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INTESTINAL TRANSLOCATION: INTRODUCTION TO THE TOPIC

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INTRODUCTION

At the end of the 13th Old Herborn University Seminar, which dealt with "the Role of Polyspecific Immunoglobulins in the Normal (physiological) Clearance of Micro-organisms", it was decided that the process of intestinal translocation per se (i.e. before any clearing mechanisms may become operative) should receive more attention at the next meeting. The present publication contains the proceedings of papers as presented at the 14th Old Herborn University Seminar devoted to the topic of intestinal translocation.

DEFINITION

Now what is "intestinal translocation"? In 1979, Berg and Garlington defined the term translocation as “the passage of viable bacteria from the gastro-intestinal tract to the mesenteric lymphnodes and possibly other organs”

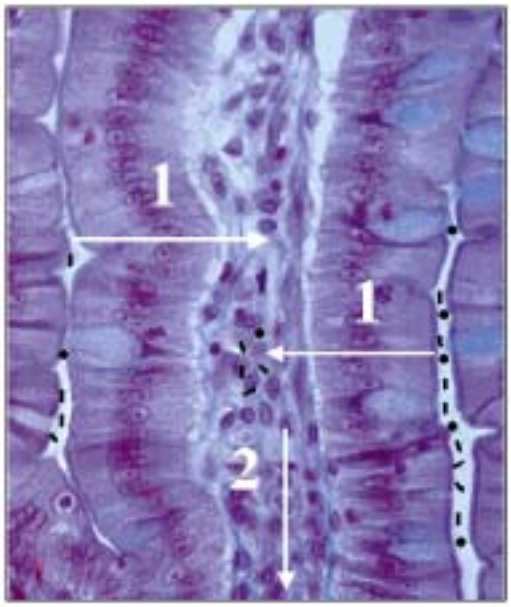

Figure 1: Photomicrograph of intestinal villus showing the two stages of bacterial translocation (arrows 1 and 2 respectively).

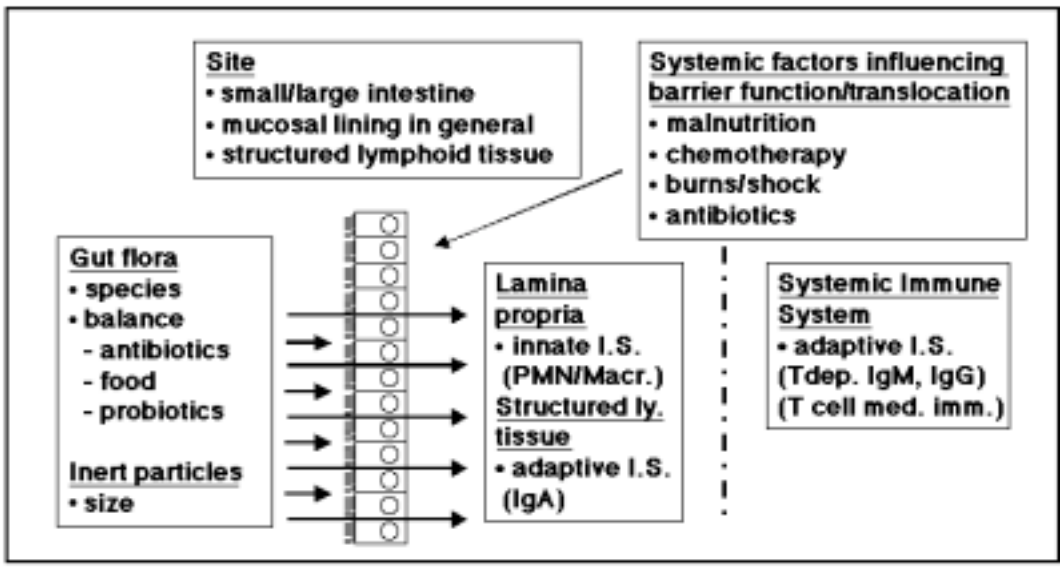

Figure 2: Factors involved in intestinal translocation as discussed in the text.
I.S.: Immune system; PMN: polymorphonuclear cells; Macr.: macrophages; T dep. IgM, IgG: T-cell dependent IgM, resp. IgG production; T-cell med. imm.: T-cell mediated immunity.

(*Berg* and *Garlington*, 1979). In this definition indigenous micro-organisms were explicitly included.

When analysing the process of translocation (Figure 1), several stages may be discriminated. Usually the mucosal lining (epithelial layer) is considered a physical barrier between the milieu extérieur and the milieu intérieur. Mutatis mutandis, the skin serves the same purpose. Crossing this barrier of epithelial cells (and as a result entering the milieu intérieur as such) could be defined as translocation in a more restricted sense (Figure 1, arrow numbered 1). Once having crossed this border (including the basement membrane) a translocating micro-organism is subject to the rules of homeostasis in the milieu intérieur which are quite different to those reigning at the site where it came from, i.e. the gut lumen. These rules now will determine whether the organism will live or die. However, with time during evolution, micro-organisms have developed several strategies to escape these rules, one being intracellular survival. If not eliminated after translocation into the lamina propria, the micro-organisms may travel on either by way of lymph or blood (Figure 1, arrow numbered 2). When the lymphatic route is chosen, the next step will be the mesenteric lymphnodes draining the gut wall (Figure 3). There again chances are that it will be eliminated. Some researchers feel that translocation to MLN is still within the boundary of physiology (as came up during the discussion), whereas others feel that reaching the MLN already is a sign of diminished resistance. However, if a micro-organism manages to get beyond the MLN, i.e. reach the blood stream through the efferent lymphatics draining into the thoracic duct, it is agreed that this is a sure sign of pathology, usually involving clinical manifestations of (serious) infection. From the blood stream in principle all organs of the body can be reached. Organs monitored for translocating micro-organisms usually include spleen, liver, kidney and brain.

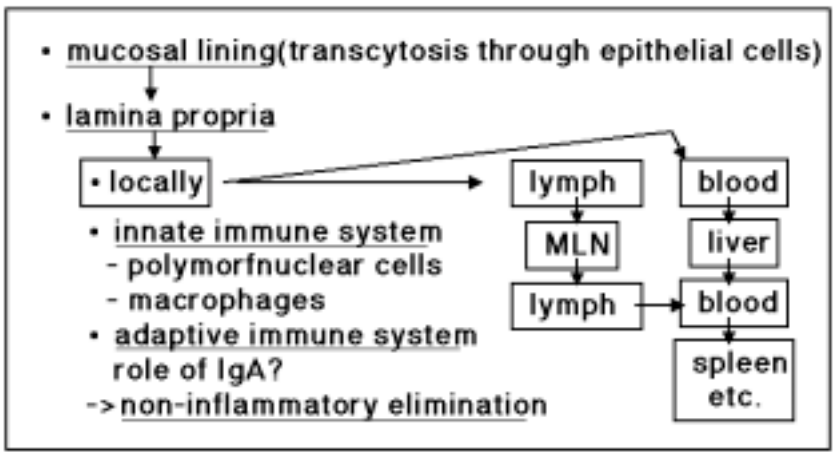

Figure 3: Events occurring after translocation across the mucosal lining in general. Arrows indicate possible routes of translocating micro-organisms.

WHAT "MATERIALS" DO TRANSLOCATE?

In principle any substance reaching the gut lumen by the oral route is eligible for translocation. This ranges from intact (macro) molecules to particles the size of tens of µ-meters. In this way, the definition as given above is extended to include all "particulate" matter crossing the epithelial border. These particles may be live or dead including inert particles like starch, carbon, latex etc. Dr. Volkheimer, and Dr. Hussain contributed papers on this issue.

Live micro-organisms like bacteria have predominantly been found to translocate. As to viruses and parasites, little information is available. In the following, intestinal translocation will be restricted to bacteria and inert particles (see also *Wells* et al., 1988).

FACTORS INVOLVED IN INTESTINAL TRANSLOCATION

Many factors are involved that determine whether a micro-organism will translocate or not and what happens once it has translocated (in a more restricted or in its broadest sense). Figure 2 shows an overview of these factors.

When considering factors involved, several compartments can be distinguished.

First (1) there is the *gut flora* itself. Aspects like species, their respective concentration, their adherence properties, whether they live under aerobic vs. anaerobic conditions and whether they are commensals or (opportunistic) pathogens, all play a role.

Under normal physiological conditions the composition of the gut flora is highly stable (dynamic equilibrium). This equilibrium, however, can be disturbed by the use of antibiotics both orally as well as systemically. Thus colonisation resistance may change resulting in overgrowth of resistant species thus enhancing chances of their translocation. Drs. Wadström, Herías, and Van der Waaij contributed papers related to this part.

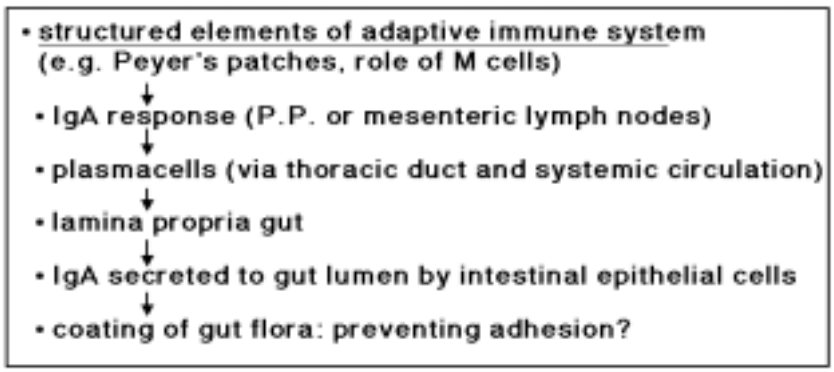

Figure 4: Events occurring after translocation at the level of structured lymphoid tissue. P.P.: Peyer's patches

In addition, the issue of manipulation of the gut flora in a positive way, i.e. to increase resistance to infection, was addressed. Special attention was given to the role of *Lactobacillus* species in this field. In a broader sense the possible beneficial role of prebiotics and probiotics were discussed. Related papers were presented by Drs. Bengmark and Bovée-Oudenhoven.

When preparing this seminar it seemed logical to pay special attention to the issue of translocation of inert particles in comparison with live micro-organisms as a different kind of particulate matter that may occur in the gut lumen. Is there an essential difference or are mechanisms involved virtually the same? (Dr. Volkheimer, Dr. Hussain; see above).

Second (2) there is the *intestinal barrier* itself. In a broad sense, elements of the innate immune system, like polymorphonuclear cells, macrophages and the adaptive immune system (especially IgA) as present in the lamina propria may be considered to be part of this barrier.

Issues like site of translocation i.e. ileum vs. jejunum vs. colon as well as mucosal lining in general vs. the specific M-cells associated with structured lymphoid tissue like Peyer's patches, were worthwhile considering.

Upon crossing the border both effector cells and molecules of the innate immune system (polymorphonuclear cells, macrophages, opsonising lectins, polyspecific IgM (?)) as well as effector cells and molecules of the adaptive immune system (T-cells, IgA) come into play (Figures 3 and 4). Assuming that under steady state conditions, translocation is a normal phenomenon, apparently translocated micro-organisms are eliminated in a non-inflammatory way. This process, however, still remains elusive. A major question here is if and to what extent locally secreted IgA is instrumental: opsonisation leading to non-inflammatory elimination, export of IgA coated bacteria through the epithelial lining back to the gut lumen? Or does IgA "only" play a role in the gut lumen by preventing adhesion? Papers in this area were contributed by Drs. Berg, Jepson, Pabst and -in the discussion- Bos.

Lastly (3) *systemic factors* may determine whether translocation may lead to pathology. In immunocompromised patients, (part of) the defence mechanisms as present in the lamina propria may fail. Malnutrition and chemotherapy may affect these mechanisms but may also affect the quality of the epithelial barrier. In critically ill patients e.g. due to extensive burn wounds, the ini-

tial hypovolaemic shock may lead to local ischaemia in the lamina propria consequently affecting the barrier function. As mentioned above, both oral and systemic administration of antibiotics may disturb the gut flora equilibrium thus facilitating translocation of now dominating species. To this area Drs. Alexander and Feltis contributed papers.

LITERATURE

Berg, R.D. and Garlington, A.W.: Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. Infect. Immunol. 23, 403-411 (1979).

Wells, C.L., Maddaus, M.A., and Simmons, R.L.: Proposed mechanisms for the translocation of intestinal bacteria. Review of Infectious Diseases 10, 958-979 (1988).