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World J Gastroenterol 2003;9(11):2385-2389
World Journal of Gastroenterology
 ISSN 1007-9327

• REVIEW •

Gut in diseases: Physiological elements and their clinical significance

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Received: 2003-03-05 **Accepted:** 2003-06-02

Abstract

The intestinal barrier function of GI tract is very important in the body except for the function of digestion and absorption. The functional status of gut barrier basically reflects the stress severity when body suffers from trauma and various stimulations. Many harmful factors such as drugs, illnesses, trauma and burns can damage the gut barrier, which can lead to the barrier dysfunction and bacterial/endotoxin translocation. The paper discusses and reviews the concepts, anatomy, pathophysiology of gut barrier and its clinical relations.

Ding LA, Li JS. Gut in diseases: Physiological elements and their clinical significance. *World J Gastroenterol* 2003; 9(11): 2385-2389

http://www.wjgnet.com/1007-9327/9/2385.asp

INTRODUCTION

The gut has long been thought to be quiescent or inactive during illnesses. It has not been paid much attention and not protected just like other organs such as the heart, lung, and kidney in ICU patients. It is generally considered that biochemical metabolism of the body takes place mainly in the liver. Developments in studying technology and advances in surgical skills have led to a better understanding of nutrients metabolism, anatomic architecture and physiological functions of the gut. Gastrointestinal (GI) tract has functions not only to digest and absorb nutrients, but also to modulate systemic immunity and to prevent enteric bacterial/endotoxin' s invasion, so-called gut barrier function. Functional status of the gut sometimes determines the patients' prognosis and recovery from diseases. Some traditional managements are not beneficial or completely harmful to intestinal barrier capability, and aggravate the primary diseases the body suffers. There is a practical significance to further study the physiological functions of GI tract. An overall understanding of the mechanisms of pathophysiological changes of the gut in illness would make us take measurable treatments to patients clinically. This review deals with a series of new concepts and advances in research of intestinal barrier that might be helpful to clinicians.

INTESTINAL BARRIER AND RELATED CONCEPTS

Intestinal barrier function

The definition of intestinal barrier function means that the gut can prevent the harmful materials in intestinal lumen such as bacteria and endotoxin from entering other aseptic organs, tissues and blood circulation through intestinal mucous membrane. The gut barrier is chiefly composed of three components: mucous epithelia, intestinal flora, and secreting immunoglobulin and gut associated lymphatic tissues (GALT)[1], namely the ecological barrier (normal inhabitant flora within intestine), mechanical barrier (mucous epithelia) and immune barrier (or secreting IgA, miscellaneous immune cells including intraepithelial lymphocytes and macrophages, neutrophils, natural killer cells underlying the mucous membrane, Payer' s nodes and mesenteric lymph node). Among them mucous epithelium is the most important one that establishes a mechanical barrier between the lumen and blood circulation. The gut barrier in general term means this structural epithelia[2-5].

Architecture of intestinal barrier

There are two pathways for materials in the lumen when entering into the blood circulation through mucous membrane. One is the transcellular route, the other is the paracellular route, which occupies 5 % of the total intestinal surface area. These two configurations are the main constituents of epithelial barrier[3,6]. It is considered that there are dispersively nonpolarized holes which are full of water and have a radius of 0.3-0.8 nm on the top of villous cells and a tight-junction of 0.95 nm in radius between villous cells. Substances with different sizes of radius get across intestinal epithelia through transcellular or paracellular way when entering into the body. Molecules smaller than 0.3-0.8 nm in radius could enter into the mucous membrane through these holes. Molecules bigger than those such as disaccharides (lactulose and cellobiose etc) and ^{51}Cr-EDTA seem to enter into epithelia through paracellular tight-junctions. Based on this mechanism the intestinal permeability is measured by combining the smaller (such as monosaccharide) and bigger molecules (such as disaccharide) clinically and experimentally[3,6,7]. The two accesses are influenced by alterations of absorbing intestinal area. Substanecs absorbed by the intestine would reduce after atrophy of villi or bowel resection[3, 5-7].

Bacterial translocation

Bacteria come into aseptic tissues from the bowel lumen through mucosal barrier and colonize in tissues such as mesenteric lymph node, liver, spleen and blood. This process is called bacterial translocation (BT). Studies in experimental rodents showed that translocated bacteria seen most oftenly within intact epithelial cells were *Candida*, *E. coli*, *Proteus mirabilis*, *Enterococcus faecalis* and so on, whereas *E. coli* was common and anaerobes and fungi were rare in human beings[1,8]. Endotoxin could pass through bowel wall into the body easier than bacteria in the lumen[9].

Mechanisms of intestinal barrier damage

Hunger, malnutrition and longer parenteral nutrition could cause intestinal mucosa atrophy and impair the mechanical bowel barrier[1,3,10,11]. Shock, ischemia/reperfusion damage, endotoxin of bacteria are the factors that lead to deterioration of intestinal barrier[4,12]. It was found that changes in

prostaglandin and related enzymes-Ca^{++} and cAMP system within cells affected significantly the structure of gut barrier. Non-steroid anti-inflammatory drugs (NSAIDs) could destroy the system and increase the intestinal permeability. Thus it caused bacteria/endotoxin translocating from intestinal lumen into blood circulation and other aseptic tissues, and sepsis would ensue[2,6]. Because of the increments of intestinal permeability, a series of alterations occurred, such as edema of tissues underlaid mucous membrane, microvasculature compression, stasis of blood circulation and thrombosis in microvasculature system. These patho-physiological changes impaired the microvasculature underlaid mucosa and aggravated further the damage of mucosal barrier[2]. Animal experiments showed that treatment with non-steroid anti-inflammatory drugs in aseptic rats did not cause impairment of intestinal mucous membrane. The clinical symptoms were remitted evidently by treatment with metronidazol to human bowel lesions caused by NSAIDs[13]. Managements with antibiotics in rats (it decreased the bacteria load within the intestine) also prevented NSAIDs from inducing intestine inflammation. In addition, the method of fasting for reducing bacterial antigen in alimentary tract could counteract inflammatory intestinal lesions that caused by NSAIDs either[2,14]. Studies showed that factors causing alterations in hormones secreted by mucous enterocytes and changes of related enzymatic system caused damage of intestinal barrier, and the enteric bacteria and endotoxin reinforced the damage. Prabhu *et al*[15] concluded from researches in rats that surgical stress in the small intestine caused structural and functional alterations in the brush border membrane (BBM) through oxidative stress which could affect gut barrier integrity and the generation of arachidonic acid, might mediate distal organ dysfunction. Activation of phospholipase A2 during the process was considered as a pivotal step. Other investigations discovered that the increment of intestinal permeability was mainly due to the relaxation of the tight-junction between intestinal epithelial cells, indicating that there are close connections between changes in tight-junction and cytoskeleton. Any drugs or chemical materials that could impact on cytoskeleton such as lipopolysaccharide, growth factors, cytokines, and hormones, would affect the intestinal permeability[16].

Nitric oxide and intestinal barrier

Nadler *et al*[12] considered that various insults working on human body could cause overexpression of inducible nitric oxide synthase (iNOS) and hence a redundant production of nitrix oxide (NO) occurred. This higher concentration of NO could lead to deposition of protein salts of nitrite-peroxide (and nitric-peroxide) on mitochondrial membrane, impair mitochondrial membrane potential (or permeability) or decrease ATP production. It would destroy the cellular respiratory function and aggravate cellular apoptosis, thus resulting in a breakage in mucous epithelial continuity and "bare area". Bacteria entering through the "bare area", so-called bacterial translocation takes place. A number of researches have shown that endotoxin increases NO over-production with intestinal barrier damages[17-20]. Our animal experiments confirmed this finding (data not published).

Gut is a central organ for surgical stress

The gut has long been thought to be quiescent or inactive during illnesses[29]. A large number of animal experiments and clinical investigations have suggested that functional changes in gastrointestinal mucous mumbrane occur during illness. Bacteria and endotoxin within the lumen enter into the other aseptic tissues and blood circulation through disordered functional and/or disorganized structural mucous epithelia, which influence greatly on occurrence, progress and transformation of illnesses[1-4,6,10-12,21-30]. In recent decades based on large amounts of animal experiments and clinical investigations, a series of new functions concerning gut metabolism and nutrition, intestinal barrier and immunity function, have been recognized. Following the elucidation on mechanisms of systemic inflammatory response syndrome (SIRS) and multiple-organ dysfunction syndrome (MODS)[4,11,29,31-37], the action of the gut as a central organ for surgical stress has also been put forward[29,30,32,35]. It is now known that the gastrointestinal tract contains about 50 % of reticular endothelia and other immune cells, and occupies about 80 % of the total humoral immunity of a human body. It is therefore the largest immune organ of the body[32-35]. Various insults such as trauma, burn, infection, shock, ischemia/reperfusion, irradiation therapy, chemical therapeutical medicines, and SIRS, could directly or indirectly cause an overgrowth of bacteria in bowel and lead to deterioration of intestinal barrier. Hence translocation of enteric bacteria and/or endotoxin, SIRS, sepsis and even MODS ensue[8,38-40], suggesting that the function of the gut in illness determines the patient' s prognosis[38, 41]. Based on this theory and clinical practice above, Wilmore *et al* put forward that gut was a reservoir of pathogens in illness and a central organ for surgical stress[29, 41]. This has been accepted by most scholars[8,38].

EVALUATION OF GUT BARRIER

There are many ways for measuring intestinal barrier function, but no one is perfect. Three regular approaches are often used to measure the function of gut barrier. The first is to examine the morphologies of mucous membrane such as thickness of mucosa, depth of crypts, architecture of villi, proliferating cellular nuclear antigen (PCNA) and intraepithelial lymphocytes (IELs). The second is to test translocation of bacteria/endotoxin, or bacteria growth and endotoxin concentration in mesenteric lymph node (MLN), liver, spleen, portal vein and/or systemic circulation. The third is to measure intestinal permeability[5,6], which is often carried out by using some labeling substances in experimental and clinical researches. Such substances could be water-soluble, nontoxic, and freely permeated through numerous small ' water pores' in the cell membranes of mucosal enterocytes. There is few or no such substances in body tissues that could not be metabolized. They should be excreted rapidly in an easily measured form. The substances matching with conditions mentioned above are lactulose, mannitol, ^{51}Cr-EDTA, PEG400 and inulin[2,6,42]. The approches that are most frequently used to examine intestinal permeability are the two-sugar test, or lactulose/mannitol test. There are two pathways for the subtances to get across the bowel mucous membrane, transcellular (through plasma membrane of enterocyte in the tip) and paracellular (the tight-junction between cells) routes. Smaller molecular substances (such as monosaccharide) pass through enterocytes by transcellular route, whereas bigger molecules (such as disaccharide) get across enterocytes by paracellular pathway. Thus, the increase of small intestinal permeability reflects the "leakeage degree" of mucous enterocytes [2,5-7].

DISEASES AND FACTORS CAUSING GUT BARRIER DYSFUNCTION

Any insults that lead to an overgrowth of enteric bacteria, an impairment of immune defence function and a damage to mechanical barrier of the gut would result in disorders of the intestinal barrier, and bacteria/endotoxin translocation would ensue[1,4,6,10,11,27]. Followings are the causes that lead to an increase of intestinal permeability.

Infection
This includes intestinal and intraperitoneal infections[38] and infections out of the intestinal tract (such as pneumonia)[43].

Parenteral nutrition
The issue has been confirmed by many animal experiments and clinical researches[10,11,21,25,44,45]. The reason is that 70 % of nutrients are absorbed directly from gut lumen, whereas only 30 % is provided by arterial blood supply[1]. Thus parenteral nutrition makes intestinal mucous membrane in a hunger state and leads to gut mucosa atrophy.

Mulnutrition
Mulnutrition could cause atrophy of intestinal mucosa, an insufficiency of protein synthesis and deficiency of body immunity. These would impair the gut barrier[3-27,28,32,34].

Overgrowth of enteric bacteria
Drugs or infection caused by some pathogens could lead to the overgrowth of intestinal bacteria and hence injures the gut barrier[8,27,39,45, 46].

Endotoxin
Endotoxin could increase NO production in the body and lead to impairment of intestinal barrier function[27,46,47]. Our animal experiments were in accordance with this (not shown).

Surgical stress
Various injuries such as burn/scald[10], organ transplantation (reperfusion injury), surgery and trauma[48-50], haemorrhagic shock and many other insults that lead to SIRS, would bring about an increment of intestinal permeability and damage of gut barrier[4,21].

Drugs
Oral administration of castor oil would cause a physical damage of intestinal mucous membrane in mice. Diabetes mellitus induced by streptozotocin in mice caused an overgrowth of enteric bacteria and an immunity injury of the body. Cyclo-oxygenase inhibitors of prostglandin such as mezolin can block production of prostacyclin in bowel mucous membrane, which increases the permeability of mucous epithelium and bacterial translocation[2,14]. It can also bring about intestinal pathological changes[13,51]. Immunosupressive agents such as chemotherapy drugs, anti-transplant rejection drugs[4,52], and antiacids can destroy gut mucosal barrier[53].

Multiple illnesses
Various abdominal diseases could cause an increase of intestinal permeability. One of these is inflammatory bowel disease (IBD)[2,9,42]. Others are intestinal obstruction, biliary block[4,9], leukemia, endotoxemia, parenteral and enteral nutrition[1, 4,10,11].

Physical injury
It includes radioactive intestinal damage[54].

AGENTS DECREASING INTESTINAL PERMEABILITY
Enteral nutrition could alleviate intestinal atrophy of mucous membrane during stress and could lower gut permeability, improve mucosal immunity. These have been confirmed by experiments and clinical practices[11,37]. Treatments with some special nutrients or immune-modulating drugs for patients with parenteral nutrition could also ameliorate intestinal barrier function[2,3,21].

Glutamine
Except for nutrient digestion and absorption, one of the functions of intestinal mucosa is to prevent enteric bacteria and endotoxin from entering into other parts and blood circulation of the body. It is now considered that gut barrier dysfunction is an important cause for infectious complications when patients suffer from hyper-metabolism after surgery and trauma[1,4,10,27,29,31]. It is still unclear what pathological mechanisms lead to gut barrier failure. It is taken for granted that two important factors causing intestinal barrier failure are the damage of intestinal blood supply and the lack of nutrient support[21]. It has been discovered from animal models and septic patients that the state is associated with insufficiency of perfusion (including disorders of microcirculation) and lack of essential nutrients (including glutamine) in their mucosa[2, 21]. Except for antimicrobial therapy of selective decontamination aiming at getting rid of enteric pathogens, it has been carried out to protect gut barrier function from being injured or have been injured in patients threatened by enterogenous infection. A promising approach is to use glutamine parenterally, which is an essential nutrient for the gut in stress and decreases sharply in illness. A series of experiments and clinical researches showed that nutritional support supplemented with glutamine could improve gut barrier function and enhence the body immunity[8,10,21,32,34,42,44,55-58].

Glutamine exerts its effects on the body in many ways. It supplies fuels for mucous enterocytes and strengthens the barrier structure of the gut on the one hand, and increases secretion of IgA by regulating IL-4 and IL-10 on the other hand, thus preventing enteric bacteria from adhesion to intestinal mucosa and subsequent bacterial translocation[59].

Arginine
Arginine influences the body immune system extensively. First, it is the precursor of polyamines and nucleic acids, which are essential for cell hyperplasia and differentiation. Second, it can produce hydroxyproline through metabolism to promote collagenation. Third, it can stimulate different human cells to secrete hormones such as growth hormone, glycagon, insulin-like growth factor 1 and insulin etc., which have various effects on the immune reactions of the body. In addition, arginine is also a precursor of nitric oxide, an important immune molecule[32,44], and has functions to kill bacteria, protect or impair intestinal barrier[32,44,60,61]. Some scholars reported that arginine could alleviate the secondary damage of gut barrier[62,63], whereas others held a completely different opinion, which had also confirmative evidences[50, 64]. Further investigations on the effects and mechanisms of arginine on the body are needed.

Recombinant human growth hormone (rhGH)
Growth hormone has many biological functions[22,44,64-66]. It could decrease intestinal permeability and improve gut barrier function in illness[39,58,69-71]. Possible mechanism of this may be that it promotes hyperplasia of intestinal epithelia[72], or enhances the mechanical barrier of mucous membrane.

Insulin-like growth factor-(IGF-I)
The main effects of IGF-I on the body are basically the same as rhGH[73, 74]. It promotes hyperplasia of mucous membrane of the intestine, and increase the uptake and utilization of glutamine by the bowel when in sepsis[70].

Nucleic acid
Kishibuchi *et al*[75] observed the alterations of cellular ultrastructure under electronic microscope, variations of intestinal permeability and changes of protease in bowel

mucous membrane, which showed that intestinal barrier function was significantly improved.

Others

Epidermal growth factors (EGF) have positive effects on the proliferation of mucous epithelia[76].

REFERENCES

1 **MacFie J**. Enteral versus parenteral nutrition: the significance of bacterial translocation and gut-barrier function. *Nutrition* 2000; **16**: 606-611
2 **Mohajer B**, Ma TY. Eicosanoids and the small intestine. *Prostaglandins Other Lipid Mediat* 2000; **61**: 125-143
3 **Van Der Hulst RR**, Von Meyenfeldt MF, Van Kreel BK, Thunnissen FB, Brummer RJ, Arends JW, Soeters PB. Gut permeability, intestinal morphology, and nutritional depletion. *Nutrition* 1998; **14**: 1-6
4 **Berg RD**. Bacterial translocation from the gastrointestinal tract. *Trends in Microbiol* 1995; **3**: 149-154
5 **Daugherty AL**, Mrsny RJ. Regulation of the intestinal epithelial paracellular barrier. *Pharm Sci Technol Today* 1999; **2**: 281-287
6 **Travis S**, Menzies I. Intestinal permeability: functional assessment and significance. *Clin Sci* 1992; **82**: 471-488
7 **Bijlsma PB**, Peeters RA, Groot JA, Dekker PR, Taminiau JA, Van Der Meer R. Differential *in vivo* and *in vitro* intestinal permeability to lactulose and mannitol in animals and humans: a hypothesis. *Gastroenterology* 1995; **108**: 687-696
8 **MacFie J,** O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut* 1999; **45**: 223-228
9 **Van Deventer SJ**, ten Cate JW, Tytgat GN. Intestinal endotoxemia. Clinical significance. *Gastroenterology* 1988; **94**: 825-831
10 **Sugiura T**, Tashiro T, Yamamori H, Takagi K, Hayashi N, Itabashi T, Toyoda Y, Sano W, Nitta H, Hirano J, Nakajima N, Ito I. Effects of total parenteral nutrition on endotoxin translocation and extent of the stress response in burned rats. *Nutrition* 1999; **15**: 570-575
11 **Kompan L**, Kremzar B, Gadzijev E, Prosek M. Effects of early enteral nutrition on intestinal prmeability and the development of multiple organ failure after multiple injury. *Intensive Care Med* 1999; **25**: 157-161
12 **Nadler EP,** Ford HR. Regulation of bacterial translocation by nitric oxide. *Pediatr Surg Int* 2000; **16**: 165-168
13 **Bjarnason I**, Hayllar J, Smethurst P, Price A, Gumpel MJ. Metronidazole reduces intestinal inflammation and blood loss in nonsteroidal anti-inflammatory drug induced enteropathy. *Gut* 1992; **33**: 1204-1208
14 **Robert A**, Asano T. Resistance of germ freerats to indomethacin-induced intestinal lesions. *Prostaglandins* 1977; **14**: 331-341
15 **Prabhu R**, Anup R, Balasubramanian KA. Surgical stress induces phospholipid degradation in the intestinal brush border membrane. *J Surg Res* 2000; **94**: 178-184
16 **Gasbarrini G**, Montalto M. Structure and function of tight junctions. Role in intestinal barrier. *Ital J Gastroenterol Hepatol* 1999; **31**: 481-488
17 **Dickinson E**, Tuncer R, Nadler E, Boyle P, Alber S, Watkins S, Ford H. NOX, a novel nitric oxide scavenger, reduces bacterial translocation in rats after endotoxin challenge. *Am J Physiol* 1999; **277**(6 Pt1): G1281-1287
18 **Unno N**, Wang H, Menconi MJ, Tytgat SH, Larkin V, Smith M, Morin MJ, Chavez A, Hodin RA, Fink MP. inhibition of inducible nitric oxide synthase ameliorates endotoxin-induced gut mucosal barrier dysfunction in rats. *Gastroenterology* 1997; **113**: 1246-1257
19 **Mishima S**, Xu D, Deitch EA. Increase in endotoxin-induced mucosal permeability is related to increased nitric oxide synthase activity using the Ussing chamber. *Crit Care Med* 1999; **27**: 880-886
20 **Forsythe RM**, Xu DZ, Lu Q, Deitch EA. Lipopolysaccharide-induced enterocyte-derived nitric oxide induces intestinal monolayer permeability in an autocrine fashion. *Shock* 2002; **17**: 180-184
21 **Foitzik T**, Kruschewski M, Kroesen AJ, Hotz HG, Eibl G, Buhr HJ. Does glutamine reduce bacterial translocation? A study in two animal models with impaired gut barrier. *Int J Colorectal Dis* 1999; **14**: 143-149
22 **Eizaguirre I**, Aldazabal P, Barrena MJ, Garcia-Arenzana JM, Ariz C, Candelas S, Tovar JA. Effect of growth hormone on bacterial translocation in experimental short-bowel syndrome. *Pediatr Surg Int* 1999; **15**: 160-163
23 **O'Boyle CJ**, MacFie J, Dave K, Sagar PS, Poon P, Mitchell CJ. Alterations in intestinal barrier function do not predispose to translocation of enteric bacteria in gastroenterologic patients. *Nutrition* 1998; **14**: 358-362
24 **Heys SD**, Ashkanani F. Glutamine. *Br J Surg* 1999; **86**: 289-290
25 **Pierro A**, van Saene HK, Donnell SC, Hughes J, Ewan C, Nunn AJ, Lloyd DA. Microbial translocation in neonates and infants receiving long-term parenteral nutrition. *Arch Surg* 1996; **131**: 176-179
26 **O'Dwyer ST**, Michie HR, Ziegler TR, Revhaug A, Smith RJ, Wilmore DW. A single dose of endotoxin increases intestinal permeability in healthy humans. *Arch Surg* 1988; **123**: 1459-1464
27 **Deith EA**, Ma WJ, Ma L, Berg RD, Specian RD. Protein malnutrition predisposes to inflammatory-induced gut-origin septic states. *Ann Surg* 1990; **211**: 560-567
28 **Welsh FK**, Farmery SM, MacLennan K, Sheridan MB, Barclay GR, Guillou PJ, Reynolds JV. Gut barrier function in malnourished patients. *Gut* 1998; **42**: 396-401
29 **Wilmore DW**, Smith RJ, O'Dwyer ST, Jacobs DO, Ziegler TR, Wang XD. The gut: a central organ after surgical stress. *Surgery* 1988; **104**: 917-923
30 **Marshall JC**, Christou NV, Meakins JL. Immunomodulation by altered gastrointestinal tract flora. The effects of orally administered, killed Staphylococcus epidermidis, Candida, and pseudomonas on systemic immune responses. *Arch Surg* 1988; **123**: 1465-1469
31 **Bengmark S**, Gianotti L. Nutritional support to prevent and treat multiple organ failure. *World J Surg* 1996; **20**: 474-481
32 **Hulswe KW**, Van Acker BA, von Meyenfeldt MF, Soeters PB. Nutritional depletion and dietary manipulation: effects on the immune response. *World J Surg* 1999; **23**: 536-544
33 **Goris RJ**, te Boekhorst TP, Nuytinck JK, Gimbrere JS. Multiple-organ failure. Generalized autodestructive inflammation? *Arch Surg* 1985; **120**: 1109-1115
34 **McCauley R**, Kong SE, Heel K, Hall JC. The role of glutaminase in the small intestine. *Int J Biochem Cell Biol* 1999; **31**: 405-413
35 **Brandtzaeg P**, Halstensen TS, Kett K, Krajci P, Kvale D, Rognum TO, Scott H, Sollid LM. Immunobiology and immunopathology of human gut mucosa: humoral immunity and intraepithelial lymphocytes. *Gastroenterology* 1989; **97:** 1562-1584
36 **Alverdy J**, Stern E, Poticha S, Baunoch D, Adrian T. Cholecystokinin modulates mucosal immunoglobulin A function. *Surgery* 1997; **122**: 386-393
37 **Keith Hanna M**, Zarzaur BL Jr, Fukatsu K, Chance DeWitt R, Renegar KB, Sherrell C, Wu Y, Kudsk KA. Individual neuropeptides regulate gut-associated lymphoid tissue integrity, intestinal immunoglobulin A levels, and respiratory antibacterial immunity. *J Parenter Enteral Nutr* 2000; **24**: 261-269
38 **Marshall JC**, Christou NV, Meakins JL. Small-bowel bacterial overgrowth and systemic immunosuppression in experimental peritonitis. *Surgery* 1988; **104**: 404-411
39 **Fukushima R**, Saito H, Inoue T, Fukatsu K, Inaba T, Han I, Furukawa S, Lin MT, Muto T. Prophylactic treatment with growth hormone and insulin-like growth factor I improve systemic bacterial clearance and survival in a murine model of burn-induced gut-derived sepsis. *Burns* 1999; **25**: 425-430
40 **Swank GM**, Deitch EA. Role of the gut in multiple organ failure: bacterial translocation and permeability changes. *World J Surg* 1996; **20**: 411-417
41 **Carrico CJ**, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple-Organ-Failure Syndrome. *Arch Surg* 1986; **121**: 196-208
42 **Juby LD**, Rothwell J, Axon AT. Lactulose/mannitol test: an ideal screen for celiac disease. *Gastroenterology* 1989; **96**: 79-85
43 **Yu P**, Martin CM. Increased gut permeability and bacterial translocation in *Pseudomonas* pneumonia-induced sepsis. *Crit Care Med* 2000; **28**: 2573-2577
44 **Ziegler TR**, Leader LM, Jonas CR, Griffith DP. Adjunctive therapies in nutritional support. *Nutrition* 1997; **13** (9 Suppl): 64S-72S
45 **Pappo I**, Polacheck I, Zmora O, Feigin E, Freund HR. Altered

gut barrier function to candida during parenteral nutrition. *Nutrition* 1994; **10:** 151-154
46 **Mishima S**, Xu D, Lu Q, Deitch EA. Bacterial translocation is inhibited in inducible nitric oxide synthase knockout mice after endotoxin challenge but not in a model of bacterial overgrowth. *Arch Surg* 1997; **132**: 1190-1195
47 **Steinberg S**, Flynn W, Kelly K, Bitzer L, Sharma P, Gutierrez C, Baxter J, Lalka D, Sands A, Van Liew J, Hassett J, Price R, Beam T, Flint L. Development of a bacteria-independent model of the multiple organ failure syndrome. *Arch Surg* 1989; **124:** 1390-1395
48 **Reynolds JV**, Kanwar S, Welsh FK, Windsor AC, Murchan P, Barclay GR, Guillou PJ. Does the route of feeding modify gut barrier function and clinical outcome in patients after major upper gastrointestinal surgery? *J Parenter Enteral Nutr* 1997; **21**: 196-201
49 **Anup R**, Aprana V, Pulimood A, Balasubramanian KA. Surgical stress and the small intestine: Role of oxygen free radicals. *Surgery* 1999; **125**: 560-569
50 **Baue AE**. The role of the gut in the development of multiple organ dysfunction in cardiothoracic patients. *Ann Thorac Surg* 1993; **55**: 822-829
51 **Allison MC**, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1992; **327**: 749-754
52 **Nakamaru M**, Masubuchi Y, Narimatsu S, Awazu S, Horie T. Evaluation of damaged small intestine of mouse following methotrexate administration. *Cancer Chemother Pharmacol* 1998; **41**: 98-102
53 **Basaran UN,** Celayir S, Eray N, Ozturk R, Senyuz OF. The effect of an H_2-receptor antagonist on small-bowel colonization and bacterial translocation in newborn rats. *Pediatr Surg Int* 1998; **13**: 118-120
54 **Vazquez I**, Gomez-de-Segura IA, Grande AG, Escribano A, Gonz áez-Gancedo P, Gomez A, Diez R, De Miguel E. Protective effect of enriched diet plus growth hormone administration on radiation-induced intestinal injury and on its evolutionary pattern in the rat. *Dig Dis Sci* 1999; **44**: 2350-2358
55 **Van Der Hulst RR**, Van Kreel BK, Von Meyenfeldt MF, Brummer RJ, Arends JW, Deutz NE, Soeters PB. Glutamine and the preservation of gut integrity. *Lancet* 1993; **341**: 1363-1365
56 **Burke DJ**, Alverdy JC, Aoys E, Moss GS. Glutamine-supplemented total parenteral nutrition improves gut immune function. *Arch Surg* 1989; **124**: 1396-1399
57 **Li JY**, Lu Y, Hu S, Sun D, Yao YM. Preventive effect of glutamine on intestinal barrier dysfunction induced by severe trauma. *World J Gastroenterol* 2002; **8**: 168-171
58 **Gu Y**, Wu ZH. The anabolic effects of recombinant human growth hormone and glutamine on parenterally fed, short bowel rats. *World J Gastroenterol* 2002; **8**: 752-757
59 **Kudsk KA**, Wu Y, Fukatsu K, Zarzaur BL, Johnson CD, Wang R, Hanna MK. Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels. *J Parenter Enteral Nutr* 2000; **24**: 270-275
60 **Moncada S**, Higgs EA. Endogenous nitric oxide: physiology, pathology and clinical relevance. *Eur J Clil Inves* 1991; **21**: 361-374
61 **Nadler EP**, Ford HR. Regulation of bacterial translocation by nitric oxide. *Pediatr Surg Int* 2000; **16**: 165-168
62 **Hutcheson IR**, Whittle BJ, Boughton-Smith NK. Role of nitric oxide in maintaining vascular integrity in endotoxin-induced acute intestinal damage in the rat. *Br J Pharmacol* 1990; **101**: 815-820
63 **Brooks EC**, Mahr NN, Radisavljevic Z, Jacobson ED, Terada LS. Nitric oxide attenuates and xanthine oxidase exaggerates lung damage-induced gut injury. *Am J Physioly* 1997; **272**(4Pt1): G845-852
64 **Mishima S**, Xu D, Deitch EA. Increase in endotoxin-induced mucosal permeability is related to increased nitric oxide synthase activity using the Ussing chamber. *Crit Care Med* 1999; **27**: 880-886
65 **Tritos NA**, Mantzoros CS. Recombinant human growth hormone: old and novel uses. *Am J Med* 1998; **105**: 44-57
66 **Inoue Y**, Copeland EM, Souba WW. Growth hormone enhances amino acid uptake by the human small intestine. *Ann Surg* 1994; **219**: 715-724
67 **Byrne TA**, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. *J Parenter Enteral Nutr* 1995; **19**: 296-302
68 **Zhou X,** Li YX, Li N, Li JS. Effect of bowel rehabilitative therapy on structural adaptation of remnant small intestine: animal experiment. *World J Gastroenterol* 2001; **7**: 66-73
69 **Scopa CD**, Koureleas S, Tsamandas AC, Spiliopoulou I, Alexandrides T, Filos KS, Vagianos CE. Beneficial effects of growth hormone and insulin-like growth factor I on intestinal bacterial translocation, endotoxemia, and apoptosis in experimentally jaundiced rats. *J Am Coll Surge* 2000; **190**: 423-431
70 **Balteskard L,** Unneberg K, Mjaaland M, Jenssen TG, Revhaug A. Growth hormone and insulinlike growth factor 1 promote intestinal uptake and hepatic release of glutamine in sepsis. *Ann Surg* 1998; **228**: 131-139
71 **Chen K**, Nezu R, Inoue M, Wasa M, Iiboshi Y, Fukuzawa M, Kamata S, Takagi Y, Okada A. Beneficial effects of growth hormone combined with parenteral nutrition in the management of inflammatory bowel desease: An experimental study. *Surgery* 1997; **14**: 212-218
72 **Zhou X**, Li N, Li JS. Growth hormone stimulates remnant small bowel epithelial cell proliferation. *World J Gastroenterol* 2000; **6**: 909-913
73 **Huang KF**, Chung HD, Herndon DN. Insulinlike growth factor 1 (IGF-1) reduces gut atrophy and bacterial translocation after severe burn injury. *Arch Surg* 1993; **128**: 47-53
74 **Chen K**, Okuma T, Okamura K, Tabira Y, Kaneko H, Miyauchi Y. Insulin-like growth factor-I prevents gur atrophy and maintains intestinal integrity in septic rats. *J Parenter Enteral Nutr* 1995; **19**: 119-124
75 **Kishibuchi M**, Tsujinaka T, Yano M, Morimoto T, Iijima S, Ogawa A, Shiozaki H, Monden M. Effects of nucleosides and a nucleotide mixture on gut mucosal barrier function on parenteral nutrition in rats. *J Parenter Enteral Nutr* 1997; **21**: 104-111
76 **Chen DL**, Wang WZ, Wang JY. Epidermal growth factor prevents gut atrophy and maintains intestinal integrity in rats with acute pancreatitis. *World J Gastroenterol* 2000; **6**: 762-765

Edited by Zhang JZ and Wang XL