Gut 1994; 35: 231–235

Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases

C Cellier, T Sahmoud, E Froguel, A Adenis, J Belaiche, J-F Bretagne, C Florent, M Bouvry, J-Y Mary, R Modigliani, and the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives

Abstract

The relationships between clinical activity, endoscopic severity, and biological parameters in Crohn's disease have not been thoroughly investigated and a link was therefore sought between these three elements. The following parameters were determined simultaneously in 121 consecutive patients with colonic or ileocolonic Crohn's disease: Crohn's disease activity index, Crohn's disease endoscopic index of severity, and serum albumin, α_2-globulin, α_1-antitrypsin, orosomucoid, C reactive protein, erythrocyte sedimentation rate, platelets, lymphocyte and polymorphonuclear cell counts, haematocrit, and faecal α_1-antitrypsin concentration. The distribution of these parameters was studied and transformation was used so that data matched the normal distribution closely. A weak but significant correlation ($r=0{\cdot}32$; $p<0{\cdot}001$) was found between clinical and endoscopic indices in the whole group of patients and this correlation seemed to be homogenous in various patient subgroups (clinically quiescent or active disease, pure colonic disease, untreated patients). Endoscopic or clinical indices were also found to be weakly linked with biological parameters ($r<0{\cdot}50$). Stepwise linear regression identified C reactive protein as predictive of the clinical index, and, successively, α_2-globulin, erythrocyte sedimentation rate, faecal α_1-antitrypsin, serum orosomucoid, and α_1-antitrypsin as predictive of the endoscopic index. Both predictions were poor – the biological variables accounting for only 22 and 44% respectively of the clinical and endoscopic index variations. In conclusion, Crohn's disease clinical activity seems to be virtually independent of the severity of the mucosal lesions and biological activity.

(*Gut* 1994; 35: 231–235)

Hôpital St Louis, Paris
C Cellier

INSERM U 263, Paris
T Sahmoud

Hôpital Claude Huriez, Lille
A Adenis

Domaine Universitaire du Sart Tilman, Liège, Belgium
J Belaiche

CHU Pontchaillou, Rennes
J-F Bretagne

Hôpital St Antoine, Paris
C Florent

Hôpital René Dubos, Pontoise
M Bouvry

Correspondence to:
Dr R Modigliani, Hôpital St Louis, 1 Avenue C Vellefaux, 75010 Paris, France.

Accepted for publication 16 June 1993

Treatment of Crohn's disease is frequently monitored by repeated endoscopic and biological assessments, a costly practice with no scientific basis. Relationships between clinical activity, endoscopic severity, and laboratory tests of inflammation have not yet been thoroughly studied in Crohn's disease. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID) has recently developed, on a multicentre basis, a standardised procedure for endoscopic data collection in Crohn's disease, measured interobserver variations in endoscopic findings,[1] and elaborated and validated a Crohn's disease endoscopic index of severity (CDEIS).[2] In a previous study,[3] no correlation was found between clinical severity and the surface area or severity of endoscopic lesions in 142 patients with acute episodes (Crohn's disease activity index >200). This prospective study aimed to search for a link between the clinical activity, endoscopic severity, and the degree and type of biological abnormality in a large series of consecutive patients with quiescent or active colonic or ileocolonic Crohn's disease.

Patients and methods

PATIENTS

The inclusion criteria were as follows: (1) a firm diagnosis of Crohn's disease according to usual criteria[4]; (2) colonic involvement; and (3) need for colonoscopy according to the gastroenterologist in charge of the patient. Patients with proctitis only or colonic lesions limited to the caecum were excluded from the study.

DATA COLLECTION-ENDOSCOPIC PROCEDURE

The clinical, biological, and endoscopic variables collected are shown in Table I. Clinical activity was measured by the Crohn's disease activity index (CDAI) (second version).[5] α_1-antitrypsin was assayed by radical immunodiffusion in serum and fresh faecal specimens; serum orosomucoid and C reactive protein (CRP) were measured by automated nephelometric immunochemistry system, except in three centres where serum CRP values were measured by radial immunodiffusion. To take into account anticipated interassay variations, CRP and orosomucoid serum values were expressed as 'n times' the normal value of each laboratory. To check that this method did not introduce a bias, 'raw' CRP and orosomuocoid values for 31 patients from the same centre were analysed separately.

Endoscopic findings were recorded in a standardised manner, as previously reported.[1] In brief, they included the nature and frequency of nine elementary lesions (Table I), as well as the lesion and ulceration surface area. The Crohn's disease endoscopic index of severity (CDEIS) was derived from these data.[2]

TABLE I *Variables collected on entry into the study*

Clinical variables (n=13):
- Sex
- Age
- Age at CD onset
- Time elapsed between CD onset and diagnosis
- Time elapsed between diagnosis and present study
- First attack
- Previous intestinal resection
- Previous proctologic surgery
- Previous medical treatment
- Medical treatment in the month preceding present study
- Small bowel disease
- Anal lesions
- CDAI

Biological variables (n=11):
- Serum albumin (g/l)
- Serum α2 globulin (g/l)
- Serum α1 antitrypsin (g/l)
- Serum orosomucoid (n times the normal value)
- Serum C reactive protein (n times the normal value)
- Hematocrit (%)
- ESR (mm/h)
- Platelets (10^6/mm^3)
- Lymphocytes (10^3/mm^3)
- Polymorphonuclear (/mm^3)
- Faecal α_1 antitrypsin (mg%)

Endoscopic variables (n=12):
- Frequency of nine elementary lesions (pseudopolyp, healed ulceration, frank erythema, frankly swollen mucosa, aphthoid ulceration, superficial or shallow uleration, deep ulceration, non-ulcerated stenosis and ulcerated stenosis)
- Lesion and ulceration surfaces
- Crohn's disease endoscopic index of severity (CDEIS)

STATISTICAL ANALYSIS

Relationships between clinical, biological, and endoscopic variables were evaluated using Spearman's classical correlation coefficient – on raw data for comparison with other series and after transformation to match as closely as possible the normal distribution necessary for statistical testing.[6] Departure from the normal distribution was assessed through skewness and kurtosis coefficients, indices measuring asymmetry and deviation from the normal.[7] Transformation (square root or logarithm) was chosen for minimising skewness and kurtosis coefficients.[7] Tests were performed on the classic correlation coefficient after the appropriate transformation and were confirmed by the non-parametric Spearman's rank test.[8] When examining these relations in different subsets of patients, the homogeneity of correlation coefficients determined in the subgroups was checked after Fisher's transformation.[6] To avoid the pitfalls caused by multiple testing, within-group correlations were tested only when heterogeneity had been shown. Since a few biological data were missing, clinical, endoscopic, and biological data were compared in patients with and without missing values by means of χ^2 and Mann-Whitney U tests.[8] Stepwise multiple linear regression analysis[9] was used, after variable transformation, to try to predict clinical or endoscopic scores by using a linear combination of the 11 laboratory parameters. The clinical (or endoscopic) index was the dependent variable, and the laboratory parameters the independent variables. The quality of the prediction was assessed by the square of the multiple correlation coefficient (corrected estimate),[9] which represents the proportion of the variability of the dependent variable explained by the independent variables introduced into the regression. The Statistical Package for the Social Sciences (SPSS) was used for data description and analysis.

TABLE II *Description of the study sample (n=121): clinical and endoscopic data*

Characteristic	*(%)*
Female	64
First attack	21
Previous intestinal resection	11·5
Patients receiving no treatment in the month preceding inclusion	33
Crohn's disease intestinal location:	
Colon only	44
Small bowel and colon	51
Colon and gastroduodenal location	5
Active anal lesion	27
Age (y) (mean (SD), (range))	32 (13) (13–86)
Crohn's disease activity index (mean (SD), (range))	242 (114) (24–654)
Crohn's disease endoscopic inflammation score (mean (SD), (range))	9·2 (6·6) (0·5–38)

TABLE III *Description of the study sample: biological parameters*

	Mean (SD)	*No*
Serum albumin (g/l)	34·6 (6·7)	120
Serum α_2 globulin (gl)	8·3 (2·4)	120
Serum α_1 antitrypsin (g/l)	3·7 (1·1)	92
C reactive protein (×normal value)	5·3 (7·1)	111
Orosomucoïd (×normal value)	1·8 (1·4)	108
Polymorphonuclear cells (10^3/mm^3)	7100 (3100)	111
Lymphocytes (10^3/mm^3)	1900 (900)	109
Platelets (10^6/mm^3)	450 (170)	118
Erythrocyte sedimentation rate (mm in first h)	45 (29)	118
Haematocrit (%)	36 (6)	121
Faecal α_1 antitrypsin concentration (mg%)	160 (290)	82

No=sample size.

Results

Altogether 121 consecutive patients were included in the study. The patient sample is described in Tables II and III. Ninety five (78·5%) patients underwent total colonoscopy. The procedure was incomplete in 26 patients because of poor tolerance (n=2), colonic stenosis (n=14), or the decision of the endoscopist (n=10). The terminal ileum was explored in 73 (60%) patients. On average, 4·3 of the 5 ileocolonic segments defined[1] were explored. Patient subsets with or without missing biological data did not show statistically significant difference for any of the variables listed in Tables II and III (data not shown).

RELATIONSHIPS BETWEEN CLINICAL ACTIVITY, ENDOSCOPIC SEVERITY, AND BIOLOGICAL PARAMETERS

Square root or logarithmic transformation was used when appropriate as shown in Tables IV and V and the Figure. The correlation coefficients between the raw data are also given for comparison with other published series. Skewness and kurtosis were especially noticeable for faecal α_1-antitrypsin, orosomucoid, and CRP (standardised skewness coefficients of 10·0, 30·7, and 14·9 and kurtosis coefficients of 21·3, 138·0, and 34·7 respectively).

Using the appropriate variable transformations, significant correlations were found between the following (1) CDAI and CDEIS, in the whole population (Figure) and in the different subsets of patients (Table VI) which were found to be homogeneous. (2) CDAI and all biological parameters except polymorphonuclear

TABLE IV *Correlations between Crohn's disease activity index and biological parameters (evaluated through classic correlation coefficient values without (r') or with transformation (r))*

	Serum albumin	*Serum α_2 globulin*	*Serum α_1 antitrypsin*	*Serum orosomucoid*	*Serum CRP*	*Platelet counts*	*Polymorphonuclear counts*	*Lymphocyte counts*	*ESR*	*Faecal α_1 antitrypsin*
Transformation	*Ln*	*None*	*Sq root*	*Ln*	*Ln*	*Ln*	*Sq root*	*Sq root*	*Sq root*	*Sq root*
No	120	120	92	108	111	118	111	109	118	82
r'	−0·28	0·18	0·32	0·16	0·35	0·22	0·07	0·13	0·37	0·12
r	−0·32	0·19	0·34	0·32	0·48	0·25	0·06	0·14	0·42	0·21
p	0·001	0·02	0·001	0·001	0·001	0·004	NS	NS	0·001	NS

None=no transformation; Ln=logarithmic transformation; Sq root=square root transformation; p=degree of significance of correlation coefficient value after transformation; NS=non-significant; No=sampe size.

TABLE V *Correlations between Crohn's disease endoscopic index of severity and biological parameters (evaluated through classic correlation coefficient values without (r) or with transformation (r'))*

	Serum albumin	*Serum α_2 globulin*	*Serum α_1 antitrypsin*	*Serum orosomucoid (a)*	*Serum CRP (a)*	*Platelet counts*	*Polymorphonuclear count*	*Lymphocyte count*	*ESR*	*Haematocrit*	*Faecal α_1 antitrypsin*
Transformation	*Ln*	*None*	*Sq root*	*Ln*	*Ln*	*Ln*	*Sq root*	*Sq root*	*Sq root*	*None*	*Sq root*
No	120	120	92	108	111	118	111	109	118	121	82
r	−0·28	0·48	0·37	0·04	0·11	0·27	0·13	−0·04	0·34	−0·13	0·26
r'	−0·30	0·44	0·39	0·13	0·20	0·28	0·14	−0·03	0·40	−0·16	0·37
p'	0·001	0·001	0·001	NS	0·02	0·001	NS	NS	0·001	0·04	0·001

None=no transformation; Ln=logarithmic transformation; Sq root=square root transformation; p=degree of significance of correlation coefficient value after transformation; NS=non-significant; No=sample size.

cell and lymphocyte counts (Table IV). (3) CDEIS and all biological parameters except polymorphonuclear and lymphocyte counts and serum orosomucoid (Table V). (4) In 31 patients from the same centre, CDAI and CDEIS were correlated with serum levels of orosomucoid (g/l) and CRP (mg/l). For CDAI, correlation coefficient values of orosomucoid and CRP were 0·12 (NS) and 0·30 ($p<0·005$) respectively and for CDEIS, 0·05 (NS) and 0·18 (NS) respectively. All these correlations were loose, however, with values not exceeding 0·50. The results obtained with non-parametric Spearman's correlation coefficients were consistent in all cases with those obtained with classical correlation coefficients using variable transformations (data not shown).

Stepwise linear regression on transformed variables selected the following: (a) CRP to predict CDAI (haematocrit, an item included in the CDAI, was excluded from this regression); CRP accounting for 22% of CDAI variation; (b) serum α_2 globulin level, erythrocyte sedimentation rate, faecal α_1-antitrypsin level, orosomucoid, and serum α_1-antitrypsin level to predict CDEIS (these five variables accounting for 44% of CDEIS variation).

TABLE VI *Correlations of Crohn's disease activity index (CDAI) v Crohn's disease endoscopic inflammatory score (CDEIS) in various subgroups (evaluated through classic correlation coefficient value (r) after square root transformations)*

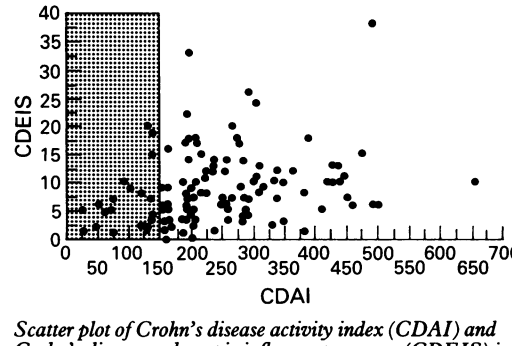
	CDAI <150	*CDAI >150*	*Pure colonic localisation*	*Ileocolonic localisation*	*With intestinal resection*	*Untreated patients*
No	21	100	53	62	14	40
r	0·31	0·24	0·40	0·21	0·39	0·25

No=samples size.
Statistical testing did not show heterogeneity between: (a) patients with CDAI <150 *v* CDAI >150; (b) patients with pure colonic and total colonoscopy *v* ileocolonic location; (c) resected and unresected patients; (d) treated and untreated patients.

Discussion

The evaluation of Crohn's disease activity has mainly been based on clinical indices, especially in controlled therapeutic trials. The search for more objective biological markers has led to a profusion of published studies but little consensus.[10] CDEIS is so far the only validated endoscopic index for Crohn's disease.[2]

In this study, links between clinical activity and endoscopic severity were weak in the overall patient population (n=121) and in various subsets (clinically quiescent or active Crohn's disease, pure colonic disease, untreated patients). In a previous study of patients during an acute episode, we were unable to find a significant correlation between CDAI and CDEIS.[3] Other attempts to correlate the clinical and endoscopic severity of CD are rare and based on rudimentary endoscopic scores.[11,12] Radiographic findings[13] and the depth of ulceration measured on colectomy specimens[14] in patients



Scatter plot of Crohn's disease activity index (CDAI) and Crohn's disease endoscopic inflammatory score (CDEIS) in the whole sample of 121 patients. The shaded area shows patients with clinically quiescent disease. Correlation values: without transformation: 0·26; after square root transformation: 0·32 ($p<0·001$).

with acute colitis have also been shown to correlate poorly with clinical severity. Links between clinical activity or endoscopic severity and laboratory parameters were weak or absent. On the contrary, the published reports abound with studies seeking relationships between clinical and biological parameters. There are, however, wide discrepancies, probably because of (1) the use of different indices of disease activity[15 16]; (2) possible selection bias owing to small sample size[17 18]; (3) statistical pitfalls, such as the inclusion of the same patient several times for analysis of correlation[17 19]; (4) the use of raw variables whose distribution could deviate from the normal distribution, making inappropriate the use of classical correlation tests. On the whole, levels of correlation were low, except in one study that reported a strong link between faecal clearance of α_1 antitrypsin and CDAI,[20] a finding not confirmed by others.[21-23]

A number of methodological points in our study warrant discussion. Firstly, the whole colon was explored endoscopically in 78·5% of the patients and the ileum in 60% of cases, and the potentially missed lesions might have blurred the correlations. This is probably not the case since correlation levels were similar in the subgroup of patients with purely colonic disease who underwent total colonoscopy. Secondly, a treatment induced bias is ruled out by the low correlation value found in untreated patients. Thirdly, serum orosomucoid and CRP values were expressed as multiples of normal values, but using the raw values in 31 patients did not improve correlations with the clinical and endoscopic indices. Lastly, α_1-antitrypsin assay in fresh faecal samples instead of lyophilised material, as in another study,[18] may be influenced by stool dilution.

Data transformation seemed to be important for orosomucoid, CRP, and faecal α_1 antitrysin when studying their relationships with CDAI and CDEIS. Indeed, some very low correlation coefficients found with the raw data could increase to significance after transformation. This illustrates a general problem which can arise with biological variables, particularly when they are skewed to the right, as was the case for these three variables. Moreover, the results obtained after variable transformation were validated through non-parametric rank correlation which gave similar results.

In sum, our results show that clinical, endoscopic, and biological findings are poorly correlated in Crohn's disease. The following explanations are suggested. (1) Clinical severity may depend more upon transmural inflammation typical of this disease than upon superficial lesions accessible by the endoscopist. In this context, assessment of the transmural pathological process by ultrasound endoscopy or leukocyte scan[12] may be of interest. (2) The inflammatory proteins measured in this study are produced by the liver. Direct determination of mediators released by gut associated lymphoid tissue, for example, lymphokines and their soluble receptors, may provide insights into the process taking place in the gut wall.[24]

Previous studies by the GETAID have shown that endoscopic findings have no predictive value for either the response to steroid treatment of an acute attack,[3] or the clinical course after steroid withdrawal.[25] It is thus clear from these data and from the present results that monitoring of Crohn's disease patients with repeated colonoscopies is currently unwarranted, with the possible exception of recently resected patients.[26]

These results may form the basis for considerable savings in terms of financial cost, health resources, and patient discomfort.

Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives: other participating physicians were: Jean-Frédéric Colombel, Antoine Cortot, Dominique Lescut (Lille), Alain Bitoun (Hôpital Saint-Lazare, Paris), Marc Lémann, Marcelo Salmeron, Jean-Paul Thérond, Bernard Vernisse (Hôpital Saint-Louis, Paris), Antoine Sée (Pontoise), Jean-Luc Raoul (Rennes).

This work was presented in part at the annual meeting of the American Gastroenterological Association (New Orleans, May 1991).

The authors thank V Delrieu for her skilful secretarial help.

1 Modigliani R, Mary JY, GETAID. Reproducibility of colonic findings in Crohn's disease: a prospective multicenter study of interobserver variation. *Dig Dis Sci* 1987; **32**: 1370–9.
2 Mary JY, Modigliani R, GETAID. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. *Gut* 1989; **30**: 983–9.
3 Modigliani R, Mary JY, Simon JF, *et al.* Clinical biological and endoscopic picture of attacks of Crohn's disease; evolution on prednisolone. *Gastroenterology* 1990; **98**: 811–18.
4 Bernades P, Hecketsweiler P, Benozio M, Descos L, Geffroy Y, Hemet J, *et al.* Proposition d'un système de critères pour le diagnostic des entèrocolites inflammatoires (maladie de Crohn et rectocolite hémorragique). Une étude coopérative du GREC. *Gastroentérol Clin Biol*, 1978; **2**: 1047–54.
5 Best WR, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's disease activity index (CDAI). *Gastroenterology* 1979; **77**: 843–6.
6 Morrison DF. *Multivariate statistical methods.* 2nd ed. New York: McGraw Hill, 1976: 102–5.
7 Kendall MG, Stuart A. *The advanced theory of statistics.* 3rd ed, vol 1. New York: Hafner, 1973: 85–6.
8 Siegel S. *Non parametric statistics for the behavioral series.* New York: McGraw Hill, 1956: 116–26/202–15.
9 Draper NR, Smith H. *Applied regression analysis.* New York: John Willey & Sons. 1966: 117/171–2.
10 Beck IT. Laboratory assessment of inflammatory bowel disease. *Dig Dis Sci* 1987; **32** (suppl): 26–41.
11 Gomes P, Du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. *Gut* 1986; **27**: 92–5.
12 Saverymuttu SH, Peters AM, Lavender JP, Pepys MB, Hodgson HJF, Chadwick VS. Quantitative fecal indium 111-labeled leukocyte excretion in the assessment of Crohn's disease. *Gastroenterology* 1983; **85**: 1333–9.
13 Prantera C, Luzi C, Olivotto P, Levenstein S, Cerro P, Fanucci A. Relationship between clinical and laboratory parameters and length of lesion in Crohn's disease of small bowel. *Dig Dis Sci* 1984, **29**: 1093–7.
14 Bucknell NA, Williams GT, Barham CI, Lennard-Jones JE. Depth of ulceration in acute colitis. Correlation with outcome and clinical and radiologic features. *Gastroenterology* 1980; **79**: 19–25.
15 Andre C, Descos L, Landais P, Fermanian J. Assessment of appropriate laboratory measurements to supplement the Crohn's disease activity index. *Gut* 1981; **22**: 571–4.
16 Van Hees AM, Van Elteren PH, Van Lier HJJ, Van Tongeren JHM. An index of inflammatory activity in patient with Crohn's disease. *Gut* 1980; **21**: 279–86.
17 Fagan EA, Dyck RF, Maton PN, *et al.* Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. *Eur J Clin Invest* 1982; **12**: 351–9.
18 Meyers S, Wolke A, Field SP, Feuer EJ, Johnson JW, Janowitz HD. Fecal alpha1-antitrypsin measurement: an indicator of Crohn's disease activity. *Gastroenterology* 1985; **89**: 13–8.
19 Sachar DB, Smith H, Chan S, Cohen LB, Lichtiger S, Messer J. Erythrocyte sedimentation rate as a measure of clinical activity in inflammatory bowel disease. *J Clin Gastroenterol* 1986; **8**: 647–50.
20 Florent C, L'Hirondel C, Desmasures C, Giraudeaux V, Bernier JJ. Evaluation de l'évolutivité de la maladie de Crohn et de la rectolite hémorragique par la mesure de la clairance fécale de l'alpha1 antitrypsine. *Gastroentérol Clin Biol* 1981; **5**: 193–7.
21 Fischbach W, Becker W, Mössner J, Koch W, Reiners C. Faecal alpha1 antitrypsin and excretion of 111 Indium granulocytes in assessment of disease activity in chronic inflammatory bowel diseases. *Gut* 1987; **28**: 386–93.
22 Karbach U, Ewe K, Bodenstein H. Alpha1 antitrypsin, a reliable endogenous marker for intestinal protein loss and its application in patients with Crohn's disease. *Gut* 1983; **24**: 718–23.

23 Karbach U, Ewe K, Dehos H. Antiinflammatory treatment and intestinal alpha1-antitrypsin clearance in active Crohn's disease. *Dig Dis Sci* 1985; **30:** 229–35.
24 Mueller Ch, Knoflach P, Zielinski C. T-cell activation in Crohn's disease: Increased levels of soluble interleukin-2 receptors in serum and in supernatants of stimulated peripheral blood mononuclear cells. *Gastroenterology* 1990; **98:** 639–46.
25 Landi B, Nguyen Anh T, Cortot A, Soule JC, Rene E, Gendre JP, *et al.*, and the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. *Gastroenterology* 1992; **102:** 1647–53.
26 Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **98:** 956–63.