Faecal diversion for Crohn's colitis: a model to study the role of the faecal stream in the inflammatory process

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Abstract
The high incidence of clinical remission after faecal diversion for Crohn's colitis suggests the faecal stream may play a part in the inflammatory mechanism. The effect of faecal diversion (n=22) and restoration of intestinal continuity (n=10) was assessed in patients with Crohn's colitis and compared with controls. Faecal diversion produced significant improvement in the disease activity index mean (SEM) (before 176 (9); after 114 (9), $p<0.01$) and serum albumin concentrations (before 33 (3.0); after 38 (3.0), $p<0.05$) in all patients with Crohn's colitis. The crypt cell production rate (CCPR) was maintained after faecal diversion for Crohn's colitis but fell in the control group (before=3.6 (0.8)), at two (1.4 (0.4), $p<0.02$), and six weeks (1.6 (0.4), $p<0.05$). Mucosal glucosamine synthetase activity, reflecting glycoprotein synthesis, was significantly lower in patients with Crohn's colitis (analysis of variance $p<0.05$) after diversion but was maintained in the control group. Restoration of intestinal continuity failed to produce reciprocal changes. The sustained cellular proliferation and fall in glycoprotein synthesis in Crohn's colitis after faecal diversion may represent the end of an exaggerated protective response and regenerative hyperplasia after exclusion of the faecal stream. This study suggests the faecal stream may participate in the inflammatory process in Crohn's colitis. The underlying mechanism is unknown.
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The management of Crohn's colitis by external faecal diversion provides not only a therapeutic alternative to resection in selected cases¹⁻⁴ but also a unique model to evaluate the role of the faecal stream in the pathogenesis of Crohn's disease.

There are both clinical and laboratory data to implicate a constituent of the faecal stream in perpetuating colonic Crohn's disease. The use of elemental diets has been associated with disease remission.^{5,6} Simple faecal diversion is also associated with symptomatic relief^{2-4,7-10} with a high incidence of disease relapse on restoration of intestinal continuity^{1,2,7,9-11}. A luminal constituent may also be implicated from the finding that improvement in perianal disease may be induced by metronidazole¹²⁻¹⁵ and the presence of an exaggerated proliferative response by tissue lymphocytes to gut related bacterial antigens.¹⁶

The faecal stream has also been implicated in small bowel disease recurrence. Rutgeerts *et al*¹⁷ described five patients having ileocolonic resection with a proximal diverting ileostomy who only developed recurrence in the neoterminal ileum after restoration of intestinal continuity. The authors concluded that recurrence is faecal stream dependant with the reflux of colonic contents probably important. Metronidazole has also been reported to reduce the incidence of endoscopic recurrence after surgery and significantly reduce its severity.¹⁸

Only one previous study to evaluate the role of the faecal stream in Crohn's colitis has been reported.^{19,20} The reintroduction of crude ileostomy effluent into the defunctioned colon of patients with Crohn's colitis treated by a split ileostomy produced a clinical response in nine of 15 patients studied, associated with a significant lymphopaenia and increase in erythrocyte sedimentation rate, while the reintroduction of a sterile ultrafiltrate failed to produce any objective change.

The aim of this study was to assess the effect of faecal diversion and restoration of intestinal continuity on colonic mucosa and peripheral blood activity indices in patients with Crohn's colitis compared with a control group with macroscopically normal colonic mucosa. The influence of disease activity on peripheral blood indices was assessed by measurement of a modified disease activity index, haematological indices, serum albumin, acute phase protein, and immunoglobulin concentrations. Changes in mucosal inflammation were assessed by recording the macroscopic and microscopic appearance of the rectum and measuring colonic cellular proliferation and glycoprotein synthesis.

TABLE 1 Details of the control group receiving faecal diversion and restoration of intestinal continuity

Indication	Previous surgery	Synchronous surgery
Faecal diversion		
Incontinence		Loop ileostomy
Hirschsprung's disease	Subtotal colectomy	Loop ileostomy
Sigmoid carcinoma		Hartmann's procedure
Incontinence		Loop ileostomy
Incontinence		Loop ileostomy
Sigmoid carcinoma		Sigmoid colectomy/loop ileostomy
High fistula in ano		Loop colectomy
Slow transit constipation	Subtotal colectomy	Loop ileostomy
Incontinence		Loop ileostomy
Incontinence		Loop colectomy
Incontinence		Loop colectomy
High fistula in ano		Loop colectomy
Sigmoid carcinoma		Sigmoid colectomy/loop ileostomy
Restoration of intestinal continuity		
Sigmoid carcinoma	Sigmoid colectomy/loop ileostomy	
Diverticular disease	Hartmann's procedure	
Solitary rectal ulcer	Rectopexy/loop ileostomy	
Enterocutaneous fistula	Sigmoid colectomy/loop ileostomy	
Diverticular disease	Hartmann's procedure	
Sigmoid carcinoma	Sigmoid colectomy/loop ileostomy	
High fistula in ano	Loop ileostomy	
Incontinence	Loop ileostomy	

TABLE II Details of patients with Crohn's colitis receiving faecal diversion and restoration of intestinal continuity

	Site of disease	Previous surgery	Synchronous surgery	Stoma
Faecal diversion	Crohn's proctocolitis	Rectosigmoid	Subtotal colectomy	Loop ileostomy
		Rectosigmoid	Subtotal colectomy	Loop ileostomy
		Rectum		Loop ileostomy
		Proctocolitis		Loop ileostomy
		Rectosigmoid	Subtotal colectomy	Loop ileostomy
		Proctocolitis	Subtotal colectomy	End ileostomy
		Proctocolitis	Right hemicolectomy	Loop ileostomy
		Proctocolitis	Subtotal colectomy	End ileostomy
		Proctocolitis	Subtotal colectomy	End ileostomy
		Proctocolitis		Loop ileostomy
		Proctocolitis		Loop ileostomy
		Proctocolitis	Subtotal colectomy	End ileostomy
		Proctocolitis		Loop ileostomy
		Left colon	Right hemicolectomy	Loop ileostomy
		Right colon		Loop ileostomy
		Left colon	Transverse colectomy	Right colostomy
Crohn's colitis and rectal sparing	Left colon	Right hemicolectomy		Loop ileostomy
	Transverse colon			Loop ileostomy
	Colitis			Loop ileostomy
	Perianal			Loop ileostomy
	Colitis			Loop ileostomy
	Perianal			Loop ileostomy
				Loop ileostomy
				Loop ileostomy
				Loop ileostomy
				Loop ileostomy
	Site of disease	Previous resection	Synchronous resection	
Restoration of continuity	Left colon	Right colon	-	
	Right colon	-	-	
	Proctocolitis	Right hemicolectomy	-	
	Left colon	Transverse colectomy	Left hemicolectomy	
	Colitis	Right hemicolectomy	-	
	Colitis	Right hemicolectomy	-	
	Rectosigmoid	Subtotal colectomy	-	
	Rectosigmoid	Subtotal colectomy	-	
	Rectosigmoid	Subtotal colectomy	Anastomotic resection	
	Proctocolitis	-	-	

Patients and methods

PATIENTS
All patients (Tables I and II) entered the study after written informed consent and were evaluated before faecal diversion and at two, six, and 12 weeks later. Patients with Crohn's colitis were subdivided according to the macroscopic state of the rectum: proctocolitis (n=12), normal rectum (n=10). All patients stopped treatment for two weeks before assessment. The control group consisted of 13 patients having faecal diversion who had a macroscopically normal rectum and no evidence of inflammatory bowel disease.

Two groups of patients were studied at the same time points after restoring intestinal continuity. Patients with defunctioned Crohn's colitis (n=10) and controls (n=8), originally defunctioned for a non-inflammatory condition, were not classified by the macroscopic appearance of the rectum as the presence of superimposed defunctioned proctitis could not be excluded.

METHODS
Disease activity was assessed by a modification of the Dutch activity index²¹ reported by Pettit *et al*²² to make allowance for previous extensive resections and stomas.
Haematological indices were measured on an S-plus Coulter counter. The differential white cell count was assessed using the Romanowsky stain and the erythrocyte sedimentation rate was evaluated by the Westergreen method. Serum IgG, IgA, and IgM concentrations were quantitatively estimated by single radial immunodiffusion²³ using Immunoplates (Unipath,

Birmingham). Serum albumin concentrations were estimated by absorbance estimation using bromocresol purple on a multichannel analyser. C reactive protein was measured by an immunoturbidimetric method²⁴ using a Cobas Bio centrifugal analyser (Roche Diagnostics, UK). α_1 Acid glycoprotein, α_2 macroglobulin, and α_1 antichymotrypsin were assessed by radial immunodiffusion using Nor-Partigen and M-Partigen plates (Behringwerke) respectively.

The macroscopic and histological state of the rectum was assessed by one observer using a standard score²⁵ at a reference point 10 cm from the posterior anal verge.

Colonic cellular proliferation was assessed by an *in vitro* stathmokinetic technique with vincristine to induce metaphase arrest.²⁶ Rectal biopsy specimens, taken 10 cm from the anal verge, were placed in organ culture dishes (Becton-Dickinson, England) semisubmerged, on wire grids (Industrial Wire Products, USA), in organ culture medium RPMI 1640 (Gibco Ltd) containing 10% fetal calf serum, penicillin (100 IU/ml) and gentamicin (40 μ g/ml) at 37°C, and equilibrated with 95% O₂ and 5% CO₂. After 16 hours the medium was replaced with identical medium containing vincristine sulphate (0.5 μ g/ml), which produces complete metaphase arrest without degeneration. Duplicate biopsy specimens were removed from dishes at 60, 100, 130, and 140 minutes, fixed in Carnoy's solution, and stained with the Fuelgen reaction. Ten individual crypts were microdissected from each biopsy specimen and the number of metaphase arrest figures counted. The mean number of metaphase arrest figures/10 crypt was plotted against time and the slope of the line was determined by linear regression analysis to give the crypt cell production rate (CCPR) in number metaphases/crypt/h.

Glycoprotein synthesis was evaluated by assessment of glucosamine synthetase activity (L-glutamine-D-fructose-6-phosphate-amino-transferase EC2.6.1.16). The glucosamine synthetase assay was performed in a manner similar to that described by Goodman,²⁷ a modification of the method of Winterburn and Phelps.²⁸

Rectal biopsy specimens were homogenised in fresh phosphate buffer (50 mM NaH₂PO₄/Na₂HPO₄ at pH 7 containing 100 mM KCl and 1 mM EDTA) and incubated at 37°C with 0.2 ml of substrate buffer containing 8 μ mol fructose-6-phosphate disodium, 3.2 μ mol L-glutamine, and 40 μ mol gentamicin. After three hours the reaction was stopped with 10% perchloric acid. Incubates were centrifuged at 2500 rpm for 15 minutes. Some 0.3 ml of the supernatant was removed and the pH was adjusted to between 6 and 11. Then, 0.2 ml borate buffer (1.12 mol boric acid and 0.56 ml KOH/L, pH 9.2) followed by 0.05 in acetic anhydride 1.5% wt/vol in acetone was added to 0.2 ml of supernatant, which was then placed in a boiling water bath for three minutes and an ice water bath for five minutes. Dimethylaminobenzaldehyde (DAB) (1.6 ml) in glacial acetic acid containing 1.25 ml concentrated HCl was added to each tube, which were then immediately placed in a water bath at 37°C for 20 minutes. The intensity of the

Figure 1: Effect of faecal diversion and restoration of continuity on the modified disease activity index (MAI) in patients with Crohn's proctocolitis (CP) and Crohn's colitis with rectal sparing (CCRS). CD= Crohn's disease, ANOVA= analysis of variance.

purple colour formed during this, the Morgan-Elson reaction,²⁹ was immediately read in a spectrophotometer (Unicam SP500 at 545 nm) against standard solutions of glucosamine hydrochloride (0.05–0.3 mM).

STATISTICAL ANALYSIS
All data were evaluated by non-parametric means unless a normal distribution was shown. The change in indices within groups and between groups with time was assessed by a one way analysis of variance and by a balanced two factor hierarchical classification respectively.

Results
Faecal diversion produced a significant reduction in the modified activity index in both groups of patients with Crohn's colitis (Fig 1). The restoration of intestinal continuity in patients with defunctioned Crohn's colitis did not produce a significant increase in the activity index (Fig 1).

HAEMATOLOGICAL INDICES
The preoperative haemoglobin, total, and differential white cell count was similar in all groups, while the preoperative platelet counts and the erythrocyte sedimentation rate were significantly increased in both groups with Crohn's colitis receiving faecal diversion (Table III). Values were not significantly influenced by faecal diversion or restoration of continuity.
The preoperative values of IgA and IgM were significantly raised in patients with Crohn's colitis receiving diversion (Table III) but there was no significant change after diversion or restoration of continuity.

TABLE III Preoperative platelet count, erythrocyte sedimentation rate (ESR), and immunoglobulin concentrations in patients with Crohn's colitis and controls

	Control group	Crohn's colitis and rectal sparing	Crohn's proctocolitis
Platelet count ($\times 10^9/l$)	297 (114)*†	493 (131)*	558 (130)†
ESR (mm/in first hour)	12 (3)‡	54 (53)†	52 (33)†
IgA (g/l)	2.0 (0.4)§	3.3 (0.6)	3.7 (0.8)§
IgM (g/l)	3.6 (0.8)	4.5 (1.1)	6.9 (0.8)
IgG (g/l)	13.2 (2.6)	13.7 (1.1)	17.9 (2.6)

*p<0.01 unpaired t test; †p<0.05 unpaired t test; ‡p<0.02 unpaired t test; §p<0.05 Mann-Whitney U test; ||p<0.01 Mann-Whitney U test; values given as mean (SEM).

ALBUMIN AND ACUTE PHASE PROTEINS
The prediversion concentrations of serum albumin were significantly reduced in both groups of patients with Crohn's colitis and rose significantly after diversion (Table IV). There was no significant change in the control group after diversion and no significant change in either group after restoration of continuity (Tables IV and V).
Prediversion concentrations of α_1 -acid glycoprotein were significantly increased in the group with Crohn's colitis and fell in the group with Crohn's colitis and rectal sparing after diversion. No other significant change occurred in any group after diversion or restoration of continuity (Tables IV and V).
C reactive protein, α_1 -macroglobulin, and α_1 -antichymotrypsin values were similar in all groups before surgery. α_1 Antichymotrypsin values fell significantly in patients with Crohn's colitis and rectal sparing after diversion. No other significant change occurred after excluding or reintroducing the faecal stream (Tables IV and V).
MACROSCOPIC AND HISTOLOGICAL ASSESSMENT
Faecal diversion was not associated with any significant overall change in the macroscopic appearance of the rectal mucosa in the control group. After three months of faecal diversion there was a significant deterioration in the macroscopic appearance in patients with Crohn's colitis and rectal sparing ($p<0.05$ rank sign test) with a trend to improvement in the Crohn's proctocolitis group. Restoration of intestinal continuity was associated with a significant improvement in the macroscopic appearance of the Crohn's disease group ($p<0.05$).
Neither faecal diversion nor restoration of continuity was associated with significant changes in histological assessment of the rectum.

RECTAL CELLULAR PROLIFERATION
There was no significant difference in the pre-operative rectal crypt cell production rate between the control group and patients with Crohn's colitis irrespective of the state of the rectum (Fig 2). Faecal diversion in the control group was associated with a significant transient fall in the CCPR at two and six weeks after diversion. Analysis of variance over the whole time period failed to show an overall significant change. In patients with Crohn's colitis, irrespective of the state of the rectum, there was no significant change in colonic cellular proliferation (Fig 2). Reintroduction of the faecal stream was not associated with a significant change in cellular proliferation in any group.

RECTAL GLYCOPROTEIN SYNTHESIS
There was no overall significant difference in the preoperative values of glucosamine synthetase activity between patients with Crohn's proctocolitis and the control group. When classified according to epithelial state, patients with proctocolitis and epithelial preservation had significantly increased glucosamine synthetase

TABLE IV The influence of faecal diversion on serum albumin and acute phase protein concentrations in a control group (C) and patients with Crohn's proctocolitis (CP) and Crohn's colitis with rectal sparing (CCRS)

	0 Weeks			12 Weeks		
	C	CP	CCRS	C	CP	CCRS
Albumin (g/l)	40.9 (1.8)*†	28.6 (2.4)*‡	34.4 (2.0)†§	39.6 (0.8)	34.3 (2.5)‡	40.7 (0.9)§
α ₁ Acid glycoprotein (g/l)	1.1 (0.1)*	1.9 (0.2)*	1.9 (0.2)*	1.0 (0.1)	1.4 (0.2)	1.1 (0.1)
C reactive protein (g/l)	5.4 (0.4)	46.4 (24)	44 (18)	5.0 (0.1)	21.2 (11)	8.9 (4.0)
α ₂ Macroglobulin (g/l)	2.6 (0.9)	2.2 (0.3)	2.0 (0.9)	2.3 (0.5)	2.3 (0.4)	2.6 (0.3)
α ₁ Antichymotrypsin (g/l)	0.7 (0.1)	1.2 (0.2)	1.1 (0.1)*	0.6 (0.2)	0.9 (0.2)	0.5 (0.1)*

*p<0.001; †p<0.05; ‡p<0.02; §p<0.01 Students t test; values given as mean (SEM).

TABLE V Influence of the restoration of intestinal continuity on serum albumin and acute phase protein concentrations in a control group and patients with Crohn's disease

	0 Weeks		12 Weeks	
	Control	Crohn's disease	Control	Crohn's disease
Albumin (g/l)	39.5 (0.8)	39.5 (1.3)	38.5 (0.9)	39.7 (2.5)
α ₁ Acid glycoprotein (g/l)	1.2 (0.1)	1.1 (0.1)	1.0 (0.1)	1.2 (0.3)
C reactive protein (g/l)	6.8 (1.6)	7.2 (3.1)	5.0 (0.1)	16.0 (7.0)
α ₂ Macroglobulin (g/l)	2.0 (0.2)	2.3 (0.2)	2.2 (0.2)	2.3 (0.2)
α ₁ Antichymotrypsin (g/l)	0.7 (0.1)	0.7 (0.1)	0.5 (0.1)	0.8 (0.2)

Values given as mean (SEM).

activity mean (SEM) (controls=2.60 (3.7), proctocolitis and epithelial depletion=23.9 (2.5), proctocolitis and epithelial preservation=34.4 (4.2), p<0.02). Glucosamine synthetase activity in patients with Crohn's colitis and rectal sparing was also significantly greater than controls (37.2 (5.0), p<0.02).

In the control group, faecal diversion failed to produce a significant change in glucosamine synthetase activity (Fig 3). In patients with Crohn's colitis and rectal sparing, glucosamine synthetase activities fell after diversion and remained significantly lower throughout the study period (analysis of variance p<0.05). In patients with Crohn's proctocolitis, activities were transiently lower two and six weeks after diversion with a return towards normal values at 12 weeks (analysis of variance, NS) (Fig 3). This phenomenon was not associated with a significant change in epithelial cell density. Analysis by a two factor unbalanced hierarchical classification showed a significant difference in the overall trend between the two groups with Crohn's colitis (p<0.05). Restoration of intestinal continuity was associated with a transient increase in glucosamine synthetase activity in both patients with Crohn's colitis and controls. There was no overall significant change by analysis of variance.

Figure 2: Effect of faecal diversion and restoration of intestinal continuity on rectal cellular proliferation rates (mean (SEM)). A = p<0.02, B = p<0.05, paired t test. CCPR = colonic cellular proliferation rate; other abbreviations as in Figure 1.

Discussion

The subjective improvement in both groups of patients with Crohn's colitis after faecal diversion corresponded with a significant fall in the modified disease activity index. The lack of change after restoration of intestinal continuity confirmed the clinical impression of continued disease remission. The relation between disease activity and mucosal inflammation, however, seems tenuous with a poor correlation between disease activity index and macroscopic or histological assessment.^{25 30}

Standard peripheral blood indices proved insensitive as markers of colonic inflammation and disease activity. The lack of significant change in haemoglobin values after diversion and restoration of continuity and the poor correlation between the absolute and differential white cell count and disease activity index do not support their use as an indicator of disease activity as previously suggested.^{21 31 32} The erythrocyte sedimentation rate and platelet count have been advocated as the most sensitive laboratory indices of disease activity,^{22 31 33-36} particularly in the presence of active colonic involvement.³⁷ Despite a significant increase in the prediversion erythrocyte sedimentation rates and platelet values in patients with Crohn's colitis, there was a poor correlation with the modified activity index concurring with previous reports.^{34 38 39} The findings of normal concentrations of serum IgG and raised IgM and IgA concentrations confirm previous studies in Crohn's disease.⁴⁰⁻⁴³ Their use as activity markers, however, is compounded by the fact that circulating immunoglobulin concentrations may be profoundly influenced by steroid administration,⁴¹ disease duration,⁴⁰ and changes in nutritional state.⁴⁴

The low preoperative concentrations of serum albumin in patients with Crohn's colitis may reflect disease extent and severity.⁴⁵ The increase after diversion, however, is likely to represent improved nutrition as well as reflect changes in disease activity.^{22 32} The variable acute phase protein response to exclusion and reintroduction of the faecal stream and poor correlation with a disease activity index and histological assessment²⁵ do not support the suggestion that serial assessment provides an accurate assessment of clinical state.^{36 38 39}

The relation between the macroscopic and histological appearance of the colonic mucosa and disease activity remains contentious with clinical remission infrequently mirrored by histological improvement.^{25 46 47} This, in part, may represent the focal and transmural nature of the disease although the improvement in the

Figure 3: Effect of faecal diversion and restoration of intestinal continuity on rectal glucosamine synthetase activity (mean (SEM)). A = $p < 0.05$, B = $p < 0.01$, paired t test. Other abbreviations as in Figure 1.

macroscopic appearance of the rectum in patients with proctocolitis suggests that faecal diversion may be associated with some improvement in morphological indices. The deterioration in the macroscopic state of the rectum in the group with Crohn's colitis and rectal sparing after faecal diversion may represent the onset of diversion proctitis.^{48,49} This is further supported by the macroscopic improvement in the appearance of the rectum in patients with defunctioned Crohn's colitis after restoration of intestinal continuity because the only diagnostic feature of diversion proctitis is its resolution on reintroducing the faecal stream.

The similarity between the cellular proliferation rates of rectal mucosa in patients with Crohn's colitis, irrespective of the state of the rectum, and the control group is in contrast with the findings in ulcerative colitis where increased rates are found in both remission and relapse.²⁶ This, in part, may explain the reduced risk of developing a colitis induced carcinoma in Crohn's disease.

The effect of faecal diversion in the CCPR of the rectum of the control group suggests the faecal stream has a tropic effect on human colonic cellular proliferation. The return to normal values three months after diversion may represent transient homeostatic mechanisms mediated by enterotropic hormones^{50,51} as prolonged defunction is reported to be associated with considerable hypoplasia in both man⁵² and the laboratory animal.^{53,54}

In contrast with the diversion induced hypoplasia of the control group, exclusion of the faecal stream in patients with Crohn's disease had no significant influence on cellular proliferation. This sustained rate of turnover in actively inflamed mucosa may represent an intrinsic defect in cellular homeostatic mechanisms in Crohn's disease or a hyperplastic response to chronic injury with regeneration in the absence of the faecal stream. A similar phenomenon is seen in ulcerative colitis in remission.⁵⁵ The mechanism by which this reactive hyperplasia occurs is unknown. It may occur secondary to reduced cell death or a persistent abnormality in mucosal structure or function after removal of the inflammatory stimuli. The finding of sustained proliferation in macroscopically normal mucosa suggests that the adaptive responses are not dependent on the presence of

an overt inflammatory reaction but may occur secondary to the interaction between a faecal constituent and the colonic epithelium.

The lack of change in cellular proliferation on restoration of intestinal continuity is in contrast with the effect of reintroducing the faecal stream in the laboratory animal⁵⁶ and suggests that the reintroduction of enteric luminal contents may not have a significant stimulatory effect on colonic proliferation in man.⁵⁷ In Crohn's colitis such a finding implies that the faecal stream does not have an acute stimulatory effect on colonic cellular proliferation, which would concur with the finding of normal proliferative rates before diversion.

The main protective mechanism of the gastrointestinal epithelium is dependant on the glycocalyx and local mucin production. Mucin, and to a lesser extent immunoglobulin and secretory component, production is reflected by the rate of glycoprotein synthesis. Glucosamine synthetase is the rate limiting step in the biosynthesis of gastrointestinal glycoprotein and thus mucin production.²⁷ The significant increase in rectal glucosamine synthetase activity in Crohn's colitis compared with a control group confirms the findings of Goodman *et al*⁵⁸ and suggests that enzymatic changes may represent a sensitive index of intestinal cellular disturbances. It supports the concept that enzyme abnormalities in Crohn's disease may exist without any obvious histological abnormality⁵⁹ and confirms the diffuse nature of the primary abnormality. The reason for increased glycoprotein synthesis in Crohn's disease is unclear. It may represent an inherent abnormality in gastrointestinal mucosa or a protective response to a faecal factor.⁵⁸

The lack of change in rectal glucosamine synthetase activity in the control group after faecal diversion suggests that the presence of faeces in the normal colon has little influence on glycoprotein synthesis and is in keeping with the reported lack of change in other mucosal enzymes after proximal diversion or small bowel resection.⁶⁰⁻⁶²

The sustained fall in glucosamine synthetase activity after diversion in patients with Crohn's colitis and rectal sparing does not support the concept that there is an inherent abnormality in enzyme activity. It suggests that in Crohn's disease the faecal stream has a strong stimulatory effect on glycoprotein synthesis, even in macroscopically normal tissue. A similar phenomenon is seen in the Crohn's proctocolitis group. The secondary rise that occurs in this group after six weeks corresponds with a similar rise seen in patients recovering from an acute attack of ulcerative colitis⁵⁸ and that seen in rat liver after partial hepatectomy⁶³ and may represent a regenerative response.

The transient increase in glucosamine synthetase activity in the control group after restoration of intestinal continuity may represent a normal response to the sudden reintroduction of a large antigenic load or a regenerative response after resolution of defunctioned proctitis which was present in four patients.

The similarity of the response in the Crohn's disease group suggests that any exaggerated response to a faecal constituent is not an acute

phenomenon but a longterm response to a chronic mucosal insult.

The increase in mucosal glucosamine synthetase activity in patients with Crohn's colitis and the reciprocal changes in colonic cellular proliferation and glycoprotein synthesis after faecal diversion supports the concept that the faecal stream may participate in the inflammatory process. Whether the effect is caused by a single constituent or represents a non-specific inflammatory stimulus is at present unclear. Further assessment of mucosal indices of disease activity with simultaneous instillation of subfractions of ileostomy effluent into the defunctioned colon may help to determine the role of individual faecal constituents in disease pathogenesis.

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