Clinical significance of translocation

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Abstract

The gastrointestinal tract, besides being the organ responsible for nutrient absorption, is also a metabolic and immunological system, functioning as an effective barrier against endotoxin and bacteria in the intestinal lumen. The passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa is called bacterial translocation. Equally important may be the passage of bacterial endotoxin through the mucosal barrier. This article reviews the evidence that translocation of both endotoxin and bacteria is of clinical significance. It summarises recent published works indicating that translocation of endotoxin in minute amounts is a physiological important phenomenon to boost the reticuloendothelial system (RES), especially the Kupffer cells, in the liver. Breakdown of both the mucosal barrier and the RES capacity results in systemic endotoxaemia. Systemic endotoxaemia results in organ dysfunction, impairs the mucosal barrier, the clotting system, the immune system, and depresses Kupffer cell function. If natural defence mechanisms such as lipopolysaccharide binding protein, high density lipoprotein, in combination with the RES, do not respond properly, dysfunction of the gut barrier results in bacterial translocation. Extensive work on bacterial translocation has been performed in animal models and occurs notably in haemorrhagic shock, thermal injury, protein malnutrition, endotoxaemia, trauma, and intestinal obstruction. It is difficult to extrapolate these results to humans and its clinical significance is not clear. The available data show that the resultant infection remains important in the development of sepsis, especially in the critically ill patient. Uncontrolled infection is, however, neither necessary nor sufficient to account for the development of multiple organ failure. A more plausible sequelae is that bacterial translocation is a later phenomenon of multiple organ failure, and not its initiator. It is hypothesised that multiple organ failure is more probably triggered by the combination of tissue damage and systemic endotoxaemia. Endotoxaemia, as seen in trauma patients especially during the first 24 hours, in combination with tissue elicits a systemic inflammation, called Schwartzmann reaction. Interferon γ , a T cell produced cytokine, is thought to play a pivotal part in the pathogenesis of this reaction. This

reaction might occur only if the endotoxin induced cytokines like tumour necrosis factor and interleukin 1, act on target cells prepared by interferon γ . After exposure to interferon γ target cells become more sensitive to stimuli like endotoxin, thus boosting the inflammatory cycle. Clearly, following this line of reasoning, minor tissue damage or retroperitoneal haematoma combined with systemic endotoxaemia could elicit this reaction. The clinically observed failure of multiple organ systems might thus be explained by the interaction of tissue necrosis and high concentrations of endotoxin because of translocation. Future therapeutic strategies could therefore focus more on binding endotoxin in the gut before the triggering event, for example before major surgery. Such a strategy could be combined with the start of early enteral feeding, which has been shown in animal studies to have a beneficial effect on intestinal mucosal barrier function and in traumatised patients to reduce the incidence of septic complications.

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Today the gastrointestinal tract is not only regarded as a system where nutrient absorption takes place, but also as an important metabolic and immunological system functioning as an effective barrier against intraluminal pathogens entering the circulation.¹ The maintenance of normal epithelial cell structure prevents transepithelial migration of particles from the gut lumen and the preservation of tight junctions prevents movements through the paracellular channels.²

A variety of immunological mechanisms support this system. The Peyer's patches of the intestinal wall, together with lymphocytes, macrophages, and local IgA production combined with the IgA present in bile, provides a special defence system.³ Finally, the Kupffer cells and endothelial cells of the liver serve as a cellular back up system before entrance into the systemic circulation. Bacterial particles entering the circulation can also be cleared and detoxified to some extent in the serum. Serum proteins, predominantly lipopolysaccharide binding protein, bactericidal/permeability increasing protein, and high density lipoprotein, play an important part in this system.

Translocation is the migration of bacteria or endotoxins across the mucosal barrier. Recent publications have focused increasingly on the role of the gastrointestinal tract as a reservoir of pathogens that can enter the circulation by translocation, initiating the

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septic process and eventually leading to multiple organ failure.

Until recently, most experimental studies have been performed in animal models and have quantified translocation by the recovery of viable micro-organisms from the mesenteric lymph nodes and other tissue by means of culture techniques. The importance of the rate of translocation and distribution of organisms that are actually killed by the different host defence mechanism, has not hitherto been the subject of study. Moreover, little recent work has been performed to define the clinical importance of translocation of endotoxin.

Systemic endotoxaemia was proposed as a cause of disease in humans more than 20 years ago by Ravin *et al.*⁴ Because of the difficulty, however, of measuring systemic endotoxin with a reliable assay, the concept fell into disfavour. Nevertheless, there is sufficient evidence that translocation of endotoxin plays an important part in sepsis.

The purpose of this paper is to review the evidence that translocation of both endotoxin and bacteria is of clinical significance.

Translocation of endotoxin

ENDOTOXIN IN RELATION TO THE RETICULOENDOTHELIAL SYSTEM

Endotoxins are lipopolysaccharide constituents of the outer membrane of Gram negative bacteria consisting of a core region, an O-antigen side chain, and a lipid moiety, lipid A. Animal and clinical studies have identified endotoxin as the main trigger of septic shock in Gram negative infection. Immunocompetent cells, such as monocytes and macrophages, are the main cellular targets of endotoxin and many of the symptoms associated with septic shock are mediated through endotoxin induced cytokine production by these cells.

Endotoxin has several biological effects, some of which are very harmful to the host. Among these effects are, the induction of intravascular coagulation,⁵ haemodynamic disturbances leading to hypotension,⁶ metabolic derangements,⁷ damage to the vascular endothelium,⁸ and cholestasis.⁹ In addition, suppression of cellular immunity^{10 11} and increased muscle protein degradation are seen when systemic endotoxaemia is present.¹²

The polysaccharide chain of lipopolysaccharide has been reported to play an important part in the colonisation of the gut by Gram negative bacteria.¹³ In the normal human gut, outer membrane fragments are constantly shed from these micro-organisms during replication and endotoxins are present in large quantities, without obvious harmful effects. There is now good evidence that portal vein endotoxaemia of gut origin in minute amounts is a normal physiological phenomenon.^{14 15} In the normal animal this low grade endotoxaemia of gut origin is rapidly cleared by the cells of the reticuloendothelial system (RES) of the liver.^{16 17}

Uptake of endotoxin or endocytosis by endothelial and Kupffer cells takes place by

both receptor dependent and receptor independent (pinocytotic) mechanisms. Receptor dependent internalisation of immune complexes or pathogenic particles entails binding to complement (C3) or Fc receptors, or both. Binding to C3 receptors or Fc receptors alone produces modest phagocytosis, while attachment to both receptor types synergistically induces rapid phagocytosis. The number of Fc and C3 receptors correlates with the capacity of the liver to clear particles that can bind to these receptors. It seems that stimulation of the liver RES by endotoxin from the gut may be an important physiological phenomena in maintaining its phagocytic function.¹⁸ Longterm endotoxin administration has been proved to prime the RES by increasing its activity. An increase in the RES capacity has also been seen in patients with peritonitis.¹⁹ The increase in the RES phagocytic function in response to endotoxin may be related to the activating effect of endotoxin on C3 receptor function.²⁰ Endotoxin does not induce the hyperphagocytosis immediately after intravenous injection, but first gives rise to a transient decrease of the RES phagocytotic capacity, possibly because of antigenic or particle overload. Twenty four hours after the injection the RES function increases. The same effects are seen when endotoxin is injected intraperitoneally.²¹

In experimental studies, transient RES depression is seen after burn, trauma, surgery, and even anaesthesia.²²⁻²⁵ This depression lasts 12 to 18 hours,²⁶ but is followed by a rapid recovery. RES depression is also seen after liver transplantation in obstructive jaundice and after partial hepatectomy.¹⁰⁻¹²

ENDOTOXAEMIA IN BOWEL DISEASE

Although the appearance of endotoxin in the peripheral circulation may be due to a decrease in RES function, some evidence suggests that gut derived endotoxin may also enter the systemic circulation after translocation across the bowel wall into the peritoneal cavity.²⁷

Severely burned patients, who often initially present in hypovolaemic shock before resuscitation, do not manifest systemic endotoxaemia until a few days after injury, when RES function has returned to normal values.^{28 29}

As discussed above, the absorption of endotoxin by the normal gut is probably a physiological phenomena; the diseased gut, however, can translocate endotoxin in large amounts. For example, in patients who had abdominal surgery for Crohn's disease and ulcerative colitis, systemic endotoxaemia was commonly seen.³⁰ Systemic endotoxaemia was also present in a high percentage of patients with acute inflammatory bowel disease, who were admitted to hospital and a correlation between the severity of bowel ulceration and the incidence of systemic endotoxaemia was found.³¹ Gastrointestinal disorders in new born children, either primary or secondary, may be associated with systemic endotoxaemia.³² Endotoxaemia was reported in 23 of 47 febrile episodes in 45 children with

necrotising enterocolitis, whereas only three of them had true Gram negative bacteraemia.³³

Severe translocation takes place when the intestinal wall is damaged, which can occur as a consequence of a number of events, including ischaemia, trauma, hyperthermia, the presence of vasoactive agents or ionising radiation. Recently, in a pilot study with patients having cardiopulmonary bypass, Oudemans (personal communication) showed a clear relation between the post-perfusion syndrome and endotoxin translocation from the gut. An increase of endotoxin concentration was seen after release of the aortic cross clamp. In addition, a close relation was seen between oxygen consumption and blood endotoxin concentrations. It was concluded that hypoperfusion of the gut during cardiopulmonary bypass, combined with a decreased blood flow through the liver depressing its RES were the probable factors leading to systemic endotoxaemia. Moreover, it was postulated that the development of pulmonary and renal dysfunction together with bleeding disorders may, in some patients, be related to this endotoxaemia.³⁴

ENDOTOXAEMIA IN LIVER DISEASE

Systemic endotoxaemia without evidence of Gram negative infection occurs in liver disease in humans. It has been reported in cirrhosis and fulminant hepatic failure and it is suggested that the endotoxaemia is pathogenetically related to extrahepatic symptoms in these conditions such as disorders in renal function and blood coagulation.

Studies by Farao *et al*³⁵ performed in cirrhotic patients, showed endotoxin in ascitic fluid in 40% and in plasma in 75% of this patient group. The mortality at six months was significantly higher in the patients with endotoxaemia, compared with those without endotoxaemia.³⁵ Increased absorption of lipopolysaccharide of clinical importance has been reported in cirrhotic patients during significant bleeding. Bigatello *et al*³⁶ identified measurable endotoxin in the plasma of 36 of 39 cirrhotic patients admitted without evidence of sepsis. Moreover, he found that in 21 patients with hepatic coma as a result of bleeding, significant endotoxaemia was present, the concentrations being highest in the cirrhotic patients with poorly compensated liver disease. Endotoxin concentrations correlated with the severity of coma and higher values of endotoxin were found in those patients who died compared with those who survived. He concluded that higher values of endotoxin were clearly associated with encephalopathy and death.³⁶ These studies were confirmed by Wilkinson *et al*,³⁷ who reported that 14 of 22 consecutive patients with fulminant hepatic failure showed endotoxaemia without bacteraemia and in this study there was a close correlation between endotoxaemia, impaired renal function, haemorrhagic diathesis, and death.³⁷ Similar findings were seen in Rey's syndrome.³⁸

Recently, studies by van Leeuwen *et al*¹² strongly showed that intestinal endotoxin

played an important part in the pathophysiology of hepatic failure after hepatic resection and that in turn the endotoxaemia initiated an accelerated catabolic response to the surgical injury. These events were associated with increased release of glutamine from skeletal muscle, accelerated uptake of glutamine by the gut, and concomitant production of ammonia. Significant hepatic injury and a high death rate occurred in conjunction with these changes. Changing the gut contents before operation through administration of lactulose or cholestyramine reduced the level of endotoxaemia, blocked the catabolic response, and protected the liver with an enhanced survival.¹² In obstructive jaundice, the RES is also known to be depressed. Clinical studies on the treatment of pancreatic carcinoma showed that obstructive jaundice is an important risk factor in postoperative complications.³⁹ A high bilirubin concentration not only predicts a higher death rate, but is also associated with an enhanced frequency of renal insufficiency, septic complications, and postoperative bleeding. Postoperative renal failure occurs in 4–18% of jaundiced patients and the death rate is between 4 and 40%.⁴⁰ Furthermore, postoperative bleeding is seen, as is septic shock and intra-abdominal sepsis together with severe impairment in immunological function.^{41–43}

It seems that most of these complications, if not all, are related to systemic endotoxaemia⁴¹ and that part of the complications can be prevented by binding endotoxin.⁴³ Nakagawa *et al*³⁴ suggested that jaundice alone does not produce any increase in endotoxin concentrations, however, after major surgery performed in these patients, a considerably increased and prolonged endotoxin concentration was seen.

In obstructive jaundice the RES function is thought to be depressed for a longer period of time, even after relief of the bile obstruction. Based upon these results it may be concluded that an increase in the incidence of liver failure and multi organ failure after surgery in patients with cirrhosis or obstructive jaundice is most probably related to a significant increase in blood endotoxin.

Bacterial translocation

It is now widely recognised that normal bacterial flora can leave the intestinal lumen and enter the systemic circulation in several ways such as retrograde migration into the lung, direct transmucosal migration across the bowel wall, and migration to the mesenteric lymph nodes, liver, and spleen by lymphatic or vascular channels. Experimental studies have repeatedly shown that the mesenteric lymph node is the most reliable site to culture for the purposes of monitoring bacterial translocation.⁴⁶

Translocation from the gut is probably controlled by its own flora, a process called 'colony resistance'. According to this hypothesis, the normal intestinal anaerobic flora acts as a control mechanism for the translocation of the enterobacteria. Van de Waay *et al*⁴⁷ have claimed that gut wall associated anaerobic flora

functions to control the intestinal colonisation and translocation of the gut wall associated aerobic flora.

The frequency with which bacterial translocation occurs may be influenced by the ability of the translocating micro-organism to be absorbed by intestinal epithelial cells. Strictly anaerobic bacteria are not readily taken up by enterocytes and stay attached to the epithelium at receptor sites. This hypothesis is consistent with the finding that translocation of anaerobic bacteria is facilitated in those situations where there is severe histological damage; damage to the intestinal epithelium and thereby damage to the receptor sites.⁴⁸ Bacterial species that translocate more readily are those considered to be facultative intracellular organisms such as *Salmonella* species and *Listeria monocytogenes*. These species can survive and replicate within host blood cells and translocate after a simple oral inoculation. Pathogenic aerobic flora translocate with much difficulty to other sites, and it is these flora that are most commonly cultured in critically ill patients.

Extensive work on bacterial translocation has been done in experimental animal models and has been shown to take place in haemorrhagic shock, thermal injury, malnutrition, endotoxaemia, trauma, and intestinal obstruction.⁴⁹ Consequently, it can be concluded that the following important mechanisms probably promote bacterial translocation: (1) Changed permeability of the intestinal mucosa as seen with haemorrhagic shock, sepsis, injury or administration of endotoxin; (2) Decreased host defence mechanism, for instance secondary to glucocorticoid administration, immunosuppression or protein depletion; (3) An increased number of bacteria within the intestine will occur if there is bacterial overgrowth, intestinal stasis or when exogenous bacteria are applied experimentally.

It is difficult, however, to extrapolate the principles gained from results of experimental studies to humans because experiments are conducted under controlled circumstances, which can influence pathogenicity of the flora. Very few studies on bacterial translocation have been performed in humans and their significance is not clear. During laparotomy Schatten *et al*⁵⁰ cultured portal venous blood in patients with non-inflammatory bowel disease. They found that portal bacteraemia occurred in more than 30% of their 25 patients.

The incidence of culture positive lymph nodes is higher in clinical situations where the gut is damaged, as is shown in studies of Ambrose⁴⁶ and Hollander.⁵¹ In accord with these results were the findings made in another clinical study performed in a small number of patients admitted to a trauma unit. These patients all had low blood pressure without gastrointestinal injury. The investigators found a clear link between haemorrhagic shock and sepsis in this group of patients.⁵²

Bacterial translocation from the gut has also been seen during and after surgery for bowel obstruction. Thus the cultures of mesenteric lymph nodes obtained during laparotomy in

patients suffering from intestinal obstruction showed an incidence of bacterial colonisation of 59% in contrast with an incidence of 4% in patients operated on for other causes.⁵³

Border *et al*⁵⁴ retrospectively studied a group of intensive care unit patients with blunt multiple trauma. They found clear correlations between methods of artificial support such as days on a ventilator, days on enteral feeding, number of drugs prescribed, and the magnitude of the sepsis severity score. All registered deaths from sepsis occurred in the group of patients who had no enteral protein intake. They concluded that the duration and magnitude of the septic state resulted from contamination by endogenous, gut derived bacteria and that they could be decreased by enteral feeding.

Similar results were seen in a study from our group.⁵⁵ In our institute a large retrospective study of 206 critically ill trauma patients was performed to evaluate the comparative importance of factors related to the extent of multiple organ system failure and outcome. Multivariate methods were used to select independent risk factors related to the multiple organ failure score and subsequent death. Independent factors related to multiple organ failure were: age, pre-existing longterm conditions, malnutrition, injury sepsis score, coma on admission, number of blood transfusions, use of H₂ receptor blockers or antacids, and intercurrent infection. Multiple logistic regression selected advancing age, longterm disease, injury sepsis score, and multiple organ failure score as the important predictors of death.

These findings together with the predominance of enteric micro-organisms in infected patients, suggests that bacterial translocation may be important in initiating late multiple organ failure during a septic state and in aggravating the severity of existing multiple organ failure. In patients with multiple organ failure score of >1, the incidence of infection or bacteraemia was 46% and 19% respectively. In the rest of the patient group, despite the severity of multiple organ failure, no bacteria could be cultured.

Early enteral feeding in the prevention of translocation

The advantage of enteral over parenteral feeding has been a subject of discussion for some time. The prevention of gut mucosal atrophy can be regarded as the most recent rationale favouring enteral feeding. It is presumed that the preservation of the gut mucosal barrier function and intestinal immunocompetence prevents bacterial translocation.^{56 57} Alexander⁵⁸ has proposed that an intact gut barrier blocks translocation of bacteria and endotoxins, which otherwise activate the complement cascade and stimulate macrophages and neutrophils to elaborate inflammatory mediators, resulting in an amplified metabolic response to injury. Recent laboratory studies have focused on the relation of mucosal structure and permeability. Mucosal permeability to macromolecule markers increases

with intravenous feeding and starvation.⁵⁹ Li *et al*,⁶⁰ however, could not find a relation between starvation and translocation. After acute (three day) starvation or prolonged (14 day) protein malnutrition, bacterial translocation did not occur, although severe mucosal atrophy was found. Malnutrition combined with endotoxin administration, however, leads to very significant translocation of bacteria to mesenteric lymph nodes, liver, and spleen. This translocation rate was significantly higher than translocation after experimental endotoxaemia without malnutrition.⁶¹ The authors suggested that impaired cell mediated responses and RES activity might be more significant in the induction of translocation than increased mucosal permeability. A study by Fong *et al*⁶² in healthy volunteers clearly pointed out that the route of feeding affects injury and disease. They found that the counter regulatory hormone and splanchnic cytokine responses to endotoxin were enhanced after total parenteral nutrition and bowel rest compared with after enteral feeding. A lack of luminal nutrition was postulated to predispose the patient to amplification of injury induced metabolic and immunological responses.⁶²

Three recent clinical studies all highlight the beneficial effects of enteral feeding on the outcome of trauma patients.^{54 64 65} In particular, all three showed that enteral feeding decreases the incidence of septic complications in these patients. Kudsk *et al*⁶⁵ studied the importance of the route of nutrient administration on septic complications in 98 patients with blunt and penetrating trauma, randomised to either enteral or parenteral feeding within 24 hours after injury. They concluded that there was a significantly lower incidence of septic morbidity in the enterally fed patient group, and recommended early enteral feeding in the management of these patients.

By means, presumably, of preserving gut mucosal barrier function and immuno-competence, enteral feeding or luminal nutrition has proved to be an important factor in the prevention of bacterial and endotoxin translocation in experimental animal models.⁵⁸ As yet, there are no data available on the effects of enteral nutrition on translocation in humans. The above clinical studies showing that the incidence of septic complications in trauma patients is reduced by enteral feeding^{54 64 65} do provide at least indirect evidence that luminal nutrition in some clinical settings may lead to a reduction in translocation of bacteria and endotoxin. It follows that although enteral feeding has been proved to be the preferred route of nutritional support in stressed patients^{34 64 65} the full rationale for this has yet to be characterised. Popular theories suggest that the benefits occur as a consequence of preserving gut function by means of providing glutamine, fibre or the products of fibre degradation short chain fatty acids.^{1 58 63} The specific effects of other nutrients, however, on intestinal blood flow and endotoxin translocation, may turn out to be of greater importance.

Discussion

It can be concluded that occult infection remains an important diagnostic consideration in the critically ill patient, who develops unexplained organ dysfunction. Uncontrolled infection, however, is not necessary or sufficient to account for the development of multiple organ failure. Experimental studies have shown that the changes during the septic response are produced by a complex cascade of molecular mediators, including cytokines, prostaglandins, and intermediates of oxygen and nitrogen. These substances are generated by host cells, mostly macrophages, in response to a variety of stimuli including ischaemia.

Maessen *et al*⁶⁶ provided evidence that ischaemic injury in combination with inflammatory mechanisms can lead to systemic complications. These authors showed that after 60 minutes of renal occlusion, severe renal failure was seen and when combined with experimentally induced systemic endotoxaemia death resulted.⁶⁶

A number of cytokines, including tumour necrosis factor, IL-1, and interferon γ have shown that they can replace part of the original endotoxin mediated stimuli. It is tempting to speculate that the two stimuli concept attributed to Schwartzmann participates in the interaction of endotoxaemia and ischaemic tissue necrosis. Interferon γ , a T cell produced cytokine, is thought to play a pivotal part in the pathogenesis of the Schwartzmann reaction. This reaction might occur only if the endotoxin induced cytokines, tumour necrosis factor and IL-1 act on target sites prepared by interferon γ . Thus after exposure to interferon γ target cells become more sensitive to stimuli like endotoxin so boosting the inflammatory cycle.^{67 68}

Such an explanation could explain the results of the experiments performed by Lehmann *et al*⁶⁹ who showed that treatment of mice with D-galactosamine, a known hepatotoxic agent induced a considerable sensitisation of the animals to lipopolysaccharide, which at very low doses had a lethal effect. Treatment with either substance alone was without effect on outcome. In other animal experiments⁶⁶ neither tumour necrosis factor treatment nor experimentally induced renal failure affected death at 48 hours. Combination treatment, however, resulted in a 50% more deaths at the same time period.

Taking this thinking one step further forward, it is possible that the multi organ failure syndrome in trauma patients could develop as a consequence of the effects of tissue necrosis combined with the endotoxaemia that results from the intestinal translocation of endotoxin.⁷⁰ Based on the results of the animal studies discussed above,⁶⁶ tumour necrosis factor may play a part in the combined effect of ischaemic tissue injury and endotoxaemia.

If this type of hypothesis is shown to be a tenable explanation for the development of multiple organ failure, then the possibility might exist that bacterial translocation is a late phenomenon during multiple organ failure and

does not participate in its pathogenesis.⁷¹ Selective decontamination treatment may therefore be too late to be effective in the prevention of multiple organ failure in some groups of intensive care unit patients because multiple organ failure has already been induced by translocated endotoxins acting in a combination with coexisting tissue injury. Future strategies for preventing the onset of multiple organ failure in traumatised or injured patients might be advised to combine a policy of early luminal nutrition with methods of binding luminal endotoxin and preventing its translocation.

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