

# Nutritional Support of Bone Marrow Transplant Recipients: A Prospective, Randomized Clinical Trial Comparing Total Parenteral Nutrition to an Enteral Feeding Program<sup>1</sup>

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## ABSTRACT

Although standard supportive care for bone marrow transplant (BMT) recipients includes total parenteral nutrition (TPN), it has not been shown that this is the most appropriate method of nutritional support. To determine whether current BMT recipients require TPN during the early recovery period, we conducted a prospective, randomized clinical trial comparing TPN and an individualized enteral feeding program (counseling, high protein snacks and/or tube feeding). Nutritional assessment included measurement of serum proteins, anthropometry, and body composition analysis. For the latter, total body water and extracellular fluid were measured by standard radioisotope dilution techniques and used to quantitate body cell mass and body fat plus extracellular solids (FAT + ECS). In 27 TPN patients, body composition 28 days after BMT, expressed as a percentage of baseline, was body cell mass, 100%, extracellular fluid, 108%, FAT + ECS, 108%, and in 30 enteral feeding program patients, was body cell mass, 93%, extracellular fluid, 104%, and FAT + ECS, 94%. Only the difference in FAT + ECS was statistically significant ( $p < 0.01$ ). Compared to the enteral feeding program, TPN was associated with more days of diuretic use, more frequent hyperglycemia, and more frequent catheter removal (prompted by catheter-related complications), but less frequent hypomagnesemia. There were no significant differences in the rate of hematopoietic recovery, length of hospitalization, or survival, but nutrition-related costs were 2.3 times greater in the TPN group. We conclude that TPN is not clearly superior to individualized enteral feeding and recommend that TPN be reserved for BMT patients who demonstrate intolerance to enteral feeding.

## INTRODUCTION

BMT<sup>3</sup> is a rigorous therapeutic modality used for the treatment of patients with severe aplastic anemia, leukemia, and certain other malignancies (1-3). The cytotoxic regimens designed to cure patients with these diseases are so intensive that without bone marrow rescue, the regimens produce lethal bone marrow failure. Individuals undergoing bone marrow transplantation do not usually eat adequate p.o. diets because of the adverse nutritional consequences associated with BMT. These toxicities, which include anorexia, fever, nausea, vomiting, mucositis, and diarrhea may be due to the preparative cytoreductive chemotherapy and total body irradiation, infection, or graft-versus-host disease (4-6). Since right atrial catheters for i.v. access have been demonstrated to be safe and well-tolerated by BMT recipients, standard supportive care now includes TPN (6, 7).

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<sup>3</sup> The abbreviations used are: BMT, bone marrow transplant; BCM, body cell mass; ECF, extracellular fluid; EFP, enteral feeding program; FAT + ECS, body fat plus extracellular solids; TPN, total parenteral nutrition.

It has not been shown that TPN is required by all bone marrow transplant recipients to recover hematological and immunological function. In fact, marrow grafts are successful in well-nourished mice unless they are totally deprived of protein and energy after BMT (4). Furthermore, TPN is an expensive therapeutic modality that is associated with risks and toxicities such as injury during catheter placement, volume overload, venous thrombosis, and infection. Nutritional support by the enteral route, however, eliminates the toxicities and costs specifically due to TPN. With individualized nutritional support programs that take advantage of current enteral feeding technology (e.g., one-on-one counseling, meal-by-meal menu selection, positive reinforcement techniques, specially prepared between meal snacks, commercial supplements, and tube feeding), it may be possible to use the enteral route to support patients recovering from BMT.

One of the greatest problems confronting the physician prescribing therapeutic nutrition is the lack of sensitive and practical methods to monitor the effects of nutritional therapy. Changes in body composition have obvious value as indicators of changes in overall nutritional status for patients who undergo nutritionally depleting therapies or who receive therapeutic nutritional support (8). Anthropometric measurements (skinfold thickness and limb circumference) are frequently used to determine body composition, but this method has been criticized as insensitive, error prone, and inaccurate (9, 10). In addition, standards have not been clearly established (11). More sophisticated methods such as neutron activation analysis (12, 13), underwater-weighing (14, 15), and determination of total body potassium by measurement of <sup>40</sup>K (16, 17) are impractical in acutely ill hospitalized patients. We have shown (18, 19), however, that isotope dilution analysis of body composition (8) can be used effectively in such patients.

In this study of BMT recipients, we compared TPN and an individualized EFP for their effectiveness in preserving body composition and for clinical outcomes including frequency of catheter-related complications, medication use, abnormalities in serum chemistries, rate of bone marrow recovery, length of hospitalization, survival, and cost.

## MATERIALS AND METHODS

### Patient Population

This study was approved by the Joint Committee on Clinical Investigations of the Johns Hopkins University School of Medicine, and written consent was obtained from all patients or their guardians after they were informed of the nature, purpose, and possible risks involved with the study. The study was conducted from January 1, 1984 through July 10, 1986; patients 10-58 years of age were enrolled during the calendar year 1984. Minimum follow-up was 555 days. Patients were stratified by type of transplant (allogeneic or autologous) and randomized to one of the two feeding methods (TPN or EFP).

### Bone Marrow Transplantation

Bone marrow transplantation was carried out according to standard protocols as previously described (1-3). Briefly, patients were treated with high dose chemotherapy (busulfan and/or cyclophosphamide) with or without total body irradiation, followed by infusion of bone marrow from a histocompatible donor or by reinfusion of previously cryopreserved autologous bone marrow. In addition to nutritional support, standard supportive care during the recovery phase included reverse isolation, antimicrobial therapy, blood product support, and physical therapy. By convention, the day of transplant is designated "day 0", days before transplant "minus days", and days following transplant "plus days" (e.g., day -1 is the day before BMT; day 7 is 1 week following BMT).

### Study Protocol

The baseline body composition analysis and standard nutritional assessment were performed following randomization and before the day of BMT. The assigned nutritional therapies were started on day -1 and continued through day 28 unless the patient was discharged or died before day 28, or unless the patient was declared a treatment failure (see below). Patients failing the assigned nutritional treatment arm received the alternate treatment for the remainder of the study. Repeat body composition analysis and nutritional assessment studies were performed on day  $10 \pm 1$  (SD) day and on day  $28 \pm 1$  day after BMT. Patients were monitored daily for nutrient intake, potential treatment-related toxicities, and clinical outcome parameters (e.g., WBC, absolute neutrophil count, infection status). Data on patient infections were collected by epidemiologists who were blind with respect to treatment group assignments. Infectious episodes were scored using accepted criteria (20) for oncology patients.

In order to have venous access adequate for the infusion of antibiotics, blood products, cyclosporine, and the TPN solution, allogeneic patients assigned to the TPN group had a total of three lumens placed, while those assigned to the enteral feeding group required only two lumens. All autologous patients had two lumens. All patients had single and/or double lumen in-dwelling Silastic central venous Hickman-Broviac catheters placed before day -1. In addition, polyurethane central venous catheters were placed percutaneously without tunneling in eight TPN and one EFP patient.

### Treatment Groups

**Total Parenteral Nutrition.** TPN patients received 35 kcal/kg/day and 1.4 g protein/kg/day from the standard TPN solution. This solution contained 25% dextrose, 4.25% amino acids (FreAmine III; Kendall McGaw), electrolytes, vitamins (MVI-12; USV Laboratories), and trace minerals (MTE-4; LyphoMed). The nutrient prescription and/or composition of the TPN solution was modified when clinically indicated (e.g., nutrients were concentrated to reduce the fluid intake in patients with fluid overload). TPN patients were allowed to eat *ad libitum*. When the patient's p.o. intake of protein was  $>0.5$  g/kg/day for an evaluation period (3-4 days), the TPN intake was reduced. The patient was considered a treatment failure and crossed over to the EFP if, because of infection or malfunction, the central venous catheter had to be removed and could not be replaced.

**Enteral Feeding Program.** The EFP was an individualized program designed to provide at least the minimum nutrient intake necessary to support hematological and early immunological reconstitution while taking into consideration the preferences of individual patients. Nutrient goals were the same as those for TPN patients. Depending on the needs of particular patients, the nutritional care plan might have included one-on-one counseling, meal-by-meal menu selection, positive reinforcement techniques, special between-meal snacks, commercial supplements, or tube feeding. All patients received p.o. daily vitamin/mineral supplements (Daily-M; Upsher-Smith).

Patients whose voluntary p.o. intake of protein was  $<0.5$  g/kg/day for an evaluation period (3-4 days) were prescribed protein-rich between-meal snacks. In addition, to ensure that the regenerating bone marrow had an adequate supply of amino acids, these patients received i.v. amino acids (0.5 g/kg/day) until their p.o. protein intake exceeded

0.5 g/kg/day or until they were declared treatment failures. Patients whose voluntary p.o. intake continued to be inadequate after day 10 were candidates for nasoenteric tube feeding. If the minimum protein intake could not be achieved by the combination of the voluntary p.o. and nasoenteric routes or when the enteral route was contraindicated, the patient was considered an enteral feeding failure and given TPN.

### Standard Nutritional Assessment

The standard nutritional assessment included body weight, percentage ideal body weight (21, 22), serum albumin and transferrin concentrations, arm muscle and arm fat areas,<sup>23</sup> total body fat estimated from measured triceps and biceps skinfold thicknesses (24, 25), and estimation of body cell mass from measured creatinine excretion (26).

### Isotope Dilution Analysis of Body Composition

In a model of body composition modified from the descriptions of Moore (8) and Shizgal (27), body mass is composed of three major compartments: ECF; BCM, the metabolically active, functional cell mass; and FAT + ECS. In addition to body fat, the FAT + ECS compartment includes the dry bone, fascia, and tendons, which were assumed to be of relatively constant size over the planned 28-day study period. Therefore, changes in the FAT + ECS compartment were attributed to changes in body fat.

Body composition was measured by isotope dilution analysis (8, 18). Total body water and ECF were measured using tritiated water ( $^3\text{H}_2\text{O}$ , 7  $\mu\text{Ci/kg}$  body weight) and [ $^{169}\text{Yb}$ ]diethylenetriaminepentaacetate, 0.5  $\mu\text{Ci/kg}$  body weight), respectively, as tracers. Tracers were injected sequentially into the patient's i.v. catheter, and samples of blood were drawn 2, 2.5, 3, 3.5, and 4 h later. Triplicate samples of the tracers and plasma were assayed in a two-channel liquid scintillation counter. The  $^3\text{H}$  activity was corrected for the contribution of  $^{169}\text{Yb}$  activity.  $^{169}\text{Yb}$  activity was measured in a well-type gamma counter. The volume of tracer dilution was calculated using the formula of Chien and Gregersen (28)

$$\text{Volume (ml)} = \frac{[\text{Activity administered}]/(100 - (0.073) (\text{plasma total protein, g/dl}))}{(\text{Activity/g plasma}) (100)}$$

The factor  $[(100) - (0.073) (\text{plasma total protein, g/dl})]/100$  represents the correction factor for plasma water (proteins act as solids, reducing the fluid and electrolyte content in a given volume of plasma). The figure for activity/g plasma was determined by extrapolating to time = 0 the plasma  $^3\text{H}$  and  $^{169}\text{Yb}$  activities measured during the equilibrium phase (2-4 h after tracer administration). This extrapolated value represents the presumed tracer activity had isotope dilution been instantaneous.

The sizes of the other body compartments were determined as

$$\text{Intracellular fluid (kg)} = \text{Total body water (kg)} - \text{ECF (kg)}$$

$$\text{BCM} = \frac{\text{Intracellular fluid (kg)}}{0.70}$$

$$\text{FAT + ECS (kg)} = [\text{Body weight (kg)}] - [\text{BCM (kg)} + \text{ECF (kg)}]$$

The calculation of BCM from ECF was based on the assumption that 70% of cell mass can be attributed to water (29-31). The whole-body radiation absorbed dose per body composition study was approximately 30 mrad.

### Data Analysis

The primary nutritional outcomes were changes in the sizes of the BCM, ECF, and FAT + ECS compartments that occurred from baseline to day 28. Secondary outcomes included changes measured by other nutritional assessment parameters. Day 28 values were expressed as a percentage of baseline, and between-group differences were evaluated by Student's *t* test (32). All tests were two tailed and  $P < 0.05$  was considered to be statistically significant. Treatment-related differences in clinical outcome parameters (e.g., catheter-related complications,

rate of hematopoietic recovery, medication use, and length of hospitalization) were evaluated by *t* and Fisher's Exact (33) tests, as appropriate. We have reported the mean  $\pm$  SD and the *P* for the *t* test, unless otherwise indicated.

Catheter-associated infection rates were evaluated by testing the equality of the two Poisson means (34). Nonparametric methods for censored data (35, 36) were used to evaluate the differences in survival. To determine which of several factors acting simultaneously on survival were the best predictors of subsequent short-term survival, we used multivariate analysis with the Cox proportional hazards regression model (37).

## RESULTS

Sixty-five patients were entered and randomized to one of the two treatment groups; 61 (93%) actually participated in the study. Two patients did not receive bone marrow transplants and were discharged, one patient withdrew on day -5, and the other patient had an unusually complicated pretransplant course requiring major changes in her preparative regimen, and she was removed from the study on day -4.

Fifty-seven (93%) of the participating subjects could be evaluated for nutritional and other outcomes on day 28 (Table 1). Before the end of the study, three of the participating patients died of complications unrelated to nutrition therapy. Except in the analysis of survival and catheter-related complications, these three patients were not evaluated further. One patient was removed from the study on day 23 because of major protocol violations and was not evaluated on day 28.

**Baseline Characteristics.** With respect to demographic characteristics (Table 1) and baseline nutritional status (Table 2), the two treatment groups were comparable. Although many patients reported a small recent weight loss, nutritional status at the time of admission was good in most patients. Body composition measurements showed that patients had normal

Table 2 Baseline nutritional status of the 61 patients as originally assigned

Variable	TPN	EFP
Body composition (% body wt)		
Body cell mass	47 $\pm$ 8 <sup>a</sup>	50 $\pm$ 9
Extracellular fluid	27 $\pm$ 6	25 $\pm$ 5
Fat + extracellular solids	30 $\pm$ 10	26 $\pm$ 9
Anthropometry		
Arm muscle area (% standard)	95 $\pm$ 21	88 $\pm$ 23
Arm fat area (% standard)	108 $\pm$ 44	101 $\pm$ 57
Total body fat (% body wt)	28 $\pm$ 8	25 $\pm$ 7
Other		
Serum albumin (g/dl)	3.8 $\pm$ 0.4	3.9 $\pm$ 0.5
Serum transferrin (mg/dl)	204 $\pm$ 42	219 $\pm$ 39
% ideal body wt	105 $\pm$ 13	107 $\pm$ 11
% usual wt	94 $\pm$ 10	96 $\pm$ 7
Lean body mass from creatinine excretion (% body wt)	69 $\pm$ 20	68 $\pm$ 19

<sup>a</sup> Mean  $\pm$  SD.

quantities of lean tissue and adequate fat stores. Albumin and transferrin concentrations and anthropometric measurements were within normal limits.

**Treatment Failures.** Four (13%) of the 31 patients randomized to TPN were declared failures because i.v. feeding catheters could not be placed successfully. These patients were crossed over to the EFP and did not receive TPN. Two of the four were evaluated on day 28, one patient died too early to be evaluated (day 11), and the other was removed from the study because of protocol violations. During the period of this study, there were no instances of TPN failure once i.v. feeding had been started. In each case where infection or mechanical complications resulted in the removal of a patient's central venous catheter, it was possible to replace the catheter and continue feeding.

Of the 30 patients randomized to the EFP, there were seven (23%) whose voluntary p.o. intake of protein was consistently  $<0.5$  g/kg/day. Three of these patients were not candidates for tube feeding because of severe nausea and vomiting or diarrhea. In four patients, tube feeding was attempted, but unsuccessful (in three patients, because of nausea, vomiting or diarrhea; one patient refused tube feeding). These seven patients were crossed over to TPN. One of these patients died too early (day 26) to be evaluated; the others were evaluated with those EFP patients who had not failed the enteral program.

There were no demographic or baseline nutritional status characteristics that could be used to predict which patients were likely to fail either TPN or the EFP. In addition, EFP failures could not be identified from changes in nutritional status that occurred from baseline to day 10 (data not shown).

Data were analyzed in two ways: in the more conservative analytical approach, patients were analyzed according to their originally assigned groups; in the second analysis, the TPN failures who never received TPN and who could be evaluated on day 28 were analyzed with the group of patients originally assigned to the EFP. The magnitude and direction of the observed treatment-related differences were the same, irrespective of the analytical method. Only the results of the latter method have been reported below.

**Energy and Protein Intakes.** The total intake (i.v. plus enteral) and enteral intake of energy and protein were compared by BMT day for the 30 patients who actually received the EFP and the 27 TPN patients who were not declared TPN failures. Mean p.o. intakes were similar (15 kcal/kg/day; 0.4 g protein/kg/day) during the week before BMT; but following transplant, the p.o. intake of EFP patients was 15–20 kcal/kg/day and 0.5–0.7 g protein/kg/day; in TPN patients, p.o. intake was 5–10 kcal/kg/day and 0.1–0.4 g protein/kg/day. However, the

Table 1 Demographic characteristics of the participating 31 TPN and 30 EFP patients

	TPN	EFP
Diagnosis		
Acute myelogenous leukemia	9 (8) <sup>a</sup>	9
Acute lymphocytic leukemia	10 (9)	6 (5)
Chronic myelogenous leukemia	4	7 (6)
Other <sup>b</sup>	8	8
Preparative regimen		
Busulfan-cyclophosphamide	10 (8)	12
Cyclophosphamide-total body irradiation	18	15 (13)
Cyclophosphamide-cyclosporine	3	3
Age group		
Adult ( $\geq 19$ yr)	21 (19)	21 (19)
Child ( $< 19$ yr)	10	9
Sex		
Male	14 (13)	18 (16)
Female	17 (16)	12
Race		
White	25 (23)	29 (27)
Nonwhite	6	1
Type of transplant		
Allogeneic	23 (21)	23 (22)
Autologous	8	7 (6)
Remission no.		
0	3	4
1	6 (5)	7
2	8	3 (2)
3+	14 (13)	16 (15)

<sup>a</sup> Numbers in parentheses, the 57 patients who could be evaluated on day 28.

<sup>b</sup> Other: six aplastic anemia; six non-Hodgkin's lymphoma; one breast cancer; one rhabdomyosarcoma; one malignant histiocytosis; one preleukemia.

total intake of EFP patients was about one-half that of TPN patients (20–25 kcal/kg/day and 0.5–1.0 g protein/kg/day in EFP patients; 40–45 kcal/kg/day, 1.4–1.6 g protein/kg/day in TPN patients). Twenty-two (73%) EFP patients required i.v. amino acid supplements for an average of  $7 \pm 5$  days. The mean total intake of i.v. amino acid supplements in these EFP patients was  $0.1 \pm 0.1$  g/kg/day as compared to  $1.3 \pm 0.3$  g/kg/day in TPN patients.

**Changes in Nutritional Status.** Although baseline body weight was similar in both treatment groups, patients in the TPN group gradually gained weight, whereas patients in the EFP group lost weight. In the TPN group, body weight on day 28 was  $108 \pm 9\%$  of baseline; in the EFP group, body weight was  $96 \pm 5\%$  of baseline ( $P < 0.0001$ ). TPN patients gained weight primarily in the FAT + ECS and ECF compartments. EFP patients lost weight from both the BCM and FAT + ECS compartments, while the ECF compartment expanded slightly (Fig. 1). Of the treatment-related differences, only those in FAT + ECS and total body weight were statistically significant ( $P < 0.01$ ). With 95% confidence, the true change in BCM from baseline to day 28 in EFP patients could have been a loss of 1–13% and for TPN patients a gain of 4% to a loss of 4%. These body composition changes (from baseline to day 28) were also detected by the standard nutritional assessment (Fig. 2); however, the changes were within the error of measurement. In

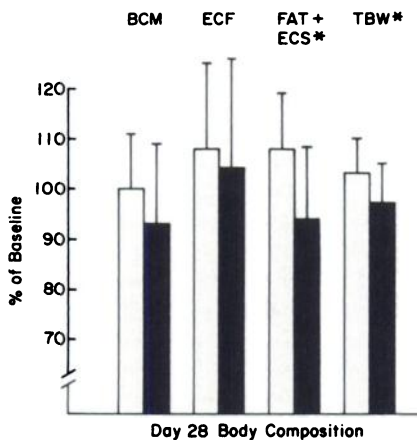


Fig. 1. Body composition of the 27 TPN (□) and the 30 EFP patients (■) who were evaluated by isotope dilution analysis on day 28. Values are a percentage of baseline [mean  $\pm$  SD (bars)]. \*,  $P < 0.05$  (*t* test; two tailed). TBW, total body weight.

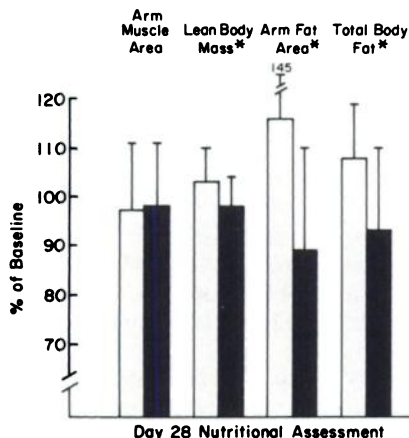


Fig. 2. Standard nutritional assessment parameters on day 28. Values are a percentage of baseline [mean  $\pm$  SD (bars)] for the evaluated TPN (□) and EFP (■) patients. \*,  $P < 0.05$  (*t* test; two tailed).

both treatment groups, the serum concentrations of albumin and transferrin fell equally to 90–92% of baseline.

When TPN patients were compared with only those EFP patients who did not fail the program, the direction and magnitude of the differences were the same as those seen when TPN patients were compared with all EFP patients. There were no significant differences in BCM and body weight on day 28 in those EFP patients who failed the feeding program and in those who did not fail. However, patients who failed the EFP lost less fat ( $100 \pm 28\%$  of baseline versus  $86 \pm 13\%$ ) and TBW ( $100 \pm 10\%$  of baseline versus  $97 \pm 7\%$ ) than did patients who did not fail the EFP, although the differences were not statistically significant.

**Medication Use.** There were no treatment-related differences in the total number of days of analgesic, antiemetic, or i.v. antibiotic use during the 28-day study period. TPN patients received diuretics more frequently than did EFP patients ( $11 \pm 6$  days for TPN patients;  $4 \pm 5$  days for EFP patients;  $P < 0.0001$ ). TPN patients required exogenous insulin for  $8 \pm 11$  days, while EFP patients required supplemental insulin for only  $1 \pm 1$  day ( $P < 0.001$ ). In fact, supplemental insulin was only required by those EFP patients who had failed the EFP and were crossed over to TPN.

Patients who failed the EFP program required more days of analgesia ( $9 \pm 7$  versus  $3 \pm 4$  days;  $P < 0.04$ ) and more days of antiemetics ( $14 \pm 10$  versus  $7 \pm 7$  days;  $P < 0.06$ ) than did patients who did not fail the EFP.

**Abnormalities in Clinical Laboratory Tests.** Despite continuous infusions of electrolytes and minerals in the TPN patients and only occasional i.v. supplements in the EFP patients, only two statistically significant differences were observed: TPN patients were less often hypomagnesemic (serum magnesium  $< 1.5$  meq/liter) than EFP patients ( $6 \pm 7$  versus  $15 \pm 7$  days;  $P < 0.0001$ ); TPN patients were more often hyperglycemic (plasma glucose  $> 150$  mg/dl) than were EFP patients ( $9 \pm 8$  versus  $2 \pm 3$  days;  $P < 0.0002$ ). In fact, hyperglycemia was seen only in those EFP patients who failed the feeding program and were started on TPN.

Although the mean serum concentrations of alanine aminotransferase, total bilirubin, and alkaline phosphatase rose to 200–600% of baseline, there were no treatment-related differences.

During the period of the study, there were no observed instances of severe hypoglycemia, hypophosphatemia, hyponatremia, or hypernatremia. Hyperkalemia, hyperphosphatemia, and elevations in serum creatinine were observed in the 10 TPN and 5 EFP patients with renal dysfunction (serum creatinine  $> 2.0$  mg/dl for at least 2 consecutive days).

**Catheter-related Complications.** Catheter-related infections, complications associated with catheter placement (e.g., malpositioned catheters, pneumothorax, hemothorax, chylothorax) and mechanical problems associated with catheter maintenance (e.g., leaking catheters, subclavian vein thrombosis) were more frequent, but not significantly so, in TPN patients (Table 3). However, catheter-related complications were more likely to result in catheter removal in TPN patients (22 lumens in 13 TPN patients and 8 lumens in 3 EFP patients;  $P < 0.007$ , Fisher's Exact test).

There were no complications associated with the placement of nasogastric feeding tubes.

**Hematological Recovery.** The mean time from BMT to day of WBC count  $\geq 1000$  cells/ $\mu$ l was  $19 \pm 9$  days in TPN patients and  $20 \pm 9$  days in EFP patients ( $P > 0.56$ ) and to day of absolute neutrophil count  $\geq 500$  cells/ $\mu$ l was  $21 \pm 11$  and  $22 \pm$

Table 3 Catheter-related complications

Because all patients had multipurpose central venous catheter(s) and TPN patients had an additional TPN catheter, it was not always possible to assign a complication to a specific catheter (multipurpose *versus* TPN). Therefore, values represent the number of all catheter-related complications in each treatment group. The three TPN patients who were crossed over immediately to the EFP because of catheter placement failure were included in the TPN group for placement complications. These three patients had no complications other than the catheter placement failure. The patient who was removed from the study because of protocol violations was not included in this analysis.

	TPN	EFP
Total catheter-patient days	756	883
Infections (no. of episodes)		
Bacteremia	3	2
Catheter insertion/exit site	8	3
Total	11 (8 patients) <sup>a</sup>	5 (5 patients) <sup>a</sup>
Other complications		
Placement	6	5
Mechanical	14	7
Total	20 (14 patients)	12 (11 patients)
Catheter removal		
No. of patients requiring catheter removal and replacement because of catheter complications	13 <sup>b</sup>	3 <sup>b</sup>
No. of patients not requiring catheter removal	14	30
Total	27	33

<sup>a</sup>  $P > 0.1$  ( $\chi^2$  goodness-of-fit to the Poisson distribution).

<sup>b</sup>  $P = 0.002$  (Fisher's Exact Test).

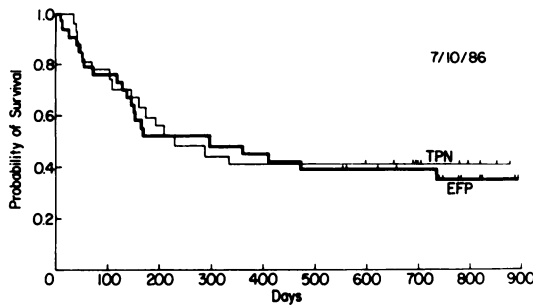


Fig. 3. Kaplan-Meier survival plot. Probability of survival for the 27 TPN and 33 EFP patients. (The patient who violated the study protocol was not included in this analysis.) Indicated are the censored data points.

8 days for the TPN and EFP groups, respectively ( $P > 0.50$ ). One patient in each treatment group never recovered hematological function and died in aplasia. There was no difference in hematological recovery day in patients who failed the EFP program and those who did not.

**Graft-versus-Host Disease.** During the 28-day study period, four of 27 TPN patients and three of 30 EFP patients developed acute graft-versus-host disease and were treated with high-dose methylprednisolone and cyclosporine (2).

**Length of Hospitalization and Survival.** The mean time from BMT to discharge from the hospital was  $36 \pm 18$  days for TPN patients and  $33 \pm 15$  days for EFP patients ( $P > 0.40$ ). For patients who failed the EFP and those who did not, mean time from BMT to discharge was  $48 \pm 31$  and  $30 \pm 9$  days, respectively ( $P < 0.34$ ).

There were no treatment-related differences in short-term (100 days) or long-term survival ( $P > 0.70$ ; logrank and Generalized Wilcoxon test) (Fig. 3). When adults (age  $\geq 19$  years) and children (age  $< 19$  years) were evaluated separately for survival, there were no treatment-related differences ( $P > 0.45$ ; logrank and Generalized Wilcoxon test).

In the proportional hazards model, adults were at greater risk of death than were children ( $P < 0.05$ ); allogeneic patients who did not receive prophylactic cyclosporine were at greater risk

than were autologous patients or allogeneic patients who received cyclosporine ( $P = 0.05$ ). After adjustment for age and cyclosporine, we found that neither the nutritional treatment ( $P > 0.38$ ) nor a loss of BCM  $> 10\%$ , from baseline to day 28 ( $P > 0.90$ ), was associated with increased risk of death.

**Cost Analysis.** Charges were classified as those related to the placement of central venous feeding catheters (average \$572/TPN patient; 40 catheters in 27 patients; \$32/EFP patient; 4 catheters in 4 patients), those related to i.v. nutrients (amino acids, dextrose, trace elements, vitamins, and lipid emulsions; i.v. electrolytes were not included in the cost analysis; \$1686/TPN patient; \$337/EFP patient), those related to i.v. infusion devices (tubing, cassettes for infusion pumps, and dressing change kits; infusion pumps were not included in the cost analysis; \$311/TPN patient; \$89/EFP patient), and those related to the enteral diet (additional dietary personnel to prepare and deliver special food items, vitamins, commercially prepared nutrient formulas, feeding tubes, feeding pumps, special food items purchased from outside the hospital; the cost of regular patient trays was not included in the analysis; \$6/TPN patient; \$681/EFP patient). The average cost for the 28-day study period was \$2575/TPN patient and \$1139/EFP patient.

## DISCUSSION

For many years we have used TPN to support the patients undergoing bone marrow transplantation at our institution. This approach was adopted at a time when patients referred for marrow transplantation routinely presented with residual leukemia (even after multiple courses of aggressive antineoplastic therapy) and malnutrition. I.v. nutritional support was considered necessary because the intensive treatment that these patients faced would limit their voluntary p.o. intake and compromise their already poor nutritional status.

Our BMT patient population has changed, however. Now, most patients are in remission and well nourished, and the goal of nutritional support is no longer nutritional repletion but maintenance of nutritional status. In addition to the change in the BMT patient population, improvements have been made in enteral feeding technology and nutritional assessment methodology, making this clinical trial possible.

As we had expected, the patients who participated in this study were well nourished at the time of hospital admission, confirming the descriptions of BMT recipients published by other transplant centers (38, 39).

The nutrient prescription (35 kcal/kg/day; 1.4 g protein/kg/day) was based on the results of an earlier study (40) in which we estimated the energy intake necessary to maintain the nutritional status of BMT recipients. However, this level of intake could not be achieved by the enteral route alone. Patients in both treatment groups complained that their ability to eat was limited because of anorexia, nausea, vomiting, diarrhea and pain, problems commonly occurring in BMT recipients (41–44) and other patients undergoing aggressive antineoplastic therapy (45, 46). Nevertheless, the enteral intake (15 kcal/kg/day; 0.6 g protein/kg/day) of EFP patients was greater than that of TPN patients and much greater than that (1–5 kcal/kg/day; 0 g protein/kg/day) reported by the Seattle BMT unit (6, 47).

We found that with the TPN program (TPN plus *ad libitum* p.o. diet), the nutrient intake goals were achieved and BCM was preserved. However, on this carbohydrate-rich TPN solution, body fat and ECF were increased. Patients in the enteral feeding program were not able to achieve the same level of

energy and protein intake as patients in the TPN group and during the 28-day study period, EFP patients lost weight (BCM and FAT + ECS).

Similar results have been reported by other groups conducting clinical trials to determine whether the routine use of TPN in patients undergoing antineoplastic therapy was better than the "best hospital diet." In some studies, no nutritional benefit could be demonstrated in unselected patients (48–50). In other studies, nitrogen balance or serum proteins were better maintained in TPN patients (51, 52). Most studies, however, demonstrated that the use of TPN only resulted in weight gain, particularly in the fat compartment (53–60). Furthermore, the nutritional "benefits" of TPN were only temporary. Patients usually lost weight and lean body mass, and serum protein levels fell when TPN was discontinued (59, 60).

Investigators have suggested that without TPN, hematological recovery after chemotherapy is slower in patients with sarcoma (61) and leukemia (62). However, the results of our study demonstrate that despite the difference in total energy and protein intake, TPN did not shorten the duration of marrow aplasia after BMT. Furthermore, the difference in nutrient intake and the observed changes in body composition did not influence other clinical outcomes (length of hospitalization or survival).

The results of other clinical trials have failed to show a consistent advantage in hematological recovery or survival in the patients supported with TPN (49, 50, 52, 53, 55–57, 63–65). It is particularly noteworthy that in these clinical trials, as already discussed, there were no real nutritional benefits from TPN. Therefore, it is not surprising that no survival advantage could be derived from the indiscriminate use of TPN.

In the only reported trial evaluating TPN in BMT recipients (66), TPN was initiated prior to chemotherapy and total body irradiation and continued through day 28. The control group received no TPN and apparently no specialized enteral feeding program. The energy and protein intakes of TPN patients were comparable to those achieved in our TPN patients; however, the energy (enteral and total) intake in control patients was considerably less than that achieved in our EFP patients. These investigators found that survival and disease-free interval were significantly greater in TPN patients, but not until after day 100. These results imply that TPN acts to potentiate the effects of antineoplastic therapy rather than to support recovery. Similar observations have been made in tumor model systems in animals (67, 68). The results of our study also support this theory. When nutritional treatments were begun after antineoplastic therapy, no survival advantage could be observed in the TPN group. One might argue that routine TPN is indicated only during the period of cytoreductive therapy and may not be required after BMT in most patients who receive individualized enteral feeding programs. This hypothesis requires further testing.

Catheter-related infectious episodes have been reported to occur in 3–8% of patients on TPN (69–71). These low rates have been achieved by careful catheter care and by limiting the use of central venous catheters to infusions of nutrient solutions. Unfortunately in the treatment of BMT and other critically ill patients, central venous catheters cannot always be used exclusively for TPN. Hickman *et al.* (7) and Colombani *et al.* (72) have reported that multipurpose catheters do not necessarily increase the risk of TPN-related infections. In our study, the incidence of catheter-related infections was high, but no patient died directly as a result of a catheter infection. Complications during catheter placement and mechanical problems associated

with catheter maintenance were also more common in TPN patients. Because of the frequency of catheter-related complications, TPN patients more often required catheter removal and replacement at a time in their course when they are particularly susceptible to catheter placement complications.

The only complication associated with nasogastric feeding was occasional feeding tube occlusion that required tube replacement. There were no bleeding or infectious complications in this thrombocytopenic, granulocytopenic patient population. Although cases of aspiration and infection in granulocytopenic patients have been reported (73), with the use of soft-weighted feeding tubes and with careful monitoring, tube feeding appears safe even in BMT recipients (74).

Biochemical abnormalities were seen in both treatment groups. The most frequent abnormalities were hyperglycemia (requiring exogenous insulin) in TPM patients and hypomagnesemia in EFP patients. Hypomagnesemia was, in fact, seen in both treatment groups; however TPN patients received much more magnesium than did EFP patients because the standard TPN solution contained 16 meq/liter.

Elevations (2–4 times normal) in tests of liver function have been reported in patients supported with TPN (75, 76), but these abnormalities are usually temporary, even if TPN is not discontinued. In this study, similar changes were noted, but abnormalities in liver function were as frequent in EFP patients as they were in TPN patients, suggesting that factors other than TPN were responsible.

In this study we demonstrated that TPN was effective in preserving body cell mass in critically ill patients recovering from bone marrow transplantation, but TPN was associated with certain complications and costs. Although the enteral feeding program was less effective in maintaining body cell mass, important clinical outcomes such as hematopoietic recovery rate, length of hospitalization, and survival were unaffected. Furthermore, with the use of the enteral program, most of the toxicities and costs due to TPN were avoided. Thus, we have concluded that TPN is not clearly superior to the enteral feeding program and recommend that TPN be reserved for those BMT recipients who fail enteral methods (including nasogastric tube feeding).

We would caution clinicians about extrapolating the results of this study to BMT recipients younger than 10 years or to patients undergoing other forms of aggressive antineoplastic treatment. In addition, attention to the needs and wishes of individual patients and an expanded food service were required to achieve these results. Finally, patients must be monitored daily to ensure that goals are being met or to introduce alternate methods of nutritional support when the original plan is not working. We found that this type of care was, in fact, cost effective in the patient population we studied, where TPN had been the standard nutritional therapy.

We recommend that future studies of TPN be prospective randomized clinical trials in which TPN is compared to the best methods of enteral support available. Nutritional status should be assessed by objective, accurate methods, and nutritional outcomes should be correlated with clinical outcomes.

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## REFERENCES

- Santos, G. W., and Kaizer, H. Bone marrow transplantation in acute leukemia. *Sem. Hematol.*, 19: 227-239, 1982.
- Santos, G. W., Tutschka, P. J., Brookmeyer, R., Saral, R., Beschorner, W. E., Bias, W. B., Braine, H. G., Burns, W. H., Eifenbein, G. J., Kaizer, H., Mellits, D., Sensenbrenner, L. L., Stuart, R. K., and Yeager, A. M. Marrow transplantation for acute non-lymphocytic leukemia after treatment with busulfan and cyclophosphamide. *N. Engl. J. Med.*, 309: 1347-1353, 1983.
- Kaizer, H., Stuart, R. K., Brookmeyer, R., Beschorner, W. E., Braine, H. G., Burns, W. H., Fuller, D. J., Korbaling, M., Mangan, K. F., Saral, R., Sensenbrenner, L. L., Shaddock, R. K., Shende, A. C., Tutschka, P. J., Yeager, A. M., Zinkham, W. H., Colvin, O. M., and Santos, G. W. Autologous bone marrow transplantation (BMT) in acute leukemia: a phase I study of *in vitro* treatment of marrow with 4-hydroperoxycyclophosphamide (4HC) to purge tumor cells. *Blood*, 65: 1504-1510, 1985.
- Stuart, R. K., and Sensenbrenner, L. L. Adverse effects of nutritional deprivation on transplanted hematopoietic cells. *Exp. Hematol.*, 7: 435-442, 1979.
- Aker, S. N., Cheney, C. L., Sanders, J. E., Lenssen, P. L., Hickman, R. O., and Thomas, E. D. Nutritional support in marrow graft recipients with single versus double lumen right atrial catheters. *Exp. Hematol.*, 10: 732-737, 1982.
- Yamanaka, W. K., Tilmont, G., and Aker, S. N. Plasma fatty acids in marrow transplant recipients on fat-supplemented parenteral nutrition. *Am. J. Clin. Nutr.*, 39: 607-611, 1984.
- Hickman, R. O., Buckner, C. D., Clift, R. A., Sanders, J. E., Stewart, P., and Thomas, E. D. A modified right atrial catheter for access to the venous system in marrow transplant recipients. *Surg. Gynecol. Obstet.*, 148: 871-875, 1979.
- Moore, E. D. Energy and the maintenance of the body cell mass. *J. P. E. N.*, 4: 228-260, 1980.
- Burkinshaw, L., Jones, P. R. N., and Krupowicz, D. W. Observer error in skinfold thickness measurements. *Hum. Biol.*, 45: 273-279, 1973.
- Haas, J. D., and Flegal, K. M. Anthropometric measurements. In: G. R. Newell and N. M. Ellison (eds.), *Nutrition and Cancer: Etiology and Treatment*, pp. 123-140. New York: Raven Press, 1981.
- Bishop, C. W., Bowen, P. E., and Ritchey, S. J. Norms for nutritional assessment of American adults by upper arm anthropometry. *Am. J. Clin. Nutr.*, 34: 2530-2539, 1981.
- Cohn, S. H., Ellis, K. J., and Wallach, S. *In vivo* neutron activation analysis—clinical potential in body composition studies. *Am. J. Med.*, 57: 683-686, 1974.
- Hill, G. L., McCarthy, I. D., Collins, J. P., and Smith, A. H. A new method for the rapid measurement of body composition in critically ill surgical patients. *Br. J. Surg.*, 65: 732-735, 1978.
- Behnke, A. R., Feen, B. G., and Welham, W. C. The specific gravity of healthy men. *JAMA*, 118: 495-498, 1942.
- Siri, W. E. The gross composition of the body. *Adv. Biol. Med. Phys.*, 4: 239-280, 1956.
- Allen, T. H., Anderson, E. C., and Langham, W. H. Total body potassium and gross body composition in relation to age. *J. Gerontol.*, 15: 348-357, 1960.
- Forbes, G. B., Gallup, J., and Hursh, J. B. Estimation of total body fat from potassium-40 content. *Science (Wash. DC)*, 133: 101-102, 1961.
- Szeluga, D. J., Stuart, R. K., Utermohlen, V., and Santos, G. W. Nutritional assessment by isotope dilution analysis of body composition. *Am. J. Clin. Nutr.*, 40: 847-854, 1984.
- Szeluga, D. J., Stuart, R. K., Brookmeyer, R., Utermohlen, V., and Santos, G. W. Nutritional support of normally nourished bone marrow transplant (BMT) recipients: TPN or enteral feeding? *J. P. E. N.*, 10 (Suppl.): 9a, 1986.
- Center for Disease Control. *Outline for Surveillance and Control of Nosocomial Infections*, pp. 17-19. Atlanta, GA: Center for Disease Control, 1972.
- Metropolitan Life Insurance Company. *Desirable weights of adults, 1959*. In: *Scientific Tables*, p. 712. Ardsley, NY: Geigy Pharmaceuticals, 1970.
- National Center for Health Statistics. *Growth Charts, 1976*. Rockville, MD: Health Resources Administration, Department of Health, Education, and Welfare publication No. HRA 76-1120, 1976.
- Frisancho, A. R. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am. J. Clin. Nutr.*, 34: 2540-2545, 1981.
- Durnin, J. V. G. A., and Womersley, J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br. J. Nutr.*, 32: 77-97, 1974.
- Dugdale, A. G., and Griffiths, M. Estimating fat body mass from anthropometric data. *Am. J. Clin. Nutr.*, 32: 2400-2403, 1979.
- Forbes, G. B., and Bruining, G. J. Urinary creatinine excretion and lean body mass. *Am. J. Clin. Nutr.*, 29: 1359-1366, 1976.
- Shizgal, H. M. Body composition by multiple isotope dilution. In: *Nutritional Assessment—Present Status, Future Directions and Prospects*, pp. 94-99. Columbus, OH: Ross Laboratories, 1981.
- Chien, S., and Gregersen, M. I. Determination of body fluid volumes. In: W. L. Nastuk (ed.), *Physical Techniques in Biological Research*, pp. 1-105. New York: Academic Press, Inc., 1962.
- Moore, F. D., Olesen, K. H., McMurrey, J. D., Parker, H. V., Ball, M. R., and Boyden, C. M. Interpretation and calculation. In: *The Body Cell Mass and its Supporting Environment*, pp. 13-42. Philadelphia: W. B. Saunders Co., 1963.
- Graham, J. A., Lamb, J. F., and Linton, A. L. Measurement of body water and intracellular electrolytes by means of muscle biopsy. *Lancet*, 2: 1172-1176, 1967.
- Novarini, A., Borghi, L., Curti, A., Elia, F., Montanari, M., Roncoroni, L., Violi, V., Borghetti, A., and Peracchia, A. Extracellular water, electrolyte and nitrogen balance after postoperative parenteral nutrition and intracellular involvement in muscle. *Acta Chir. Scand.*, 149: 651-656, 1983.
- Snedecor, G. W., and Cochran, W. B. *Statistical Methods*, pp. 59-62. Ames, IA: Iowa State University Press, 1967.
- Gail, M., and Gart, J. J. The determination of sample sizes for use with the exact conditional test in  $2 \times 2$  comparative trials. *Biometrics*, 29: 441-448, 1973.
- Armitage, P. *Statistical Methods in Medical Research*, pp. 391-393. London: Blackwell Scientific Publications, 1971.
- Mantel, N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother. Rep.*, 50: 163-170, 1966.
- Gehan, E. A. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika*, 52: 203-223, 1965.
- Cox, D. R. Regression models and life-tables. *J. R. Statistical Soc. (Ser. B)*, 34: 187-202, 1972.
- Schmidt, G. N., Blume, K. G., Bross, K. J., Spruce, W. E., Waldron, J. C., and Levine, R. Parenteral nutrition in bone marrow transplant recipients. *Exp. Hematol.*, 8: 506-511, 1980.
- Layton, P. B., Gallucci, B. B., and Aker, S. N. Nutritional assessment of allogeneic bone marrow transplant recipients. *Cancer Nurs.*, 4: 127-135, 1981.
- Szeluga, D. J., Stuart, R. K., Brookmeyer, R., Utermohlen, V., and Santos, G. W. Energy requirements of parenterally-fed bone marrow transplant recipients. *J. P. E. N.*, 9: 139-143, 1985.
- Dreizen, S., McCredie, K. G., Dicke, K. A., Zander, A. R., and Peters, L. J. Oral complications of bone marrow transplantation in adults with acute leukemia. *Postgrad. Med.*, 66: 187-196, 1979.
- Aker, S. N. Oral feedings in the cancer patient. *Cancer (Phila.)*, 43: 2103-2107, 1979.
- Reed, M. D., Halpin, T. C., Herzog, R. H., and Gross, S. Cyclic parenteral nutrition during allogeneic bone marrow transplantation. *J. P. E. N.*, 5: 37-39, 1981.
- Lenssen, P., Moe, G. L., Cheney, C. L., Aker, S. N., and Deeg, H. J. Parenteral nutrition in marrow transplant recipients after discharge from the hospital. *Exp. Hematol.*, 11: 974-981, 1983.
- Stuart, R. K., and Sensenbrenner, L. L. Adverse effects of nutritional deprivation on transplanted hematopoietic cells. *Exp. Hematol.*, 7: 435-442, 1979.
- DeWys, W. D., Costa, G., and Henkin, R. Clinical parameters related to anorexia. *Cancer Treat. Rep.*, 65: 49-52, 1981.
- Clemans, G. W., Yamanaka, W., Flournoy, N., Aker, S. N., Thomas, E. D., Hutchinson, M. L., and Cheney, C. Factors affecting the development of essential fatty acid deficiency (EFAD) in bone marrow transplant (BMT) patients. *J. P. E. N.*, 5: 221-225, 1981.
- Heatley, R. V., Williams, R. H. P., and Lewis, M. H. Pre-operative intravenous feeding—a controlled trial. *Postgrad. Med. J.*, 55: 541-545, 1979.
- vanEys, J., Copeland, E. M., Cangir, A., Taylor, G., Teitell-Cohen, B., Carter, P., and Ortiz, C. A clinical trial of hyperalimentation in children with metastatic malignancies. *Med. Pediatr. Oncol.*, 8: 63-73, 1980.
- vanEys, J., Wesley, M. N., Cangir, A., Copeland, E. M., Donaldson, S. S., Ghavimi, F., Shils, M., Suskind, R., Jaffe, N., and Filler, R. Safety of intravenous hyperalimentation in children with malignancies: a cooperative group trial. *J. P. E. N.*, 6: 291-294, 1982.
- Valerio, D., Overett, L., Malcolm, A., and Blackburn, G. L. Nutritional support for cancer patients receiving abdominal and pelvic radiotherapy: a randomized prospective clinical experiment of intravenous versus oral feeding. *Surg. Forum*, 29: 145-148, 1978.
- Muller, J. M., Brenner, U., Dienst, C., and Pichlmaier, H. Preoperative parenteral feeding in patients with gastrointestinal carcinoma. *Lancet*, 1: 68-71, 1982.
- Holter, A. R., Rosen, H. M., and Fischer, J. E. The effects of hyperalimentation on major surgery in patients with malignant disease: a prospective study. *Acta Clin. Scand. Suppl.*, 466: 86-87, 1977.
- Issell, B. R., Valdivieso, M., Zaren, H. A., Ducrick, S. J., Freireich, E. J., Copeland, E. M., and Bodey, G. P. Protection against chemotherapy toxicity by i.v. hyperalimentation. *Cancer Treat. Rep.*, 62: 1139-1143, 1978.
- Lim, S. T. K., Choa, R. G., Lam, K. H., Wong, J., and Ong, G. B. Total parenteral nutrition versus gastrostomy in the preoperative preparation of patients with carcinoma of the oesophagus. *Br. J. Surg.*, 68: 69-72, 1981.
- Sako, K., Lore, J. M., Kaufman, S., Razack, M., Bakamjian, V., and Reese, P. Parenteral hyperalimentation and chemotherapy for stage III testicular cancer: a randomized study. *J. Surg. Oncol.*, 16: 391-402, 1981.
- Valdivieso, M., Bodey, G. P., Benjamin, R. S., Barkley, H. T., Freeman, M. B., Ertel, M., Smith, T. L., and Mountain, C. F. Role of intravenous hyperalimentation as an adjunct to intensive chemotherapy for small cell bronchogenic carcinoma. *Cancer Treat. Rep.*, 65: 145-150, 1981.
- Samuels, M. L., Selig, D. E., Ogden, S., Grant, C., and Brown, B. I.v. hyperalimentation and chemotherapy for stage III testicular cancer: a randomized study. *Cancer Treat. Rep.*, 65: 615-627, 1981.
- Donaldson, S. S., Wesley, M. N., Ghavimi, F., Shils, M., Suskind, R. M., and DeWys, W. D. A prospective randomized clinical trial of total parenteral nutrition in children with cancer. *Med. Pediatr. Oncol.*, 10: 129-139, 1982.
- Shike, M., Russell, D. McR., Detsky, A. S., Harrison, J. E., McNeill, K. G., Shepherd, F. A., Feld, R., Evans, W. K., and Jeejeebhoy, K. N. Changes in body composition in patients with small-cell lung cancer: the effect of total parenteral nutrition as an adjunct to chemotherapy. *Ann. Int. Med.*, 101: 303-309, 1984.

61. Shamberger, R. C., Pizzo, P. A., Goodgame, J. T., Lowry, S. F., Maher, M. M., Wesley, R. A., and Brennan, M. F. The effect of total parenteral nutrition on chemotherapy-induced myelosuppression. *Am. J. Med.*, *74*: 40-47, 1983.
62. Hays, D. M., Merritt, R. J., White, L., Ashley, J., and Siegel, S. E. Effect of total parenteral nutrition on marrow recovery during induction for acute non-lymphocytic leukemia in childhood. *Med. Pediatr. Oncol.*, *11*: 134-140, 1983.
63. Kinsella, T. J., Malcolm, A. W., Bothe, A., Valerio, D., and Blackburn, G. L. Prospective study of nutritional support during pelvic irradiation. *Int. J. Radiat. Oncol. Biol. Phys.*, *7*: 543-548, 1981.
64. Popp, M. B., Fisher, R. I., Wesley, R., Aamodt, R., and Brennan, M. F. A prospective randomized study of adjuvant parenteral nutrition in the treatment of advanced diffuse lymphoma: influence on survival. *Surgery*, *90*: 195-203, 1977.
65. Moloney, M., Moriarty, M., and Daly, L. Controlled studies of nutritional intake in patients with malignant disease undergoing treatment. *Hum. Nutr. Appl. Sci.*, *37A*: 30-35, 1983.
66. Weisdorf, S., Lysne, J., Wind, D., Schissel, K., Sharp, H., Goldman, A., Haake, R., McGlave, P., Ramsay, R., and Kersey, J. Influence of prophylactic total parenteral nutrition (TPN) on long term outcome of bone marrow transplantation (BMT). *J. P. E. N.*, *10* (Suppl.): 5a, 1986.
67. Torosian, M. H., Mullen, J. L., Miller, E. E., Zinsser, K. R., Stein, T. P., and Buzby, G. P. Enhanced tumor response to phase-specific chemotherapy by parenteral amino acid administration. *J. P. E. N.*, *7*: 337-345, 1983.
68. Torosian, M. H., Mullen, J. L., Stein, T. P., Miller, E. E., Zinsser, K. R., and Buzby, G. L. Enhanced tumor response to cycle-specific chemotherapy by pulse total parenteral nutrition. *J. Surg. Res.*, *39*: 103-113, 1985.
69. Mullen, J. L. Complications of total parenteral nutrition in the cancer patient. *Cancer Treat. Rep.*, *65*: 107-113, 1981.
70. Snyderman, D. R., Murray, S. A., Kornfeld, S. J., Majka, J. A., and Ellis, C. A. Total parenteral nutrition-related infections: prospective epidemiological study using semiquantitative methods. *Am. J. Med.*, *73*: 695-699, 1982.
71. Thompson, J. S., Madison, K. L., and Hodges, R. E. The incidence and prevention of complications of total parenteral nutrition. *Nebr. Med. J.*, *68*: 321-325, 1983.
72. Colombani, P. M., Dudgeon, D. L., Buck, J. R., Miller, D. M., Ghory, M. J., Bulckloo, C., and Haller, J. A. Multipurpose central venous access in the immunocompromised pediatric patient. *J. P. E. N.*, *9*: 38-41, 1985.
73. deVries, E. G. E., Mulder, N. H., Houwen, B., and deVries-Hospers, H. G. Enteral nutrition by nasogastric tube in adult patients treated with intensive chemotherapy for acute leukemia. *Am. J. Clin. Nutr.*, *35*: 1490-1496, 1982.
74. Freeman, J. B., and Fairfull-Smith, R. J. Current concepts of enteral feeding. *Adv. Surg.*, *16*: 75-112, 1983.
75. Lowry, S. F., and Brennan, M. F. Abnormal liver function during parenteral nutrition: relation to infusion excess. *J. Surg. Res.*, *26*: 300-307, 1979.
76. Grant, J. P., Cox, C. E., Kleinman, L. M., Maher, M. M., Pittman, M. A., Tangrea, J. A., Grown, J. H., Gross, E., Beazley, R. M., and Jones, R. S. Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. *Surg. Gynecol. Obstet.*, *145*: 573-580, 1977.