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# Fiber: Effect on Bacterial Translocation and Intestinal Mucin Content

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**Abstract. Total parenteral nutrition (TPN) and elemental diet (ED) produce intestinal atrophy and increase bacterial translocation (BT) to mesenteric lymph nodes. The increased rate of BT may be due to alterations in mucosal structure, enzyme activity, or mucin content. Fiber improves intestinal structure and function in rats and may reduce the rate of BT. This study determined whether the addition of fiber to TPN or ED would maintain intestinal integrity and decrease BT to the mesenteric lymph nodes. Fifty-six adult male Sprague-Dawley rats underwent placement of jugular catheters and were assigned to one of five dietary groups: TPN, TPN + oral oat fiber (TPNF) 2 g/day, ED, ED + oral oat fiber (EDF) 2 g/day, or AIN-76 (control); they were pair-fed for 7 days. On day 8 the mesenteric lymph nodes were removed for bacterial cultures; and jejunal mucosal weight, DNA, protein, alkaline phosphatase, maltase, and jejunal mucin content were measured. Enteral nutrition significantly decreased BT when compared to parenteral feeding, and fiber significantly decreased BT when administered to rats receiving TPN or ED. Improvements in intestinal mucosal structure were not consistently associated with decreased rates of BT. Additionally, BT occurred independently of jejunal mucin concentration. Mechanisms other than maintenance of mucosal structure or mucin content are important in the mediation of fiber-induced decreased BT in rats receiving TPN or ED.**

Bacterial translocation (BT), the extraluminal relocation of indigenous gut microflora, is increased in animal models of stress and critical illness, such as shock, sepsis, burn injury, and malnutrition [1–4]. Many critically ill patients with intestinal dysfunction and a predisposition to BT receive total parenteral nutrition (TPN) or an elemental diet (ED). The provision of nutrients as either TPN or ED increases BT to mesenteric lymph nodes [5, 6] and may serve as an early index of intestinal epithelial dysfunction. It has been proposed that the increased rate of BT with these diets is due, in part, to a deficiency of important enteral nutrients [6]. Moreover, investigators showed that the addition of fiber to animals receiving TPN or ED decreases BT, suggesting that supplemental fiber maintained the intestinal mucosal barrier [7, 8].

The gastrointestinal mucosal barrier is structurally complex and consists of enterocytes, colonocytes, goblet cells, immune cells, and their by-products. Mucus, the viscous gel covering the gastrointestinal mucosa, is an important part of this barrier. It contains mucin, electrolytes, water, bacteria, and sloughed cells [9]. Mucin, the gel-forming glycoprotein in mucus, protects the intestine in part by acting as a physical barrier to bacterial invasion. Mucin is increased with fiber feeding in some animal models [10, 11]. We hypothesized that the decreased rate of BT with fiber may be due to improvement in jejunal mucosal structure, the mucin content, or both.

The aims of this study were to: (1) confirm that the rate of BT differs when nutrition is provided as either TPN, ED, or chow; (2) investigate whether oral oat fiber decreases BT when given to rats receiving TPN or ED; and (3) determine whether a decrease in BT with fiber is associated with changes in jejunal mucosal structure or mucin content (or both).

## Materials and Methods

Fifty-six adult male Sprague-Dawley rats weighing 350 to 450 g (Charles River Laboratories, Portage, Michigan, U.S.A.) were housed in individual cages and given rat chow and water ad libitum to allow acclimatization for at least 5 days prior to the start of the experiment. The study was approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania.

Rats were placed in individual cages with raised wire floors to limit coprophagia and maintained in a light, humidity, and temperature-controlled environment. Water was provided ad libitum throughout the study. On the day of surgery rats were anesthetized with pentobarbital (50 mg/kg body weight IP) and jugular venous catheterization was performed. The venous catheters were tunneled subcutaneously, exteriorized at the interscapular area, and connected to swivel devices (Instech, Plymouth Meeting, Pennsylvania, U.S.A.) to allow concurrent infusion and ambulation within the cage. Animals not fed parenterally also received central venous catheters. Animals were randomized to one of five dietary groups: AIN-76 (control, $n = 11$), TPN ($n = 11$), TPN with oral oat fiber 2 g/day ($n = 11$) (Mead Johnson, Evansville, Indiana, U.S.A.), ED (oral TPN, $n = 11$), and ED with oat fiber 2 g/day ($n = 12$). The ED and TPN were identical solutions containing 50% dextrose, 10% Aminosyn, electrolytes (Abbott Laboratories, Chicago, Illinois, U.S.A.), vitamins, and

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**Table 1.** Effects of diet on body weight change, jejunal structure, and enzyme activity.

| Diet | Body wt. change (g) | Mucosal wt. (g) | DNA ($\mu g/cm^2$) | Protein (mg/cm) | Alkaline phosphatase (U/mg protein) | Maltase (unit/g protein) |
|---|---|---|---|---|---|---|
| AIN-76 | 0 ± 6 | 0.299 ± 0.033[a] | 119 ± 9[b] | 5.8 ± 1.1 | 1.71 ± 0.21[a] | 274 ± 5[a] |
| TPN | 1 ± 5 | 0.136 ± 0.013[b] | 67 ± 5[a] | 2.9 ± 0.3 | 0.67 ± 0.07[b] | 146 ± 22[b] |
| TPNF | −3 ± 9 | 0.161 ± 0.014[b,c] | 105 ± 10[b] | 3.8 ± 0.4 | 0.75 ± 0.12[b] | 157 ± 34[b] |
| ED | −10 ± 4 | 0.227 ± 0.022[d] | 66 ± 5[a] | 3.4 ± 0.3 | 1.05 ± 0.14[b] | 323 ± 48[a] |
| EDF | 6 ± 5 | 0.197 ± 0.021[d,c] | 88 ± 8[c] | 4.6 ± 0.5 | 1.68 ± 0.3[a] | 273 ± 22[a] |

U: micromoles of substrate hydrolyzed per minute; unit: micromoles of glucose liberated per minute.
$p < 0.05$ for unlike superscripts by ANOVA and Fisher's protected least significant difference test.

minerals (LyphoMed Inc, Rosemont and Melrose Park, Illinois, U.S.A.). The fiber was administered daily as a pellet consisting of 2 g oat fiber and 2 g sucrose (for palatability). The animals not receiving fiber consumed a pellet of 2 g sucrose each day. All pellets were completely consumed throughout the study. Control rats (AIN-76) were fed ad libitum, whereas the remaining animals were pair-fed in an isocaloric, isonitrogenous (approximately 200 kcal/kg/day, 1.5 g N/kg/day), isovolemic manner for 7 days. Animals were killed by asphyxiation after 7 days of dietary delivery.

Immediately after sacrifice, 1 ml of blood was withdrawn by cardiac puncture for culture, the abdomen was opened, and the peritoneal cavity was swabbed. The blood and peritoneal cavity swabs were placed in tryptic soy broth and incubated at 37°C for 24 hours. The mesenteric lymph nodes (MLNs) were dissected from the bowel and fat and were homogenized (Polytron, Brinkman Instruments, Rexdale, Canada). Aerobic cultures were performed on blood and McConkey lactose agar in duplicate for all blood, peritoneal, and MLN samples. The culture plates were examined after 48 hours of incubation at 37°C. Plates containing MLNs were rated positive for BT if more than 10 colony-forming units/g MLN were present. Animals with positive blood or peritoneal cultures were excluded from the study due to the possibility of contamination.

A 10 cm segment of proximal jejunum was opened longitudinally, and the mucosa was scraped with a glass slide. Intestinal length was determined by suspending the bowel with a 3 g weight. Samples were then homogenized and assayed spectrophotometrically for DNA [12], protein [13], alkaline phosphatase [14], and maltase [15].

Proximal jejunum (1 cm) was removed and placed in 10% buffered formalin for histologic analysis of mucin. Sections were stained with alcian blue (pH 2.5), and the total mucosal surface area and mucin surface area were determined with a light microscope and Java Threshold 0-182 Software Image Analysis (Jandel Scientific, California, U.S.A.). Percent mucin surface area was determined by dividing the mucin surface area by the total surface area and multiplying by 100. The subsequent 25 cm of jejunum was removed for mucin content analysis. Sections of bowel were opened longitudinally and placed into tubes containing 5 ml of cold phosphate-buffered saline (PBS) with 0.2% azide. Tubes were shaken vigorously and the supernatant saved. The bowel was rewashed with 3 ml PBS with 0.2% azide, and the wash was added to the supernatant and stored at −20°C for lumin mucin measurements [11]. For tissue mucin determinations, the jejunal mucosa was scraped off with a glass slide and placed in a tube containing PBS with 0.2% azide. The contents were homogenized for 30 seconds and centrifuged (International Centrifuge, International Equipment, Needham Heights, Massachusetts, U.S.A.) at 3000 × *g* for 10 minutes. The supernatant was removed and stored at −20°C for tissue mucin analysis. The mucin contents were determined by an ELISA. The antibody was prepared by injection of purified mucin with Freund's complete adjuvant into New Zealand rabbits [16]. The ELISA technique was modified from that of Teerlink et al. [17] as described previously [11, 18]. The amount of mucin was calculated from the standard curves and expressed as mucin units per microgram of protein. One mucin unit is equivalent to 1 ng of mucin protein.

Statistical analyses were performed with the NWA Stat PAK Program Software (Northwest Analytical, Portland, Oregon, U.S.A.). The incidence of BT was evaluated by chi-square analysis. Other statistical analyses were completely randomized one-way analysis of variance. If significant differences were found, a Fisher's protected least significant differences test was performed for multiple comparisons. *p* values of less than 0.05 were considered significant.

## Results

There were no significant differences in body weight change among groups (Table 1). Dietary intake of calories and nitrogen did not vary significantly among the TPN and ED groups.

### *Bacterial Cultures*

There were no significant differences among groups in terms of the number of animals with positive blood or peritoneal cultures, and these animals were excluded from the study. BT to MLNs was significantly increased with TPN and ED when compared to the control diet, and BT was significantly greater in TPN than ED animals. The supplementation of oral fiber to animals receiving TPN and ED significantly decreased BT (Fig. 1).

### *Jejunal Structure*

Mucosal weight was significantly decreased with TPN and ED when compared to the control diet. The addition of fiber to either diet did not significantly increase mucosal weight. There were no significant differences among groups in terms of mucosal protein content. Mucosal DNA was significantly decreased with TPN and ED when compared to control. Fiber significantly increased mucosal DNA with TPN and ED when compared to respective controls. Mucosal alkaline phosphatase was significantly decreased by TPN and ED when compared to controls. Fiber maintained alkaline phosphatase at control levels in animals

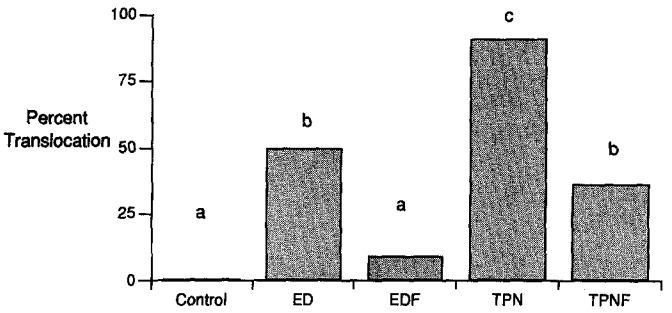


**Fig. 1.** Percent bacterial translocation to mesenteric lymph nodes observed in groups after 7 days of diet. Significant differences are indicated by different letters (a,b,c). $p < 0.05$ for unlike letters by chi-square.

receiving ED but not TPN. Mucosal maltase was significantly decreased by TPN but it was not significantly increased by fiber.

*Mucin*

There were no significant differences in mucin among groups as measured by percent surface area and content in the lumen or the tissue (Table 2).

**Table 2.** Jejunal mucin content.

| Diet | Mucin surface area (%) | Mucosal mucin (units/$\mu$g protein) | Luminal mucin (units/$\mu$g protein) |
|---|---|---|---|
| AIN-76 | 3.7 ± 0.4 | 171 ± 37 | 96 ± 34 |
| TPN | 3.7 ± 0.6 | 187 ± 42 | 166 ± 31 |
| TPNF | 3.2 ± 0.4 | 95 ± 40 | 234 ± 43 |
| ED | 4.3 ± 0.3 | 210 ± 35 | 200 ± 28 |
| EDF | 2.9 ± 0.3 | 64 ± 15 | 174 ± 57 |

## Discussion

This study demonstrated that TPN and ED increased BT when compared to control diet. Bacterial translocation was greater in rats receiving TPN than ED. The addition of fiber to rats receiving ED or TPN decreased BT, and fiber decreased BT to control levels in rats receiving ED. Jejunal mucosal weight, DNA content, alkaline phosphatase, and maltase activity were significantly decreased by ED and TPN, whereas fiber significantly increased jejunal mucosal DNA and alkaline phosphatase. Jejunal mucin content was not significantly altered by TPN, ED, or fiber supplementation.

Many critically ill patients are treated with bowel rest, including TPN and ED. TPN and ED cause gut atrophy and are associated with decreased intestinal mucosal cellularity, proliferation, and brush border enzyme activity [19–21]. TPN and ED also produce functional deficits such as increased stool liquidity and BT [5, 22]. Therefore it may be beneficial to supplement these diets with nutrients that improve gut growth and function.

Enteral nutrients such as fiber are important stimuli for normal gut growth and function. Fiber supplementation to TPN and ED improves mucosal structure and absorptive function [7, 23]. The bulk effect of fiber itself and the fermentation products of fiber, short chain fatty acids, are presumed to mediate its structural and functional effects [24]. Oat fiber contains both the bulking and fermentation properties of fiber, even though it is mainly nonfermentable. Oat fiber is soluble in liquid diets commonly prescribed for hospitalized patients and is easily administered by feeding tube.

Inasmuch as the administration of fiber to animals receiving TPN or ED improves intestinal structure and function, fiber may also enhance the barrier function of the gut. The gastrointestinal mucosa normally is an efficient barrier that prevents transepithelial invasion of microorganisms. Bacterial invasion may be a marker of increased intestinal permeability and damage. The clinical significance of BT is controversial, but it has been suggested to be an important trigger for multiple organ failure in certain groups of critically ill patients [25]. A recent study evaluated the association between proximal gastrointestinal colonization and multiple organ failure in critically ill surgical patients. It concluded that the gastrointestinal tract is an important reservoir of organisms causing intensive care unit acquired infections and is associated with the development of multiple organ failure in critically ill patients [26]. Therefore BT may be an important cause of multiple organ failure in selective patients.

Bacterial translocation was significantly increased with TPN and ED when compared to control diet. Our findings are consistent with the results of other rat studies with TPN and ED [5–7, 27, 28]. An additional finding in the present experiment was that translocation was greater in animals receiving TPN than ED. The diets were identical in nutrient content but differed only in terms of the route of administration: oral versus parenteral. Enteral nutrients are the primary stimuli for maintenance of intestinal epithelium [20], and the direct mucosal contact of nutrients may be essential for normal gut barrier function. These results agree with a similar experiment in which BT rates were measured with rats fed oral or parenteral diets [5]. BT was increased in animals regardless of route of diet administration and was significantly increased by parenteral delivery when compared to the oral route.

The addition of fiber to animals receiving TPN or ED significantly decreased bacterial translocation in the present study. Other investigations have demonstrated decreased BT with fiber [7, 8, 29]. In one of these experiments, cellulose 2.5 g/day was given to rats fed oral or venous TPN [7]. Cellulose significantly decreased BT in rats given both venous and oral TPN. In contrast to these findings, another study did not demonstrate decreased BT with fiber supplementation [30]. In this investigation, however, 2% psyllium was used as the fiber source. Psyllium is more fermentable to short chain fatty acids than cellulose or oat fiber. These studies together with the present one suggest that the bulk property of fiber may be more important than the generation of short chain fatty acids for prevention of BT.

No consistent associations were noted between abnormal mucosal structure and BT. TPN and ED significantly decreased mucosal weight, DNA, alkaline phosphatase, and maltase; and fiber significantly improved only DNA in both groups. Despite the lack of structural improvements of most of the indices measured, BT was decreased with fiber in both groups and maintained at control levels in ED. BT was greater in TPN rats than ED rats without associated increases in mucosal DNA or alkaline phosphatase. These data agree with other studies that failed to demonstrate a consistent association between structural improvements and BT [31, 32]. These findings suggest that although

maintenance of mucosal structure with fiber may have some effect on BT there are other mechanisms involved. The latter may include ultrastructural improvements or nonstructural functional mechanisms, such as maintenance of ionic transport, improved motility, or toxin binding.

Gastrointestinal mucin is an important component of the protective mucosal barrier. Mucin may protect the mucosa by the formation of a physical barrier to toxins, the provision of alternate binding sites for microorganisms, or the formation of a link to the immune system by the inclusion of immunoglobulins [33]. Because fiber reduced BT and did not improve mucin content, it is unlikely that jejunal mucin mediates the effects of fiber on BT. These results disagree with other studies demonstrating increased mucin with fiber feeding [10, 11]. Fiber sources other than oat were used in both of these studies. Additionally, animals were not fed TPN or ED in the other studies. Therefore fiber may affect mucin content in animals on diets other than TPN or ED. Additional studies are necessary to identify which dietary manipulations alter gastrointestinal mucin content and to determine if mucin content in other parts of the gut correlates with changes in BT.

In the present study, enteral feeding and fiber decreased BT without consistently improving mucosal cellularity, enzyme activity, or mucin content. Other potential mechanisms for decreased BT include alterations in gut microflora, improvements in immune responsiveness, induction of trophic hormones, changes in gastrointestinal transit time, and toxin binding. Studies have demonstrated bacterial overgrowth with TPN or ED [5, 7]. Fiber does not decrease this overgrowth but still reduces BT, suggesting that altered gut microflora is not an important mechanism in the reduction of BT with fiber [7]. The induction of various hormones may mediate the effect of fiber on BT. It has recently been shown that elemental diet-induced BT and the beneficial effects of fiber supplementation can be hormonally modulated [32]. Somatostatin analog reversed the protective effect of fiber on BT in rats [32]. Future studies are necessary to determine the most important mechanisms for reducing BT.

In conclusion, translocation of enteric bacteria to mesenteric lymph nodes was significantly increased by TPN and elemental diet and was most frequent with administration of parenteral nutrients. Fiber supplementation to rats receiving TPN or elemental diet significantly reduced bacterial translocation. Mucosal cellularity, enzyme activity, and mucin content were not consistently associated with changes in bacterial translocation. Mechanisms other than mucosal structural alterations are important to the fiber-induced reduction in bacterial translocation.


## Résumé

La nutrition parentérale totale (NPT) et la nutrition entérale élémentaire (NE) sont responsables d'atrophie intestinale et une augmentation de la translocation bactérienne (TB) vers les ganglions mésentériques (GM). L'augmentation de la TB pourrait être la conséquence d'altérations de la structure muqueuse, de l'activité enzymatique, ou d'une modification du contenu en mucine. L'ingestion de fibres améliore la structure et la fonction intestinales chez le rat et pourrait réduire la TB. Cette étude avait comme but de déterminer si l'introduction des fibres au cours de la NPT ou de la NE pourrait maintenir l'intégrité intestinale et diminuer la TB vers les GM. Cinquante-six rats Sprague-Dawley adultes ont eu un cathéter jugulaire et ont été assignés à un de cinq groupes: NPT, NPT + 2g/jour de fibres (avoine) (NPTF), NE, NE + 2g/jour de fibre (avoine) (NEF) ou AIN-76 (contrôles) et ont été alimentés par paires pendant sept jours. Au jour 8, les GM ont été enlevés pour culture bactérienne et on a mesuré le poids de la muqueuse jéjunale, de l'ADN, de la protéine, des phosphatases alcalines, de la maltase, et du contenu en mucine. La nutrition entérale a diminué de façon significative la TB lorsque des fibres ont été inclues dans l'alimentation que ce soit par NPTF ou par NEF. L'amélioration de la structure de la muqueuse intestinale ne s'est pas produite de façon constante. De plus, la TB s'est produite de façon indépendante de la concentration jéjunale en mucine. D'autres mécanismes pour maintenir la structure de la muqueuse ou le contenu en mucine sont importants dans la médiation d'une diminution par des fibres de la TB chez le rat recevant une NPT ou une NE.

## Resumen

La nutrición parenteral total (TPN) y la dieta elemental (ED) producen atrofia intestinal e incrementan la translocación bacteriana (BT) a los ganglios linfáticos mesentéricos. La aumentada tasa de BT puede deberse a alteraciones en la estructura de la mucosa, a actividad enzimática o a contenido de mucina. La fibra administrada por vía oral mejora la estructura y la función intestinales en las ratas y puede reducir la BT. El presente estudio tuvo como propósito determinar si la adición de fibra oral a los regímenes de TPN o ED podría mantener la integridad intestinal y disminuir la BT a los ganglios linfáticos. Sesenta y una ratas macho Sprague-Dawley fueron sometidos a la colocación de catéteres yugulares y asignados a 1 de 5 grupos dietarios: TPN, TPN+2g/día fibra de avena oral (TPNF), ED, Ed+2g/dia fibra de avena oral (EDF), o AIN-76 (control) durante 7 dias. En el día 8 se resecaron ganglios linfático mesentéricos para cultivos bacterianos, también se determinaron el peso de la mucosa duodenal y las concentraciones yeyunales de DNA, proteína, fosfatasa alcalina, maltasa y mucina. La nutrición enteral disminuyó significativamente la BT en comparación con la alimentación parenteral, y la fibra oral disminuyó significativamente la BT cuando fue administrada a las ratas en TPN o ED. La mejoría en la estructura de la mucosa intestinal no apareció consistentemente asociada con disminución de la BT. Además, la BT ocurrió en forma independiente de la concentración de mucina yeyunal. Otros mecanismos diferentes del mantenimiento de la estructura de la muscosa o del contenido de mucina tienen importancia en cuanto a la mediación de la disminución de la BT por la fibra en ratas que reciben TPN o DE.



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# Invited Commentary

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The manuscript by Frankel and colleagues examines the effect of the dietary oat fiber on bacterial translocation in animals fed otherwise identical diets either enterally or parenterally. Correlations between translocation and jejunal mucosal weight, DNA, protein, alkaline phosphatase, maltase, and jejunal mucin content were made at the time of sacrifice after seven days of pair feeding. As might be expected from previously published studies, enteral nutrition with a highly defined but nutritionally inadequate diet increased bacterial translocation, and bacterial translocation was further increased by feeding this same diet by the parenteral route. Also, as indicated by prior studies, the addition of fiber to the diet decreased the incidence of translocation in both enterally and parenterally fed animals. Surprisingly, however, neither mucin content nor measurements of jejunal structure nor enzyme activity were consistently associated with decreased rates of bacterial translocation.

This well constructed, tightly controlled study is an important contribution because it showed no association between mucin production and bacterial translocation, a mechanism which has often been proposed but not often studied because of the