

TEN versus TPN following Major Abdominal Trauma— Reduced Septic Morbidity

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Recent animal models suggest that enteral feeding (TEN) compared to parenteral nutrition (TPN) improves resistance to infection. This prospective clinical trial examined the impact of early TEN vs. TPN in the critically injured. Seventy-five patients with an abdominal trauma index (ATI) >15 and <40 were randomized at initial laparotomy to receive either TEN (Vivonex TEN) or TPN (Freamine HBC 6.9% and Trophamine 6%); both regimens contained 2.5% fat, 33% branched chain amino acids, and had a calorie to nitrogen ratio of 150:1. TEN was delivered via a needle catheter jejunostomy. Nutritional support was initiated within 12 hours postoperatively in both groups, and infused at a rate sufficient to render the patients in positive nitrogen balance.

The study groups (TEN = 29 vs TPN = 30) were comparable in age, injury severity and initial metabolic stress. Jejunal feeding was tolerated unconditionally in 25 (86%) of the TEN group. Nitrogen balance remained equivalent throughout the study period, at day 5 TEN = -0.3 ± 1.0 vs. TPN 0.1 ± 0.8 gm/day.

Traditional nutritional protein markers (albumin, transferrin, and retinol binding protein) were restored better in the TEN group. Infections developed in 5 (17%) of the TEN patients compared to 11 (37%) of the TPN group. The incidence of major septic morbidity was 3% (1 = abdominal abscess) in the TEN group contrasted to 20% (2 = abdominal abscess, 6 = pneumonia) with TPN.

This clinical study demonstrates that TEN is well tolerated in the severely injured, and that early feeding via the gut reduces septic complications in the stressed patient.

Nutritional support of seriously injured patients is an integral component of critical care. The injury stress response is characterized by a hypercatabolic, hypermetabolic state. If not supported by exogenous nutrients, the obligatory protein turnover will erode critical visceral mass, producing subclinical organ dysfunction as well as impair host defenses, and thus set the stage for inexorable multiple system organ failure (MOF) (7). A second insult, whether ischemic or septic, will precipitate the full-blown syndrome. Animal studies (23, 35) and subsequent clinical trials (1, 29) have established that aggressive nutritional support attenuates this cascade of events which predispose to MOF. Acknowledging the benefit of early nutritional support, the next question is the preferred route of substrate delivery; i.e., enteral (TEN) or parenteral (TPN). Recent recognition of the

gut as a metabolically active (39, 41), immunologically important (2, 24), and bacteriologically decisive (3, 11-13, 22, 34) organ during critical illness has strengthened the argument for enteral feeding (4, 29). This prospective clinical trial was designed to compare the impact of immediate TEN versus TPN following major abdominal injury.

MATERIALS AND METHODS

Study Protocol. During the 28-month period ending August 1988, all adult patients undergoing emergency celiotomy at the Denver General Hospital (DGH) with an abdominal trauma index (ATI) (30) >15 and <40 were entered into a prospective, randomized study comparing total enteral nutrition (TEN) and total parenteral nutrition (TPN). Upon regaining consciousness, each patient was informed about the study, and verbal consent was obtained. This study design was approved by the Investigation Review Board at DGH. Patients were excluded from study with pelvic fractures requiring >6 units of blood in the first 12 hours postinjury, total blood loss >25 units in the first 24 hours, or repeat laparotomy or death within 72 hours.

Management of abdominal trauma was uniform throughout the study period. Patients with blunt trauma were explored promptly for signs of peritoneal irritation and evaluated by

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diagnostic peritoneal lavage if equivocal findings existed. Stab wound patients without overt signs of visceral injury underwent selective laparotomy based on local wound exploration and peritoneal lavage. Patients sustaining gunshot wounds were explored routinely unless the missile tract was unequivocally superficial to the peritoneum. Broad-spectrum antibiotics were administered in the emergency department, and continued for 5 days if the distal ileum or colon was violated. The midline abdominal fascia was approximated with a continuous 0-polypropylene suture. The skin and subcutaneous fat were left open for delayed primary closure in the presence of fecal contamination.

Eligible patients, randomized by computer assignment, had either a needle catheter jejunostomy (NCJ) or central venous catheter placed at initial laparotomy, and then received TEN or TPN within 12 hours of surgery. Our technique for NCJ placement has been detailed in a previous report (28). TEN consisted of an elemental diet (Vivonex TEN, Norwich Eaton Pharmaceuticals, Inc., Norwich, NY). This is a low-residue, high-nitrogen elemental diet containing 33% branched-chained amino acids (BCAA), 2.5% calories from fat, 82% calories from simple carbohydrates, and macro- and micronutrients known to be required for nutritional maintenance. Vivonex TEN has a nonprotein calorie to nitrogen ratio of 149:1, a BCAA to aromatic amino acid (AAA) ratio of 7.4:1, an essential to nonessential amino acid ratio of 1:1, and an osmolality of 650 mOsm/kg of water. At normal dilution, the diet provides 1 kcal/ml. Infusion of TEN via the NCJ was begun at 12 to 18 hours postoperatively. The solution was initiated at one-quarter strength (0.25 kcal/ml) at a rate of 50 ml/hr. Patients were observed for distention while the rate and then concentration were advanced at 8-hour intervals to deliver the targeted nutritional goal with three-quarter strength formula at 72 hours. Nasogastric decompression was maintained for a minimum of 72 hours.

The TPN solution, nutritionally equivalent to Vivonex TEN, was prepared by the hospital pharmacy from Trophamine 6% and Freamine HBC 6.9% (Kendall-McGaw Laboratories, Irvine, CA). The combined solution contained 33% BCAA's, 2.2% calories from fat, 84% calories from carbohydrate, and required amounts of micro- and macronutrients. This TPN formula had a nonprotein calorie to nitrogen ratio of 148:1, a BCAA to AAA ratio of 7.5:1, and an essential to nonessential amino acid ratio of 1:1. This solution provided 1.0 kcal/ml. The TPN administration rate was designed to be isocaloric with the enteral protocol. Our standard protocol for central venous catheters mandates strict aseptic technique for all catheter manipulations and daily dressing changes. The intravenous lines are changed over a wire every 5 days and the tip sent for semiquantitative culture. Criteria for line sepsis include a site with purulent drainage, the same organism identified on catheter tip and blood cultures, and two sequential positive catheter tip cultures or two positive blood cultures without an obvious source in conjunction with pain and erythema at the catheter site. Ongoing monitoring of this protocol has demonstrated a catheter infection rate consistently below 3.5%.

Basal energy expenditure (BEE) was calculated by the Harris-Benedict equation, and caloric needs were estimated at a stress factor $1.5 \times$ BEE and confirmed by indirect calorimetry (Biochem RAS 1000, Wauskega, WI). The 24-hour nitrogen loss was calculated from the measured daily urine urea nitrogen (UUN) excretion plus an estimated stool and obligatory nitrogen loss of 4 grams. Nitrogen balance was determined on postinjury days 1, 5, and 10. TEN or TPN was continued at rates sufficient to meet these caloric and nitrogen demands until oral intake was adequate. Venous blood was obtained within 12 hours of laparotomy as a baseline pretreatment (day 1) sample and again on postinjury days 5 and 10. Blood for

standard nutritional indices was sent directly to the hospital central laboratory, and sera were analyzed by techniques detailed in an earlier report (29). Laboratory analysis included a complete blood count with differential, transferrin, retinol binding protein, bilirubin, alkaline phosphatase, amino acid profile, and insulin levels.

Patients were characterized by standard trauma scoring (9) to permit study group comparison. The Revised Trauma Score (RTS) of Champion profiled the physiologic status of the patients by combining the Glasgow Coma Scale, systolic blood pressure, and respiratory rate. The magnitude of intra-abdominal injuries was quantitated at laparotomy by the Abdominal Trauma Index (ATI). The Injury Severity Score (ISS) of Baker provided an overall assessment of multisystem trauma. The TRISS Score of the ACS Committee on Trauma estimated survival probability. Septic complications were categorized as major or minor. Major infections included documented intra-abdominal abscess or pneumonia. Intra-abdominal abscess was defined as a purulent collection requiring operative or radiologic drainage. The diagnostic criteria for pneumonia included fever, leukocytosis, purulent sputum samples, and a new infiltrate on chest X-ray studies. Minor infections included wound, urinary tract, catheter, and other peripheral sites.

Mean \pm SEM are recorded in the tables but comparisons between the diet groups were tested using a nonparametric statistical method (Wilcoxon) due to non-normality of the data. For discrete variables the Chi-square test was used to examine the differences between diet groups. When conditions for the Chi-square test were not met Fisher's exact test was used to obtain *p* values. Ten risk factors were tested for their ability to predict pneumonia: injury mechanism, head trauma, chest trauma, splenectomy, major liver injury, shock, ATI, ISS, RTS, and route of nutrition. Univariate and multivariate tests were used to identify effects alone and in combination with the other factors. Multivariate analysis consisted of fitting a multiple logistic regression model of the outcome, pneumonia.

RESULTS

Study Groups. Seventy-five patients (39 TEN, 36 TPN) of 407 undergoing emergent laparotomy were prospectively randomized into the study; 16 patients were subsequently excluded from the study, leaving 59 evaluable subjects (29 TEN, 30 TPN). The reasons for exclusion from analysis were early death (four patients), reoperation within 72 hours (three patients), significant chronic medical disease (three patients), an ATI > 40 (two patients), head injury requiring fluid restriction (two patients), mechanical failure of TEN delivery (one patient), and early transfer (one patient). The salient characteristics of the evaluable patients are shown in Table I. The study groups were comparable at presentation with respect to age, sex, injury mechanism, injury severity (ISS, ATI) and physiologic status (RTS). Equivalent TRISS scores further corroborate comparability.

UUN values were increased to the same level at day one, reflecting the anticipated hypercatabolic state. Additional nutritional indices for the two study groups are shown in Table II. Day one caloric intake, nitrogen intake, and nitrogen balance were similar. Of the evaluable TEN patients, four (14%) subjects failed to tolerate the protocol increments in the enteral diet. Three patients responded to manipulation in the feeding schedule,

TABLE I
Randomization homogeneity of TEN versus TPN study groups following major abdominal trauma

	TEN (n = 29)	TPN (n = 30)	p value
I. Demographics*			
Age (years)	28 ± 2	32 ± 2	NS
Sex	22M/7F	23M/7F	NS
Blunt trauma	8 (28%)	11 (36%)	NS
Penetrating trauma	21 (73%)	19 (64%)	NS
II. Stress assessment*			
RTS	6.9 ± 0.2	6.9 ± 0.3	NS
ATI	24.7 ± 1.1	24.0 ± 1.0	NS
ISS	28.7 ± 2.3	25.1 ± 1.0	NS
TRISS	0.49 ± 0.05	0.55 ± 0.04	NS
UUN (gm/d)	8.6 ± 0.8	9.4 ± 0.9	NS
BEE (Kcal)	1,641 ± 42	1,731 ± 58	NS

* Mean ± SEM; NS, not significant; RTS, Revised Trauma Score; ATI, Abdominal Trauma Index; ISS, Injury Severity Score; TRISS, probability of survival; UUN, day 1 urinary urea nitrogen; BEE, 24-hr basal energy expenditure.

TABLE II
Nutritional data from TEN versus TPN study groups following major abdominal trauma

	TEN (n = 29)	TPN (n = 30)	p value
Caloric intake*			
Day 1	150 ± 15	180 ± 25	NS
Day 5	1,847 ± 123	2,261 ± 60	0.01
Nitrogen intake (gm)*			
Day 1	1.1 ± 0.1	1.2 ± 0.2	NS
Day 5	12.4 ± 0.8	15.4 ± 0.4	0.01
Nitrogen balance (gm)*			
Day 1	-11.5 ± 0.8	-12.2 ± 0.9	NS
Day 5	-0.3 ± 1.0	0.1 ± 0.8	NS

* Mean ± SEM; NS, not significant, caloric intake = nonprotein calories.

while the remaining patient was transitioned to TPN on day 7 due to moderate intolerance in the face of persistent hypermetabolism. All were retained in the TEN group for analysis. On day 5, caloric and nitrogen intake were higher in TPN patients compared with the patients receiving TEN. Despite this slight advantage in protein-calorie intake via the parenteral route, no significant differences for nitrogen balance were noted between the two groups at day 5.

The laboratory data results for days 1, 5, and 10 are summarized in Table III. Differences occurred in the traditional nutritional protein markers over time. Albumin, transferrin, and retinol binding protein levels increased throughout the study period in patients receiving TEN, and decreased in patients receiving TPN. At day 5, the difference between treatment groups reached statistical significance for albumin. By day 10, albumin and transferrin were significantly higher in the TEN patients. Abnormalities in liver function were observed and, of note, bilirubin and alkaline phosphatase were higher in patients receiving TPN. Glucose levels also tended to

TABLE III
Laboratory results of TEN versus TPN study groups following major abdominal trauma*

	TEN (n = 29)	TPN (n = 30)	p value
Total protein (gm/dl)			
Day 1	5.0 ± 0.1	5.2 ± 0.1	N.S.
Day 5	5.9 ± 0.1	5.2 ± 0.1	0.03
Day 10	6.3 ± 0.2	5.5 ± 0.3	N.S.
Albumin (gm/dl)			
Day 5	3.3 ± 0.1	3.1 ± 0.2	0.01
Day 10	3.4 ± 0.1	2.7 ± 0.2	0.01
Transferrin (mg/dl)			
Day 1	190 ± 10	192 ± 7	N.S.
Day 5	190 ± 10	170 ± 5	N.S.
Day 10	216 ± 25	150 ± 18	0.05
Retinol binding protein (mg/dl)			
Day 1	2.8 ± 0.1	2.7 ± 0.1	N.S.
Day 5	2.5 ± 0.1	2.2 ± 0.3	N.S.
Day 10	3.1 ± 0.3	2.0 ± 0.3	0.06
Bilirubin (mg/dl)			
Day 1	1.6 ± 0.2	1.2 ± 0.1	N.S.
Day 5	0.9 ± 0.1	1.4 ± 0.2	0.03
Day 10	0.8 ± 0.3	2.9 ± 1.2	N.S.
Alkaline phosphatase (units)			
Day 1	61 ± 4	59 ± 4	N.S.
Day 5	83 ± 5	92 ± 6	N.S.
Day 10	135 ± 29	220 ± 96	N.S.
Glucose (mg/dl)			
Day 1	152 ± 8	162 ± 10	N.S.
Day 5	144 ± 10	190 ± 17	N.S.
Insulin (uU/ml)			
Day 1	23.5 ± 3.2	29.3 ± 5.3	N.S.
Day 5	66.0 ± 9.3	93.3 ± 8.3	0.02
Glutamine (nmol/ml)			
Day 1	275 ± 31	266 ± 18	N.S.
Day 5	241 ± 31	178 ± 20	N.S.
Alanine (nmol/ml)			
Day 1	370 ± 40	372 ± 35	N.S.
Day 5	472 ± 52	490 ± 39	N.S.

* Mean ± SEM; NS, not significant; Day 10 data based on 10 patients in each group. Normal fasting glutamine level = 400-500 nmol/ml, alanine level = 350-370 nmol/ml, and insulin level < 20 uU/ml.

be higher in the TPN patients, but failed to reach statistical significance. However, glucose levels were maintained at acceptable levels by exogenous insulin in five (17%) of the TPN group compared to one (3%) of the TEN group and insulin levels by day 5 were significantly elevated in patients receiving TPN.

Complications occurred in ten (34%) TEN patients compared to 17 (57%) TPN patients. Seven patients in the TPN group and six patients in the TEN group experienced nonseptic complications; these included pancreatitis (five patients), atelectasis (three patients), recurrent pneumothorax (one patient), partial small bowel obstruction (one patient), biliary fistula (one patient), breakdown of exteriorized colon repair (one patient), and CSF leak (one patient). Septic complications are summarized in Table IV. The overall incidence of septic morbidity was five (17%) patients in the TEN group and 11 (37%) patients in the TPN group. There

TABLE IV
Septic complications of TEN versus TPN study groups following major abdominal trauma

Complications	TEN (n = 29)	TPN (n = 30)	p value
Major infections			
Abdominal abscess	1	2	0.03*
Pneumonia	0	6	
Minor infections			
Wound	3	1	NS
Catheter	0	2	
Urinary	0	1	
Miscellaneous	1	2	
Total patients	5 (17%)	11 (37%)	NS

* Fisher's exact test; NS, not significant.

was a significant difference with respect to major infections (pneumonia and intra-abdominal abscess): one (3%) patient among the TEN group compared to six (20%) patients in the TPN group. Of interest, all six pneumonias occurred in the TPN group. The mechanism of injury for these patients was blunt in three and GSW in three, the mean ATI was 27.8 ± 2.2 , and the mean ISS was 25.0 ± 3.7 . One patient had an associated chest injury; two others underwent splenectomy. Three (50%) had early pneumonias; i.e., developing within 5 days postinjury. Pathogens identified by sputum culture included two *Staphylococcus aureus*, and one each of *Escherichia coli*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*, and *Citrobacter* species. Table V presents the univariate analysis of risk factors for the development of pneumonia. As isolated variables, TPN was the only factor correlated significantly with pneumonia. A multiple logistic regression model analysis of the independent variables also identified TPN as the sole significant risk factor.

DISCUSSION

Nutritional support of the seriously injured patient is an essential component of postinjury critical care. The early postinjury period is characterized by hypercatabolism and hypermetabolism—the “injury stress response.” This exaggerated demand for substrate, if not satisfied by exogenous supply, must be generated from endogenous protein breakdown. Even in the previously well nourished individual, the obligatory protein turnover will erode critical visceral mass, compromise immune defense, and fundamentally set the stage for inexorable multiple organ failure (7). Generally, a second ischemic or septic episode is necessary to culminate in the full-blown syndrome. Experimental work (23, 35) and recent clinical studies (1, 29) suggest that immediate nutritional support is beneficial in preventing this cascade of events. In our previous prospective trial of patients seventy-five of 371 patients undergoing emergent laparotomy had an ATI>15 and were randomized to receive 5% dextrose in

TABLE V
Pneumonia risk factors

Characteristics	Pneumonia	p value
Mechanism		
Blunt	3/19 (15%)	NS
Penetrating	3/40 (8%)	
Head trauma		
Yes	0/4 (0%)	NS
No	6/55 (11%)	
Chest trauma		
Yes	1/13 (8%)	NS
No	5/46 (11%)	
Splenectomy		
Yes	2/8 (25%)	NS
No	4/51 (9%)	
Major liver injury		
Yes	0/8 (0%)	NS
No	6/51 (12%)	
ER shock (BP < 90)		
Yes	4/28 (14%)	NS
No	2/31 (6%)	
ATI		
16-25	2/33 (6%)	NS
≥26	4/26 (15%)	
Injury Severity Score		
<20	3/19 (16%)	NS
>20	3/40 (8%)	
Revised Trauma Score		
≤6	5/50 (10%)	NS
>6	1/9 (11%)	
Route of nutrition		
TEN	0/29 (0%)	0.02
TPN	6/30 (20%)	

NS, not significant.

water for 5 days followed by TPN as needed or enteral nutrition, via NCJ, begun 12-18 hours postoperatively (29). While the overall complication rate was similar, septic morbidity was significantly greater ($p < 0.025$) in the control group. Nine (29%) of the control group developed postoperative infections consisting of abdominal abscess in seven and pneumonia in two, compared to three (9%) septic events among the enteral fed group, all of whom developed an abdominal abscess. Based on this work, we believe that patients sustaining major trauma warrant aggressive nutritional support within the first 72 hours of injury. Alexander's study (1) of early nutritional support in pediatric burns corroborates this concept.

Acknowledging the benefit of early nutrition in high-risk patients, the next question is the preferred route of substrate delivery; i.e., enteral (TEN) or parenteral (TPN). Safety, convenience, and cost are the commonly stated advantages of enteral nutrition, but alleged inconvenience has largely erased these considerations (5, 36). The gut has been inappropriately perceived as a dormant organ following stress. Nasogastric decompression is typically required for 1-2 days postinjury due to loss of gastric motility, while colon peristalsis is impaired for 3-5 days, but small bowel motility and absorption remain functionally intact despite laparotomy or acute stress.

With the advent of nasojunal tubes and the needle catheter jejunostomy to access the small bowel plus refinement in enteral diets, immediate postoperative jejunal feeding has been shown to be simple, safe, and effective in a wide variety of surgical patients (8, 20, 28, 36). Recent work establishing the gut as a metabolically active (39, 41), immunologically important (2, 24), and bacteriologically decisive (3, 11-13, 22) organ in critical illness has strengthened the argument for aggressive enteral feeding.

Central to this evolving concept has been the documentation of bacterial translocation from the gastrointestinal (GI) tract of stressed patients (34) as well as experimental animals under a variety of environmental modifications (3, 11-13, 22). Bacterial translocation is defined as the migration of viable indigenous gut organisms through intact epithelial mucosa into mesenteric lymph nodes (MLN) and ultimately to other organs and the blood stream. Transmural migration of intestinal bacteria was proven experimentally nearly 40 years ago. In 1950 Fine et al. (37) reported a canine model of chemical peritonitis which documented peritoneal seeding with gut derived I^{131} -tagged *E. coli*. Indeed, this group completed a number of innovative studies from which they concluded that the absorption of endotoxin from the GI tract in conjunction with reduced hepatic detoxification was the fundamental basis for irreversible post-injury shock (16). During the past 5 years, there has been an enormous resurgent interest in this unifying pathophysiological concept of MOF.

Rush et al. (22, 34) conducted an enlightening series of studies in a rat model of hemorrhagic shock. Blood cultures became positive at 2 hours into the shock period and bacteremia continued throughout the ensuing 48 hours of observation (22). *Pseudomonas* and *Enterococcus* predominated, and cultures became polymicrobial with time. As a clinical correlate, blood was sampled within 3 hours of admission in 50 acutely injured patients (34). Cultures were positive in 56% of the 18 patients with an initial systolic blood pressure (SBP) <80 torr contrasted to one (4%) among 25 patients with a SBP > 110 torr. Of the ten positive cultures, six were Gram-positive organisms, two were Gram-negative, and two were mixed. These studies confirm that severe hemorrhagic shock is associated with early bacteremia.

Deitch et al. (3, 11-13) have also completed an instructive series of studies in a rat shock model. These animals were sacrificed at 24 hours postshock and their mesenteric lymph nodes (MLN), spleens, and livers cultured quantitatively. Bacterial translocation was virtually uniform into MLN and occurred in 60% of spleens and livers in the animals subjected to shock for 90 minutes. In another series, mice were studied to characterize factors which promote translocation of bacteria (13). Neither 72 hours of starvation nor 21 days of protein deprivation was associated with transmural migration. However, when *E. coli* endotoxin was administered, bacteria

were recovered in 80% of the MLN and 60% of the livers and spleens. The organisms migrating from the gut, in decreasing frequency, were *E. coli*, *Klebsiella*, *Enterobacter*, *Staphylococcus epidermis*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa*. Wells et al. (40) observed bacterial translocation into experimental abdominal abscesses. Additional enteric bacteria were recovered from more than half of fibrin clot/*Bacteroides fragilis* inocula within a week; the most frequent organisms were *Enterococci*, *E. coli*, and *Staphylococci*. Inoue et al. (19) also demonstrated the translocation of *Candida albicans* across gut mucosa into MLN of guinea pigs, and correlated this with the severity of burn injury. Of interest, there have been a number of clinical reports describing the emergence of *Enterococcus*, *Staphylococcus epidermis*, and *Candida albicans* in the blood stream of surgical patients developing MOF without an identifiable septic focus (6). Collectively, these studies suggest that the bacteremia associated with acute shock may be perpetuated by a number of cofactors common to critically injured patients; i.e., endotoxemia (13), malnutrition (13), immunosuppression (24), and altered gut microflora (12) due to ileus and antibiotic administration.

Bacterial translocation is a widely accepted concept, but its precise role in the development of postinjury MOF remains to be established. Secondary endotoxemia appears to be the most plausible link (Fig. 1). Presumably the same elements that favor bacterial translocation will promote escape of their toxic cell membrane from the gut lumen. In the hemorrhage model of Rush et al. (34), endotoxin was documented in 33% of the rats after 30 minutes of shock and in 88% after 2 hours. Also in this study, half the acutely injured patients presenting with SBP < 80 torr had endotoxemia. In other studies, oral nonabsorbable antibiotics have attenuated the endotoxemia associated with intestinal ischemia (18). Gram-negative lipopolysaccharide (LPS) has been invoked as a precipitating factor in the development of MOF as well as lethal sepsis (6, 7, 10, 14, 26, 34). In fact, endotoxin-specific antibodies have reduced mortality in hemorrhagic shock models (17). LPS has been shown to recruit, activate, and "prime" neutrophils; damage endothelium and alter receptors; and trigger the complement and clotting cascades (6, 10, 26, 34). Cerra et al. (21) have showed in a rat cell culture preparation that endotoxin-activated Kupffer cells modulate adjacent hepatocytes to markedly reduce protein synthesis. The Kupffer cells lining the vast hepatic sinusoidal network represent more than 80% of the reticuloendothelial mass, are positioned strategically to interact with gut-derived endotoxin and may serve a critical role in detoxifying portal LPS.

Fixed tissue monocytes, primarily the Kupffer cell and alveolar macrophage, are also a rich source of inflammatory mediators; i.e., tumor necrosis factor (TNF), interleukin-1 (IL-1), products of arachidonic acid metabolism, and platelet-activating factors (6, 10, 14, 17, 34). Wilmore et al. (26) found that plasma TNF increased 90

Gut: The Starter for MOF Liver: The Motor for MOF

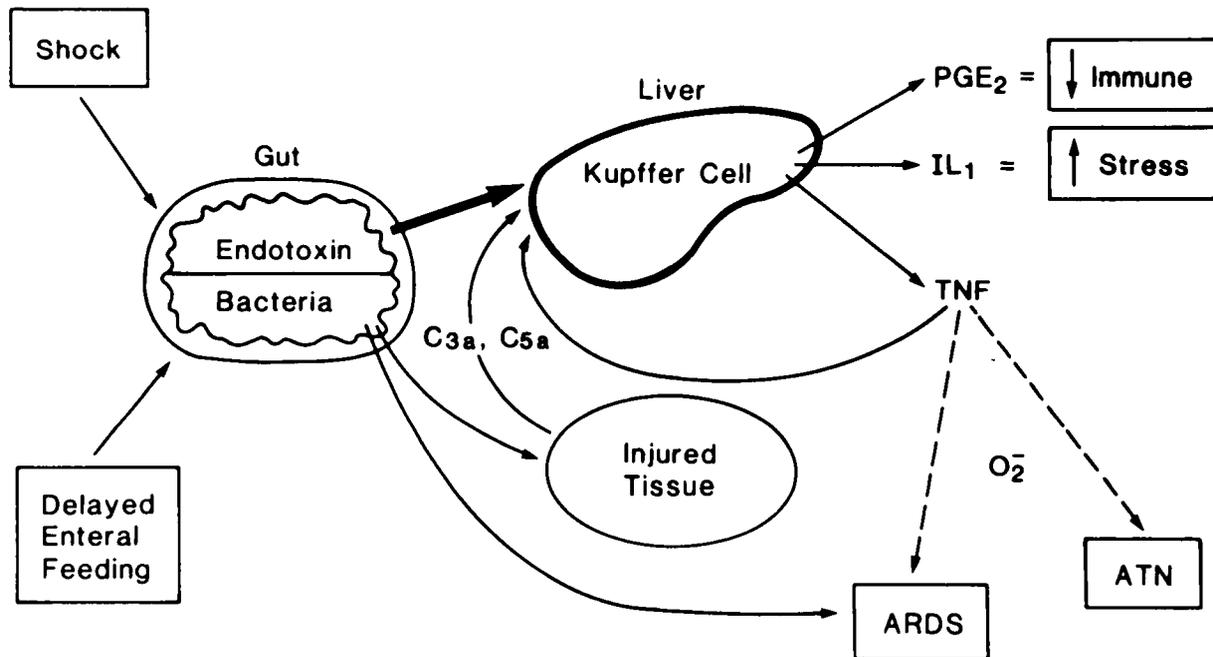


FIG. 1. Diagram of development of multiple organ failure.

to 180 minutes after intravenous administration of *E. coli* endotoxin to otherwise healthy men. Previous animal studies have shown that monoclonal antibodies to TNF will reduce the lethal effects of endotoxin as well as live *E. coli* (10, 17). Prostaglandin E₂ (PGE₂), an immunosuppressant, is elevated following major torso injury and is presumed to be a product of activated macrophage (15, 27). Of note, increased PGE₂ has been identified in rat ileum after a hypotensive insult (31). Christou et al. (25) designed an animal model to ascertain the impact of Kupffer cell modulation on systemic immune response. *E. coli* at a concentration of 10⁸ per ml infused into the portal vein of rats resulted in suppressed delayed-type hypersensitivity (DTH); whereas the same *E. coli* challenge infused via the infrarenal vena cava had no effect on DTH. Finally, these inflammatory mediators will promote additional bacterial translocation and endotoxemia by compromising the gut mucosal barrier as well as prime the target organs of MOF for greater insult when flooded by endotoxin.

Animal models comparing TEN versus TPN have shown that early enteral alimentation reduces postburn hypercatabolism (35) and improves host resistance to a peritoneal septic challenge (23), presumably by preservation of gut mucosal integrity. To test this hypothesis we examined the reprioritization of hepatic protein synthesis (38), a process that accelerates the production of acute-phase proteins at the expense of normal constitutive proteins. These previously published data (33) suggest that TEN ameliorates reprioritization following ma-

ior abdominal trauma. The present report, a continuation of the above trial, focuses upon the clinical impact. Indeed, TEN provided a significant advantage in reducing major septic complications. The striking incidence of pneumonia in patients maintained on TPN is consistent with our understanding of postoperative pulmonary morbidity. A midline laparotomy places the acutely injured patient at moderate risk to develop a nosocomial pneumonia. If enteral nutrition is delayed, gut bacterial translocation would serve as a source of contamination for the impaired lung.

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DISCUSSION

DR. JERRY M. SHUCK (Cleveland, Ohio): Invitation to discuss a paper at this meeting is an honor; particularly when it is a good paper. The subject is timely, and the study was well performed by the Brothers Moore and associates. Understanding of the role of altered intestinal tract as a focus for translocation, sepsis, and eventual organ failure is rapidly evolving. The perturbing factors in these phenomena have included mucosal changes in shock, starvation, shifts in luminal bacterial flora, toxins, oxygen radicals, and even genetic predisposition.

This paper addresses the pragmatic issue of the best method by which to deliver nutrition to trauma patients: TPN versus TEN. Enteral nutrition resulted in fewer major complications and in higher albumin and transferrin levels. I have some questions here: Do you see wound infections as minor complications, or were all your wound infections truly minor? The pneumonias were all in the TPN group. Do you believe that the pneumonias were secondary to translocation, despite the bacteriologic data in your paper that would hardly support that conclusion?

These authors are actually in the right field at the right time. Would they care to speculate on how they might confirm the mechanisms for the alleged benefits in the clinical situation of acute trauma that they presented? Are other studies planned?

I am kind of sorry that Jacob Fine, whose observations were ignored for decades, is not here to see this evolve once again. However, many important contributors to the scientific bases of your study are here. I see Doctors Deitch, Alexander, Carrico, and others. This excellent paper deserves their comments. Therefore, I will terminate my remarks.

Thank you. [Applause]

DR. TURNER ÖSLER (Albuquerque, New Mexico): I wonder if this study actually compares two routes of delivery or two substantially different diets.

Thank you.

DR. J. W. ALEXANDER (Cincinnati, Ohio): I certainly enjoyed this paper. It was a wonderful clinical study. We have done a study in burned guinea pigs, using total parenteral nutrition versus enteral nutrition and found very similar findings.

One other study that we did found that the use of intact protein, however, was much better than the use of free amino acids as a source of nitrogen in the solutions.

I wonder if the authors had considered using any other type of dietary formulation that had intact protein rather than free amino acids.

Finally, last year at this meeting we showed that even a single bolus feeding of diet could prevent translocation of *Candida albicans* in the burned guinea pig model.

I have two questions. One is that since it has been shown that early feeding can prevent the hypermetabolic response and even the type of feeding can alter it, was the metabolic response measured in these patients? And also, since translocation seems to be a central issue as a potential cause for the hypermetabolic response and the adverse effect of total parenteral nutrition, did the authors measure endotoxin in their patients?

Thank you.

DR. CHARLES E. WILES, III (Baltimore, Maryland): Two questions. One, is there the possibility that there is a relationship in the incidence of pneumonia to another factor not reported on such as the control of gastric pH in the TPN group?

The second question is: what influence, if any, the relatively low level of fat replacement had on the results in this study.

DR. EDWIN A. DEITCH (Shreveport, Louisiana): My comments are similar to those of Doctor Wiles. In our work on bacterial translocation, we have not found lung invasion by the translocating bacteria. Since bacteria can reach the lung via the micro-aspiration of oral or gastric fluid, have you any information on the extent of gastric or hypopharyngeal bacterial colonization in these patients?

DR. MICHAEL HAWKINS (Augusta, Georgia): I wonder since they made a point of starting enteral feeding within 12 hours postop, if as an adjunct to this study they looked at patients who did not require laparotomy. Should we be starting tube feedings within 12 to 24 hours in these patients?

DR. PAUL SCHLOERB (Kansas City, Kansas): One of your slides showing serum albumin decreasing with TPN and rising with enteral nutrition, was attributed to the nutritional superiority of enteral feeding.

Please address the alternative interpretation that the fall in albumin over a relatively short period of time reflected dilution and the rise in albumin was due to diarrhea and dehydration.

DR. GEORGE M. WATKINS (Easton, Pennsylvania): Of course I liked Doctor Moore's paper since I like enteral nutrition as opposed to parenteral.

There is one particular concern in an otherwise well controlled study. You very loosely define when and how much you started the feeding in the two groups. One of the most important things may be timing of when and how much. Did you look at the quantity given and when it was started in TPN versus enteral nutrition groups?

DR. JAMES C. THOMPSON (Galveston, Texas): Whenever you get different results from studies in which you use two different routes of nutrition, I think one of the questions that you have to ask is: what different signals are transmitted by the two different routes, and certainly a strong candidate to be considered are the various growth factors that protect mucosal integrity that are dependent upon stimulation by the introduction of food into the gut.

I know that several groups are addressing this exact problem. Certainly David Herndon and Courtney Townsend are looking into this, and I know several others are. I suspect that we may, in fact, find at least part of our answers in the categorization of the different endogenous effects by supplying calories by the different routes.

DR. JORGE L. RODRIGUEZ (Buffalo, New York): To continue Doctor Wiles' remarks, there is another factor that is not discussed in the paper. The incidence of an increase in pneumonia is due to the length of intubated days. One wonders whether the TEN group versus the TPN group had a difference in intubated days.

Number two, the increase in metabolic rate might be an expected factor of the amino acid infusion which was shown by the John Kinney group; amino acids increase metabolic rate. One has to wonder whether this paper is actually stating that the TEN route can increase metabolic rate in comparison to TPN, which is an expected response.

DR. C. JAMES CARRICO (Seattle, Washington): Could I just ask one clarification question? Was the incidence of multiple organ failure different in the two groups?

DR. FREDERICK A. MOORE (Closing): Doctor Shuck, thank you for your thoughtful comments. We leave the skin and subcutaneous tissue open in the face of colonic or distal ileal

injury, and consequently, rarely encounter major wound infections. The incidence of pneumonia found in this study is consistent with our understanding of postoperative pulmonary complications. Early atelectasis is virtually routine in these patients following extensive abdominal surgery with a long midline laparotomy incision. The question is how does enteral nutrition prevent atelectasis from progressing to an infectious pneumonia. First, diminishing bacterial translocation may limit contamination of the impaired lung. The organisms identified in the TPN group were consistent with gut origin. Second, if enteral nutrition blunts hypermetabolism and provides more effective nitrogen utilization there will be better maintenance of somatic muscle. Respiratory function is especially sensitive to skeletal muscle mass and it is well known that acutely malnourished individuals die of pneumonia. In regard to studying mechanisms, as of December 1, we will be collaborating in a comprehensive NIH Score Grant identifying patients at risk to develop ARDS, which will include assaying potential mediators in the first 72 hours postinjury. This study will include patients randomized to TEN versus TPN.

Doctor Osler, as outlined in the presentation, when designing this study considerable effort was made to assure the two formulas were nutritionally equivalent. With exception to glutamine, which is not present in parenteral formulas, there were no substantial differences. Of interest, serum glutamine levels measured on day 5 were not statistically different.

Doctor Alexander, we recognize your enormous contributions to this area of research and appreciate your comments. In regard to our preference of an elemental diet, we have had problems with clogging of the needle catheter jejunostomy when using other diets. As you know, hypermetabolism is difficult to document in the ICU setting. Not all of our study patients had pulmonary artery catheters to allow O₂ consumption measurement by the Fick equation, and few remained intubated to document increase O₂ consumption by indirect calorimetry. Counterregulatory hormone levels were measured, but large variations made interpretation difficult. We are currently measuring TNF and endotoxin, but this has only been instituted recently.

Doctor Wiles and Doctor Deitch, it is standard protocol in our ICU to control gastric pH by antacids. When two-hour dosing fails, H₂ blockers are added. Although interesting, recent data supporting sucralfate as a means of stress gastritis prophylaxis are inconclusive. We have not cultured patients' oropharynxes or stomachs, but recognize this may be a source of bacterial contamination and rationale for selective decontamination.

Doctor Hawkins, we have considered immediate enteral nutrition in trauma patients who have not undergone laparotomy, but we have not found a easy reliable means to access the small bowel. In the acute setting nasogastric feeding is hazardous; the risk of aspiration is prohibitive. Doctor Schloerb, in a recent manuscript we analyzed 130 consecutive postinjury patients who were randomized to TEN over the past 8 years. While 13% were intolerant to jejunal feeding, we were unable to correlate this to serum albumin.

Doctor Watkins, we designed our study to ensure that initial TPN administration was isocaloric with jejunal feeding. Subsequent needs were titrated by UUN determinations and indirect calorimetry. Doctor Rodriguez, some of these patients required prolonged intubation due to initial injuries. We believe complications lead to increased intubation time, not the reverse. Doctor Carrico, many of these patients had pulmonary, hepatic, and renal abnormalities in the early postinjury period. It was difficult to separate out those changes due to injury from those influenced by nutritional route. Of course, pneumonia may simply represent a sign of ARDS and subclinical multiple organ failure.