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Leading article

Crohn's disease – a permeability disorder of the tight junction?

Despite extensive efforts the aetiology of Crohn's disease has yet to be established. Studies have concentrated on possible infectious or immunological causes, but have not provided a clear explanation of the pathogenesis of this disease. Many infectious agents such as bacteria, viruses, mycoplasma, and mycobacteria have been considered as possibly causing Crohn's disease.[1–3] So far none of the infectious agents have fulfilled Koch's postulates or been consistently confirmed as a causative agent of this disease. Possible immunological abnormalities have also been studied.[4] Numerous investigators have looked for either primary immunological abnormalities[5] or abnormalities of immune response.[6] Again, none of these efforts have consistently identified immunological abnormalities as the cause of Crohn's disease.[7 8]

Prostanoid metabolism has recently received extensive scrutiny in the search for the aetiology of Crohn's disease. Numerous investigators have been able to show increased PGE_2 concentrations in inflamed colonic mucosa[9 10] or colonic lumenal contents from patients with Crohn's disease.[11] Increased elaboration of other prostanoids[9 12 13] and leucotrienes[10] has also been reported in patients with Crohn's disease. The consensus of opinion is that changes in prostanoid metabolism in Crohn's disease are probably secondary to the inflammatory process itself and not an underlying aetiological factor.[14]

While the aetiology and pathogenesis of Crohn's disease is complex, I propose that increased intestinal permeability through abnormal tight junctions could play a role. I am not proposing that increased intestinal permeability is the only aetiological factor in the development of Crohn's disease; rather, I am proposing that increased intestinal permeability could allow the penetration of antigenic or infectious agents into the intestinal wall and thus start the process which in susceptible individuals culminates in Crohn's disease. The proposal that increased intestinal permeability could be important is not new.[15] Recent new clinical and experimental evidence,[16–21] however, is sufficient to suggest serious consideration of this proposal as a working hypothesis.

The term permeability needs clarification and definition. Normally the intestinal epithelium is able to act as a selective entry gate into the body. The intestinal epithelium which absorbs needed nutrients, fluids, and electrolytes with a very high degree of efficiency can also selectively prevent the absorption of water soluble compounds larger than 0·4 nm in diameter.[22] Such size considerations do not apply to lipid soluble molecules, because they penetrate the absorptive cell membrane directly.[23] Strictly speaking, small water soluble charged molecules can also be absorbed by a process which is also sometimes referred to as permeability.[24] The penetration of the intestinal epithelium by sodium ions is an example for such a process. For

the purpose of using the term permeability as relevant to the aetiology of Crohn's disease, however, I will restrict its use to the passive penetration of the intestinal epithelium by medium and large sized water soluble non-charged molecules, greater than 0·4 nm in cross-sectional diameter. Examples of such molecules include the monosaccharide rhamnose, the disaccharide lactulose, polymers such as polyethylene glycol and macromolecules such as inulin, or albumin.[25 26] The concept of altered permeability implies that the absorption of these molecules has increased in comparison with their absorption rate by the normal intestine. The barrier to the absorption of these molecules may be disrupted and thus no longer prevents their penetration into the intestinal mucosa.

Information about the normal regulation of intestinal permeability is extremely limited. The two possible routes of intestinal permeability are the cellular and paracellular routes. It is clear that small ions can penetrate the epithelium through the paracellular tight junctions, or through the absorptive cells themselves.[27] We also know that large macromolecules such as horseradish peroxidase can penetrate the cell membrane by endocytosis.[28] The route of intestinal permeation of medium sized, non-charged molecules such as lactulose, polyethylene glycol (PEG), and viral or bacterial particles has not been established. If a compound cannot normally permeate across the cell membrane, it must traverse the intestine by the paracellular tight-junction.[27 29 30] It is for this reason that the hypothesis favoured at present assigns a defective tight-junction as the cause of abnormal intestinal permeability; however, permeation across an abnormal membrane or membrane channels has not been ruled out.

What is the evidence for abnormal permeability as an aetiological factor in Crohn's disease? It is morphological and physiological.

Morphological study of intestine from Crohn's patients has included tissue from involved inflamed intestine and from segments without gross inflammation.[31–33] If morphological studies are to be considered of significance in the aetiology of Crohn's disease, the tissue must not be from inflamed areas because inflammation could cause secondary morphological changes. The studies by Marin[31] and Dvorak,[32 33] provide information about mucosal abnormalities in uninflamed areas of the intestine from patients with Crohn's disease. In these studies, the tight junctions appear to be abnormal with increased separation between cells and abnormalities in the structural strands of the tight junctions. These findings provide support to the hypothesis that one of the underlying abnormalities in Crohn's disease is increased permeability secondary to abnormal paracellular tight junctions.

Recent studies show that intestinal permeability of patients with Crohn's disease is greater than that of normal controls or patients with ulcerative colitis.[16–21] Such evidence is based on measurements of urinary excretion of poorly absorbed, water-soluble, orally given compounds unable to be metabolised. In these comparative studies, patients with Crohn's disease showed increased intestinal permeability by the non-metabolised sugar, lactulose,[19] and of markers such as 51Cr-EDTA[18] and of PEG 400.[16 34] In recent studies we found that clinically healthy relatives of patients with Crohn's disease also have increased permeability to PEG 400 compared with non-related healthy controls.[16] This finding suggests that the permeability abnormality in patients with Crohn's disease is not secondary to intestinal inflammation, but rather, may be an aetiological factor in the disease. This

finding also suggests that the abnormal intestinal permeability of patients with Crohn's disease may be genetically determined and is in concert with the known familial aggregation of the disease.

The validity of these observations of abnormally high intestinal permeability in patients with Crohn's disease and in their healthy relatives needs additional testing with different permeability markers and populations. The factors which control permeability also need more study. Nevertheless, the hypothesis that abnormal intestinal permeability is an aetiological factor in Crohn's disease has sufficient support to provide direction for future research in the disease. The goal of research now should be to increase the understanding of the physiological regulation of permeability, in order to design diagnostic and therapeutic approaches to the disease based on the new observations about permeability changes in Crohn's disease.

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