Catabolic States and Immune Dysfunction: Relation to Gastrointestinal Feeding

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Critical injury and illness induce a number of metabolic, immunologic, and functional responses which influence clinical outcome and normal defenses. Raised levels of counterregulatory hormones, immobilization, respiratory failure, and violation of host defenses with intravenous catheters and endotracheal intubation alter the balance between the bacterial assault and immunologic host defenses. One of the largest surfaces vulnerable to assault by pathogenic organisms is the gastrointestinal tract, which contains between 1 and 1.5 kg of bacteria, the total number of which exceeds the total number of cells in the body by an order of magnitude. Normally, the single layer of columnar epithelium, along with associated specific and nonspecific immune defenses, maintains an effective barrier between luminal contents and the internal areas of the body. The metabolic perturbations induced by injury and illness, and changes in the normal oral intake of nutrients, affect the integrity of this gut barrier system. Clinical studies suggest that enteral feeding reduces infection on moist mucosal surfaces of the body by helping to maintain these barriers. In this overview I will focus on the clinical and experimental data that have accumulated on the mechanisms involved.

Metabolic Changes

Protein breakdown is accelerated in skeletal muscle and other protein-containing tissues in response to increased levels of the counterregulatory hormones, epinephrine, norepinephrine, and cortisol, as well as circulating inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin
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(IL)-1, IL-2, and IL-6. The counterregulatory hormones and cytokines induce protein catabolism within skeletal muscle and accelerate branched chain amino acid metabolism within the skeletal muscle, increasing the production and release of glutamine and alanine into the circulating amino acid pool [1]. Alanine is recirculated into glucose as the waste nitrogen is ultimately transformed into urea in the liver, to be excreted by the kidneys. Glutamine serves as a fuel source for enterocytes, macrophages, lymphocytes, and neutrophils, and is the primary oxidative fuel for rapidly growing cells. Low levels of glutamine impair the function of neutrophils and monocytes, depress proliferative responses in lymphocytes, and depress cell surface receptors for the recognition and presentation of antigens. This hormonal and cytokine response also affects protein synthesis. IL-6, for example, is released by macrophages, lymphocytes, fibroblasts, and endothelial cells and stimulates production of hepatic acute phase proteins such as α1 acid glycoprotein, C-reactive protein, and fibronectin. The gastrointestinal tract appears to be an important producer of IL-6, as portal levels are higher than systemic levels and peak at 24–48 h following stress [2]. The IL-6 response correlates positively with acute phase protein production and inversely with the production of the transport proteins, albumin and prealbumin.

This metabolic response is well tolerated by the body if it is short lived, resulting in satisfactory clinical outcome and healing of wounds while maintaining immunologic defenses. However, when the response is prolonged owing to the onset of complications, a gradual deterioration of lean body mass occurs which depletes the vigor of the metabolic response. Under these circumstances, nutrition support can be therapeutic in two ways. First, nutrients delivered either enterally or parenterally supplement body reserves of protein and fat and prevent the starvation-induced aspect of nutritional status during injury and illness. Second, early delivery of nutrients through the gastrointestinal tract upregulates immunity, resulting in a reduced incidence of pneumonia or intra-abdominal abscess in susceptible critically injured patients, in addition to providing substrate for the body [3, 4]. As these complications occur between 4 and 7 days after injury and long before malnutrition plays an important role, enteral feeding appears to preserve host defenses and immunologic barriers against bacterial assaults.

**Mucosal Changes with Lack of Enteral Feeding**

Lack of enteral stimulation rapidly produces mucosal atrophy. In rats starved for 6 days, loss of weight and protein from the gastrointestinal tract is out of proportion to weight loss from the body [5]. Even if malnutrition is prevented with parenteral nutrition, a 30–40% reduction in mucosal thickness, mucosal protein, and mucosal DNA occurs in rats, with the change mainly occurring in the proximal two thirds of the small intestine [6]. Gastrointestinal tract mass and protein is partially preserved by providing total parenteral nutrition (TPN) solution enterally, but normal histology and protein are only preserved by the
administration of complex enteral diets. Interestingly, when protein is provided to the fasted, atrophied gastrointestinal tract of rats, the intestinal mucosa withholds a disproportionate amount of the protein to allow mucosal recovery before transporting significant quantities into the body [7]. Although in the human and the mouse, mucosa thickness does decrease when enteral stimulation is lacking, the degree of atrophy is much less than in the rat. At most, the mucosa of parenterally fed humans atrophies by 10–15% in the upper gastrointestinal tract after a week. The provision of the specific nutrient glutamine intravenously can blunt the cellular atrophy and hypoplasia induced by lack of enteral feeding in both humans and rats, but normal architecture is not achieved, and the improvement is modest [8].

**Alterations in Permeability to Macromolecules and Bacteria**

Intestinal permeability to the macromolecules lactulose and mannitol increases following burns and severe trauma and during the onset of sepsis. Within 24 h of an acute burn, permeability increases threefold compared with unburned controls [9]. Permeability increases in chronically burned patients in parallel with the clinical manifestations of sepsis [10]. Following acute trauma, intestinal permeability increases significantly in approximately one third of patients in proportion to increases in IL-6 and the acute phase protein response. By day 7, however, permeability returns to normal, suggesting a short duration in altered permeability [11]. During this period, investigators have documented positive blood cultures (growth of enteric organisms) and the presence of bacterial DNA (measured by polymerase chain reaction) in serum samples. The former is consistent with translocation of bacteria from the intestinal lumen.

Experimentally, various factors result in translocation of bacteria from the gastrointestinal lumen to the mesenteric lymph nodes (Table 1). Hemorrhagic shock, overgrowth of bacteria secondary to antibiotics, and parenteral nutrition increase this phenomenon. Surprisingly, starvation alone does not result in bacterial translocation as long as there is no other insult; however, if an inflammatory focus is induced following starvation, translocation becomes widespread, with positive cultures in mesenteric lymph nodes, liver, spleen, and blood [12]. In humans, bacterial translocation has been noted in bowel obstruction, inflammatory bowel disease, shock, and trauma; however, it appears to have no association with clinical outcome and does not correlate with the development of extraintestinal infections. In trauma patients requiring celiotomy, samples of blood following placement of portal vein and systemic catheters showed a very low incidence of bacterial translocation and no correlation with outcome or multiple organ dysfunction syndrome [13]. Bacteria translocate to mesenteric lymph nodes, lung, and spleen in organ donors, and correlate with the use of vasoactive drugs, starvation, antibiotics, and hypotension. Endotoxin was also found within the abdominal fluid in over half of a group of donors [14].
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<th>Table 1. Factors affecting bacterial translocation in experimental conditions</th>
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Bacterial translocation can occur, there is no evidence to suggest that it influences clinical outcome or the development of subsequent complications such as organ dysfunction or development of infection.

**Normal 'Physiology' of Mucosal Immunity**

The immunologic systems that have developed to protect against bacterial assault across moist mucosal surfaces are very similar in all organisms with an intestinal tract. Although the complexity increases with higher phylogeny, the strategy of these key defenses is to prevent attachment of pathogens to the mucosal surfaces. If attachment is prevented, invasive infection does not occur. These defenses appear to be both specific and nonspecific, and recent work in the mouse model shows that the integrity of the specific immune system depends upon enteral stimulation. It is unclear at present whether the immunologic vigilance of this system is derived from the nutrients themselves or is a side effect of enteral delivery of nutrients.

**Innate, Nonspecific Factors**

There are several innate nonspecific proteins that provide protection against bacterial invasion without the use of antibodies (Table 2) [15]. Many of these have been well investigated in their function as a first line of defense against bacterial assault [16]. Lactoferrin has a long list of biologic functions and is found both in exocrine secretions and in blood and white blood cells. It exists in several isoforms and is bacteriostatic, bacteriocidal, fungicidal, or viricidal. Levels are increased significantly during inflammation, suggesting importance as an antioxidant by binding Fe$^{3+}$ to prevent oxidative metabolism by bacteria. Bacterial growth is inhibited by reducing the availability of iron.

Peroxidases are derived from neutrophils and eosinophils, and are also released onto moist mucosal surfaces through exocrine glands. This family of agents catalyzes peroxidation of halides (for example, Cl$^-$, Br$^-$), generating products with antibacterial properties. These are found in high concentrations in human
Table 2. Innate mucosal defenses

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saliva and human milk and protect mucosal surfaces by preventing growth and the normal metabolic processes of potentially pathologic organisms.

Defensins are peptides containing 30–40 amino acid residues which serve as broad-spectrum microbicides [17]. They increase the permeability of microbial cell membranes by disrupting transmembrane potential. Over 75 α- and β-defensins have been identified across various animal species. These defensins are found in the neutrophils in humans, and high concentrations occur in sites that are rich in neutrophils. In addition, they play an important role as endogenous intestinal antibiotics to limit bacterial concentrations in the upper gastrointestinal tract.

These innate defenses, as well as others, incorporate diverse, nonspecific activities which keep bacterial growth and metabolism in check. While the metabolism and function of these important mechanisms have been described, their role in normal physiology and the effect of nutrition or malnutrition has not been studied and remains a fertile ground for research.

Specific Immunity

Approximately 50% of total body immunity lies just below the mucosal surfaces of the upper and lower respiratory tracts and the gastrointestinal tract. This immunologic tissue is responsible for 70–80% of immunoglobulin production by the body. The primary effector in this system is IgA, an immunoglobulin produced by lamina propria cells and immediately attached to secretory component on the basal surface of the mucosal cell for transport onto the mucosal surface. While 80–90% of serum IgA is monomeric, external secretions are either dimers or tetramers in a ratio of approximately 3:2 in these polymeric forms [18]. IgA functions by binding to surface antigens on specific bacteria and preventing their attachment to the mucosa without activating complement or inducing an inflammatory response. In the occasional circumstance of IgA deficiency in humans, IgM takes over this important role in mucosal defense.

Experimental studies in animal models show that enteral feeding of complex diets influences the size and function of this important immunologic defense. As a research tool, parenteral nutrition allows the study of alterations in this complex system when enteral feeding is interrupted, while avoiding the confounding variable of progressive malnutrition associated with intestinal ‘starvation’. As
a result, the implications of enteral nutrition and the mechanisms for this impor-
tant mucosal defense can be studied over periods of time which are impossible
in small animal starvation models.

Alverdy et al. [19] first described the drop in rat IgA levels owing to lack of
enteral nutrition. Biliary IgA levels fell precipitously during parenteral feeding
but recovered when animals were provided with enteral nutrients. More recent
work has focused on the mouse as it better reflects human mucosal immunity
for several reasons. The majority of IgA released by gut associated lymphoid
tissue (GALT) in rats is secreted into the portal system and is cleared by the
liver after attachment to hepatocyte receptors. Approximately 85% of IgA within
the gut lumen of rats arrives through the biliary tract. In mice and humans, on
the other hand, approximately 85% of the IgA reaches the lumen by transport
directly across the mucosa. As a result, the mouse has been the standard model
for studying the interaction of nutrition and this important immunologic defense.

GALT consists of affector and effector sites, constituting four main anatomic
units: the Peyer’s patches, mesenteric lymph nodes, the lamina propria, and
the intraepithelial space. Circulating naive B and T cells recognize the high
endothelial venule of Peyer’s patches and, as they pass through this structure,
are sensitized to intraluminal antigens that have been taken up from the lumen
by specialized M cells and processed by antigen-presenting cells. After migra-
tion to the mesenteric lymph nodes, they proliferate in response to a favorable
cytokine milieu and release daughter cells into the thoracic duct and the vascular
tree for distribution to sites beneath moist mucosal surfaces throughout the body.
Migration appears to be directed by adhesion molecules. For example, within
the gastrointestinal tract, sensitized cells home to the lamina propria by way
of the α-4 β-7 integrin on the lymphocyte and the MAdCAM-1 marker on
vascular endothelial cells [20]. This distribution to both intestinal and nonin-
testinal surfaces after sensitization in the gut has been termed the ‘common
mucosal immune hypothesis’.

With ad libitum chow oral intake, normal B- and T-cell populations are
maintained within Peyer’s patches, mesenteric lymph nodes, and the lamina
propria [21]. The lamina propria is the primary effector site for IgA produc-
tion, and at this site the T cells have a CD4/CD8 ratio of approximately 2:1
and produce high levels of IL-4, IL-5, IL-6, and IL-10 [22]. These cytokines
stimulate IgA production by B cells (or plasma cells) residing in close prox-
imity. Under normal conditions of feeding, these cytokine levels are adequate
to counterbalance the inhibitory effects of interferon-γ (IFNγ) and TNFβ, two
IgA-inhibiting cytokines within the GALT.

The final anatomic unit, the intraepithelial space, has been less extensively
studied. The cells are primarily CD8+, have a lifespan similar to that of the
epithelium, and there appears to be no local proliferation of cells. Distribution
of intraepithelial lymphocytes varies along the gastrointestinal tract. Within the
jejenum, one of every five epithelial cells is an intraepithelial lymphocyte, but
this number is gradually reduced distally to 5% in the colon. These cells appear
to function as cytotoxic agents against parasites and viruses, and their primary lymphokine secretion is IFN-γ, IL-2, and TNFα. When stimulated, they may recruit neutrophils and macrophages as well as stimulate crypt cell function. In addition, intraepithelial lymphocytes may play an important role in controlling junctions between mucosal cells.

Lack of enteral stimulation leads to a rapid deterioration in all GALT populations within the intestinal tract (Fig. 1) [21]. The absolute numbers of B and T cells are reduced within Peyer’s patches and the lamina propria within three days. The normal CD4/CD8 ratio of 2:1 in the lamina propria is reduced to 1:1, and concentrations of two of the important IgA-stimulating cytokines, IL-4 and IL-10, fall while no change occurs in IFNγ levels [22]. It is presumed that this loss of pro-IgA cytokine stimulation, together with the reduction in numbers of B and T cells, produces the fall in intestinal IgA levels. This system is extremely dynamic and responds rapidly to the reintroduction of enteral stimulation [23]. Significant increases in Peyer’s patch and lamina propria total cell yield, B-cell yield, and T-cell yield occur within 2 days of enteral feeding, and within 3 days, lamina propria CD4/CD8 ratios return to normal as intestinal IgA levels approach normal values.

Within the intestine, these changes exert functional alterations in intestinal integrity and gut barrier function which increase the permeability to bacteria. In data obtained from both mice and rats, lack of enteral stimulation increased bacterial translocation to mesenteric lymph nodes. In general, experimental models associated with increases in bacterial translocation are associated with overgrowth of aerobic bacteria and simultaneous decreases in intestinal IgA levels. Manipulations which increase intestinal IgA levels also normalize bacterial populations and eliminate bacterial translocation.

Extraintestinal mucosal immunity also deteriorates with lack of enteral stimulation consistent with the common immune hypothesis. After establishing IgA-mediated immunity against the H1N1 virus following intranasal inoculation, lack of enteral stimulation impairs this established defense (Fig. 2) [24]. Normally, within two weeks of an initial challenge with the virus, established immunity completely eliminates a subsequent dose of virus from the nasal passages within hours. Lack of enteral nutrition (in association with parenteral feeding to avoid malnutrition) reduces respiratory IgA levels within two days and IgA-mediated antiviral immunity is lost in 50–75% of animals by 5 days [25]. This immunity recovers within five days of enteral feeding, confirming that memory to the antigens remains intact but the functional ability to mount a defense is lost [23]. Similar results are found after establishing immunity against pseudomonas organisms using liposomes incorporating pseudomonas antigens for immunization. Immunization reduces mortality to a lethal dose (in unimmunized mice) of intratracheal pseudomonas from 90–100 to 10% [26]. Lack of enteral stimulation completely obliterates this established protection to the pseudomonas organism given intratracheally. Clinically, these findings are consistent with the much higher incidence of pneumonia noted in critically injured trauma patients.
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Fig. 1. GALT changes with parenteral nutrition. Lack of enteral stimulation reduces total cell yield in Peyer’s patches and the lamina propria in association with fall in intestinal IgA levels and intestinal interleukin-4 and interleukin-10.
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Fig. 2. After establishing immunity to either the H1NI virus (left) or pseudomonas bacteria (right), animal immunity was severely impaired if nutrients were not provided enterically, resulting in impairment of ability to eliminate virus from the upper airway and a high mortality to intratracheal pseudomonas. Results with nonimmunized animals are also shown. IV-TPN-Intravenous total parenteral nutrition.
who are not fed enterally. Studies of respiratory IgA levels in this patient population are currently underway.

**Surrogates of Enteral Feeding**

Both glutamine and intestinal neuropeptides are associated with a reduction in bacterial translocation, increases in intestinal IgA levels, and normalization of microbiologic colonization patterns, and each has been studied for its effect upon mucosal immunology.

**Glutamine**

Glutamine is an important fuel for enterocytes and various cells of the immune system. A 2% glutamine supplementation of parenteral nutrient solution partially preserves mucosal immunity. Total cell yield, B-cell populations, and T-cell populations within the Peyer’s patches, intraepithelial sites, and lamina propria, as well as IgA levels within the intestine, are restored with glutamine supplementation; this improvement occurs with either the free glutamine (amino acid), or when it is given as the dipeptide, glycyl-glutamine [27]. However, some defects in the infectious models still remain. Although IgA-mediated antiviral defenses and survival following pseudomonas infection improve with glutamine supplementation of parenteral nutrition, approximately 20–30% of animals have persistent defects in protection against respiratory pathogens (Fig. 3) [28]. Clinically, parenteral glutamine supplementation of intravenous nutrition given to bone marrow transplant patients reduces viral infections and normalizes microbial colonization patterns. Glutamine supplementation holds promise in preserving immunologic defenses against potential pathogens but requires further testing in broader patient populations.

**Neuropeptides**

The gastrointestinal tract is richly innervated by the enteric nervous system. The number of neurons in the enteric nervous system is comparable with that in the spinal cord. Every cubic millimeter of intestinal tissue is infiltrated with approximately 2 m of nervous tissue. Ninety-nine percent of these nerve fibers lie within 13 µm of the mucosa providing stimulation to the surrounding cell populations. These nerve fibers release various neuropeptides such as gastrin-releasing peptide, vasoactive intestinal polypeptide, cholecystokinin, neurotensin, and gastrin which are important in the digestive functions of the gastrointestinal tract. These peptides also influence the GALT mass and function.

Bombesin is a tetradecapeptide obtained from the skin of frogs and is analogous to gastrin-releasing peptide in man. The seven amino acids that determine its function are identical to those in gastrin-releasing peptide; the remaining peptides identify the species of origin. Bombesin stimulates the release of various gastrointestinal hormones and increases intestinal IgA, eliminates TPN-induced
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Supplementation of total parenteral nutrition (TPN) solution with either glutamine (GLN) or bombesin (BBS) improves mucosal defenses. GLN provided partial improvement; BBS completely reversed immunologic defects to microbial challenges.

Fig. 3. Supplementation of total parenteral nutrition (TPN) solution with either glutamine (GLN) or bombesin (BBS) improves mucosal defenses. GLN provided partial improvement; BBS completely reversed immunologic defects to microbial challenges.

intestinal atrophy, prevents bacterial translocation, and improves mortality in a lethal enterocolitis model. Supplementation of parenteral nutrition with this neuropeptide prevents the deleterious effects induced by lack of enteral feeding in mouse GALT models. Normal T- and B-cell populations are maintained within the Peyer’s patches, intraepithelial space, and lamina propria of animals given this neuropeptide [29]. In animals with existing atrophy of the GALT secondary to lack
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of enteral stimulation, bombesin administration leads to recovery of cell populations in the lamina propria, Peyer’s patches, and intraepithelial cells within 3 days and increases intestinal and respiratory IgA levels to normal. After immunization with the H1N1 virus [30] or with pseudomonas antigen/liposome complex [29], bombesin together with parenteral feeding maintains IgA-mediated antiviral defenses and produces mortality rates comparable to those in chow-fed animals. As this neuropeptide normalizes mucosal immune function at both intestinal and extraintestinal sites, the important factor in mucosal defense with enteral feeding may not only be nutrient availability as an energy or protein source, but the ability of enteral nutrient formulas to elicit a neuropeptide/hormonal response inducing specific and, possibly, nonspecific immunologic defenses.

Conclusion

Increased vulnerability to infection occurs at moist mucosal surfaces in critically ill and critically injured patients. These vulnerabilities appear to be reduced by delivery of nutrients through the gastrointestinal tract. Experimentally, the important immunologic organ protecting humans at these surfaces is the GALT generated in the small intestine and generalized throughout the body, through a common mucosal immune system. Enteral delivery of specific nutrients preserves the integrity of this system, perhaps by inducing normal neuropeptide/hormonal responses.

References

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Discussion

*Dr. Grimble:* You’ve partly explained why chow animals have always done so well in published reports, but could it not also be due to the way in which you present the diet? Chow is a hard diet that is chewed and undergoes a certain pattern of gastric emptying, whereas the TPN diets are liquid diets.
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Dr. Kudsk: Intermittency does not seem to be that important, because the complex enteral diets are given as a continuous infusion and for the most part the animals do just as well as with chow, with all the other things that are in it. So the important factor seems to be the complexity – with perhaps the ability to secrete neuropeptides, or stimulate them. I don’t think the hardness of the diet makes a difference.

Dr. Bentsen: There may be interesting things happening in the extracellular matrix, particularly because that is also the area where you find nerves, and you will probably see interactions between neuropeptides and inflammatory peptides within the extracellular matrix. You showed the numbers of intraepithelial lymphocytes going down and also the numbers of anti-inflammatory cells in the lamina propria and in Peyer’s patches. You also briefly mentioned that the number of cells within the mesenteric lymph nodes did not go down. Could you speculate on what that might mean?

Dr. Kudsk: One point is that the cells that decreased were not inflammatory cells. These lymphocytes are part of the normal host defense; that is a non-inflammatory system. The mesenteric lymph nodes may merely be a temporary lodging point of fixed size; the cells fill up the sites and then just traffic off into the upper thoracic duct. So the fact that the site stays filled may either reflect duration of residence time, or just the fact that when the whole system gets downregulated the cells don’t get pushed on to the next region. We’ve never looked for cytokine changes in the mesenteric lymph nodes, because there are so many other areas where things are dramatically occurring.

Dr. Silk: The bombesin data are clearly of key importance here. In your TPN ± bombesin experiments, was the dose of bombesin that you gave physiological or pharmacological?

Dr. Kudsk: That is a very good question, because at present we don’t know what the receptor is seeing in the way of levels, and I’ve not been able to find out. So I can’t tell you whether the dose is physiologic for that receptor or pharmacologic.

Dr. Freedman: Bombesin does so many things. For example it can affect cholecystokinin (CCK) release and we know that’s a very trophic hormone. Have you tried CCK alone, or other hormones, to really tease out what bombesin is doing? And also along those lines, I’m curious about whether you’ve looked at other cytokines or chemokines to determine their role in the process. Different strains of mice have very different responses to infectious agents.

Dr. Kudsk: We’ve been looking at the downstream cytokines: CCK, gastrin and neurotensin were the three we chose. We found that reductions in GALT were more prominent in the distal half of the gastrointestinal tract (40%) than in the proximal half (25%). We also noticed that it takes a larger number of animals to reach statistical significance with neurotensin than with bombesin, but CCK will bring the GALT back to normal and protect against pneumonia. Gastrin will do the same. Neurotensin will help with the distal GALT but it does nothing for survival following pneumonia when given as a parenteral supplement.

Dr. Barbul: What do we know specifically about the effects of individual components or amino acids on the secretion of these mediators?

Dr. Kudsk: There have been a few studies looking at the hormone response to enteral feeding [1–3]. For example, if you feed into the stomach you get maximum CCK and secretin response. When you feed into the duodenum the response is blunted by half. If you feed directly into the small intestine, CCK is the only one that increases, though not by very much. Can anyone else shed any light on this?

Dr. Freedman: I can tell you that in the pancreas the situation is complicated, but amino acids turn out to be a pretty major drive of pancreatic exocrine secretion through CCK. Peptides don’t stimulate very much response. Full-length proteins turn secretion full on, as do full length triglycerides.
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*Dr. Barbul:* Did you focus on this particular type of neural ending in the gut because it’s numerically the most significant? Have you looked at the other neural systems within the gut and seen what possible effect they may have?

*Dr. Kudsk:* I’m not aware of other neural systems. The reason for our study was that we had preliminary data showing that bombesin increased IgA and a number of other things. Some of these peptides are secreted not only by the enteric nervous system but also by specialized enterochromaffin cells, and it’s not clear to me at all how much of their effects are neurally related and how much are specialty cell related.

*Dr. Millward:* It seems to me that one of the key questions about your work relates to the issue of what the nutrients are that drive the activity of the GALT. You didn’t actually tell us what your TPN solution comprised. Is there lipid in it? Is it complete in terms of micronutrients? You could start with that and through a process of adding constituents you could do a titration. You have the outcome measurements to define the requirements.

*Dr. Kudsk:* We’ve not added lipid to it. The reason we didn’t do that at the beginning was because there’s a major controversy as to whether intravenous lipid is immunosuppressant. Thus any changes that we saw could have been secondary to lipids. So it contains only carbohydrate plus a standard amino acid solution, though we have to add trace metals and vitamins to meet the mouse’s need. It’s given at a dose that meets the nutrient, nitrogen and energy needs of a mouse of 30 g weight. Yes, we could add individual nutrients, and it may be important to do so, but it’s not on the drawing board at the moment.

*Dr. Wernerman:* How much enteral diet is needed?

*Dr. Kudsk:* There are no clinical data on that as far as I’m aware. In a burn model by Nelson et al. [4] it seemed that around 50% of the calculated dose of enteral feeding was necessary to eliminate bacterial translocation following a burn. I would say at this point that we should try to get 50% of the nutrient goals in somehow.

*Dr. Wernerman:* What dosage of glutamine did you use in that particular study?

*Dr. Kudsk:* You can only get 2% to go into solution, so we use a 2% glutamine solution, which is typically what is given to patients as well.

*Dr. Silk:* My feeling is that we have probably emphasized the concept of malnutrition too much, and should really be focusing rather more on mal-eating, in other words, how much nutrition we are taking in. The reason I say that is that in our studies of oral dietary supplements in postoperative patients, we seem to have obtained a similar reduction in the incidence of infection, which I agree seems very interestingly to be mainly pneumonia, just by adding 300 or 400 kcal/day and the equivalent amount of nitrogen over the normal ward diet. My guess is that there is a threshold here; it’s not malnutrition *per se*. There may be a required threshold, at least in response to some traumas such as surgery, which might be in the region of 1000 or 1200 kcal/day, at which you activate all the systems you’ve been telling us about, while if you’re below that threshold you don’t. I think we should be considering this as a concept, as well as malnutrition *per se*. This may be particularly relevant with regard to your patients, who are like ours: they start off well-nourished but run into problems on the fourth to the seventh day. I’ve had very similar experiences.

*Dr. Wernerman:* 1200 kcal is quite sufficient for an elderly population but not for a young population. What age were you referring to?

*Dr. Silk:* Ours is a mixed population so I can’t tell you. The data are pooled, so I haven’t analyzed it that way around.

*Dr. D´echelotte:* There have been very interesting data in experimental animals fed only with bulk chow with no calories at all, and this had some preventive effect. We know that gastric or intestinal distension can induce secretion of many peptides. Do you think the effect of chow could be due only to mechanical distension of the gut?
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Dr. Kudsk: Oh I think that’s very likely. When you give chow, the mechanical distension results in secretion of these neural peptides. That’s what increases motility. They tell the body to start secreting certain enzymes to digest food, but they also increase motility to move it through. And as a side effect seem to say, ‘upregulate your immunity because you don’t know what’s coming down’.

Dr. Jackson: On your list of factors that work in a beneficial way in terms of mucosal immunity you have fiber, but you haven’t said anything at all about that. How does fiber fit into the picture or is it just there as an unknown extra?

Dr. Kudsk: I think fiber plays a role in several ways. One is distension which we mentioned. I think it plays another role in that it is metabolized downstream. I’ve not added fiber to these diets but there are good data showing that fiber reduces bacterial translocation (5–7).

References