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Intestinal permeability and the prediction of relapse in Crohn's disease

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To see whether intestinal permeability (IP) predicted relapse in Crohn's disease, we measured IP in 72 patients with quiescent Crohn's disease using the lactulose-mannitol test. The permeability index (lactulose/mannitol) was significantly higher in patients than in controls (0·046 [SEM 0·005] *vs* 0·018 [SEM 0·002], respectively). Patients were followed for 1 year after the test. 26 of the 37 patients with raised permeability, but only 6 of the 35 with normal permeability relapsed within 1 year after the test ($p<0·001$). The sensitivity of the permeability test as a predictor for relapse was 81%. A significant correlation was found between the value of the permeability index and the probability of relapse ($p<0·01$). These results show that increases in intestinal permeability precede clinical relapses in Crohn's disease and so are an indicator of subclinical disease. The measurement of intestinal permeability may lead to a better understanding of the pathogenesis of Crohn's disease.

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Introduction

It is not possible accurately to predict the clinical course of Crohn's disease: about 60% of patients relapse within the first year after successful treatment of an acute episode;[1] the rest may stay in remission for several years. Relapses cannot be predicted, but a way of doing so would help select patients for maintenance treatment and spare patients who do not require such treatment the side-effects of the drugs used. Increased intestinal permeability (IP) is a consistent finding in patients with active Crohn's diease.[2,3] We investigated whether this increase precedes relapse of Crohn's disease, and whether measurement of IP could predict relapses.

Patients and methods

Patients

72 patients with quiescent Crohn's disease (diagnosed by generally accepted clinical, radiological, endoscopic, and histological criteria[1]) who attended the outpatient clinic participated in this study (table I). Crohn's disease had been in remission (Crohn's disease activity index [CDAI] below 150)[4] in all patients for a minimum of 6 months. None received maintenance treatment. 30 healthy age-matched volunteers served as controls. Informed consent was obtained from all patients.

TABLE I—CLINICAL FEATURES OF PATIENTS

—	Relapsed <1 yr	Not relapsed at 1 yr	Total
Sex			
Male	12 (16)	15 (21)	27
Female	20 (28)	25 (35)	45
Age	34 [2]	39 [2]	37 [2]
Intestinal resection			
Yes	7 (9)	15 (21)	22
No	25 (35)	25 (35)	50
Site of disease			
Small bowel	10 (14)	16 (22)	26
Small bowel and colon	14 (20)	11 (15)	25
Colon	7 (9)	14 (20)	21
CDAI	75 [7]	50 [7]	61 [5]
PI	0·074 [0·010]	0·024 [0·002]	0·046 [0·005]

No of patients, (%), [SE]; CDAI = Crohn's disease activity index; PI = permeability index.

Intestinal permeability test

After an overnight fast, each subject provided a specimen of urine (to be checked for possible endogenous mannitol production), before drinking a solution containing 5 g mannitol, 10 g lactulose, 22 g glucose, and water to 150 ml (osmolarity $\simeq$ 1300 mOsmol/L). Urine was collected for the next 5 h, with sodium azide as preservative. The subjects went without food during the test but were allowed to drink water after the first 2 h. Urine was stored at −80°C.

Patient follow-up

After the test, patients were seen regularly for 1 year in the outpatient clinic, and asked to return if they become ill before their next appointment. CDAI > 150 was considered as a relapse.

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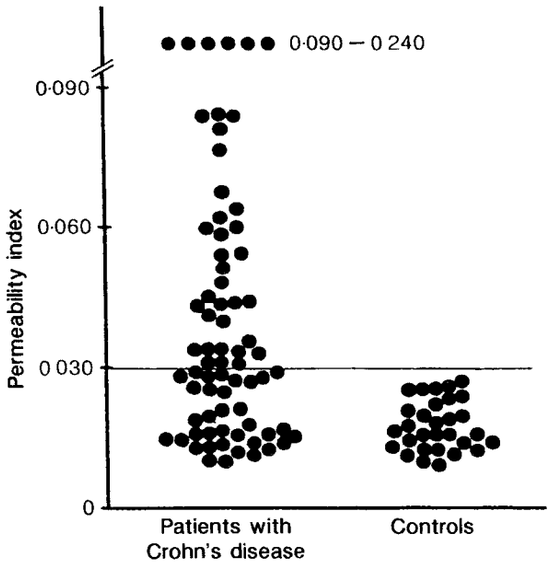

Fig 1—Permeability index (PI) in patients with Crohn's disease (n = 72) and controls (n = 30).

Biochemical analysis

Protein was removed from urine with sulfosalicilic acid; the urine was centrifuged, the supernatant treated with Amberlite MB-3 resin in the acetate form, swirled for 10 min, and then centrifuged. Lactulose and mannitol were measured in the supernatant by high performance liquid chromatography; lactulose by the method of D'Amboise et al[5] with turanose as internal standard, mannitol by the method of Delahunty and Hollander[6] with dulcin as internal standard. Results were expressed as the percent recovery of the ingested dose of lactulose (L) and mannitol (M) in urine over 5 h. The permeability index (PI) was the ratio L/M.

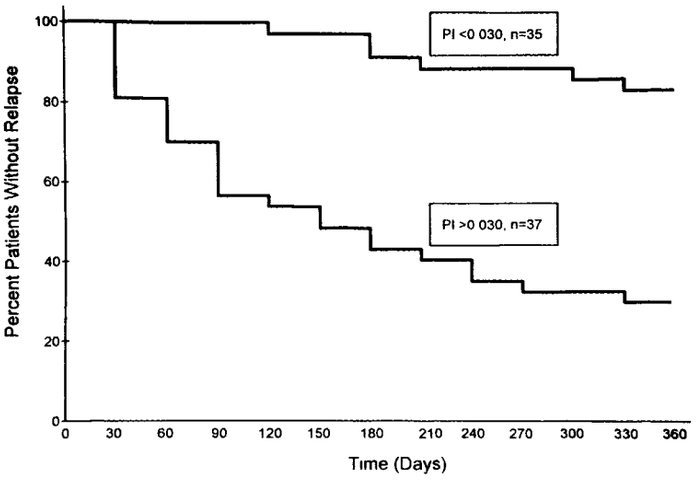

Fig 2—Percentage of patients without a relapse over 1 year.

PI = permeability index.

Statistics

Data are expressed as means (SEM). Proportions of patients without relapse at various intervals were estimated by the Kaplan-Meier method;[7] the curves were compared by the Mantel-Cox test.[8] A logistic regression[9] was calculated to estimate the probability of a relapse within 1 year depending on the different values of PI. A Hosmer-Lemeshow goodness-of-fit test[10] was used to test how well the logistic regression fits the actual data. Sensitivity, specificity, and accuracy were calculated[11] by classifying PI in two groups: PI < 0·03 and PI > 0·03. Comparison of the PI test in the different groups was done by Chi-square or Wilcoxon tests.

TABLE II—CUMULATIVE RELAPSES ACCORDING TO INITIAL PERMEABILITY INDEX (PI)

Days	Cumulative no of relapses (%)		
	Normal PI (PI < 0·030, n = 35)	Raised PI (PI > 0·030, n = 37)	Total (n = 72)
0	0 (0)	0 (0)	0
90	0 (0)	16 (43)	16
180	3 (9)	21 (56)	24
270	4 (11)	25 (67)	29
360	6 (17)	26 (70)	32

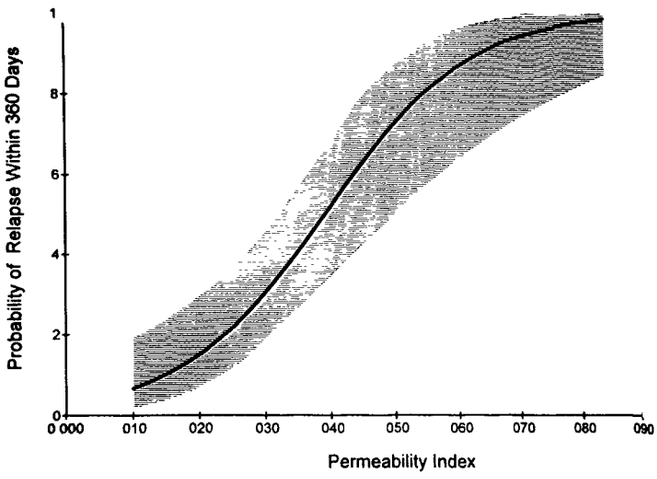

Fig 3—Probability of a relapse within 1 year.

The shaded area represents the 95% confidence interval.

Results

In 30 healthy volunteers, excretion of mannitol over 5 h was about 12% of the ingested dose, about 50 times higher than the excretion of lactulose: 12·71 ± 1·18% mannitol and 0·22 ± 0·02% lactulose. Variation within the group was low (fig 1). A PI of up to 0·030—the mean of the PI of controls plus 2 SD—was judged the upper limit of normal. In patients with Crohn's disease, permeability for mannitol was similar to that of healthy volunteers (11·51 ± 0·67%). Permeability for lactulose was higher (0·50 [0·07]%, $p < 0·01$) resulting in a higher mean PI (0·046 [0·005], $p < 0·0001$). PI varied considerably within the patient group (0·236–0·010, fig 1). 35 of the 72 patients had a normal PI. 32 (44%) relapsed within 1 year.

To test the predictive vaue of PI, the results from patients were divided into groups with normal (< 0·030) and raised (> 0·030) PI. Significantly more patients with raised PI had relapses than those with normal PI ($p < 0·001$, Mantel-Cox test, fig 2). The cumulative number who relapsed is shown in table II. The sensitivity of the PI as predictor of relapse was 81%; the specificity was 73%. Correct prediction of the course of the disease for 1 year by a single measurement of intestinal permeability could be made in 76%. We considered whether the probability of a relapse increased with PI. A logistic regression was calculated and a highly significant correlation was found (fig 3). The regression parameters representing the intercept and the effect of PI, were estimated as $\beta_0 = 3·54$ and $\beta_1 = -90·63$, both significant at $p < 0·0001$ (deviance = 39·53 with df = 1). To test for a lack of fit of the model, the Hosmer-Lemeshow goodness-of-fit test was used, which indicated no significant deviation from the real data ($p < 0·985$). The Mantel-Cox and Chi-square test did not show a difference in the probability of relapse between patients with disease at different sites, nor between those with and without bowel resections.

Discussion

Provided an increase in PI represents a deterioration in intestinal function, our results show for the first time that in

Crohn's disease, PI predicted relapse in 76% of patients, and the probability of relapse increased with increasing PI. Several attempts have been made to predict the course of Crohn's disease. Concentrations of acute phase proteins in the plasma have been suggested,[12] but in only one study was a reliable predictive index established by combining the results of several laboratory tests.[13] The PI test differs from other indices because it is not based on concentrations of proteins in plasma, but rather represents functional changes in the intestinal mucosa. The test may be useful to assess the effects of treatment and to follow the course of the disease. Our results also suggest that increases in IP may occur early in relapses of Crohn's disease, or even initiate them: increased permeability may lead to the absorption of endotoxin and lipopolysaccharides from the lumen. Both these substances are potent stimulators of acute-phase reactions and liberation of interleukin-6, which has been shown to be an important mediator of inflammation in Crohn's disease.[14] What causes the increase in permeability, however, is unknown.

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SHORT REPORT

Colorectal cancer in patients with X-linked agammaglobulinaemia

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Primary immunodeficiency disorders can predispose to certain malignancies but hitherto no such relation has been established for X-linked agammaglobulinaemia (XLA). We have diagnosed rapidly progressive colorectal cancer in 3 unrelated young adults with XLA. We could find no explanation for the tumours. Since the calculated incidence of rectosigmoid cancer is increased 30-fold in patients with XLA, we advise the screening of these individuals, and perhaps people with other agammaglobulinaemias, for colorectal cancer.

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Gastrointestinal ailments are common in patients with primary agammaglobulinaemia.[1] Intestinal infections with *Giardia lamblia*, *Campylobacter jejuni*, and *Salmonella* spp are frequent.[1,2] Giardiasis may lead to malabsorption, while *C jejuni* infection may result in recurrent fever.[3,4] In late-onset agammaglobulinaemia (LOA), lymphonodular hyperplasia is common; the aetiology and pathogenesis of this abnormality are not known. Antral gastritis with abnormal gastrin production capacity is also a common finding in people with LOA,[5] whose risk of developing gastric cancer is some 47-fold greater than that of the normal population.[6] Malignant lymphoma is also 30 times more common in people with LOA.[6] An increased risk of developing cancer is less well established for the other common types of agammaglobulinaemia (X-linked [XLA] and early-onset agammaglobulinaemia).[1,6–9] Here we describe 3 unrelated patients with XLA who developed colorectal cancer at an early age.

Patient A was born in 1959 and agammaglobulinaemia was diagnosed at an early age. Our diagnosis of XLA was based on family history, absence of B lymphocytes, and very low serum concentrations of immunoglobulins (IgG 0·6 g/L, IgA and IgM not detectable). 3 brothers with the same disorder had died of pulmonary complications, and an affected male cousin survives. There was no family history of colorectal or other cancers. The patient did well on intramuscular gammaglobulin until October, 1984, when he complained of abdominal distension, cramps, and diarrhoea. During the next few months he lost 16 kg and he was cachectic when admitted to hospital in March, 1985. He was pale with a pulse rate of 100/min, but there were no other abnormalities on physical examination. He had a haemoglobin concentration of 6·9 mmol/L, microcytic red blood cells, serum iron concentration of 1 mmol/L, and thrombocytosis (760×10^9/L). Serum albumin and IgG were 30 g/L and 1·3 g/L, respectively. A jejunal biopsy revealed complete villus atrophy, but no *G lamblia* infection. 2 weeks after admission an acute abdomen with hyperperistalsis developed. An abnormal mass was palpated on rectal examination. Subphrenic gas was seen on a chest radiograph. At laparotomy, a nonresectable rectal carcinoma was found together with a perforation and carcinomatous peritonitis. An adenocarcinoma was