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A New Treatment for Patients with Short-Bowel Syndrome

Growth Hormone, Glutamine, and a Modified Diet

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Objective
The purpose of this study was to initially determine if growth hormone or nutrients, given alone or together, could enhance absorption from the remnant small bowel after massive intestinal resection. If clinical improvement were observed, this therapy would then be used to treat patients with the short-bowel syndrome over the long term.

Summary Background Data
Patients who undergo extensive resection of the gastrointestinal tract frequently develop malabsorption and require long-term parenteral nutrition. The authors hypothesized that the administration of growth factors and/or nutrients could enhance further compensation of the remnant intestine and thereby improve absorption. Specifically, animal studies have shown that there is enhanced cellularity with the administration of growth hormone (GH) or glutamine (GLN), or a fiber-containing diet.

Methods
Initially, 17 studies were performed in 15 total parenteral nutrition (TPN)-dependent short-bowel patients over 3 to 4 weeks in the clinical research center; the first week served as a control period, and during the next 1 to 3 weeks, the specific treatment was administered and evaluated. Throughout the study, food of known composition was provided and all stool was collected and analyzed to determine absorption across the remaining bowel. The effect of a high-carbohydrate, low-fat diet (DIET), the amino acid glutamine (GLN) and growth hormone (GH) administered alone or in combination with the other therapies (GH + GLN + DIET) was evaluated. The treatment was expanded to 47 adults (25 men, 22 women) with the short-bowel syndrome, dependent on TPN for 6 ± 1 years. The average age was 46 ± 2 years, and the average jejunal-ileal length was 50 ± 7 cm (median 35 cm) in those with all or a portion of colon and 102 ± 24 cm (median 102 cm) in those with no colon. After 28 days of therapy, the patients were discharged on only GLN + DIET.

Results
The initial balance studies indicated improvement in absorption of protein by 39% accompanied by a 33% decrease in stool output with the GH + GLN + DIET. In the long-term study, 40% of the group remain off TPN and an additional 40% have reduced their TPN requirements, with follow-up averaging a year and the longest being over 5 years.

Conclusion

GH + GLN + DIET offers a potential method for providing cost-effective rehabilitation of surgical patients who have the short-bowel syndrome or other complex problems of the gastrointestinal tract. This therapeutic combination also may be useful to enhance bowel function in patients with other gastrointestinal diseases and those requiring extensive intestinal operations, including transplantation.

Intestinal resection is a commonly performed operation that is usually without complications. Occasionally, however, removal of large segments of the small bowel with or without a portion of the colon is necessary because of thrombosis of a mesenteric vessel, progressive inflammatory disease, major abdominal injury, or the presence of congenital abnormalities. These operative procedures result in short-bowel syndrome, a disorder characterized by an intestinal absorptive surface area that is insufficient to support the host. This intestinal loss results in malabsorption of fluid, electrolytes, and other essential nutrients; severe diarrhea; dehydration; and progressive malnutrition.[1]

Surgeons have long been aware of the ability of the small bowel to compensative after massive intestinal resection. This response, first described by Flint[2] in 1912 and later characterized in greater detail by many others,[3-5] is accompanied by elongation and dilation of the remnant bowel and hypertrophy of the intestinal villi, resulting in a greater absorptive surface area and prolonged transit time. With bowel compensation, absorption of enteral nutrients is gradually enhanced and diarrhea and malabsorption are reduced[6]; occasionally the clinical problems resolve. Although this adaptive response may support normal hydration and nutrition in individuals with resection of up to 80% of the small bowel, patients with less than 50 to 70 cm of jejunum–ileum (approximately 1½–2½ ft) with an intact duodenum and a portion of colon in continuity usually require total parenteral nutrition (TPN) for life.[1,7] Other factors, such as normal structure and function of other gastrointestinal organs, health of the intestinal mucosa, the presence and length of the remaining colon, and the age of the individual, also determine the ability of a patient to adapt and become independent of parenteral support.

Although TPN is regarded as lifesaving to patients after massive bowel resection,[8] data emerging over the past 20 years have detailed both short- and long-term complication rates of this therapy,[9-11] described the effect of nightly infusions on the disruption of a normal lifestyle,[12] and quantitated the costs associated with the therapy.[13] All of these factors have limited more comprehensive rehabilitation and shortened longevity, and investigators are now seeking alternative methods of care for this group of patients. Reconstructive procedures on the remnant bowel and intestinal transplantation are areas of special interest to surgeons working in this field.

This report provides details of the evolution of a treatment program that enhances absorption of nutrients from the remnant bowel through the use of growth factors and specialized nutrients. Absorption has been enhanced by using a combination of therapeutic agents, and this approach has now been applied to a larger group of patients with short-bowel syndrome to reduce or eliminate the need for TPN for prolonged periods.

MATERIALS AND METHODS

Absorption Studies

Patients

Seventeen studies were performed in 15 patients (9 women, 6 men; mean age, 44 years; range, 24–68 years) with severe short-bowel syndrome. All patients had previously undergone extensive bowel resection for trauma, mesenteric infarction, or inflammatory bowel disease with or without colonic resection. The average length of jejunum–ileum in the group, as determined from operative reports and confirmed by perioperative radiographs, was 54 cm (range, 8–120 cm) in the 12 patients with a portion of colon in continuity and 60 cm (range, 40–100 cm) in those without a colon. All patients were chronically dependent on specialized nutritional support. The patients were ambulatory, clinically stable, and did not demonstrate evidence of infection or active inflammatory bowel disease. In addition, they had no extradigestive organ failure, were free of cancer and diabetes, and did not have a history of cancer for the past 5 years. All patients were able to tolerate an *ad libitum* oral diet; however, without parenteral support they were unable to adequately maintain hydration and/or nutritional status. The protocol was approved by the Brigham and

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Women's Hospital's Committee for the Protection of Human Subjects from Research Risks, and informed consent was obtained from all subjects.

Study Design

The patients were admitted to the Clinical Research Center of the Brigham and Women's Hospital for a 21 to 35 day stay. For the patients receiving a high-carbohydrate low-fat (HCLF) diet alone or diet plus growth hormone plus glutamine, the first week served as a control period during which time the patients' nutritional (parenteral feedings, tube feedings, and *ad libitum* oral intake) and medical management (antidiarrheal agents, etc.) simulated their usual home therapy. The patients were instructed to consume the quantity and type of foods and beverages that best represented their usual eating habits and food preferences. Only foods and beverages of known nutrient composition were provided. Meals and snacks were made available six times per day and beverages were readily available on an *ad lib* basis. During the control period, the infusions of parenteral nutrients and fluid volumes were matched to those prescribed by the patient's physician.

During the remaining 3 weeks, these patients received a diet high in complex carbohydrates and low in fat but nearly isocaloric and isonitrogenous to that which the patient received during the control period. The diet was targeted to provide approximately 60% of total calories from carbohydrate, 20% from fat, and 20% from protein. Calories and protein were divided into six feedings and provided as meals or snacks throughout the day. Near-isotonic fluids containing glucose and sodium (Gatorade, The Gatorade Company, Chicago, IL, and Pedialyte, Ross Laboratories, Columbus, OH) replaced both hypo-osmolar and hyperosmolar fluids and served as the primary source of enteral hydration.

Two of these 10 patients received the modified diet (HCLF diet) only. The remaining eight patients received recombinant methionyl growth hormone (Protropin, Genentech, Inc., San Francisco, CA) at a dose of 0.14 mg/kg/day by parenteral administration. They also received supplemental parenteral and/or enteral L-glutamine (given as an average dose of 0.6 g/kg/day (Ajinomoto USA, Raleigh, NC).

The seven additional studies examined the effects of administering glutamine alone or growth hormone alone. The patients received a fixed diet throughout the entire 21 to 28 day period, which involved foods of their choice on a 2-day rotational schedule. After the first week, either glutamine or growth hormone was provided as described above and the diet continued. Intravenous feedings, fluid volume, calories, and protein were maintained at a constant level of intake throughout the entire study period.

During all investigations, all enteral intake and stool output was weighed and the nitrogen, water, and sodium contents determined. Enteral nutrient balance and absorption were then calculated from the measured enteral intake and stool losses. Body weight was recorded daily. Blood samples were analyzed biweekly to monitor the response to therapy and to adjust electrolytes added to the parenteral solution.

Determination of Nutrient Intake

All food and fluid was weighed and prepared by the Clinical Research Center's metabolic kitchen. The total daily intake of protein, calories, carbohydrate, fat, sodium, and water (including the water content of all foods and beverages) was determined by a computer program (GCRC Diet Planner, Version 2.03, Clinical Study Center, University of California, San Francisco, CA), which translated the gram weight of intake into nutrient composition. For foods not analyzed or available on the computer program, nutrient values were determined by referring to Handbook 8[14] or other standards.[15] On random days of the study, duplicate patient trays were prepared and analyzed to confirm the nitrogen, fat, and sodium content of the diet.

Measurement of Nutrient Losses

All stool was collected for consecutive 24-hour periods between 7:30 A.M. and 7:30 A.M. beginning on the morning after admission and continuing until completion of the study. Samples were prepared frozen at −20 C and analyzed for water, nitrogen, sodium, and, in selected patients, fat and calories as previously described.[16] Body weight was recorded each morning to the nearest 0.1 kg using a leveled platform scale (model SR2MI01, Acme Scale, Oakland, CA). All blood chemical and urine analyses were determined using standard hospital analytical techniques.

Calculations of Nutrient Absorption

The absorption of nitrogen and sodium was calculated by subtracting the quantity of the substance present in the stool from the enteral intake for each 24-hour period. Stool output was the mean of the 24-hour measurements for each week. Because nutrient intake was constant, nutrient absorption of sodium and nitrogen was calculated by subtracting the balance of the final study week from the first or control week. This was expressed as a percentage change in absorption by dividing this difference by the control value and multiplying it by 100. The percentage change in stool weight (output) was calculated in a similar manner.

Table 1. PATIENT CHARACTERISTICS AND RESPONSES TO THERAPY

Patient No.	Gender	Age (yr)	Cause of Resection	Jejunum-Ileum (cm)	ICV (+/−)	Colon Rectum	TPN (yr)	Discharge TPN	Current TPN
1	M	44	SMA thrombosis	0	−	TDR	5	Off	Reduced
2	F	40	Small bowel volvulus	0	−	TDR	4	Reduced	Reduced
3	M	29	Small bowel volvulus	0	−	TDR	13	Reduced	No change
4	F	44	Small bowel volvulus	8	+	TDR	13	No change	Reduced
5	M	47	SMA thrombosis	8	−	TDR	3	Reduced	Reduced
6	F	42	Small bowel volvulus	10	−	TDR	10	Off	No change
7	F	42	Small bowel volvulus	15	−	All	3	Reduced	No change
8	F	31	Trauma to SMA	15	−	TDR	1.5	Off	Off
9	M	48	SMA thrombosis	20	−	TDR	5	Off	Reduced
10	M	19	Malrotation	20	−	All	15	Off	Off
11	M	68	Crohn's disease	20	+	All	1	Off	Off
12	F	34	Venous ectatic disease	24	−	DR	7	No change	No change
13	M	27	Trauma	30	−	TDR	3	Off	Reduced
14	M	54	SMA thrombosis	30	−	TDR	13	Off	Off
15	F	57	Small bowel obstruction secondary to adhesions	30	+	AT	4	Off	Reduced
16	F	34	Mesenteric infarction	30	+	All	8	Reduced	Reduced
17	F	58	Portal vein thrombosis	30	−	TDR	0.6	Off	Off
18	F	50	SMA thrombosis	30	+	All	1	Off	Off
19	F	30	SMA thrombosis	30	−	TDR	6	Off	Off
20	M	71	SMA thrombosis	30	−	TDR	11*	Off	Off
21	M	47	SMA thrombosis	30	−	TDR	7	Off	Off
22	F	45	Trauma	35	−	TDR	11	Reduced	No change
23	M	44	Volvulus	40	+	All	7	Off	Off
24	M	28	Small bowel volvulus	43	−	TDR	2	Off	Off
25	F	42	Small bowel obstruction secondary to adhesions	43	−	TDR	1	Off	Off
26	M	61	Mesenteric infarction	45	−	None	4.4	No change	No change
27	M	65	SMA thrombosis	46	−	TDR	2	Reduced	No change
28	F	44	Multiple resections secondary to adhesions	46	+	AT	9	Off	Off
29	F	65	Crohn's disease	53	−	TDR	5	Reduced	Reduced
30	M	70	SMA thrombosis	58	+	TDR	9	No change	Reduced
31	M	40	Crohn's disease	60	+	All	8	No change	Reduced
32	M	54	Volvulus	67	+	All	2	Reduced	Reduced
33	M	26	Crohn's disease	75	−	TDR	3	Off	Reduced
34	M	51	Crohn's disease	75	−	TDR	10	Reduced	Reduced
35	M	57	SMA thrombosis	76	−	TDR	0.3	Off	Off
36	F	46	Crohn's disease	80	−	TDR	1	Off	Off
37	F	55	Mesenteric infarction	83	−	TDR	14	Reduced	No change
38	F	46	Crohn's disease	90	−	TDR	9	Reduced	Reduced
39	F	38	Congenital malrotation	91	+	All	10	Off	Off
40	M	76	Small bowel obstruction secondary to adhesions	91	−	None	6	Reduced	Reduced
41	F	34	Crohn's disease	100	−	TDR	6	Off	Off
42	M	48	Volvulus	100	+	All	3	Off	Off
43	F	54	Crohn's disease	112	−	None	7	No change	No change
44	M	24	Crohn's disease	122	−	DCR	9	Off	Reduced
45	M	70	Crohn's disease	137	−	TDR	10	Reduced	Reduced
46	F	30	Crohn's disease	159	−	None	8	Off	Off
47	M	53	Small bowel obstruction secondary to adhesions	240	+	TDR	5	Off	Reduced

TDR = transverse and descending colon and rectum; TPN = total parenteral nutrition; DCR = descending colon and rectum; AT = ascending and transverse colon; + = with ileal cecal valve; − = without ileal cecal valve; SMA = superior mesenteric artery.

* Received TPN and intermittent tube feedings during this time.

Bowel Rehabilitation

Patients

This portion of the clinical investigation was performed at the Brigham and Women's Hospital, Boston, Massachusetts, and at the Nutritional Restart Center, Hopkinton, Massachusetts, the latter a low-cost unit for adults and children with severe malabsorptive disorders. Study protocols were approved by the Brigham and Women's Hospital's Committee for the Protection of Human Subjects from Research Risks, and informed consent was obtained.

Forty-seven adult patients with short-bowel syndrome (25 men, 22 women, age 46 years [range, 19–76 years]) were admitted for study. The clinical characteristics and primary diagnoses of the patients are given in Table 1. All patients had undergone extensive small-bowel resection with or without colonic resection. Combined jejunoileal length of the 43 patients with a colonic remnant was 50 cm ± 7 cm. For the four patients with no colon, the combined jejunoileal length averaged 102 cm ± 24 cm. Most patients (n = 39) were referred for rehabilitative therapy while they received TPN. This group, on average, had received intravenous feedings for 6 years ± 1 year. Some patients (n = 8) were referred because of lack of central venous access and progressive malnutrition. Seven patients in this category were treated without the use of TPN. On admission, all patients were clinically stable and without evidence of infection. Patients with diabetes mellitus, cancer within 5 years of treatment, clinically active inflammatory bowel disease, symptomatic strictures or bowel adhesions, or severe gastrointestinal dysmotility that precluded oral intake were excluded from study. This series represents a group of patients studied in a consecutive manner with no other exclusions.

Method of Treatment

On the morning after the day of admission, a baseline assessment of the patient's nutritional and hydration status was performed. Weight was recorded to the nearest 0.1 kg; whole-body bioelectrical resistance (ohms) was measured by a plethysmograph (model 101A, RJL Systems, Mt. Clemens, MI), and the readings were used to calculate body water as described previously.[17] In a subgroup of 31 patients followed prospectively, blood was obtained to determine concentrations of selected nutrients (vitamins, trace elements, and essential fatty acids) and indicators of organ function using standard analytical techniques. Urine was collected to determine 24-hour volume and creatinine excretion.

Thereafter, recombinant growth hormone was administered by subcutaneous injection at a dose ranging from 0.03 to 0.14 mg/kg/day (average dose of 0.11 mg ± 0.01 mg/kg/day). Supplemental glutamine was provided by both the parenteral and enteral routes. As stool output decreased, TPN (including the quantity of intravenous glutamine) was reduced. Parenteral glutamine dose averaged 0.16 ± 0.02 g/kg/day. Because it was not possible to determine the proportion of enteral glutamine that was absorbed, a standard daily dose of 30 g was administered (5 g of enteral glutamine powder were mixed with a hypotonic, cold beverage and taken six times per day).

In addition to growth hormone and glutamine, all patients underwent extensive diet modification and nutritional education.[16] The quantity and frequency of TPN administered was gradually reduced as enteral intake and 24-hour urine volumes increased and stool output decreased. Blood was drawn biweekly to monitor serum electrolyte concentrations.

In all but three of the persons studied, body weight, total body resistance, intravenous fluid volume and calories, enteral fluid volume and calories, and stool and urine volumes were measured daily. The mean of the first 3 days (baseline) was compared with the mean of the last 3 days of treatment (discharge) to evaluate the effect of 4 weeks of therapy.

On completion of the 26-day protocol, growth hormone was discontinued and the patients were discharged home on oral glutamine (30 g/day) and the modified oral diet. The parenteral nutrient prescription on discharge was individualized for each patient, based on the individual's overall response to treatment with growth hormone plus glutamine plus HCLF diet. For those patients whose baseline nutritional assessment indicated an essential fatty acid deficiency, parenteral lipid emulsions were prescribed. Parenteral and/or enteral vitamin, trace element, and electrolyte supplements were prescribed at dosages to correct nutrient deficiencies identified during the baseline assessment and to maintain normal serum concentrations.

Follow-up data were collected at regular intervals and compared with the baseline data in the group of 31 patients entered into the prospective protocol. This evaluation included TPN requirements (days of infusion per week, volume of fluid per week, intravenous protein and calories administered per week), serum albumin concentration, and body weight. Cost of pretreatment intravenous feedings and current TPN requirements were calculated using Medicare reimbursement rates.[18]

At discharge, patients were classified into one of three categories based on their response to treatment: off, reduced, and no change. *Off* was defined as a patient who was removed from TPN at the end of therapy. In addition, patients who were referred for central line placement and received this treatment and were discharged without the need for TPN were placed in this group. However, several of these patients occasionally received

Table 2. SODIUM AND PROTEIN INTAKE AND BALANCE, AND STOOL WEIGHT DURING SPECIFIC TREATMENT PROTOCOLS

	Control Period			Final Week of Treatment Period			
	Oral Intake (g/day)	Intestinal Balance (g/day)	Stool Weight (g/day)	Oral Intake (g/day)	Intestinal Balance (g/day)	Stool Weight (g/day)	% Change with Treatment
Diet (n = 2)			1117 ± 332			1334 ± 508	+16.3 ± 10.9
Sodium	4.26 ± 0.49	+2.24 ± 0.60		4.66 ± 0.82	+2.46 ± 0.60		+10.6 ± 3.2
Protein	135.2 ± 24.8	+99.0 ± 12.8		117.5 ± 19.6	+79.4 ± 3.8		−19.0 ± 6.7
GLN (n = 3)			1953 ± 231			2197 ± 669	+8.5 ± 20.3
Sodium	3.27 ± 1.40	+1.25 ± 1.06		4.88 ± 0.84	+1.11 ± 0.86		+35.3 ± 34.9
Protein	64.2 ± 11.7	+30.9 ± 11.8		68.3 ± 10.2	+30.5 ± 11.9		+1.2 ± 14.5
GH (n = 4)			2268 ± 437			1872 ± 351	−12.9 ± 11.4
Sodium	4.52 ± 0.89	+2.77 ± 0.05		5.77 ± 1.16	+4.45 ± 0.02		+60.8 ± 3.5
Protein	118.2 ± 8.3	+70.6 ± 7.3		110.5 ± 14.8	+73.2 ± 11.0		+6.4 ± 16.5
GH + GLN + DIET (n = 8)			1783 ± 418			1308 ± 408	−33.1 ± 10.3*
Sodium	3.48 ± 0.56	+1.51 ± 0.68		3.73 ± 0.50	+2.55 ± 0.36		+37.1 ± 40.8
Protein	88.6 ± 18.8	+45.3 ± 12.3		86.7 ± 15.3	+54.2 ± 10.7		+38.8 ± 13.8*

Values are mean ± SEM.
+ = improved protein or sodium absorption; − = decreased stool loss.
* Different from other treatment groups, $p < 0.05$.

specific nutrients intravenously to treat a deficiency. In addition, these patients may have required occasional hydration fluid. Patients who continued to receive similar amounts of TPN when compared with baseline were considered unaffected by therapy. This was confirmed by analyzing costs, which also demonstrated *no change*. Patients who were classified as *reduced* were those who had a decrease in their TPN requirements and also experienced a cost reduction.

STATISTICAL ANALYSIS

Data were analyzed using standard statistical software (Statview No. 512, Abacus Concepts, Inc., Berkeley, CA, on a Macintosh SE personal computer, Apple Computer, Cupertino, CA). For normally distributed data, the paired Student's t test was used to determine differences between the control period and the last week of the treatment period. For nonnormally distributed data, the Wilcoxon signed rank test was used. Analysis of variance was used to identify between-group differences. Simple and multiple linear regression analyses were used to identify which variables significantly influenced response to therapy. A probability value of less than or equal to 0.05 was considered statistically significant. Results are expressed as mean ± SEM.

RESULTS

Absorption Studies

All patients were clinically stable throughout the study period. Weight gain over the 3 to 4 weeks of study was gradual and averaged approximately 1 kg/week. The oral dietary intake remained relatively constant throughout the study. The patients consumed about 2800 kcal/day and 100 g protein/day by the enteral route, although there were large variations among individuals due to food intolerances and preferences (calories ranged from a group average of 1800–3700 kcal/day, and protein intake ranged from 64–135 g/day).

With diet modification only, sodium and protein absorption did not change significantly, and stool output increased slightly compared with the control period (Table 2). When glutamine was added to a fixed standard diet, sodium absorption was slightly enhanced (approximately 35%, not significant), and protein absorption and stool volume were likewise unaffected. Administration of growth hormone alone also tended to improve sodium absorption and somewhat enhanced protein uptake but reduced stool output slightly. With the administration of all three treatment components (growth hormone plus glutamine plus diet) there was a 37% increase in sodium absorption (not significant) and a 38% improvement in protein absorption ($p < 0.02$). Stool loss decreased by about one third ($p < 0.05$) (Fig. 1). This decrease in stool output was accompanied by a reduction in the frequency of bowel movements and often a change in stool character from liquid to semiformed.

Response to Four Weeks of Therapy

All subjects entered into the protocol were able to complete the treatment program, and there were no

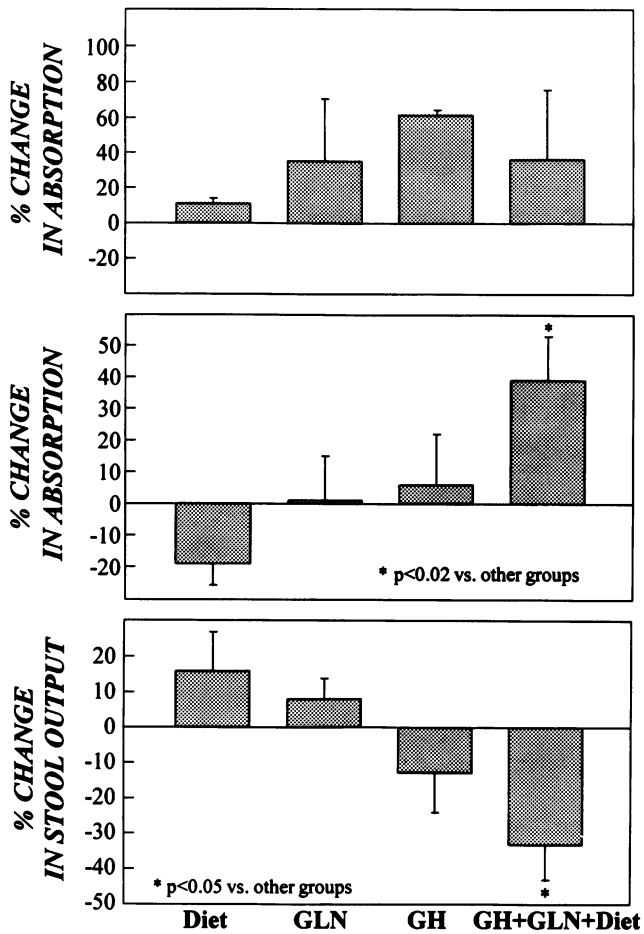

Figure 1. The effect of HCLF diet, glutamine, growth hormone, and growth hormone plus glutamine plus HCLF diet on absorption of (top panel) sodium, (middle panel) protein, and (bottom panel) stool output. An increase in absorption above the 0 balance line indicates enhanced uptake; a negative change indicates decreased absorption. A negative change in stool output indicates a reduction in stool volume.

dropouts. The major side effect of the treatment was fluid retention, manifested by peripheral edema and arthralgia, which varied depending on growth hormone dose. This problem was attenuated by limiting fluid intake, reducing the growth hormone dose, or administering diuretics. In this group of 47 patients, 15 febrile episodes occurred; many were attributable to upper respiratory tract infections, and these individuals were treated symptomatically. Patients diagnosed by culture with bacterial infections (urinary tract, sinusitis, catheter sepsis) were treated with specific antibiotics.

For the group, the 4 weeks of therapy resulted in weight gain, an increase in intake of enteral calories and fluid, maintenance of urine output, and diminished need for intravenous fluid and nutrients (Table 3). These responses were variable, however; at the end of the treatment period, 27 of the 47 patients (57%) did not require TPN, 14 (30%) had reduced TPN requirements, and 6 (13%) required approximately the same quantity of parenteral support as was necessary at the start of therapy. For each subgroup, the changes in absorption of nutrients and fluid during the 4-week treatment period are shown in Table 3. An examination of the characteristics of the subjects in each group revealed that the patients who could not be weaned from TPN were slightly older ($p = 0.02$) and had Crohn's disease as the cause of resection ($p = 0.04$) compared with the other patients who were weaned from or received reduced intravenous nutrition (Table 4). In addition, the patients who failed the therapy (no change) initially had larger stool output ($p < 0.002$) than the other two groups (Table 3). There was no significant difference in bowel length among the three groups.

Evaluation of Long-Term Effect

The length of follow-up for all patients has been between 5 months and 5 years. During this time, most of the patients have been cared for by their primary care physicians and the nutritional support team located in their immediate geographic area. Nutritional compliance was constantly reinforced and hydration state evaluated by frequent telephone interviews between ourselves and the patients. This information was conveyed to the primary care and home care providers, who likewise emphasized the nutritional plan. We cared for and followed directly a smaller group of patients who lived in the New England area. Over the past 18 months, 31 patients have been entered into a prospective study to

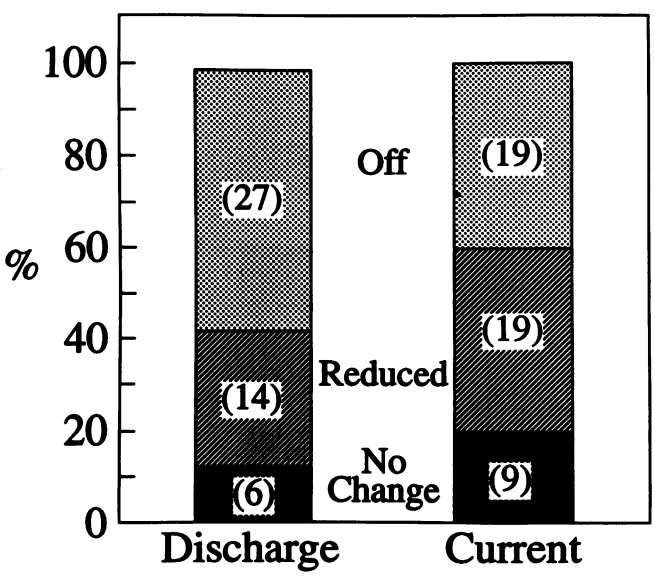

Figure 2. The TPN status of patients after discharge after 28 days of treatment and approximately 1 year after treatment. "Off" indicates no TPN, "Reduced" indicates less than what was initially given, and "No Change" indicates similar volume and calories to those initially administered.

Table 3. THE EFFECTS OF FOUR WEEKS OF GH + GLN + DIET TREATMENT ON WEIGHT, RESISTANCE, AND SOME INPUT AND OUTPUT MEASUREMENTS

	Entire Group (n = 44)*			Off (n = 25)			Reduced (n = 13)			No Change (n = 6)		
	Baseline	Discharge	p	Baseline	Discharge	p	Baseline	Discharge	p	Baseline	Discharge	p
Weight (kg)	58.4 ± 1.6	61.4 ± 1.6	0.0001	56.0 ± 1.8	59.5 ± 1.8	0.0001	62.8 ± 3.7	64.7 ± 3.9	0.016	58.8 ± 3.0	62.4 ± 3.5	0.06
Resistance (Ω)	581 ± 18	500 ± 17	0.0001	600 ± 25	496 ± 22	0.0001	559 ± 36	503 ± 35	0.007	548 ± 37	510 ± 41	NS
Oral calories (kcal/day)	2212 ± 144	2568 ± 139	0.003	2356 ± 226	2853 ± 192	0.004	1913 ± 165	2139 ± 215	0.27	2261 ± 282	2308 ± 275	NS
Oral fluid (mL/day)	2892 ± 156	3158 ± 153	0.03	3073 ± 230	3288 ± 220	0.19	2507 ± 238	2966 ± 248	0.032	2970 ± 324	3027 ± 398	NS
IV calories (kcal/day)	1358 ± 115	539 ± 108	0.0001	1284 ± 180	120 ± 60	0.0001	1440 ± 192	890 ± 202	0.003	1429 ± 204	1525 ± 232	NS
IV fluid (mL/day)	1525 ± 165	827 ± 167	0.0001	1210 ± 189	264 ± 115	0.0001	1781 ± 309	1277 ± 272	0.029	2283 ± 534	2200 ± 617	NS
Urine output (mL/day)	1705 ± 132	1814 ± 113	NS	1663 ± 183	1815 ± 156	0.25	1846 ± 269	1877 ± 227	NS	1572 ± 197	1671 ± 200	NS
Stool output (mL/day)	2078 ± 205	1749 ± 214	0.006	1806 ± 246	1336 ± 204	0.005	1902 ± 275	1911 ± 314	NS	3590 ± 726	3118 ± 1004	NS

Values are mean ± SEM.
NS = not significant.
* Complete data unavailable for three subjects: one who reduced IV feedings and two others who were removed.

evaluate periodically the effect of the therapy on long-term nutritional intake, route of feeding, costs, and nutritional status.

Eight of the 27 patients who had had TPN discontinued eventually experienced increased requirements for TPN. This occurred because of recurrence of disease in three patients (e.g., recurrence of active inflammatory bowel disease), dietary noncompliance in three patients, and inappropriate removal from TPN by the care team in two patients. With follow-up at 1 year, 40% of the group were off TPN, 40% received a reduced TPN prescription, and the remaining 20% of the patients received TPN similar to their initial pretreatment requirement (Fig. 2). At this time of follow-up (approximately 1 year), body weight and serum albumin concentration were well maintained, despite the reduction of intravenous calories and protein (Fig. 3, Table 5).

For the 31 patients followed prospectively, we could estimate the cost savings that occurred with decreased use of TPN. In those patients weaned from TPN, the annual savings was $102,270/year, and those with reduced TPN volume, calories, and protein saved approximately $25,338/year (Table 4). If one assumes that all patients would have received TPN for the coming year, applying these savings to the entire group in the proportion shown at 1 year (see Fig. 2), the money saved for TPN alone would equal $2,310,396/year, or about $49,157/patient/year.

DISCUSSION

The treatment of patients with loss of large segments of the intestinal tract has evolved rapidly over the past 30 years. In the early 1960s, it was common to simply close the abdomen of a patient after laparotomy if extensive bowel loss was identified, because no treatment was available after massive intestinal resection. The development of TPN provided a method for stabilization and support of these patients with the hope that adaptation of the remnant bowel would occur over time. Although this has occurred in many patients who have had adequate lengths of remaining small bowel, it has not been the case in many other persons with inadequate small intestine. It has been estimated that about 10,000 to 20,000 patients with short-bowel syndrome in the United States are now at home being maintained on intravenous feedings.[13] That these persons can be maintained out of the hospital over the long term is a remarkable accomplishment, and it should be realized that patients with short-bowel syndrome served as the stimulus for the growth of a new health service industry—home care—which has facilitated this process. However, the long-term experience with home TPN now reveals that a variety of short- and long-term complications occur, including repeated episodes of catheter sepsis, nutri-

Table 4. CHARACTERISTICS OF PATIENTS IN GROUPS

	Off	Reduced	No Change
n	27	14	6
Age (yr)	43 ± 3	51 ± 4	50 ± 6
Gender (male:female)	15:12	7:7	3:3
Jejunum-ileum length (cm)			
With colon (mean)	53 ± 10 (n = 26)	49 ± 11 (n = 11)	38 ± 13 (n = 4)
(median)	30	46	41
Without colon	159 (n = 1)	91 (n = 1)	78 (n = 2)
Years of TPN	5 ± 1	7 ± 1	8 ± 1

Values are mean ± SEM.
TPN = total parenteral nutrition.

tional deficiencies, progressive failure of the liver and kidneys, and severe osteoporosis. These problems, associated with the compromised lifestyle and major costs (about $100,000/year for the TPN alone), have resulted in other initiatives to solve the problems of patients with short-bowel syndrome. Surgeons are evaluating the effects of bowel reconstruction[19] and intestinal transplantation[20] in this group of patients.

In the past 10 years, however, several important experimental developments have contributed to the evolution of the approach presented in this report. First, it was discovered that glutamine was the major nutrient for the bowel. Providing parenteral feedings that contained this amino acid supported mucosal growth under a variety of conditions,[21] including mucosal hypertrophy that occurred after extensive small-bowel resection.[22] Other studies have documented improved bowel function, including absorption, when L-glutamine was provided by parenteral[23] and/or enteral feedings.[24]

Second, both animal and human studies have demonstrated that growth hormone, now available in recombinant form, stimulates intestinal growth[25] and enhances transport of nutrients across the small bowel.[26] Although we observed few significant clinical effects when these agents were administered alone, under the conditions of our study, enhanced absorption was observed when the agents were given together. Animal studies have revealed a molecular basis for this proliferative response using combined agents.[27]

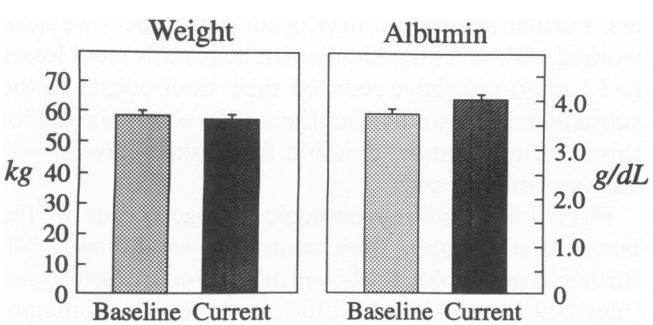

Figure 3. Body weight and albumin at baseline and currently at approximately 1 year.

The issue of optimizing dietary intake is more controversial, and investigators have differed in their preference for a low-fat[28] or a high-fat (unmodified) diet.[29] Absorption was maximized by providing a diet that contained 20% to 25% fat, similar to recent recommendations by others.[28] However, for these patients with very short segments of jejunum–ileum, we were unable to document major effects of diet alone. The exception to this finding occurred when a patient consumed a high-fat intake (>40% of total calories) during the control period and was then placed on a 20% fat diet during the treatment period. In addition, we have found that many patients were sensitive to lactose and also increased their stool output and complained of bloating with the ingestion of simple sugars (fructose and glucose). We therefore have provided a diet tailored to the individual but that provides about 60% of calories as complex carbohydrates, 20% as protein, and the remainder as fat. This is provided as six feedings given throughout the day, with nutrients distributed into three meals and three snacks. Vitamins and minerals are supplemented by the oral route. Hydrogen-blocking drugs were often helpful to diminish gastric secretion; in contrast, we have observed little benefit with the administration of somatostatin analogues, even in the patients with high stool losses.

In this clinical trial, each subject served as his or her own control. This approach was chosen because of the large variation among subjects in terms of bowel disease, length of remnant bowel, and volume of stool lost. We found that it was possible to wean a large proportion of these patients from TPN using this combined therapeutic approach; another sizable segment of this group was able to reduce their weekly TPN requirements, thus giv-

Table 5. CHANGES IN TPN REQUIREMENTS, ANNUAL COSTS, AND NUTRITIONAL INDICES BEFORE TREATMENT AND AT THE PRESENT TIME

	Off (n = 7)			Reduced (n = 16)			No Change (n = 8)		
	Baseline	Current	p	Baseline	Current	p	Baseline	Current	p
TPN days/wk	6 ± 1	0	0.0001	6 ± 0	4 ± 0	0.0001	6 ± 1	6 ± 1	NS
TPN volume/wk (L)	12 ± 2	0	0.002	12 ± 1	7 ± 1	0.0006	11 ± 2	10 ± 2	NS
TPN protein/wk (g)	387 ± 80	0	0.003	476 ± 32	259 ± 28	0.0001	392 ± 15	375 ± 72	NS
TPN calories/wk (kcal)	9451 ± 2909	0	0.018	9188 ± 1088	5744 ± 950	0.0001	7518 ± 1719	8665 ± 1953	NS
Annual costs ($/yr)	102,270	0	0.0002	107,143 ± 7117	81,805 ± 7081	0.0003	95,227 ± 12,271	107,911 ± 13,182	NS
Weight (kg)	57.7 ± 3.6	54.0 ± 2.7	NS	59.5 ± 2.7	60.4 ± 2.7	NS	62.7 ± 4.5	60.4 ± 4.5	0.02
Albumin (g/dL)	3.8 ± 0.1	3.9 ± 0.1	NS	3.6 ± 0.1	3.8 ± 0.1	0.1	3.6 ± 0.1	3.6 ± 0.2	NS

Values are mean ± SEM.
TPN = total parenteral nutrition; NS = not significant.

ing them nights off from infusion. Body weight and serum albumin, major indicators of nutritional status, were stabilized over the follow-up period, which averaged 1 year. This series represents the largest group of adult patients with short-bowel syndrome studied to date by a single group of investigators, and additional multicenter trials are in progress involving both adults and children to evaluate the effect of this approach in randomized trials.

It could be argued that the patient's response to growth hormone plus glutamine plus HCLF diet occurred because special attention was given to provide the appropriate diet or that specific nutrients were provided to satisfy deficiencies or because the investigators have a sophisticated understanding of the underlying fluid, electrolyte, and nutritional derangements that occur in this group of patients. Although this is possible, we believe our initial study in the Clinical Research Center indicates that this combination of therapeutic agents, coupled with sound nutritional and physiologic management, resulted in the responses observed—the ability to take patients off or keep them off TPN or reduce their requirements in more than 80% of this population. Numerous patients were referred to us after failure to respond to growth hormone or glutamine administered by their own physicians, and all of these patients demonstrated decreased stool output when growth hormone plus glutamine plus HCLF diet were administered in combination. In addition, 14 of 21 patients who were discharged without TPN and who have maintained their nutritional state in follow-up had less than 50 cm of jejunum-ileum. This is an important observation, because this length of intestine is consistently regarded as less than the necessary length for adequate absorption and nutritional maintenance by enteral feedings.[1,7]

Not only did the patients respond to 4 weeks of therapy, but also, many were able to maintain this state of independence during the year after the initial treatment. Our longest-term patient has been independent of TPN for 5 years (patient 8, 15 cm jejunum anastomosed to her transverse colon), and during the last year she became pregnant, carried a normal child to term, had a normal delivery, and breast-fed the infant, events that reflect her capacity to withstand additional nutritional stress. Others have been free of TPN, but short-term illness has necessitated brief intervals of intravenous support. In those eight persons who were initially weaned from TPN but who eventually required intravenous feedings, about one third were placed back on TPN because of recurrence of their underlying disease; dietary noncompliance was another cause of failure in several other persons. Care plans need to be developed allowing for all of these persons to receive appropriate long-term care to cost-effectively support the patient with short-bowel syndrome through intercurrent illness. For example, several days of intravenous fluid may be necessary during periods of viral gastroenteritis, but with resolution of the illness and adequate hydration, enteral feeding can be restarted. In addition, some patients may need to be retreated with growth hormone plus glutamine plus HCLF diet at appropriate time intervals and/or have dietary compliance frequently reinforced by their care providers. Further adaptation may occur with time—we have worked with several patients with large daily stool losses (>3 L/day) who have reduced their stool output in the subsequent 12 months after therapy to about one half of this volume while the diet and fluid intake have stayed the same or increased.

Physiologic and morphologic changes occur in the bowel after therapy. With treatment, small-bowel villi further hypertrophy, the bowel dilates and elongates, and intestinal transit time becomes prolonged. Colonic absorption is thought to be enhanced via the process of bacterial fermentation. This process stimulates fluid and

electrolyte absorption and salvages both carbohydrate and protein calories, which are malabsorbed by the small bowel remnant.[30] In addition, volatile fatty acids generated in the colon enhance mucosal growth and prolong transit time.[31]

Because the bowel is constantly renewing its surface area, this organ is ideal for modification by administration of selected nutrients and growth factors. Other hormones are also known to exert effects on the bowel, but growth hormone and glutamine are currently approved agents, readily available, safe, and reasonably inexpensive compared with the other therapeutic options. This method of treatment should be evaluated and considered for patients with inflammatory bowel disease, those undergoing intestinal transplantation, and those with dysfunctional loops of distended bowel who require rehabilitation. Various laboratory and clinical observations suggest that these therapeutic agents administered singly or in combination affect intestinal structure and function in a wide variety of conditions. These observations of patients with short-bowel syndrome may demonstrate for the first time that we can use growth factors and nutrients together to enhance the proliferative response of specific tissue and therefore improve function. This concept may have broad applications to support or enhance the growth and function of other organs and thus improve care of patients.

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Discussion

DR. JOHN L. ROMBEAU (Philadelphia, Pennsylvania): Dr. Wilmore and colleagues and a number of members of this Association have created a very exciting new area of surgical nutrition and metabolism; namely, the area of nutritional pharmacotherapy. This is broadly defined as providing some nutrients that indeed seem to have more pharmacologic effects than nutritional effects per se, in addition to giving some drugs that in turn either enhance nutrient utilization or modify the metabolic environment of the host.

We have been very interested in the effects of the amino acid glutamine on the transplanted small intestine. In a model of transplanted small intestine in the rat, we compared the effects of supplemental glutamine given either intravenously or directly into the graft on small bowel glucose absorption as measured with C-14 labeled glucose. As shown, the addition of glutamine, when compared with an isonitrogenous controlled diet balanced with a mixture of nonessential amino acids, significantly enhanced the ability of the small intestine to absorb glucose nearly equivalent to baseline pretransplant levels.

I have one question for Dr. Wilmore, and this relates to the human short bowel setting. There is very limited information obtained from intestinal biopsies in patients that have suffered from short bowel syndrome. This information shows that the small intestine seems to reach a maximal rate of adaptive hyperplasia somewhere between 2 and 3 years postoperatively.

In Dr. Wilmore's study, 10 of the 19 patients that remained off total parenteral nutrition had been on total parenteral nutrition for periods greater than 3 years. In fact, one of these patients had actually been on total parenteral nutrition for 15 years prior to the usage of this combined therapy.

My question is, what are the mechanisms by which this combined therapy enhances the absorptive function of the remaining gut in an intestine that has already had at least 3 years to adapt endogenously?

DR. PAUL R. SCHLOERB (Kansas City, Kansas): I am as impressed by this paper as I was a quarter of a century ago when Doug Wilmore, working with Dr. Rhoads, Dr. Dudrick, Dr. Vars, and others in Philadelphia, maintained an infant for many, many weeks by total parenteral nutrition for the first time.

When you have reviewed this manuscript, as I have had the privilege of doing, I think you will agree that this kind of study, with careful clinical observations and measurements, could only be carried out in a clinical research center, although it was not called that at the Brigham when Dr. Francis Moore set it up 47 years ago.

One may philosophize, I suppose, to the extent that nature has a way of correcting defects like this. The more weight that is lost, the less nutrients are required.

But it is worth emphasizing as Doug pointed out, that patients with less than 50 cm of jejunum-ileum are almost destined to require total parenteral nutrition. Two thirds of their patients in this category were taken off total parenteral nutrition.

Weight gain to the tune of approximately 1 kg per week was observed in their study. And I have to ask whether this weight was in fact water, because growth hormone does indeed produce fluid retention.

These favorable results are probably due in large measure to the effect of growth hormone, and yet the patients were discharged while not receiving growth hormone. So my question is, what did growth hormone do? What effect did it have that continued beyond the administration of growth hormone?

Whether it is pediatric cardiac surgery, orthotopic liver transplantation, or carcinoma of the pancreas, the best results are obtained by centralized patient care. I think centralization of care applies to this rather unusual circumstance of short-gut syndrome. Dr. Wilmore makes reference to the possibility of multicenter trials, and I wonder if he would share with us some of his plans and ambitions in this regard.

And finally, in terms of centralized care, I wonder, Doug, if you would acquaint us a little more with the so-called Nutritional Restart Center, which, from my limited understanding, represents a real boon to patients with short-gut syndrome.

DR. STANLEY J. DUDRICK (Waterbury, Connecticut): I thoroughly enjoyed this impressive paper, which is in an area of great personal clinical and scientific interest to me. I, too, had the opportunity to read the manuscript, which is replete with data that were not able to be presented here in its entirety. Dr. Wilmore did not have time to explain all aspects of the entry criteria and the therapy, and, therefore, I would like to ask him a few questions. To reduce some of the variables, patients with active infection and inflammatory bowel disease, cancer within 5 years of treatment, diabetes mellitus, other extra digestive organ failure, and severe gastrointestinal dysmotility, were excluded. I wonder if the team had any experience treating some of these patients that were excluded from the study? Furthermore, do you have any recommendations for how one might manage patients with those exclusionary comorbid factors?

Regarding your choice of the recombinant hormone, how did you determine the dosage used? Was the final recommended dose arrived at by trial and error? Or did you give growth hormone to the point at which you began to have complications and then back off? Or were you able to discern some optimal dose above which you had no additional beneficial effects? Additionally, what does a course of growth hormone cost?

In measuring body water, did you fractionate the total body water into intracellular and extracellular water? If so, would you share those data with us?

In the paper, you described a pregnant woman with short-bowel syndrome who came off the total parenteral nutrition