33] In this stable but depleted patient group, appropriate synthetic capacity was present to generate IGF-1 levels, which increased three to fourfold.

For over 25 years, a variety of studies have demonstrated positive effects of pituitary-derived human GH in adult patients.[34-37] Enhanced retention of nitrogen, potassium, and sodium, improved wound healing, and increased appetite have been reported with use of this agent. GH is now available in large quantities as a result of recombinant technology. This study demonstrates that GH greatly enhances the efficiency of parenteral nutrition. Positive nitrogen balance can be easily achieved and sustained when hypocaloric parenteral nutrition is combined with recombinant GH administration.

Acknowledgments

References

1. Cuthbertson DP. Physical injury and its effects on protein metabolism. *In* Munro HN, Allison JB, eds. Mammalian Protein Metabolism. New York: Academic Press, 1964; 373–414.

2. Moore FD. Energy and the maintenence of the body cell mass. JPEN 1980; 4(3):228–259.
3. Wilmore DW. The Metabolic Management of the Critically Ill. New York: Plenum Publishing Corp., 1977; 193–194.
4. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma 1987; 27(3):262–266.
5. Smith RC, Burkinshaw L, Hill GL. Optimal energy and nitrogen intake for gastroenterological patients requiring intravenous nutrition. Gastroenterology 1982; 82:445–452.
6. Jeejeeboy KN, Baker JP, Wolman SL, et al. Critical evaluation of the role of clinical assessment and body composition studies in patients with malnutrition and after total parenteral nutrition. Am J Clin Nutr 1982; 35:1117–1127.
7. Kinney J, Elwyn DH. Protein metabolism in the traumatized patient. Acta Chir Scand 1984; 522(suppl.):45–56.
8. Shaw JHF, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. Ann Surg 1987; 205(3):288–294.
9. Kehlet H. Does regional anaesthesia reduce postoperative morbidity? Intensive Care Med 1984; 10:165–167.
10. Lopes J, Russell DMcR, Whitwell J, Jeejeeboy KN. Skeletal muscle function in malnutrition. Am J Clin Nutr 1982; 36:602–610.
11. Carrico CJ, Meakins JL, Marshall JC, et al. Multiple-organ failure syndrome. Arch Surg 1986; 121:196–208.
12. Sheldon GF, Peterson SR, Sanders R. Hepatic dysfunction during hyperalimentation. Arch Surg 1978; 113:504–508.
13. Burke JF, Wolfe RR, Mullany CJ, et al. Glucose requirements following burn injury-parameters of optimal glucose infusion and possible hepatic and respiratory abnormalities following excessive glucose intake. Ann Surg 1979; 190(3):274–285.
14. Askanazi J, Rosenbaum SH, Hyman AI, et al. Respiratory changes induced by the large glucose loads of parenteral nutrition. JAMA 1980; 243(14):1444–1446.
15. Samuels ML, Selig DE, Ogden S, et al. IV hyperalimentation and chemotherapy for Stage III testicular cancer: a randomized study. Cancer Treat Rep 1981; 65(7–8):615–627.
16. Manson JMcK, Wilmore DW. Positive nitrogen balance with human growth hormone and hypocaloric intravenous feeding. Surgery 1986; 100(2):188–197.
17. Manson JMcK, Smith RJ, Wilmore DW. The effect of growth hormone on protein utilization and fuel utilization during hypocaloric parenteral nutrition. Ann Surg (in press).
18. Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. Ann Surg 1984; 200(3):264–281.
19. Juan C, Avruskin TW. A combined immunoassay of human growth hormone and insulin. J Clin Endocrinol 1971; 33:150–152.
20. Kaplan SL, Underwood LE, August GP, et al. Clinical studies with recombinant DNA-derived methionyl-human growth hormone in growth hormone-deficient children. In Raiti S, Tolman RA, eds. Human Growth Hormone. New York: Plenum Press, 1986; 267–277.
21. Reifenstein EC, Albright F, Wells SJ. The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. J Clin Endocrinol Metab 1945; 5:367–395.
22. Consolazio CF, Johnson RE, Pecora LJ. Physiological measurements of metabolic functions in man. New York: McGraw-Hill, 1963; 335.
23. Hintz RL. The somatomedin binding proteins. In Raiti S, Tolman RA, eds. Human Growth Hormone. New York: Plenum Press, 1986; 553–561.
24. Ward HC, Halliday D, Sim AJW. Protein and energy metabolism with biosynthetic human growth hormone after gastrointestinal surgery. Ann Surg 1987; 206(1):56–61.
25. Daughaday WH. The anterior pituitary. In Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. Philadelphia: W.B. Saunders, 1985; 577.
26. Defronzo RA, Cooke RC, Andres R, et al. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. J Clin Invest 1975; 55:845–855.
27. Dickerson RN, Rosato EF, Mullen JL. Net protein anabolism with hypocaloric parenteral nutrition in obese stressed patients. Am J Clin Nutr 1986; 44:747–755.
28. Clemmons DR, Snyder DK, Williams R, Underwood LE. Growth hormone administration conserves lean body mass during dietary restriction in obese subjects. J Clin Endocrinol Metab 1987; 64(5):878–883.
29. Phillips LS. Nutrition, somatomedins, and the brain. Metabolism 1986; 35(1):78–87.
30. Rechler MM, Nissley SP, Roth J. Hormonal regulation of human growth. N Engl J Med 1987; 316(15):941–943.
31. Phillips LS, Unterman TG. Somatomedin activity in disorders of nutrition and metabolism. Clin Endocrinol Metab 1984; 13:145–189.
32. Clemmons DR, Klibanski A, Underwood LE, et al. Reduction of plasma immunoreactive somatomedin-C during fasting in humans. J Clin Endocrinol Metab 1981; 53(6):1247–1250.
33. Merimee TJ, Zapf J, Froesch ER. Insulin-like growth factors in the fed and fasted states. J Clin Endocrinol Metab 1982; 55(5):999–1002.
34. Liljedahl SO, Gemzell CA, Plantin LO, Birke G. Effect of human growth hormone in patients with severe burns. Acta Chir Scand 1961; 122:1–14.
35. Soroff HS, Rozin RR, Mooty J, et al. Role of human growth hormone in the response to trauma: 1. Metabolic effects following burns. Ann Surg 1967; 166(5):739–752.
36. Bray GA, Raben MS, Londono J, Gallagher TF. Effects of triiodothyronine, growth hormone, and anabolic steroids on nitrogen excretion and oxygen consumption of obese patients. J Clin Endocrinol Metab 1971; 33(2):293–300.
37. Wilmore DW, Moylan JA, Bristow BF, et al. Anabolic effects of human growth hormone and high caloric feedings following thermal injury. Surg Gynecol Obstet 1974; 138:875–884.