MINIREVIEW

Intestinal Epithelial Barrier Dysfunction in Crohn's Disease (44099)

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Abstract. **Despite extensive research, the etiology of Crohn's disease remains unknown. Accumulating evidence suggests the possibility that a primary defect of intestinal barrier function may be present in Crohn's disease. In this review, the possible role of intestinal barrier defect in Crohn's disease is discussed. It has been recognized for some time that Crohn's patients have a defective intestinal epithelial barrier function manifested by an increase in intestinal permeability. Recent studies indicate that a subgroup of healthy first-degree relatives of Crohn's patients (a population at high risk for developing Crohn's disease) also have increased intestinal permeability. Additionally, this subgroup of patients have evidence of increased exposure to foreign antigens, suggesting a possible link between increase in intestinal permeability and increase in antigenic penetration. Furthermore, exacerbation of Crohn's disease is produced by agents that disrupt intestinal epithelial barrier function, while remission of active disease is induced by decreasing intestinal antigenic load. A "leaky gut" hypothesis is advanced which proposes that a preexisting disorder of intestinal permeability is responsible for the intestinal inflammation of Crohn's disease.**

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Crohn's disease is a chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract, from mouth to anus. Most commonly, Crohn's disease affects distal small intestine; however, the large intestine is also involved in the majority of patients (1). The overwhelming majority of Crohn's patients have recurrent exacerbation. During an exacerbation, patients frequently present with complaints of abdominal pain, fatigue, diarrhea, and weight loss related to the intestinal inflammation. The response to treatment is quite variable, and there is no cure for the disease. In many patients, the disease is difficult to control, and, not infrequently, patients develop severe complications, including fistulas, infections, and cancers.

Despite extensive research, the etiology of Crohn's disease remains unknown. Possible etiologic factors that have been suggested include infectious agents, immune dysfunction, genetic susceptibility, and various environmental factors (2–4). While a great deal of information has been gained through research efforts, we still do not understand the pathogenesis of the disease. During the past 15 years, a number of clinical studies have demonstrated an abnormal increase in intestinal permeability in Crohn's patients (5–11). There is some evidence suggesting that this disorder of intestinal permeability may play an etiologic role in the pathogenesis of Crohn's disease (8, 11). This review will examine the possibility that Crohn's disease is a primary disorder of intestinal permeability.

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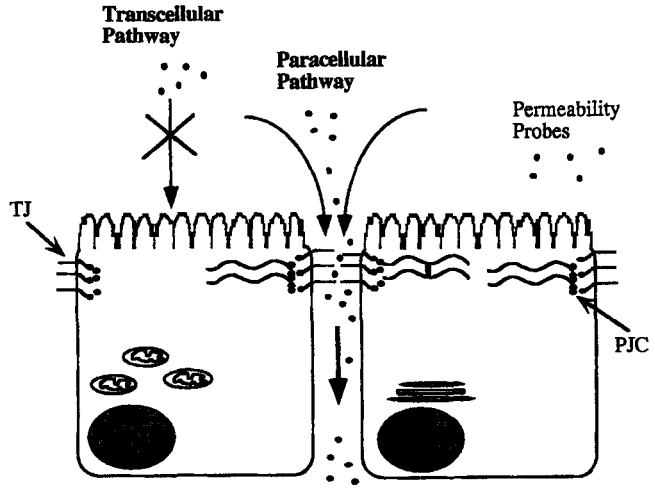

Figure 1. The permeation pathway of intestinal permeability probes. Because of their strong water solubility, permeability markers do not partition across the bi-lipid enterocyte membrane to any appreciable extent but permeate through the aqueous paracellular pathways. The tight junctional complexes (TJ) act as a restricting structural barrier or "gates" to the paracellular permeation of the probes. The opening or closure of TJ pathways appears to be regulated in part by the perijunctional cytoskeletal elements (PJC) actin and myosin filaments.

Intestinal Permeability

Intestinal permeability is an imprecise term which has been used by investigators in this area to refer to the intestinal epithelial barrier function. It has been defined as "the ability of medium and large sized water-soluble compounds to passively traverse the intestinal epithelial layer through the paracellular tight-junctional areas" (12–14). Thus, "intestinal permeability" measurements assess the intestinal epithelial paracellular barrier function to passively permeating water-soluble molecules (Fig. 1).

In clinical studies, permeability markers are given orally and intestinal permeability is measured by a quantitation of the permeability markers excreted in the urine over a designated time period (usually between 6 and 24 hrs). By definition, permeability markers must be hydrophilic and passively absorbed by the intestine. Ideally, for clinical use permeability probes should also be inert, not metabolized or endogenously produced, and should be rapidly and completely excreted in the urine in an easily measured form (12, 15). The commonly used intestinal permeability probes include lactulose, cellobiose, mannitol, rhamnose, various molecular weight polyethylene glycols (PEG), and ^{51}Cr-EDTA. Because of their hydrophilicity, permeability probes do not diffuse across the bi-lipid enterocyte membrane to any appreciable extent but permeate through the aqueous paracellular spaces (12, 15–17) (Fig. 1). As the permeability markers permeate through the aqueous pathways, their trans-epithelial flux rates are strongly dependent on convection or solvent drag, such that increasing intestinal water absorption causes an increase in intestinal flux rate of the permeability markers, and water secretory states cause a decrease in flux rate of the permeability markers (18–21). Consistent with their dependence on solvent drag, luminal introduction of drugs that increase intestinal water absorption causes an increase in intestinal epithelial permeation of the permeability probes (19, 22). Thus, factors that influence intestinal water absorption can significantly alter overall intestinal permeability.

The major cellular structures that restrict permeation through the epithelial paracellular pathways are the tight junctions (Fig. 1) (17, 23). The tight junctions act as gates to the permeation pathways (17, 24). The "tightness" of epithelial paracellular pathways is directly related to the density of tight junctional strands. For example, epithelial types that have a high number of tight junctional strands (e.g., gall bladder epithelium) have low epithelial permeability (i.e., high paracellular barrier function), and epithelial types that have a low number of tight junctional strands (e.g., intestinal epithelia) have relatively high epithelial permeability (i.e., low paracellular barrier function) (17, 23–25). As the small intestine is comprised of two distinctly different epithelia, villus and crypt, the epithelial permeability of these regions differ (12, 25). The epithelial cells lining the villi have a higher number of intercellular tight junctional strands and are more restrictive to permeability markers (12, 25). The epithelial cells lining the crypts have fewer intercellular tight junctional strands and are "leakier" to permeability markers. These differences are likely to have significant impact on the selective permeability of these regions.

The importance of tight junctions in the regulation of paracellular permeability is further evidenced by the increases in epithelial permeability following disruption of tight junctions. It had been demonstrated that various factors including ethanol (26), clostridial toxin A (27), activators of the Na-glucose transporter (28), removal of extracellular Ca^{++} (29), and γ-interferon (30) disrupt tight junctions and cause an increase in epithelial permeability. The increase in epithelial permeability directly correlates with the disruption of tight junctions (17, 23) and subsequent opening of the paracellular spaces. Previously, it was demonstrated that addition of cytochalasin B or D, or ethanol caused a disruption of tight junctions, a rapid drop in epithelial resistance, and an increase in paracellular permeability of intestinal epithelia (31–33). Upon removal of these agents from the incubation solution, there is a rapid re-tightening of the paracellular pathways and reassembly of the tight junctions (31, 32). The opening and reclosure of the tight junctional pathways did not depend on translation or transcription but required metabolic energy, indicating that the assembly and disassembly of tight junctions were not due to new protein synthesis but reassembly of

preexisting components. Additional evidence suggests that the opening and closing of tight junctional strands were mediated by actin and myosin filaments (31–33). The disturbance of these peri-junctional cytoskeletal elements (Fig. 1) were associated with disruption of tight junctions and visual opening of the paracellular spaces.

Intestinal Permeability Alteration in Crohn's Disease

In 1963, Grybosky *et al.* (34) made the observation that the rate of intestinal absorption of lactulose and sucrose was increased in Crohn's patients. It wasn't until two decades later that other investigators confirmed this earlier observation. In the early 1980s, a number of other investigators (6, 7) also reported finding increased intestinal permeability in Crohn's patients (Table I). Cobden *et al.* (53) found Crohn's patients to have an increased intestinal permeability to cellobiose. Ukabam *et al.* (6) reported significant increases in small intestinal permeability to lactulose in patients with either small intestinal or colonic involvement of Crohn's disease. Interestingly, patients with ulcerative colitis did not have significant increase in intestinal permeability to lactulose (Table II). Bjarnason *et al.* (7) also found Crohn's patients to have significant increases in intestinal permeability to ^{51}Cr-EDTA. They also did not find ulcerative colitis patients to have increase in intestinal permeability to ^{51}Cr-EDTA. A number of other investigators (8–11) have confirmed the finding of increased intestinal permeability in Crohn's patients (Table I). In contrast to Crohn's patients, ulcerative colitis patients do not have an alteration of intestinal permeability (6, 7) (Table II), indicating that the two diseases are distinctly different in this regard.

The permeability probes most commonly used to assess intestinal permeability in Crohn's patients are lactulose, ^{51}Cr-EDTA, PEG 400, and mannitol. PEG 400 is a polydispersed polymer of ethylene glycol subunits having a cross-sectional diameter of 5.3 Å and an average molecular weight of 400 g/mol (54). Mannitol is a monosaccharide with a cross-sectional diameter of 6.7 Å and a molecular weight of 343 g/mol (54). Lactulose is a disaccharide of galactose and fructose having a cross-sectional diameter of 9.5 Å and a molecular weight of 343 g/mol, and ^{51}Cr-EDTA is a metal chelating agent having a cross-sectional diameter of 11.5 Å and a molecular weight of 343 g/mol (54). The urinary recovery rate of the permeability probes with larger cross-sectional diameter-lactulose and ^{51}Cr-EDTA are in the range of 0.2%–0.7% per 6 hr after ingestion, whereas the smaller probes mannitol and PEG 400 are in the range of 10%–30% per 6 hr (6, 11, 54). Previous studies have demonstrated a linear correlation between the cross-sectional

Table I. Summary of Published Intestinal Permeability Studies of Patients with Crohn's Disease

Authors	Permeability markers				
	PEG 400	Mannitol	Lactulose	^{51}Cr-EDTA	L/M ratio
Gryboski *et al.* 1973 (34)			↑		
Ukabam *et al.* 1983 (6)		↓	↑		↑
Bjarnason *et al.* 1983 (7)				↑	
Magnusson *et al.* 1983 (35)	↓				
Peled *et al.* 1985 (36)				↑	
Hollander *et al.* 1985 (8)	↑				
Olaison *et al.* 1987 (37)	↓				
Sanderson *et al.* 1987 (38)			↑		
Jenkins *et al.* 1988 (39)				↑	
Andre *et al.* 1988 (40)		↓	↑		↑
Olaison *et al.* 1988 (41)	↑				
Ainsworth *et al.* 1989 (42)				↑	
Katz *et al.* 1989 (10)		—	↑		↑
Pironi *et al.* 1990 (43)				↑	
Resnick *et al.* 1990 (44)				↑	
Howden *et al.* 1991 (45)		—	↑*	↑	↑*
Isserman *et al.* 1992 (46)				↑	
Adenis *et al.* 1992 (47)				↑	
Ruttenberg *et al.* 1992 (48)	—				
Teahon *et al.* 1992 (9)	—		↑	↑	
Kuiper *et al.* 1993 (49)		—	↑		↑
Wyatt *et al.* 1993 (50)		—	↑		↑
May *et al.* 1993 (51)		—	↑		↑
Munkholm *et al.* 1994 (52)	—	—	—		—

Note. Published intestinal permeability studies utilizing permeability markers PEG 400, mannitol, lactulose or ^{51}Cr-EDTA were included. ↑, a significant increase in intestinal permeability compared to normal controls; —, no significant difference from controls; ↑*, increasing trend in intestinal permeability which did not reach statistical significance.

Table II. Summary of Published Intestinal Permeability Studies in Patients with Ulcerative Colitis

Authors	Permeability markers				
	PEG 400	Mannitol	Lactulose	^{51}Cr-EDTA	L/M ratio
Ukabam *et al.* 1983 (6)		—	—		—
Bjarnason *et al.* 1983 (7)				—	
Peled *et al.* 1985 (36)				—	
Jenkins *et al.* 1988 (39)				↑	
Resnick *et al.* 1990 (44)				—	
Howden *et al.* 1991 (45)				—	
Isserman *et al.* 1992 (46)				↑	
Munkholm *et al.* 1994 (52)	—	—	—	—	—

Note. Published intestinal permeability studies utilizing permeability markers PEG 400, mannitol, lactulose, or ^{51}Cr-EDTA were incubated. ↑, a significant increase in intestinal permeability compared to normal controls; —, no significant difference from controls.

diameter of the permeability probe and its intestinal permeation rate (54). As the cross-sectional diameter varies greatly between molecules with similar molecular weight, the cross-sectional diameter correlated better with the relative epithelial permeation rates of the probes than the molecular weight (55).

Of interest are the selective differences in intestinal permeability to different sized permeability markers in patients with Crohn's disease. Crohn's patients have been consistently shown to have increased intestinal permeability to the larger probes lactulose and ^{51}Cr-EDTA (5–7, 9–11) (Table I). On the other hand, Crohn's disease appears to have little effect on the smaller probes (5, 10, 52, 56, 57). Although earlier studies (before 1990) were conflicting as to whether intestinal permeability to PEG 400 was altered in Crohn's disease, more recent studies indicate that PEG 400 permeation rate is unchanged (48, 52). This difference is likely to reflect the advancement in detection methods.

The reasons for the probe size–related differences in intestinal permeability in Crohn's disease are unclear. One possible explanation relates to the relative "pore" size of the intestinal epithelium (12, 25) (Fig. 2). As mentioned above, smaller probes like mannitol readily permeate, while larger probes like lactulose only minimally penetrate across the healthy intestinal epithelium. In contrast, patients with Crohn's disease have a defective paracellular barrier either as a primary defect or secondary to intestinal inflammation allowing paracellular penetration by larger probes. In diseased states, intestinal inflammation can cause extensive damage to the mucosal surface and lead to a decrease in mucosal absorptive surface. This inflammatory injury to the epithelial surface also produces large epithelial "pores" either as a result of direct cytotoxicity or damage to the paracellular barrier. The decrease in overall absorptive surface area could have a significant negative impact on absorption of smaller probes like mannitol, whereas absorption of larger probes like lactulose would only be minimally affected. On the other hand, the increase in the size of the epithelial "pores" or permeation pathways could significantly enhance lactulose permeation. The permeation rate of the smaller probes would also be increased, but to a much smaller extent. On balance, the permeability changes caused by the intestinal inflammation of Crohn's disease would be likely to affect larger probes more than the smaller probes.

A permeability index which has been widely used in intestinal permeability studies is the lactulose/mannitol (or large probe/small probe) ratio. The presumption is that the mannitol (small probe) absorption rate indirectly reflects the intestinal absorptive capacity and by using mannitol absorption rate as a denominator, the relative permeation rate of a given probe (i.e., lactulose) per absorptive capacity (as determined by mannitol) may be calculated. Whether such assumptions are valid or useful remains to be further investigated, but studies that have utilized lactulose/mannitol absorption ratios have consistently shown this ratio to be elevated in Crohn's patients as a group (5, 10, 16, 40) (Table I).

Crohn's Disease as a Primary Disorder of Intestinal Permeability

While it is well established that Crohn's patients as a group have an increase in intestinal permeability, the clinical significance of this finding remains to be elucidated. One possibility is that the increase in intestinal permeability is an epiphenomenon of intestinal inflammation and, thus, is a resultant consequence of the intestinal inflammation of Crohn's disease. A second, more intriguing possibility is that the increase in intestinal permeability reflects a genetic disorder of intestinal epithelial barrier function of Crohn's disease and that the defective intestinal epithelial barrier function is an important etiologic factor leading to Crohn's disease. Yet another possibility is that the increase in intestinal permeability, regardless of the etiology, plays a secondary permissive role in the exacerbation or prolongation of intestinal inflammation in Crohn's disease by allowing increased antigenic penetrations.

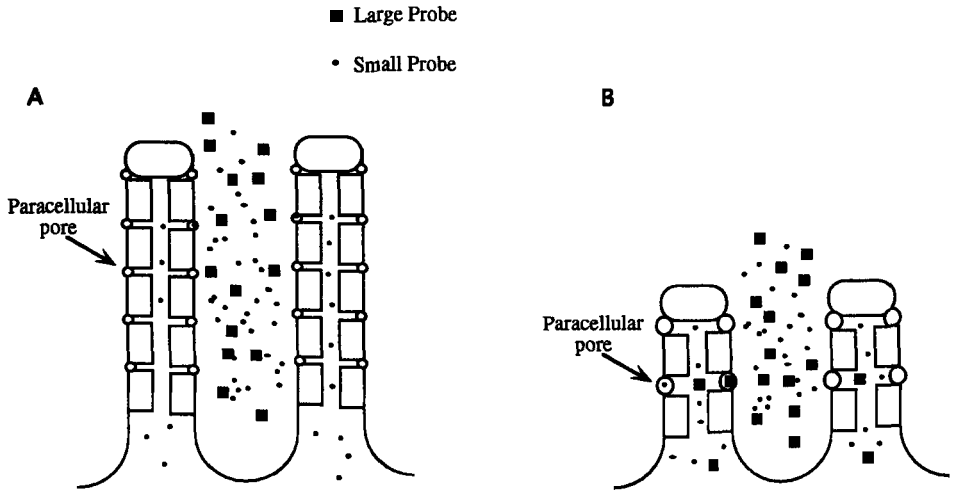

Figure 2. Proposed model of alteration of paracellular pathways or "pores" in Crohn's disease. In normal healthy intestine (A), absorptive surface is relatively large (villus adaptation), and the paracellular opening or pores are "moderate" in size. The smaller probes (e.g., mannitol and PEG 400) readily permeate (urinary recovery rate of 10%–30%/6 hr), whereas larger probes (e.g., lactulose) are mostly excluded (urinary recovery rate of 0.2–0.4%/6 hr) from permeation across the healthy intestinal epithelia. In diseased states (B), the overall surface area of absorptive surface may be diminished, but the paracellular pores are larger either as a primary defect or secondary to intestinal inflammation. The enlarged paracellular pores allow penetration of larger probes. The permeation of smaller probes are also increased but to a much smaller extent (The decrease in absorptive surface area negate the increase in permeation of smaller probes).

In 1986, Hollander *et al.* (8) performed a study to investigate the possibility that intestinal permeability disorder was an etiologic factor of Crohn's disease. They reasoned that since relatives of Crohn's patients have a genetic predisposition for Crohn's disease (2–4), if intestinal permeability disorder was an etiologic factor of Crohn's disease, this subpopulation may have clinically silent permeability disorder. In this innovative study, Hollander *et al.* (8) found that clinically healthy relatives of Crohn's patients had a significant increase in intestinal permeability to PEG 400 and concluded that the "intestinal defect in ability to exclude larger sized molecules is not secondary to clinically recognized intestinal inflammation but is a primary defect that may be an etiologic factor in this disease." Recently, other investigators have also found healthy Crohn's relatives to have increased intestinal permeability to lactulose (51, 57). It should be noted that some studies have found a nonsignificant trend toward an increase but could not demonstrate a statistically significant difference between the healthy relatives and the controls (Table III). It was suggested that the inability of these studies to reach statistical significance was due to the small number of relatives and controls studied. Since epidemiological studies indicate that about 10% of Crohn's relatives develop Crohn's disease, only a small proportion (about 10%) of the relatives would be expected to have disordered intestinal permeability (51). Therefore, it had been suggested that unless a large number of relatives and controls are studied, the probability of a type 1 error (i.e., null hypothesis is true for the population but the sample size too small to support the hypothesis) would be high. Indeed, on closer inspection, 10% or greater of relatives had abnormal intestinal permeability in majority of the studies (Table III).

It has been recognized for some time that Crohn's patients have increased systemic penetration by foreign antigens. Various investigators have noted the presence of pathogenic bacteria in the mesenteric lymph nodes, bacterial antibodies, serum antibodies to bovine serum albumin, and circulating immune complexes in Crohn's patients (58–63). A recent study by Yacyshyn and Meddings demonstrated a correlation between an increase in intestinal permeability and immunologic activation in the healthy relatives (57). A transition from CD45RA to CD45RO occurs in B cells following antigenic stimulation. This change in isoform expression of the common leukocyte antigen CD45RA has been used by some investigators as an indication of increased antigenic exposure.Crohn's patients have increased expression of CD45RO in their B cells (64). In their provocative report, Yacyshyn and Meddings demonstrated a relationship between an increase in intestinal permeability and an increased expression of CD45RO in B cells (57). All controls and relatives with normal intestinal permeability had normal levels of CD45RO expression in B cells. They found that 8 of 10 Crohn's patients with increased intestinal permeability had elevated CD45RO expression in B cells. Interestingly, all clinically healthy relatives with increased intestinal permeability had increased expression of CD45RO in their B cells. Thus, increased expression of CD45RO in B cells was found in

Table III. Summary of Published Intestinal Permeability Studies in Healthy First-Degree Relatives of Crohn's Patients

Authors	Permeability markers				
	PEG 400	Mannitol	Lactulose	^{51}Cr-EDTA	L/M ratio
Hollander *et al.* 1985 (8)	↑				
Ainsworth *et al.* 1989 (42)				—	
Katz *et al.* 1989 (10)		—	↑*		↑*
Ruttenberg *et al.* 1992 (48)	—				
Teahon *et al.* 1992 (9)	—		↑*	↑*	
May *et al.* 1993 (51)		—	↑		↑
Munkholm *et al.* 1994 (52)	—	—	↑*		↑
Yachyshyn *et al.* 1995 (57)					↑

Note. Published intestinal permeability studies utilizing permeability markers PEG 400, mannitol, or ^{51}Cr-EDTA were incubated. ↑, a significant increase in intestinal permeability compared to normal controls; —, no significant difference from controls; ↑*, an increase in intestinal permeability in 10% or greater of Crohn's relatives compared with controls.

all of the relatives with increased intestinal permeability and in none of the relatives with normal intestinal permeability. These findings suggested that intestinal permeability disorder was responsible for the increased immunologic expression of CD45RO in the B cells.

In addition to having increased baseline intestinal permeability, it was recently demonstrated that the healthy relatives of Crohn's patients also have increased susceptibility to an intestinal "permeability stressing" agent (65, 66). It has been previously shown that small doses of NSAIDs such as aspirin cause an acute increase in intestinal permeability (67). Pironi *et al.* and Hilsden *et al.* found that Crohn's relatives had greater increase in intestinal permeability following oral ingestion of aspirin (325 mg) compared with the controls (65, 66). These findings suggested that the healthy relatives (a subgroup genetically predisposed to Crohn's disease) may have an exaggerated response to a permeability stressing agent.

Other evidence that support a role of intestinal permeability disorder as a causative factor of intestinal inflammation includes studies in NSAID-associated enteropathy. Chronic and acute NSAID therapy results in a high prevalence of intestinal inflammation and ulcers (67, 68). Allison *et al.* (68) demonstrated that 10% of autopsied patients who used NSAIDs, including occasional users, had small intestinal ulcerations. It is well established that NSAIDs cause an increase in intestinal permeability (67, 69, 70). NSAID-induced increase in intestinal permeability is present shortly following oral intake of NSAIDs and precedes any inflammatory changes (69–71), indicating that the intestinal permeability increases are not caused by the inflammatory process. In this regard, neither germ-free nor fasted animals develop carrageenan-induced colitis (72). These findings indicate that bacteria- or diet-associated luminal antigenic load are a required factor for NSAID-associated intestinal inflammation. Based on these findings, it was concluded that (i) NSAIDs cause an increase in intestinal permeability; (ii) the NSAID-induced increase in intestinal permeability results in an increased permeation of luminal antigens; and (iii) increased antigenic penetration results in intestinal inflammation and injury (70, 71).

Based on the above relationship between NSAIDs and increased intestinal permeability, it follows that NSAIDs could induce exacerbation of Crohn's disease by enhancing intestinal permeability. Clinically, NSAID usage has been established as an important exacerbating factor of Crohn's disease (73, 74). It is plausible to assume that NSAID-induced exacerbation of Crohn's disease could be due to NSAID-induced increase in intestinal permeability.

In addition to the functional changes in intestinal epithelial barrier function, morphologic abnormalities of tight junctional complexes have also been demonstrated in patients with Crohn's disease (75, 76). Crohn's patients have been found to have abnormalities of intestinal epithelial tight junctions in normal appearing regions of small intestine. Examination of tight junctions in the normal appearing regions revealed irregularly distributed, fragmented, and aberrant tight junctional strands. Consistent with these findings, Hawker *et al.* (77) have also found that the intestinal tissue in "uninvolved" segments in Crohn's patients has decreased epithelial barrier function. Additionally, relapse of Crohn's disease has been shown to be associated with disruption of intercellular tight junctions. The importance of intact intestinal epithelial barrier function is further supported by the observation that relapse of Crohn's disease is often preceded by conditions that affect intestinal epithelial barrier function, such as ethanol binges, acute gastroenteritis, and NSAID usage (26, 73, 78). The importance of increased mucosal antigenic load in exacerbation or prolongation of active Crohn's disease is also suggested by improvement of the disease activity following treatment with elemental diet, antibiotics, and bowel rest (79–84). These therapeutic measures decrease the

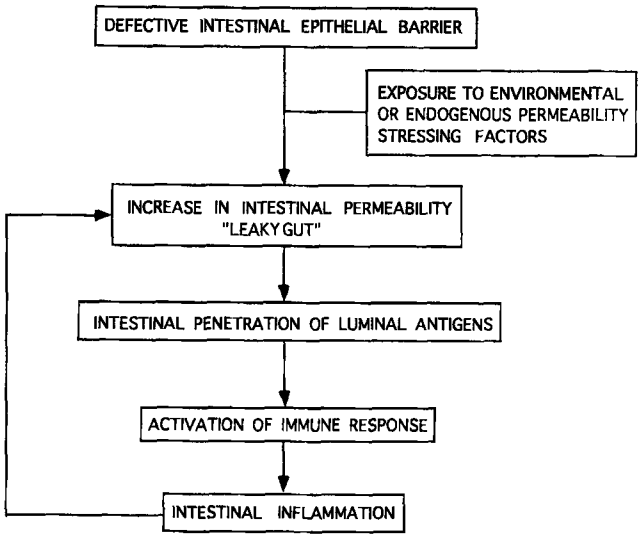

Figure 3. Proposed model of "leaky gut" hypothesis. The proposed primary defect of intestinal epithelial barrier function (increased paracellular permeability) allows increased mucosal penetration by toxic luminal antigens (including infectious agents). The antigenic penetration activates immunologic and inflammatory responses, which produce epithelial injury and further damage of the intestinal epithelial barrier function. Exposure to environmental or endogenous factors that increase intestinal permeability, such as NSAIDs, may act as a trigger for the onset or exacerbation of Crohn's disease in a susceptible population.

luminal antigenic load and decrease the mucosal antigenic penetration and intestinal inflammation, and allow repair of the "intestinal barrier" to occur.

Leaky Gut Hypothesis

Based on the above evidence, we advanced the hypothesis (85) that Crohn's disease is a primary disorder of intestinal permeability caused by a primary genetic defect in intestinal epithelial barrier function resulting in a "leaky" gut (Fig. 3). The defective intestinal epithelial barrier allows intestinal epithelial penetration of normally excluded luminal antigens including food additives, food by-products, and infectious agents and their by-products. Intestinal penetration of luminal antigens elicits an immune response culminating in intestinal inflammation and systemic circulation of toxic antigens. Various environmental and endogenous factors that abnormally increase intestinal permeability could be the trigger for the onset and the recurrent exacerbation of Crohn's disease.

Whether the defective intestinal epithelial barrier function is truly a primary etiologic factor of Crohn's disease remains to be further defined. More investigations are needed to better define the role of intestinal epithelial barrier dysfunction in Crohn's disease. An important study would be to conduct a long-term evaluation of intestinal permeability in a large number of healthy relatives and to follow those relatives having disordered intestinal permeability intermittently to determine whether the permeability disorder persists and whether these patients eventually develop Crohn's disease. Periodic evaluation of intestinal epithelial ultrastructure for alteration in tight junctions and cellular structures, and of intestinal tissue for evidence of increased antigenic penetration and immune response will also be important. Prospectively following these relatives for possible development of Crohn's disease will be crucial in establishing a cause-and-effect relationship.

Other Potential Clinical Utility of Intestinal Permeability Studies

In addition to the importance of intestinal permeability as a possible etiologic or pathogenic factor of Crohn's disease (8–11), recent clinical studies have suggested a potential clinical utility of its measurement in following clinical activity of the disease and therapeutic response, and in predicting early relapses (56, 79, 86, 87). A relationship between the level of increase in intestinal permeability and early relapse of Crohn's patients (86) has been shown. Wyatt *et al.* (56) showed that there is a direct correlation between improvement in Crohn's disease activity following therapy and a decrease in intestinal permeability to lactulose. Furthermore, persistently elevated intestinal permeability in successfully treated patients was associated with early relapse of the disease. Ito *et al.* (87) found that the normalization of intestinal permeability correlated with a therapeutic response to an elemental diet. Inca *et al.* (86) also demonstrated a significant relationship between an increase in intestinal permeability and the level of activity of Crohn's disease as defined by biochemical, endoscopic, and clinical criteria. Thus, the severity of Crohn's disease activity may be determined by intestinal permeability measurements.

Summary

Intestinal permeability is increased in Crohn's disease. Whether the alteration in intestinal permeability represents a primary genetically predetermined trait of Crohn's disease or a secondary response to intestinal inflammation and injury is unclear. More detailed studies are needed to resolve this issue. A large body of evidence has been presented above that supports the existence of a primary defect of intestinal epithelial barrier dysfunction in Crohn's disease. It appears likely that whether it is a primary or secondary process, the disruption of intestinal barrier function (alteration in intestinal permeability) promotes intestinal inflammation by allowing intestinal penetration of luminal antigens and activating immune response. In this regard, decreasing intestinal antigenic load has a therapeutic effect on Crohn's disease. There is an ongoing contro-

versy as to whether Crohn's disease is an infectious disease or a primary disorder of immune dysfunction. The leaky gut hypothesis would suggest that both are important: leaky gut allows mucosal penetration by normally excluded antigenic and infectious agents, which in turn trigger immunologic and inflammatory response.

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