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Loss of Upper Respiratory Tract Immunity with Parenteral Feeding

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Objective

The authors examine the effect of route and type of nutrition on an established upper respiratory tract immunity and investigate potential mechanisms for increased pneumonia rates in critically injured patients fed parenterally.

Summary Background Data

The primary immunologic defense against many mucosal infections is IgA. Prior work shows that mice fed total parenteral nutrition (TPN) solutions either intravenously or intragastrically had small intestinal gut-associated lymphoid tissue (GALT) atrophy along with decreased intestinal IgA compared with animals fed complex enteral diets. The small intestine is postulated to be the origin of most mucosal immunity, both intraintestinal and extraintestinal. The impact of diets affecting GALT, small intestine IgA, and upper respiratory tract immunity is studied.

Methods

Male Institute of Cancer Research mice underwent intranasal inoculation with a mouse-specific influenza virus to establish immunity. Three weeks later, the mice were randomized to chow, intragastric Nutren (Clintec, Chicago, IL), intravenous TPN, or intragastric TPN. After 5 days of feeding, mice were challenged with intranasal virus and killed at 40 hours to determine viral shedding from the upper respiratory tract.

Results

Despite similar body weights, there was significant atrophy in the Peyer's patch cells from animals fed the TPN solution intravenously or intragastrically. There was no viral shedding in any animal fed *via* the gastrointestinal tract, whereas 5 of 10 animals fed intravenous TPN had continued viral shedding.

Conclusions

The IgA-dependent upper respiratory tract immunity was preserved with enteral feeding but not with intravenous feeding. Upper respiratory tract immunity is not dependent on intestinal GALT mass but is influenced by route of nutrition. The underlying mechanisms may explain the higher pneumonia rate in critically injured patients fed parenterally.

Infectious complications are the most common cause of death after trauma in patients without severe head injuries[1] and a frequent cause of morbidity and mortality in patients who are malnourished, patients who sustain surgical complications, and medical patients who require prolonged intensive care unit stays. Despite intravenous nutrition, multiple antibiotics, and aggressive intensive care unit care, mortality from sepsis averaged 30% with a range of 20% to 60%, depending on the patient population studied.[2-6]

Septic morbidity is significantly reduced in critically injured patients when enteral feeding rather than parenteral feeding is provided, implying benefits of enteral feeding on host defenses.[7-10] The mechanisms to explain this improved recovery are poorly understood, but it is hypothesized that lack of enteral feeding leads to a breakdown in the gastrointestinal barrier, thus allowing molecules, and perhaps bacteria, to gain entry into the body, causing inflammation and distant infection.[11-15] Most investigators have studied barrier integrity by focusing on changes in gut morphology and permeability to bacteria and macromolecules.[16] Experimentally, interrelationships between levels of IgA, bacterial flora changes, and mucosal permeability have shown definite influences of route and type of nutrition on these basic defenses. With a few exceptions, bacterial overgrowth, mucosal permeability, and increased translocation of both bacteria and molecules have shown an inverse correlation with intestinal IgA levels and nutritional models that preserve IgA also appear to preserve normal GI colonization and reduce bacterial translocation.[17,18] Although systemic responses to injury do increase gut permeability in some patients,[12,13,19] data showing that this increased permeability causes infectious complications, such as pneumonia, are not convincing.

A critical component in mucosal defense and barrier integrity is the availability of secretory IgA (SIgA) in the mucin layer coating the mucosa.[20,21] SIgA binds or agglutinates bacteria, viruses, and potentially other toxic molecules, eliminating the key to invasive mucosal infection (*i.e.*, adherence of infectious agents to human mucosal cells).[20] Levels of IgA are dependent on adequate numbers of functioning immunocompetent cells in the lamina propria mucosae and a cytokine milieu appropriate to the production of IgA.[22,23] As IgA is released from plasma cells within the lamina propria mucosae, it is transported through mucosal epithelial cells by secretory component. In the mucin layer, SIgA binds and agglutinates potential noxious agents without inducing inflammation. Although intestinal SIgA levels correlate inversely with bacterial overgrowth, translocation, and intestinal permeability in animal models,[17,18] only a few investigators have studied the underlying gut-associated lymphoid tissue (GALT) responsible for IgA production.[24,25]

The GALT appears to be exquisitely sensitive to route and type of nutrition.[26] Our prior work shows that small intestine GALT is preserved in animals fed chow or a complex enteral diet, whereas intravenous (IV) total parenteral nutrition (TPN) or enteral TPN (as a model of a monomeric elemental enteral diet) produces a generalized atrophy of GALT B and T cells within the lamina propria mucosae, Peyer's patches, and intraepithelial spaces. Decreases in intestinal IgA parallel this atrophy, but no direct relationship between atrophy and susceptibility to extraintestinal infections has been documented. The concept of a common mucosal immune system may be the link between intestinal changes and extraintestinal susceptibility to infection.[27,28] According to this hypothesis, once activation of precursor IgA-producing cells occurs within the Peyer's patches, the antigen-sensitized precursor cells undergo mitotic changes, proliferate within regional lymph nodes, and migrate to the systemic circulation *via* the thoracic duct. Many of these cells home to the lamina propria mucosae and intraepithelial spaces of the small intestine and serve as the effector arm in an IgA-dependent host defense against intraluminal infectious agents. However, cells released from the Peyer's patches also populate extraintestinal sites, such as the respiratory tract and the mammary, parotid, and lacrimal glands, where they serve as the effector arm of host defense, producing IgA for transport into external secretions and protecting the epithelial surface.

This study investigates the impact of GALT-maintaining (chow and a complex enteral diet) and GALT-depleting (IV and enteral TPN) diets on IgA-mediated respiratory tract mucosal defense using a mouse-adapted influenza virus challenge. It is our hypothesis that a GALT-depleting diet will impair an established IgA-dependent mucosal defense.

MATERIALS AND METHODS

Animals

The studies reported herein conform to the guidelines for the care and use of laboratory animals established by the Animal Care and Use Committee of The University of Tennessee, and protocols were approved by that committee. Male Institute of Cancer Research mice (Harlan,

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Indianapolis, IN) were housed in an American Association for Accreditation of Laboratory Animal Care accredited conventional facility under controlled conditions of temperature and humidity with a 12:12-hour light:dark cycle. Mice were quarantined and fed commercial mouse chow (RMH 3200 Agway, Syracuse, NY) with water *ad libitum* for 2 weeks before protocol entry. During the experiments, the mice were housed in metal metabolism cages with wire-grid bottoms to eliminate coprophagy and bedding ingestion.

Virus Preparation

To generate a pool, A/PR8–Mt. Sinai (H1N1) influenza virus was grown in eggs, pooled, filtered through a 0.45-μm filter, aliquoted, and stored at −70 C. The 50% lethal dose for mice (LD_{50}) was established by the total respiratory tract inoculation of 50 μL of tenfold serial dilutions of the virus pool intranasally into anesthetized mice, generating a fatal pneumonia. The virus pool contained 10^5 LD_{50}/mL.

Experimental Protocol

Mice were inoculated with 20 μL of a 1:10 dilution of the virus pool stock of A/PR8 (H1N1), a mouse-adapted influenza virus, intranasally while awake. This route ensures infection without producing pneumonia and produces sound systemic and mucosal immunity in convalescent mice 3 weeks after inoculation.[29] Three weeks after inoculation, animals were randomized to receive chow with an IV catheter (n = 10), IV TPN (n = 10), intragastric (IG) TPN (n = 10) *via* gastrostomy, or Nutren (Clintec, Chicago, IL) (n = 11) *via* gastrostomy. The composition of TPN used has been described previously.[26] In animals randomized to gastrostomy, a sham neck incision was performed, and animals with IV lines had a sham laparotomy. Under general anesthesia (ketamine 100 mg/kg and acepromazine maleate 10 mg/kg mixture), a silicone rubber catheter (0.012-in inner diameter × 0.025-in, O.D. Baxter, Chicago, IL) was inserted into the vena cava through the right jugular vein or directly into the stomach. Twenty microliters of blood were drawn and the plasma stored at 4 C before enzyme-linked immunosorbent assay to document the presence of virus-specific serum IgG. Lines were tunneled subcutaneously from either the right jugular vein or the gastrotomy site and exited the tail at its midpoint. Animals were partially immobilized by tail restraint during infusion; this model does not produce physical or chemical evidence of stress.[30] Catheterized animals were infused immediately with saline at a rate of 4 mL/day with an increase in rate to a goal of 10 mL/day in the chow, IV TPN, and IG TPN groups and 15 mL/day in the Nutren group. For the first 2 days, animals were allowed *ad libitum* access to chow. On the third day after surgery, animals received only the assigned nutrition. The TPN solution contained 4.1% amino acids and 34.3% glucose (6455.4 kJ/L) in addition to electrolytes and vitamins. The nonprotein calorie/nitrogen ratio of the TPN solution was 663.6:1 kJ/g nitrogen. Nutren contained 12.7% carbohydrate, 3.8% fat, and 4.0% protein (4200 kJ/L) in addition to electrolytes and vitamins. The nonprotein calorie/nitrogen ratio of Nutren was 665.2:1 kJ/g nitrogen. These feedings provided approximately 63 kJ energy and 95 mg nitrogen, meeting the calculated requirements for mice weighing 25 to 30 g.[26] After 5 days of their respective diets, animals were given intranasal challenge twice successively during a 20-minute period with 10 μL of the influenza virus (20 μL total) while awake. Diets were maintained after the challenge until the animals were killed. At 40 hours, the animals were killed by exsanguination under anesthesia. The trachea was clamped at the thoracic inlet through a midline neck incision, and 600 μL cold Dulbecco's modified Eagle media supplemented with 10% fetal calf serum and antibiotics, as detailed below, infused into the proximal trachea. The wash fluid draining from the nostrils was collected in a microcentrifuge tube, placed on ice, and processed immediately for virus. The small intestine was excised from the ligament of Treitz to the ileocecal valve and rinsed three times with total 15-mL chilled Hanks' balanced salt solution, and the intestinal contents were collected in plastic tubes in an ice bath. The length of the small intestinal segments was recorded under a standardized vertical extension with a 2-g weight, and the contents were stored in a −70 C freezer for further IgA analysis. The Peyer's patches also were harvested for cell populations.

Antibody Quantitative Analysis

IgA was measured in intestinal washings in a sandwich enzyme-linked immunosorbent assay using a polyclonal goat anti-mouse IgA (Sigma, St. Louis, MO) to coat the plate, a purified mouse IgA (Sigma, St. Louis, MO) as standard, and a horseradish peroxidase conjugated goat anti-mouse IgA.

Serum influenza-specific IgG was determined by enzyme-linked immunosorbent assay as described previously.[28] Affinity-purified goat anti-mouse IgG and alkaline phosphatase-linked rabbit anti-goat antibodies were obtained from Sigma (St. Louis, MO).

Cell Isolation

Lymphocyte isolations from the Peyer's patches were performed as described previously.[26] The Peyer's patches

were excised from the serosal side of the intestine and teased apart with 18-gauge needles. The fragments were treated with type 1 collagenase (Sigma, St. Louis, MO) (50 U/mL) in minimal essential medium for 60 minutes at 37 C with constant rocking. After collagenase digestion, the cell suspensions were passed through nylon filters.

Flow Cytometric Analysis

To determine the phenotypes of the lymphocytes isolated from the Peyer's patches, 10^5 cells were suspended in 50-μL Hanks' balanced salt solution containing either fluorescein-conjugated anti-CD3 (clone 145-2C11, Pharmigen, San Diego, CA) or phycoerythrin-conjugated goat anti-mouse immunoglobulin (Southern Biotechnology Associates, Birmingham, AL) to identify T cells and B cells, respectively, or in fluorescein-conjugated anti-CD4 (clone RM4-5, Pharmigen, San Diego, CA) and phycoerythrin-conjugated anti-CD8 (clone 53–67, Pharmigen, San Diego, CA) to identify the two T-cell subsets. All antibodies were diluted to 2.5 μg/mL in Hanks' balanced salt solution containing 1% bovine serum albumin and 0.1% azide; incubations were for 30 minutes on ice. After staining, the cells were washed twice in Hanks' balanced salt solution/0.25% bovine serum albumin and were fixed in 1% paraformaldehyde (Sigma, St. Louis, MO). Flow cytometric analysis was performed on a profile I (Coulter Co., Hileah, IL).

Viral Assays

Viral samples were serially diluted (tenfold) in Dulbecco's modified Eagles media supplemented with 2.5 μg/mL amphotericin B, 50 μg/mL gentamicin, and 10% fetal calf serum. Triplicate 100-μL samples of each dilution were placed in 96-well round bottom tissue culture plates. To each well, 100 μL of a 2×10^5 cells/mL suspension of Madin-Darby canine kidney cells in antibiotic-supplemented Dulbecco's modified Eagles media 10% fetal calf serum was added. Plates were incubated at 5% carbon dioxide and 37 C. Culture fluid was removed 24 hours later and replaced with Dulbecco's modified Eagles media containing 2.5 μg/mL gentamicin, 2.5 μg/mL amphotericin B, and 2 μg/mL trypsin. Plates were incubated 4 days longer. Viral growth was determined by a hemagglutination assay. To each well, 50 μL of a 0.5% suspension of chicken erythrocytes was added. Hemagglutination was read after 1 to 2 hours in the cold, and viral titers were calculated by the method of Reed and Muench.[31]

Table 1. ANIMAL BODY WEIGHT AND WEIGHT GAIN

Group	n	Body Weight (g)	Weight Gain (g)
Chow	10	31.60 ± 1.35	2.80 ± 1.23
IV-TPN	10	28.80 ± 1.28	0.09 ± 0.91*
IG-TPN	10	28.53 ± 1.16	0.46 ± 0.74
Nutren (Clintec, Chicago, IL)	11	28.52 ± 1.22	0.40 ± 0.79

IV-TPN = animals fed total parenteral nutrition intravenously; IG-TPN = animals fed total parenteral nutrition intragastrically.
* *vs.* chow, $p < 0.05$.

Statistical Analysis

All data were expressed as the mean plus or minus the standard error of the mean. Statistical analysis was carried out by analysis of variance and Scheffe's multiple comparison and simple linear regression procedure using Statview (Brain Power, Calabasas, CA) software. The Fisher's exact test was used for analysis of virus shedding.

RESULTS

There were no significant differences in body weight at the beginning or end of the experiment, although animals randomized to chow had significantly greater weight gain during the experiment than did IV TPN animals. There were no significant differences between the animals receiving TPN and those receiving Nutren (Table 1).

There was a significant decrease in total cell yield from the animals receiving TPN, either IG ($p < 0.05$) or IV ($p < 0.05$), compared with those from the chow or Nutren group. Total T cells significantly decreased in both groups receiving TPN compared with chow ($p < 0.05$) or Nutren ($p < 0.05$) animals (Table 2). There were significant decreases in CD4 and CD8 cells in both TPN groups compared with those in the chow ($p < 0.05$) group, but only the IV TPN group had significant decreases in CD4 and CD8 cells compared with the Nutren ($p < 0.05$) group. Overall, there were no significant differences in the CD4/CD8 ratio between groups.

Although B cells decreased in both TPN-fed groups, only the IV TPN mice had significantly fewer B cells than did the chow or the Nutren ($p < 0.05$) animals. Intestinal IgA was significantly lower in both TPN groups ($p < 0.05$) than in the chow or Nutren group (Table 3).

All animals had positive serum antiviral IgG titers at the time of cannulation, documenting systemic immunity. Despite this, after 5 days of feeding, 5 of 10 IV TPN

Table 2. PEYER'S PATCHES CELL YIELD AND SUBTYPE ($\times 10^6$)

Group	Total	B	T	CD4	CD8	CD4/CD8
Chow	5.09 ± 0.40	3.05 ± 0.28	1.40 ± 0.15	1.09 ± 0.11	0.40 ± 0.05	3.04 ± 0.41
IV-TPN	3.11 ± 0.37*†	1.86 ± 0.25*†	0.86 ± 0.09*†	0.70 ± 0.07*†	0.22 ± 0.03*†	3.41 ± 0.37
IG-TPN	3.88 ± 0.34*	2.37 ± 0.21	1.03 ± 0.13*†	0.80 ± 0.10*	0.27 ± 0.03*	3.06 ± 0.29
Nutren (Clintec, Chicago, IL)	4.97 ± 0.40†	3.03 ± 0.28	1.37 ± 0.10	1.06 ± 0.09	0.40 ± 0.04	3.15 ± 0.43

IV-TPN = animals fed total parenteral nutrition intravenously; IG-TPN = animals fed total parenteral nutrition intragastrically.
* *vs.* CHOW, $p < 0.05$; † *vs.* Nutren, $p < 0.05$.

animals had positive flu virus ($p < 0.001$) cultures from nasal washes, whereas all other groups had successfully cleared the viral challenge (Table 4).

DISCUSSION

This is the first demonstration of the importance of route of nutrition on extraintestinal mucosal defenses, introducing the concept of the common mucosal immune system to the surgical literature. Although extraintestinal IgA-mediated responses are known to be influenced by the intestinal processing of antigen by the small intestinal GALT,[32] this study shows a significant influence of specialized nutrition on an IgA-mediated infection.

The infection chosen was an A/PR8 (H1N1) mouse-adapted influenza virus documented by Renegar and Small to be IgA mediated.[29,33] After inoculation of nonimmune mice, the virus proliferates within the mucosal epithelial cells and can be cultured from the respiratory tract for 7 to 10 days until normal immune mechanisms clear the virus. When convalescent (immune) mice are challenged, virus is cleared in less than 24 hours. In immune animals, serum virus-specific IgG confirms systemic immunity, but experiments devised to test passive immunity or block mucosal immunoglobulins show that respiratory tract mucosal immunity is IgA dependent. The IV administration of influenza-specific polymeric IgA induces temporary passive immunity in nonimmune mice as IgA is transported from the serum into the nasal secretions.[31] Convalescent (immune) mice challenged with virus administered with anti-IgG and anti-IgM antibodies maintain immunity and efficiently clear the virus; administration of anti-IgA antiserum with the challenge eliminates immunity.[29] These results show that IgA is the major, if not the only, mediator of mucosal immunity to A/PR8 mouse-adapted influenza virus in the intact murine nose and serves as a model for nutritional manipulation of basic IgA-mediated host defenses.

SIgA is a primitive defense used to protect moist epithelial surfaces. Specific IgA mucosal defense develops after antigen processing and migration of cells to the submucosal spaces.[33] Once initial activation of precursor IgA-producing cells occurs within the Peyer's patches, the antigen-sensitized cells undergo mitotic changes, and the resulting B lymphoblasts migrate to regional lymph nodes and eventually to the systemic circulation *via* the thoracic duct.[34] Experiments using whole bacteria, bacterial products, live or killed viruses, or modified viral antigens have shown that the antigen-sensitized precursor cells home not only to the gastrointestinal tract but also to the respiratory tract and mammary, parotid, and lacrimal glands, where they produce IgA for transport through the epithelial cells into external secretions if the

Table 3. INTESTINAL IMMUNOGLOBULIN A LEVEL

Group	Intestinal IgA (μg)
Chow	84.7 ± 8.1
IV-TPN	52.1 ± 3.3*†
IG-TPN	55.7 ± 7.1*†
Nutren (Clintec, Chicago, IL)	80.5 ± 6.8

IV-TPN = animals fed total parenteral nutrition intravenously; IG-TPN = animals fed total parenteral nutrition intragastrically.
* *vs.* chow, $p < 0.05$; † *vs.* Nutren, $p < 0.05$.

Table 4. VIRAL SHEDDING

Group	Virus Positive
Chow	0/10*
IV-TPN	5/10
IG-TPN	0/10*
Nutren (Clintec, Chicago, IL)	0/11*

IV-TPN = animals fed total parenteral nutrition intravenously; IG-TPN = animals fed total parenteral nutrition intragastrically.
* *vs.* IV-TPN, $p < 0.001$.

appropriate T-cell signals and antigenic stimulation exist.[22,27,28,35] These observations have led to the concept of a common mucosal immune system and explain the extraintestinal effects of enteral or parenteral feeding on respiratory tract immunity.

All animals fed *via* the gastrointestinal tract maintained normal immunity against the mouse-adapted virus. Despite confirmed immunity at the time of randomization to diet by the presence of antiviral IgG within the serum, 50% of IV-fed animals lost their immune defense, allowing viral proliferation in the respiratory tract. Our previous work had showed atrophy in both IV TPN- and IG TPN-fed animals (confirmed by the changes in the Peyer's patches in the current study).[26] Respiratory tract immunity appeared to be unaffected by intestinal GALT atrophy because respiratory tract immunity was intact in animals fed by IG TPN despite the GALT atrophy. This suggests that IV TPN both produces atrophy within the GALT and impairs respiratory tract immunity, whereas enteral stimulation with a monomeric "elemental" diet produces GALT atrophy but has no "toxic" effect on the respiratory tract immunity. This finding was surprising and ran counter to our hypothesis at the onset of this experiment. This does not indicate that the intestinal barrier was normal because enteral feeding of a TPN solution increases bacterial translocation,[17,18] implying an impairment in intestinal mucosal defenses, but does suggest that respiratory and intestinal barriers are interrelated yet independent.

A viral rather than a bacterial challenge was used in this experiment to test established IgA responses for several reasons. First, it ensured that animals did not have prior immunologic "experience" with the infectious challenge. Second, the assay techniques are exquisitely sensitive to specific antiviral antibody. Third, the model appears to be purely IgA mediated. A similar underlying mechanism for both anti-influenza immunity and immunity to bacterial pathogens causing pneumonia is likely. This is because in intensive care units, many pathogenic-infecting organisms, such as *Haemophilus influenzae, Streptococcus pneumoniae, Proteus mirabilis, Proteus vulgaris, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Acinetobacter, Candida albicans, Candida tropicalis,* and *Torulopsis glabrata,* have been shown to generate a specific IgA response.[21] These bacterial organisms account for a large number of the nosocomial pneumonias occurring in an intensive care setting. These organisms are usually kept in check by microflora balance, which is disrupted by antibiotic administration and by IgA defenses potentially influenced by mechanisms implicit in our animal model. Susceptibility to induced *Pseudomonas* pneumonia increases with hemorrhagic shock in a timeframe characterized by depressed respiratory IgA levels.[36]

Subsequent investigations into the cytokine milieu that controls plasma cell production of IgA and with hormonal and nutrient manipulation may allow insights into a primitive but essential protection against invasive bacterial infections. The concept of boosting natural barriers rather than attacking the offending organisms with antibiotics or administering antibodies against bacteria or bacterial products eventually may allow improved outcome without inducing serious and significant side effects of current therapy. With current methods, the pathogens continue to win.

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Discussion

DR. GEORGE F. SHELDON (Chapel Hill, North Carolina): President Thompson, Secretary Copeland. I want to congratulate the authors on this wonderful paper. The first paper I gave as a member of this organization was in a similar vein but much less developed. From the Native Americans who used to chew poison oak and poison ivy prior to going on the warpath so they could hide in bushes with these noxious plants, the tolerance through the immunoglobulin mechanism has had an application in a variety of activities, and also the polio vaccine is another manifestation of it.

This, however, is one of the first studies to show that the importance of the route of enteral feeding and maintenance of the immunoglobulin mechanisms has effects on extramucosal defense mechanisms. These studies suggest the concept of a common mucosal immune system, perhaps even governed by the gut-associated lymphoid tissue (GALT) system. In other words, we now know that the gut is an important immune organ; it may actually govern other parts of the immune system. The study also is the first one to show a significant influence on immunoglobulin A (IgA)-dependent infection. So this is a very important study.

I have two questions; one is very naive. Is it possible that the IgA phenomena, the elevation in response to the mouse virus infection, is simply a tolerance phenomena that decreases and decays quickly when the animals have a different nutritional routine? I do not think that is true, but I wish he would comment on it.

The second is, do you have a cohort of total parenteral nutrition animals that have gone through this process that you then have refed, and if so, have they regained their immunity on so doing? I would be surprised if there was not a study like that in the works, and I wonder if we could have a preview to that.

And, finally, Dr. Thompson, relevant to your comments about having to have a commitment to make a contribution, Dr. Kudsk's magnificent obsession with the gastrointestinal tract and enteral feeding has been present since he was a second-year resident. He continues to be the leader in this field. Thank you very much.

DR. JOSEF E. FISCHER (Cincinnati, Ohio): President Thompson, Secretary Copeland. I would like to thank Dr. Kudsk for supplying me with the manuscript in ample time to review it.

Dr. Kudsk and his coworkers in this very nice paper have used a viral model in which immunoglobulin A (IgA) is the dominant operative influence on noncontiguous immunity, with the emphasis on noncontiguous. The working hypothesis is that intestinal gut-associated lymphoid tissue (GALT) and IgA determine the immunity to influenza virus, which is mouse-specific. The results apparently disprove the working hypothesis.