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Beneficial Effect of Enteral Feeding

Kenneth A. Kudsk, MD
Veterans Administration Surgical Services, William S. Middleton Memorial Veterans Hospital Madison and the Department of Surgery, The University of Wisconsin-Madison

Both intravenous and enteral nutrition are used for metabolic support when patients cannot take adequate amounts of intake orally with the primary goal of avoiding progressive lean tissue catabolism due to starvation. Both enteral and parenteral nutrition can serve that function well. However, there is increasing evidence that significant benefits are gained when nutrients are delivered via the gut compared to the parenteral route. In addition to economic benefits, there exists a significant body of clinical work demonstrating reductions in septic complications when nutrients are delivered via the gastrointestinal tract[1-4]. However, generalization of these clinical observations of reduced septic complications to *every* patient, regardless of clinical condition, generates controversy- and probably should. This controyersy is reflected in several recent meta-analyses; some show a clear benefit with enteral feeding while others do not[5-6]. This is likely due to indiscriminant inclusion of different populations in these meta-analyses without appreciating and addressing the subtleties of inclusion and exclusion criteria and outcome within each specific trial. The problem is compounded when important subpopulations are not considered and divergent populations are pooled into one mathematical analysis tin an attempt to prove- or disprove- an overall effect. This technique can mislead by ignoring the critical issues in individual studies which can be used to predict whether an individual patient will or will not benefit. [7-8]

This review is meant to serve several purposes. First, it is a general review of those populations who will and will not benefit from enteral feeding. Secondly, it provides rationale for why enteral feeding significantly reduces infectious complications *in patients at risk* of those septic complications.

THE FIELD OF SPECIALIZED NUTRITION SUPPORT

In the 1960's, Rhoads, Dudrick, and Wilmore used central venous access and a concentrated nutrient solution to feed a pediatric patient who otherwise would have died, successfully[9]. This burgeoned into a multi-billion dollar industry of parenteral feeding and stimulated tremendous researched focusing on metabolism, specific nutrients and the critically ill patient. Parenteral feeding saved and saves countless lives which might otherwise have been lost due to loss of the GI tract function from prolonged ileus, gastric resection, or enterocutaneous fistulas- and to the complications inherent is major surgery and critical illness. What this technique provided was a means to deliver adequate amounts of macronutrients and micronutrients in a volume small enough to be tolerated by most patients. The early literature reflected those successes. In the early 1980's, Kudsk and Sheldon observed that animals pair fed a parenteral solution enterally and parenterally survived a septic intraperitoneal challenge significantly better when nutrients had been delivered via the gastrointestinal tract[10-11]. The results of this sentinel

Corresponding author: Kenneth A. Kudsk, MD 600 Highland Ave, H4/736 CSC. Madison, WI 53792-7375. Tel: 608-263-1396 Fax: 608-263-7562 e-mail address: kudsk@surgery.wisc.edu.

study resulted in a series of clinical trials and laboratory experiments culminating in the current concept that benefits are gained when nutrition is delivered enterally rather than parenterally.

TRAUMA TRIALS

The first clinical work focused on the trauma patient. In the first of these trials published in 1986, Moore, et al. randomized moderately injured patients to either enteral feeding with a chemically defined diet administered via a jejunostomy or IV fluids containing only dextrose[12]. This group noted the occurrence of significantly fewer intraabdominal abscesses in the enteral fed group. Critics speculated that the increased infection rate may be secondary to development of malnutrition – and increased infections- in the group receiving IV fluids alone and the study was repeated by the same group randomizing patients to either early enteral or early parenteral feeding[2]. Again, the enteral group experienced a significant reduction in infectious complications with significantly fewer pneumonias and a lowered rate of intraabdominal abscesses. In both trials, patients were excluded if they sustained very severe intraabdominal injuries, required early reoperation or a large number of transfusion or if they sustained severe pelvic fractures. These patients were excluded because one goal of the trial was to advance patients to their calculated goal rate quickly and patients with this degree of injury rarely tolerate rapid advancement of tube feeding.

In 1992, Kudsk et al. randomized patients to isonitrogenous, isocaloric formulas fed enterally via a jejunostomy or parenterally [3]. No patients expected to survive their injuries were excluded due to severity of intraabdominal injury, excessive blood loss and transfusions, need for early re-operation or severe pelvic fractures. In this trial, enterally fed patient sustained significantly fewer pneumonias and intraabdominal abscesses than patients fed parenterally. The benefit was not universally found in all subpopulations randomized in the trial however. There was no significant difference in outcome between enterally and parenterally fed patients who suffered only mild injuries- ie. those likely to have less that a 15-20% chance of septic complications. In this subgroup, the risk of septic complications was quite low in either the enterally or the parenterally fed patients - probably no nutrition support is necessary in this population, at least initially. However, in patients with a 25% or greater chance of developing septic complications due to severe intraabdominal injury, severe multisystem (ie, chest and/or head and/or abdomen and/or bony) injury, or both severe multisystem and severe intraabdominal injury, parenteral feeding resulted in a 6-11X increase in septic complications with the predominant infection being pneumonia followed by intraabdominal abscess.

Primarily as a result of these three clinical trials, the use of enteral nutrition has been the first choice for feeding in most major trauma centers whenever the gastrointestinal tract is functional and access has been obtained at a suitable site-usually post-pyloric (distal duodenum or small bowel) due to gastroparesis. The major controversy revolves around the safety and effectiveness of direct enteral access with a feeding jejunostomy placed at the time of laparotomy vs advancing a nasoenteric tube beyond the stomach into the small intestine. This is necessary since gastroparesis complicates the post-injury course of most severely injured patients for at least 4-5 days so that intragastric feeding is unsuccessful under most conditions.

In 1986, Adams et al. published a study demonstrating no significant difference in feeding route in trauma patients[13]. In that trial, patients with moderate to severe blunt injuries involving two or more body systems were randomized to parenteral or enteral feeding. Adams noted no significant difference in the occurrence of pneumonia or intraabscess formation between groups. However, the patient populations were not well matched. Patients randomized to the enteral group sustained more head and severe chest injuries, more pelvic fractures, and more soft tissue injuries. Therefore, it is hard to interpret the results of this trial.

SPECIALTY NUTRIENT FORMULAS IN TRAUMA TRIALS

In the late 1980's and early 1990's, attention focused on composition of the formulations fed to patients. The early trials had used predigested, chemical defined diets given via jejunostomy. However when experience showed that more complex diets-even those containing fiber[14]- did not clog small bore needle catheter jejunostomy tube and were tolerated by patients, investigators began to scrutinize their clinical usefulness.

About the same time, several specially supplemented enteral products appeared on the market. These diets incorporated omega fatty acids, glutamine, arginine, branch chain amino acids, and/or nucleotides in varying combinations. Each nutrient had a specific rationale for its use. Omega-3 polyunsaturated fatty acids obtained from either fish or canola oil are used to replace omega-6 fatty acids as an energy source in most of these formulas[15-18]. These polyunsaturated fatty acids incorporate into cell membranes to be released during times of stress. Activated phospholipases cleave them from the membrane and these enter metabolic pathways within the cell. Omega-6 fatty acids typically found in vegetable oil are precursors for the 2- and 4-series prostanoids which induce vasoconstriction and platelet aggravation. They are also immunosuppressive through alterations in cytokine secretion, impairment of cytotoxic T-lymphocytes, and alterations in the reticuloendothelial system. Metabolism of omega-3 fatty acids however produces metabolites of the 3- series of prostanoids and the 5- series of leukotrienes. These products are less inflammatory and less immunosuppressive. Arginine is not an normally an essential branch chain amino acid in health but it becomes an essential amino acid during periods of stress due to upregulation of arginase which rapidly degrades it[19]. Arginine is a precursor for polyamine synthesis as well as for glutamate and prolene production. It also plays a critical role in nitric oxide synthesis. It is this role of increasing nitric oxide synthesis which has led to a question of safety in critically ill or septic patients. In septic patients in particular, arginase is not upregulated and current studies are investigating its safety under those conditions where production is increased but degradation is not[20]. Under conditions of depletion, eg increased arginase but no increase production, arginine depletion inhibits Kupfer cell function and reduces wound healing. Administration of arginine to depleted animals leads to proliferation of T-cells, increases natural killer cell activity and increases macrophage cytotoxicity. Both intracellular and serum concentrations of glutamine decrease rapidly under conditions of stress[21-23]. Normally, glutamine is the most-free abundant amino acid in the cytosol. Its production is dramatically upregulated by transamination of alpha ketoglutarate in the Kreb's cycle during stress as skeletal muscle metabolizes the branched chain amino acids in cellular protein. Glutamine also provides a metabolicsubstrate for enterocytes, rapidly proliferating cells, and T lymphocytes.

These nutrients (as well as others such as nucleotides[24] and branched chain amino acids) have been added in varying combinations and concentrations to several commercial products and tested in trauma patients as well as general surgery patients (discussed later). In 1994, Moore et al. randomized moderately injured patients to a chemically defined diet (the same used in their earlier trails) or a powdered enteral diet enriched in glutamine, arginine, canola oil-based omega-3 fatty acids, nucleotides, and branched chain amino acids[25]. In this trial, Moore et al noted significantly higher levels of T lymphocytes in the group receiving the supplemented diet and significantly fewer intraabdominal abscesses in that group. Overall, the overall reduction in risk of infectious complications barely missed statistical significance in the group administered the supplemented diet. In 1996, Kudsk et al. randomized only those patients with very severe intraabdominal or total body injury to that same supplemented diet or to an isonitrogenous, isocaloric control diet[4]. This patient population was the same as that shown in the 1992 enteral vs parenteral trial to benefit from enteral nutrition. This group fed the specialty diet suffered significantly fewer intraabdominal abscesses just Moore et al had shown earlier. This specialty diet fed group received significantly fewer days of therapeutic antibiotics and

fewer hospitalization days than patients receiving the standard diet. In addition to severity of injury, placement of a feeding jejunostomy for diet administration was an entry criterion. An interesting subpopulation of patients who met eligibility for inclusion by severity of injury but who did not have jejunal access were prospectively studied. No diet- either enteral or parenteral- was given to these patients for at least 6 days. This "starved" group had the highest rate of infection, had the longest hospitalization and received significantly more therapeutic antibiotics during their hospital course that either of the fed groups.

In summary, the trauma population, particularly the severely injured trauma population with significant intraabdominal and/or total body injury, are likely to benefit from enteral feeding. In this same group, additional evidence supports the use of specialty supplemented diet to provide added benefit over and above unsupplemented enteral diets but it is unclear what particular component, combination of components or amount of these specialty nutrients provide the additonal benefit. Further research is necessary in this regard. However, a primary limiting factor appears to be access into the gastrointestinal tract since gastroparesis precludes successful intragastric feeding in many of these patients for at least 5 days. The existing evidence suggests that it is this first 5 days which is critical in maintaining host defenses in the injured host. An ideal solution would be to define some factor which can be added to parenteral nutrition which is capable of maintaining those host defenses which protect the respiratory tract and intraperitoneal cavity against bacterial assault. This requires an understanding of the mechanisms which protect these surfaces. This will be discussed in more detail later in the section on mucosal immune effects of feeding.

THE GENERAL SURGICAL POPULATION

One of the first randomized clinical trials which questioned the use of parenteral nutrition in patients undergoing general surgical or general thoracic procedures was the VA cooperative trial[26]. Patients were randomized to receive either > 85% of their calculated nutrient goals parenterally for 7-15 days prior to surgery or to no parenteral or forced enteral feedings preoperatively or during the first 72 hours postoperatively. Although the fed group had a reduction in major non-infectious complications (such as wound dehiscence, anastomotic dehiscence et al.) from 22.4% to 16.7%, this failed to reach statistical significance. However, there was a significant increase in major infectious complications from 6.4% to 14.1%. A very important concept identified in this work has usually been ignored, ie the likelihood that patients would develop the complication(s) which nutrition potentially prevents, ie malnutrition-related complications. Risks of parenteral nutrition therapy itself such as line sepsis, hyperglycemia, etc were well known prior to that study. If patients are not at risk of malnutrition-related complications but are given this fairly high technology therapy, one is unlikely to see any benefit from the therapy and only see manifestations of its risk. However, if those patients who are at risk of malnutrition-related complications are analyzed separately, the complications of parenteral nutrition will be seen but one can also determine if there is a benefit. The VA cooperative study clearly demonstrates this. Only at-risk patients benefit. In patients with borderline or very mild malnutrition, noninfectious complications were not benefited with parenteral nutrition, but there was a dramatic increase in major infectious complications in that group. in those patients who were significantly malnourished, not only was there a reduction in major infectious complications (it did not reach statistical significance) but there was a significant reduction in non-infectious healing complications with the perioperative nutrition. This concept is important when interpreting all feeding trials.

In 1997, Heslin and Brennan[27] randomized almost 200 patients undergoing resection for malignancies of the esophagus, stomach, pancreas and duodenum. Patients were randomized to either jejunal feeding using a specialty supplemented enriched in omega-3 fatty acids, nucleotides, and arginine or to IV fluids alone. There were no significant differences in length

of stay (length of stay was short in both groups compared to other trials recruiting the same population), infectious complications, or major complications between the two groups. However, the majority of these patients were well nourished. The average serum albumin preoperatively for the two groups was approximately 4 g/dLand only approximately 5-6% of the patients in either of the groups had any preoperative weight loss at all. This is in markedly different than two clinical trials performed by Daly et al[28-29]. In the first trial, they randomized patients undergoing resection of malignancies (of the same organs as the Heslin/Brennan tria) l to either a specialty supplemented diet or to a non-isocaloric, non-isonitrogenous diet. The patients receiving the specialty supplemented diet had a significant reduction in complications from 36.4% to 12% and a reduction in the length of stay from 20 days to approximately 16 days. The study was repeated using an isonitrogenous and isocaloric control diet and obtained similar results. The differences between these trials and the Heslin/Brennan trial could be related to the difference in recruited patients. While Heslin/Brennan recruited well nourished patients, patients in Daly's study had serum albumin levels between 3 and 3.3 g/dL and 30% of recruited patients had lost ≥10% body weight prior to surgery. It appears that just as in the trauma patients, feeding, and in particular enteral feeding, is beneficial in general surgery patients who are at risk of malnutrition-related complications i.e. those with significant weight loss or significant hypoalbuminemia. Some patient are likely to gain additional benefit from the use of a specialty supplemented diet. The most severely malnourished benefit from parenteral nutrition preoperatively when the enteral route cannot be used for nutitional support.

Additional support for perioperative nutrition intervention was provided by Braga et al. who randomized malnourished cancer patients with at least 10% of body weight loss to 1) preoperative and postoperative feeding with their specialty enteral diet enriched in arginine, omega-3 fatty acids and nucleotides, 2) to the specialty diet preoperatively and a standard enteral diet postoperatively, or 3) to an isonitrogenous, isocaloric unsupplemented diet in the postoperative period only[30]. Patients receiving the specialty diet pre- and postoperatively had the lowest rate of complications – both infectious and noninfectious – and the shortest length of stay compared to the other two groups. Administration of the specialty diet preoperatively but not postoperatively provided some benefit compared to patients fed a standard diet just postoperatively. In a subsequent trial, Braga[31] randomized patients undergoing surgical resection of the stomach, pancreas, and colon or rectum to 1 liter/day of specialty oral supplement for 7 days compared to patients receiving only IV fluids postoperatively. The preoperative oral supplement significantly reduced septic complications whether or not patients had preexisting malnutrition with the greatest effect in those with preexisting malnutrition.

This issue of risk stratification in surgical trials was validated by Kondrup et al.[32] who examined how nutritional risk and severity of injury affected the outcome of nutrition intervention trials. Both degree of malnutrition and severity of disease of patients recruited into the individual trials were ranked as absent, mild, moderate, or severe; these values converted to a numeric score which had been previously validated. The results showed that the likelihood of a clinical nutrition trial showing benefit with nutrition intervention was very low if the recruited populations had a very low severity of illness and very low degree of preexisting malnutrition. However, the likelihood of a trial showing positive results with nutrition intervention increased dramatically as the recruited populations suffered from greater degrees of malnutrition or greater severity of illness when entered into the trials. Thus, those patients who suffer from malnutrition or are about to undergo a significant surgical stress such as pancreatectomy, esophagectomy, et al. will likely benefit from preoperative and postoperative nutrition intervention with a reduction in infectious and non-infectious complications. Although most the severely malnourished will benefit from parenteral nutrition, there are likely to get greater benefit when nutrients are delivered via the gastrointestinal tract, if that is possible.

THERMAL TRAUMA

In 1980, Alexander et al. first noted potential benefits of enteral feeding when pediatric patients were randomized to either a standard enteral diet or a protein supplemented enteral diet following a burn injury[33]. The patients group administered the protein supplemented diet experienced significantly fewer bacteremic days and a higher survival rate then the patient receiving the standard enteral formula. Interestingly, the patients receiving the standard diet also received significantly more parenteral nutrition. Gottschlich and Alexander[34] subsequently compared a specialty enteral formula enriched in arginine, omega-3 fatty acids and nucleotides to a standard enteral formula in pediatric burned patients. There were significantly fewer wound infections in the group receiving the specialty diet. Hospital stay/ percent body burn was also reduced in this group. However, Saffle et al. noticed no significant differences in hospital stay or wound infections in adult burn patients receiving a specialty diet compared to a standard enteral diet[35]. In this study, the standard enteral diet contained very high levels of protein which possibly blunted differences between the two groups.

For the most part, there is consensus that enteral feedings are usually well tolerated and should be used as the primary form of nutrition support following severe burn injury. The important issue is institution of enteral feeding as early as possible after the burn since early administration of intragastric feeding reduces gastroparesis developing later. Patients not fed for the first 18 hours had a much higher rate of delayed gastric emptying than those fed early[36]. Once gastroparesis develops, advancement of a small bore feeding tube into the distal duodenum or proximal jejunum is often necessary to successfully feed via the gastrointestinal tract.

SEVERE HEAD INJURED PATIENTS

Data for the use of enteral feeding after closed head injury is less compelling than for other trauma populations. This may reflect the need for paralysis and heavy sedation, prolonged intubation, and prolonged immobilization associated with the injuries of the therapies for such injuries.

Rapp et al. randomized patients to either early parenteral feeding or intragastric feeding once gastric atony had resolved and nasogastric drainage was low[37]. This was usually not until 5-8 days after injury resulting in severe underfeeding of the enteral group. Of the patients randomized to enteral feeding, all received fewer than 600 calories per day during the first 10 days none received more than 1000 calories per day over the first two weeks. Mortality was higher in the group randomized to intragastric feeding and there was a high rate of septic complications but the rate of sepsis with parenteral feeding was not reported and could not be compared to the essentially starved “enteral” group. In a follow-up trial, the same clinical group randomized patients to either parenteral feeding within 48 hours of admission or enteral feeding once gastric atony had resolved and nasogastric drainage was low[38]. The enterally fed patients appeared to have a worse initial prognostic sign, but there were no significant differences between the two groups in early or late deaths or septic morbidity. A favorable outcome in CNS recovery was noted at 3 months in the parenterally fed group, but this was not substantiated in the follow-up report.

Graham et al. randomized 32 patients with head trauma to a nasojejunal tube placed fluoroscopically or to intragastric feeding after gastric resolution of gastric atony[39].. Caloric intake was significantly greater for the early fed group. Bronchitis, pneumonia, and ventriculitis appear to be lower in the group that received early feeding. Borzotta et al. studied 57 patients randomized to parenteral feeding or enteral feeding within 72 hours of severe head injury[40]. Calculated nutrient goals were met by both routes but there were no significant differences in infectious complications. Finally, Minard et al. randomized patients to either early advancement of a feeding tube into the small intestine following closed head injury or

intragastric feeding once gastric atony resolved [41]. Interestingly, intragastric tube feeding was successfully tolerated on the third postinjury day in the majority of head injured patients when close attention was paid to advancing tube feedings as soon as possible and when a residual of 200 mL or less was accepted as signs of tolerance. Many other trials did not attempt gastric feedings unless residuals were much lower. In this study of very early vs.early enteral nutrition using a specialty supplemented diet (containing omega-3 fatty acids, glutamine, and arginine), there was no significant benefit gained by advancing the tube into the small intestine in fluoroscopy.

In summary, most patient s with severe head injury tolerate enteral feeding fairly soon after their injury and it is unlikely that there is any benefit from advancing a feeding tube into the small intestine to bypass this temporary gastroparesis particularily if the patient requires transport to radiology for this procedure. In is unclear whether there is any difference between a specialty diet and a standard enteral formula in the severely head injured patient.

INFLAMMATORY BOWEL DISEASE

Both enteral and parenteral nutrition produce similar rates of disease remission in ulcerative colitis.[42] While improvements in serum albumin were noted in patients fed enterally, there is no other significant benefit noted in these trials.

In studies of Crohn's disease patients, unless bowel obstruction is an important element of the disease, enteral feeding with an elemental diet appears to show some benefit. In comparative studies investigating complete bowel rest with regimens of steroid and sulfasalazine vs an elemental diet, there appears to be some benefit to the medical approach with steroid and bowel rest. A meta-analysis of several randomized clinical trials seems to favor medical therapy.[43] Chemically defined diets have been used in patients in whom steroid therapy failed to induce remission. Success rates have been mixed since patient selection and the extent of disease may be more important. There is little evidence to support the use of a specialty supplemented enteral formula or use of an elemental diet over a standard polymeric diet at this time when enteral feeding is tolerated by the patient.

PANCREATITIS

Conventional therapy for patients with acute pancreatitis has encumbered fluid resuscitation, bowel rest, parenteral nutrition, and usually antibiotics. While the majority of patients with acute pancreatitis, resolve quickly, there is another population with severe disease due to pancreatic pseudocyst, pancreatic necrosis, and pancreatic abscess. In patients with complicated pancreatic disease, it was once considered a contraindication to obtain enteral access, but two studies have demonstrated the safety of obtaining direct small bowel access with a jejunostomy at the time of laparotomy in those patients requiring surgical therapy[44-45]. Once access is obtained distal to the ligament of Treitz, enteral feeding can usually be administered successfully with little evidence of pancreatic stimulation.

However, there is a much larger group of patients with acute pancreatitis who are unable to take a diet within several days. In this population, recent work has shown that it is safe and beneficial to these patients to administer enteral feeding. In a systematic review by McClave et al, patients admitted with acute pancreatitis and enterally fed were noted to have significant reductions in infectious morbidity and hospital length of stay[46]. While there was no effect on mortality with enteral feeding, multiple organ failure appeared to be reduced when compared with the use of parenteral feeding. A blunted metabolic response with reduced oxidative stress was implicated this this regard. Particularly in those patients in whom surgery was necessary, enteral feeding administered post operatively tended (but was not definitely shown) to reduce

mortality. Additional benefits noted in some studies included more rapid recovery, shorter duration of nutritional therapy, early resumption of oral diet, and reduced costs.

In patients who do not require operation, access into the gastrointestinal tract at a suitable site can be difficult due to the edema and swelling associated with severe pancreatitis. But in general, enteral feedings should be used whenever possible. There is no clear data suggesting that supplemental diets however are any more beneficial than standard enteral nutrition in providing this benefit.

POTENTIAL MECHANISMS FOR REDUCED SEPTIC COMPLICATIONS WITH ENTERAL FEEDING

Over the past 20 years a number of hypothesis have investigated potential explanations for why patients benefit with enteral delivery of nutrients compared patients fed parenterally or not at all. A large body of literature implicated a mucosal vulnerability induced by histologic changes occurring in the intestinal mucosa. Such changes show dramatic losses in villus height, cellular proliferation and mucosal protein in parenterally fed rats. Using this rat model, investigators focused on bacterial translocation from the gastrointestinal tract to the mesenteric lymph nodes as a potential explanation for multiple system organ failure and respiratory infections seen in critically ill and critically injured patient[47-49]. In regard to the hisologic changes, while rat mucosa atrophies to about 50% of normal in the proximal small intestine, humans do not exhibit this degree of atrophy. In regard to bacterial translocation as a source of infectious complications, Moore et al. could not document any evidence of bacterial translocation into the splanchnic system of traumatized patients in whom portal vein catheters had been placed [50]. The concept of bacterial translocation as a source of infectious bacteremia is primarily of historic interest. However, recent experimental evidence defines a cogent nutrition-related link between the intestinal and respiratory mucosal immune defenses.

The mucosal associated lymphoid tissues (MALT) are the specific arm of the immune system which protects the intestinal and extraintestinal external mucosal surfaces through production and secretion of IgA. MALT contains 50% of the body's total immune cell mass and produces more IgA than all other antibodies combined[51]. The primary site for education of these immune cells resides in the Peyer's patches of the small intestine where mucosal adressin cellular adhesion molecule-1 (MAdCAM-1) expressed on the high endothelial venules interact with molecules on T & B cells destined for the mucosal immune system[52-54]. These two specific T & B cell molecules, $\alpha_4\beta_7$ and L-selectin, are expressed on their cell surfaces and serve as ligands for MAdCAM-1 which attracts them into the Peyer's patches[55]. They are sensitized in the Peyer's patches and migrate in response to chemokines to the mesenteric lymph nodes where they mature and/or proliferate. They then migrate via the thoracic duct into the vascular system for distribution to the lamina propria of the small intestine and to extraintestinal mucosal sites such as the mammary gland, respiratory tract, and nasal passages. Within these locations, the Th-2 type IgA stimulating cytokines, IL-4, IL-5, IL-6, IL-10 and probably others – produced by the T cells stimulate IgA production by the plasma cells[56]. These plasma cells originate from the B cells under the similar cytokine influences of the T cells. There is evidence that the enteric nervous system and antigen stimulation of mucosal surfaces drive IgA defense. The T & B cells are continually repopulated with a life span of approximately 5 days.

Experimentally, this system is driven by enteral stimulation- or its lack. When animals are fed parenterally (ie. no enteral stimulation is provided), levels of MAdCAM mRNA drop within hours resulting in reduced expression of MAdCAM-1 within the Peyer's patches within 24 hours[57]. The result is a significant reduction in entry of naïve T and B cells into the Peyer's patches with their resultant atrophy in size. With this reduction, cell numbers drop in the Peyer's patches, lamina propria, and in the intraepithelial lymphocyte spaces to approximately 50% of

normal[58]. Simultaneously, two of the Th-2 type cytokines – IL-4 and IL-10 – also drop significantly resulting in lowered cytokine drive for the remaining plasma cells to produce IgA[59]. Besides the impaired migration and cytokine stimulation to the cells, mechanisms of IgA secretion into the lumen becomes compromised. Poly immune globulin receptor (pIgR), normally expressed on the basal surfaces of the mucosal cells, immediately attaches to IgA produced by cells within the lamina propria.[60] pIgR transports the IgA across the mucosal cell and extrudes it onto its cell surface for where the IgA provides protection of the mucosal surfaces. When the IgA is cleaved and relased from the transport molecule, a small fragment of the pIgR – secretory component – remains attached to the IgA molecule rendering it identifiable as secretory IgA (sIgA). pIgR levels plummet under conditions of lowered enteral stimulation[61]. The overall effect of these change are fewer cells to produce IgA, impaired cytokine levels to stimulate IgA production, lower levels of IgA transport protein, and a reduction in intestinal and respiratory IgA levels and protection [62].

These alterations generate functional changes. In the murine model, one can generate intact IgA mediated defenses against pathogens including the influenza virus and *Pseudomonas aeruginosa.* Animals previously immunized against the influenza virus rapidly neutralize a subsequent intranasal inoculation so that no viral shedding occurs and the airway becomes clear of the virus within hours[63]. Likewise, an otherwise lethal dose of intratracheal *Pseudomonas* becomes non-lethal if animals receive previous immunization with the *Pseudomonas* antigen carried in liposomes[64]. The effect of lack of enteral stimulation is dramatic. Half of the animals previously immunized against the influenza virus lose this immunity after 5 days of parenteral feeding and no enteral stimulation (which is rapidly regained when animals are chow refed for 5 days) [63]. Likewise, administration of parenteral feeding for 5 days completely destroys the anti-*Pseudomonas* defense so that previously immunized animals that might normally have a 10% mortality rate die at the same rate as non-immunized animals[64]. These observations are consistent with the increase susceptibility of parenterally fed (or unfed) trauma patients to pneumonia. .Others have focused on the peritoneal cavity and noted similar suppression of normal responses to peritoneal challenges [65].

The importance of the enteric nervous system [66] and of the amino acid glutamine[67] in preservation of at least part of these defenses has been shown experimentally. When parenteral nutrition is supplemented with a 2% glutamine solution (which serves as an energy source for enterocytes and T lymphocytes), MALT cell populations and cytokine profiles remain normal in the glutamine supplemented group improving resistance to *Pseudomonas* and virus rechallenges[67-69]. When bombesin, a neuropeptide analogous to gastrin releasing peptide in humans, is administered to parenterally fed animals three times a day, cell populations within the Peyer's patches, lamina propria, and intraepithelial spaces and IgA levels are maintained at normal levels as anti-*Pseudomonas* and anti-viral defenses are maintained intact [70-72]. While neither of these supplements returns all aspects of mucosal immunity to normal, the data demonstrates the complex response generated in response to an oral diet. Not only are nutrients themselves are important for preservation of body composition and meeting metabolic needs, the enteric nervous system and some specific nutrients preserve the immunologic responses and integrity responsible for host defenses.

SUMMARY

The last four decades have seen an explosion in nutritional research investigating both clinical and laboratory issues occurring in diverse groups of patients who cannot maintain a normal oral diet. Over the past two and a half decades, researchers have investigated how the administration of macro and micro nutrients via the gastrointestinal tract provides additional benefit over parenteral administration of similar nutrients. The administration of enteral

feeding provides effects which are far beyond those of merely administering macro- and micro-nutrients. Rather, the processing of nutrients via the gastrointestinal tract stimulates a complex response which has implications for body composition and for immunologic integrity. Route and type of nutrition are important aspects of successful patient recovery.

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