INFLAMMATORY BOWEL DISEASE

Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study

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Background and aims: The causes of relapses of ulcerative colitis (UC) are unknown. Dietary factors have been implicated in the pathogenesis of UC. The aim of this study was to determine which dietary factors are associated with an increased risk of relapse of UC.

Methods: A prospective cohort study was performed with UC patients in remission, recruited from two district general hospitals, who were followed for one year to determine the effect of habitual diet on relapse. Relapse was defined using a validated disease activity index. Nutrient intake was assessed using a food frequency questionnaire and categorised into tertiles. Adjusted odds ratios for relapse were determined using multivariate logistic regression, controlling for non-dietary factors.

Results: A total of 191 patients were recruited and 96% completed the study. Fifty two per cent of patients relapsed. Consumption of meat (odds ratio (OR) 3.2 (95% confidence intervals (CI) 1.3–7.8)), particularly red and processed meat (OR 5.19 (95% CI 2.1–12.9)), protein (OR 3.00 (95% CI 1.25–7.19)), and alcohol (OR 2.71 (95% CI 1.1–6.67)) in the top tertile of intake increased the likelihood of relapse compared with the bottom tertile of intake. High sulphur (OR 2.76 (95% CI 1.19–6.4)) or sulphate (OR 2.6 (95% CI 1.08–6.3)) intakes were also associated with relapse and may offer an explanation for the observed increased likelihood of relapse.

Conclusions: Potentially modifiable dietary factors, such as a high meat or alcoholic beverage intake, have been identified that are associated with an increased likelihood of relapse for UC patients. Further studies are needed to determine if it is the sulphur compounds within these foods that mediates the likelihood of relapse and if reducing their intake would reduce relapse frequency.

The course of ulcerative colitis (UC) is variable but the majority of patients follow a relapsing and remitting course.[1] The underlying causes of relapses of UC have not been clearly defined. Three prospective studies have identified factors that predict an increased likelihood of relapse.[2–4] Relapse was more likely to occur with higher relapse frequency,[3] less time since last relapse,[3] or a higher total number of previous relapses,[4] at least in women.[2] These observations do not allow patients to modify any factors that may be contributing to a high relapse frequency.

Several studies[5–9] have examined the association between dietary factors and onset of UC but none have systematically examined the relationship between normal dietary intake and relapses of UC. A high intake of dairy products or low dietary fibre intake may be associated with relapse[10–14] but the strongest evidence for a dietary factor is that sulphur and sulphate may be implicated in relapse of colitis.

The role of sulphur rich compounds was first suspected from animal models where sulphated dextrans, but not dextrans without sulphur, were able to induce experimental colitis in rodents.[15] The toxic effects of sulphur reducing compounds, particularly hydrogen sulphide, at concentrations commonly found in the lumen of the human colon, appear to be mediated through impaired utilisation of butyrate by colonocytes.[16] Hydrogen sulphide causes increased epithelial permeability, loss of barrier function,[17] cellular proliferation,[18] and histological changes in rat colon that are similar to those seen in humans with UC.[19] UC patients have significantly higher luminal concentrations of hydrogen sulphide than controls[20] and disease activity correlates with sulphide production rates.[21] Endogenous sources do not seem to make a significant contribution to the colonic pool of sulphur.[22] The major exogenous sources of sulphur are the sulphur amino acids (found in high protein foods such as red meat, cheese, milk, fish, nuts, and eggs) and inorganic sulphate (in Brassica vegetables and as preservatives in processed foods, particularly commercial breads, beers, sausages, and dried fruit[23]). Sulphur amino acids and inorganic sulphate reach the colon where they are converted to sulphides by fermentation with colonic bacteria or by sulphate reducing bacteria.[24 25] Faecal hydrogen sulphide concentration is increased by increasing either the sulphur amino acid content (as meat)[26] or sulphate content (as additives) of the diet.[27] Generation of hydrogen sulphide by sulphate reducing bacteria is modest compared with total faecal sulphide concentration,[20] suggesting that fermentation of sulphur amino acids may be the more important of the two mechanisms of generation of hydrogen sulphide. In a pilot study in which the intake of sulphur amino acids was limited, clinical improvement, in terms of stool frequency, was demonstrated in all four participants with UC.[28]

The aim of this study was to determine if any dietary factors postulated to influence disease activity, including dairy products, dietary fibre, and foods rich in sulphur, were associated with an increased likelihood of relapse in patients with UC.

METHODS
Design
This was an observational prospective cohort study in which patients with UC in clinical remission were followed for one year to determine the effect of diet on relapse. The outcome

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was clinical relapse or continued remission over the year, determined by a validated disease activity index.

Setting

Participants were recruited from two district general hospitals in the North East of England. The study had approval from the two local ethics committees.

Participants

Potential participants were identified between January and September 2000 through two existing databases of UC patients, compiled from histology reports or recruited from outpatient clinics and including patients currently under primary and secondary care. Inclusion criteria were: age 18–70 years; diagnosis of UC (including proctitis) established by histology with extent determined by endoscopy or barium enema; ability to give informed consent; in remission at the time of recruitment; and last relapse more than one month prior to recruitment. Exclusion criteria were active disease or pregnancy, previous colectomy, or inability to comply with weekly postal follow up.

Eligible patients gave informed consent for the study and were interviewed by one of the authors (SLJ) at recruitment. In addition to the dietary assessment, data were collected on participant non-dietary factors that could potentially alter the risk of relapse, including age and sex, disease duration and extent, smoking status, medication, prior appendectomy, and baseline disease activity, which included a disease activity score, duration of remission, and previous relapse frequency.

Measurement and validation of nutritional intake

Habitual dietary intake was measured using a food frequency questionnaire (FFQ) listing 107 types of food (for instance, ''bread and rolls'') commonly consumed in the UK, and a food atlas that contained pictorial representations of different portions of food and a range of foods not readily described using standard household measures.[29] [30] The FFQ and food photographs have been used in studies with healthy volunteers,[29] alcoholic subjects,[31] and cancer patients.[32] [33] For each food, a series of eight photographs has been validated to accurately represent portions from the 5th to the 95th centile of the distribution curve of UK portion sizes.[34–36]

Dietary intake was converted to nutrient intake depending on the specific type, amount, and preparation of food consumed, using a computerised food table (the UK Nutrient Databank, updated and modified by the Human Nutrition Research Centre, University of Newcastle (version 1.04)) derived from McCance and Widdowson's food composition tables, fifth edition with supplements.[37–42] This provides data on more than 40 composite nutrients, including macro and micronutrients, of nearly 5000 foods eaten in the UK and on their food groups. Food groups were allocated by the Royal Society of Chemistry classification, which categorises foods into food groups such as ''meat and meat products'' or ''milk and dairy products'', and subgroups such as ''red and processed meat'', which are major sources of sulphur amino acids and sulphate.

The food table provides data on the sulphur composition of some, but not all, foods. Sulphur content was listed for 29% of the foods consumed by subjects in this study. For the sulphate content of foods, data were derived from a published source[23] and added to the tables using mean values. The sulphate content of composite food and meals was calculated from the individual components using standard recipes. Using this method, sulphate values were assigned to 91% of foods reported by volunteers.

The FFQ was further validated by comparing reported energy intake and estimated energy requirements. Schofield equations[43] were used to determine the patient's basal metabolic rate (BMR), and from this a physical activity level (PAL) was calculated. PAL is the ratio by which actual energy intake is greater than BMR. PAL for an individual usually lies within the range 1.14–2.11.[44] [45]

Defining relapse and remission

The outcome measure for the study was having a relapse or maintaining remission during the year from recruitment. Because of the need for a non-invasive method of defining relapse or remission in this relatively large cohort followed in the community, the simple clinical colitis activity index (SCCAI) was the chosen outcome measure.[46] This is a symptom based disease activity index that uses six clinical parameters: daytime and nocturnal bowel frequency, urgency, amount of blood in the stool, wellbeing, and extraintestinal manifestations. The index has been validated as a measure of disease activity in UC by comparison with pre-existing disease activity indices[46] and by its ability to discriminate between different degrees of disease activity.[47] We have previously shown, in a separate cohort of participants, that a score of 5 or more accurately confirms a clinician defined relapse with 92% sensitivity, 93% specificity, 88% positive predictive value, and 95% negative predictive value when the questionnaire is self administered.[47] Conversely, a score of less than 5 defines remission with a sensitivity of 93% and a specificity of 92%.

To monitor disease activity, participants completed the six questions that made up the SCCAI and recorded their answers on preprinted stamped addressed postcards, which were returned to the study centre weekly. If a participant's score reached 5 or more, they were classified as having had a relapse. Sigmoidoscopies were not performed to confirm relapse because we had previously shown strong correlation between sigmoidoscopy and the SSCAI in defining relapse/ remission and because we wished to maximise patient participation so that the results would be more generalisable. Similarly, because a previous study suggested that the definition of relapse used had a positive predictive value of 88%,[47] stool cultures to exclude infectious agents were not performed to improve participation rates.

Statistical analysis

Nutrient data were not adjusted to energy intake because comparison of gross intake of nutrients is important in a disease such as UC where the colon is directly exposed to products of digestion. Furthermore, the relationship between certain nutrients and total energy intake is not clearly correlated and therefore adjusting nutrient intake proportionally to energy intake is likely to introduce distortions in the data.[48] Nutrient intake was compared for macronutrients (energy, fat, protein, carbohydrate, and alcohol), the Royal Society of Chemistry food groups, dietary fibre (measured as non-starch polysaccharide), sulphur, and sulphate intake. Nutrient data were categorised into tertiles, as is customary in many nutritional epidemiological studies.[49] However, as this may in itself introduce bias into the analysis, results are also presented using a linear term for dietary intake.

Dietary and non-dietary characteristics of patients who relapsed were compared with those who remained in remission using multivariate logistic regression. We initially examined the effect of potentially important non-dietary confounding factors: age, sex, disease extent and duration, baseline SCCAI score, number of relapses in the year prior to recruitment, time since last relapse, average annual relapse frequency, medication use, including non-steroidal anti-inflammatory drugs, smoking status, and prior appendectomy. The effect of each dietary factor was then examined, after controlling for the non-dietary confounders that had been found to be statistically significant and may additionally

Table 1 Non-dietary characteristics of all patients at recruitment that were associated with relapse in a multivariate logistic regression analysis

	OR (95% CI)	LRT p
SCCAI score at recruitment		<0.0001
0	1.00	
1	1.46 (0.67–3.18)	
2	5.28 (2.00–14.0)	
3 or 4	9.30 (3.50–24.7)	
Age (per 10 years)	0.74 (0.59–0.96)	0.021

SCCAI, simple clinical colitis activity index.[46]
OR (95% CI), odds ratio (95% confidence interval).
p value from likelihood ratio test (LRT).

act as a surrogate for unidentified non-dietary factors that may increase the likelihood of a relapse, plus sex, which is a potentially important determinant of dietary intake. Statistical significance was assessed using likelihood ratio tests. Odds ratios (OR) and corresponding 95% confidence intervals (CI) are reported. The fit of the logistic regression models to the data was assessed using the Pearson χ^2 goodness of fit test. Statistical analysis was performed using SPSS statistical package version 10 (SPSS Inc., Chicago, Illinois, USA).

No correction has been made for multiple analyses. Allowance for multiple analyses can be made formally with statistical methods such as Bonferroni correction. However, the validity of correcting p values for the number of analyses performed has been questioned and it has been suggested that this can lead to rejection of true associations.[50 51] Another approach is to evaluate the results with respect to the strength of the association, the biological plausibility, and any supporting evidence.

RESULTS

Recruitment and patient demographics
A total of 463 patients were invited by letter to participate in the study. Replies were received from 355, a 77% response rate. Of those who responded, 83 actively declined participation in the study and a further 81 were found to have exclusion criteria. Therefore, 191 participants were recruited to the study. There was no significant difference between participants and non-participants for age (2 years 6 months; p = 0.071, Student's t test) or sex (p = 0.759, χ^2 test).

Eight participants failed to complete the study: one withdrew because she was pregnant, one because she was receiving chemotherapy for breast carcinoma, one participant

had a prophylactic colectomy because of a high risk of malignancy, and five participants were lost to follow up. Complete follow up data were therefore available on 183 (96%) consented eligible participants. Subsequent statistical analyses were limited to these patients. Median age of participants was 51 years (interquartile range (IQR) 38–61 years) and 93 were male (51%). Median disease duration since hospital diagnosis was 6 years 7 months (IQR 2 years 10 months to 16 years 4 months). Disease extent was: proctitis 25.1%, rectosigmoiditis 34.4%, left sided disease 16.4%, and extensive disease 24.1%. At recruitment, 141 patients (74%) were using regular 5-aminosalicylic acid drugs. In a randomly chosen subgroup of 50 patients who relapsed, continued reported compliance with 5-aminosalicylic acid drugs was high (96%). Ninety six participants (52%) were defined as having had a relapse during the year of follow up because their SCCAI score reached 5 or more. As previously reported, 68 of the patients were assessed in detail to check the performance of the SCCAI in this population by comparison with their reported relapse or remission status.[47] Over the whole study, the SCCAI had 85.7% sensitivity and 84.8% specificity for defining relapse.

Validation of nutritional assessment
One hundred and twenty two patients (67%) had a PAL within the acceptable limits for an individual. Twenty four patients (13%) appeared to underreport energy intake based on PAL and 36 (20%) appeared to overreport. One patient's PAL was unavailable as their weight was not recorded.

Non-dietary differences
On multivariate analysis, non-dietary factors that were significantly different between patients who relapsed and those that remained in remission were disease activity score at recruitment, as measured by the SCCAI, and age (table 1). Relapse was more likely in those whose disease showed greater activity prior to recruitment and in younger patients. Other non-dietary variables that were examined, including use of prophylactic 5-aminosalicylic acid medication, were not statistically different between relapsers and those that remained in remission (75% v 79% for use of prophylactic medication; p = 0.488, χ^2 test).

Dietary differences
Nutrient intake was compared for each of the macronutrients, food groups, dietary fibre, sulphur, and sulphate intake in turn. These were chosen to limit the number of dietary variables that were being tested while being comprehensive and including foods for which a reasonable

Table 2 Association of dietary intake of food groups and relapse in ulcerative colitis

	Median daily consumption (g)		Categorical analysis (comparing tertiles to tertile of lowest dietary intake)			Continuous analysis	
						Linear trend	
	Relapse	Non-relapse	Medium intake OR (95% CI)	High intake OR (95% CI)	LRT p	OR/10g	(95% CI)
Cereals and cereal products	256	259	0.82 (0.37–1.82)	1.04 (0.46–2.35)	0.816	1.01	(0.99–1.04)
Milk and milk products	221	201	1.17 (0.53–2.59)	1.33 (0.60–2.97)	0.779	1.00	(0.99–1.02)
Eggs	16	13	1.78 (0.80–3.98)	2.26 (1.01–5.08)	0.119	1.05	(0.94–1.18)
Vegetables	334	345	0.68 (0.30–1.53)	1.12 (0.50–2.52)	0.439	1.01	(0.98–1.03)
Fruit	220	260	0.98 (0.44–2.19)	0.79 (0.35–1.79)	0.818	1.00	(0.98–1.02)
Fish and fish products	32	35	1.52 (0.67–3.46)	1.26 (0.56–2.81)	0.602	1.02	(0.94–1.11)
Meat and meat products	195	146	1.37 (0.60–3.13)	3.20 (1.31–7.79)	0.027	1.08	(1.03–1.12)
Red and processed meat	172	124	2.16 (0.93–4.98)	5.19 (2.09–12.9)	0.001	1.10	(1.05–1.15)
Non-alcoholic beverages	1434	1260	0.97 (0.44–2.13)	1.63 (0.73–3.61)	0.361	1.00	(1.00–1.01)
Alcoholic beverages	238	150	0.80 (0.35–1.82)	2.71 (1.10–6.67)	0.017	1.01	(1.00–1.02)
Sugars, preserves, and snacks	44	54	1.29 (0.58–2.87)	0.94 (0.42–2.12)	0.723	1.01	(0.94–1.08)

p value from likelihood ratio test (LRT).
OR (95% CI), odds ratio (95% confidence interval).

Table 3 Association of medium and high (versus lowest tertile) macronutrient and food constituent intake and relapse in ulcerative colitis

	Median daily consumption		Categorical analysis (comparing tertiles to tertile of lowest dietary intake)			Continuous analysis	
	Relapse	Non-relapse	Medium intake OR (95% CI)	High intake OR (95% CI)	LRT p	OR*	95% CI
Macronutrients							
Energy (kJ)	11567	10657	1.32 (0.57–3.06)	2.81 (1.14–6.93)	0.053	1.01	1.00–1.02
Fat (g)	100	94	1.30 (0.57–2.96)	2.52 (1.06–5.97)	0.085	1.06	0.99–1.13
Fibre (g)	21	22	1.06 (0.31–3.70)	0.88 (0.34–2.29)	0.916	1.08	0.76–1.55
Carbohydrate (g)	291	319	0.94 (0.41–2.14)	1.31 (0.56–3.06)	0.698	1.02	0.99–1.05
Protein (g)	97	88	1.38 (0.60–3.15)	3.00 (1.25–7.19)	0.034	1.13	1.01–1.26
Alcohol (g)	14	10	1.21 (0.53–2.79)	2.42 (1.04–5.62)	0.088	1.19	1.01–1.41
Food constituents							
Non-starch polysaccharide (g)	16.4	16.3	1.07 (0.48–2.39)	1.14 (0.51–2.55)	0.954	1.18	0.76–1.83
Sulphur (mg)	396	350	1.28 (0.57–2.87)	2.76 (1.19–6.40)	0.039	1.02	1.00–1.05
Sulphate (mg)	668	636	1.45 (0.64–3.30)	2.61 (1.08–6.30)	0.089	1.02	1.00–1.04

*Odds ratio per 10 units of dietary variable, except for energy for which the odds ratio is per 100 kJ.
OR (95% CI), odds ratio (95% confidence interval).
p value from likelihood ratio test (LRT).

hypothesis existed to associate them with modified disease activity. For each of these food stuffs, median intakes in the remission and relapse categories are presented (tables 2, 3). Also presented from the multivariate analyses are the ORs for relapse, adjusted for SCCAI, age, and sex, comparing medium and high intake tertiles with low tertile and ORs and corresponding confidence intervals for a linear term (tables 2, 3). A high intake of meat and meat products (particularly red and processed meats), eggs, protein, alcohol, energy, fat, sulphur, and sulphate predicted an increased likelihood of relapse.

Because 23% patients appeared to underreport or over-report energy intake based on PAL, analyses of the significant dietary factors were repeated including only those 122 patients whose PAL fell within the acceptable limits of 1.14–2.11. Relapse was still associated with a high intake of meat (OR compared with low intake 3.74 (95% CI 1.12–12.6)), particularly red and processed meat (OR 6.88 (95% CI 2.02–23.4)) and alcohol (OR 4.14 (95% CI 1.14–15.0)). No other dietary factors were statistically significant.

All models were a reasonable fit to the observed data, with the exception of the continuous analysis of the effect of dietary intake of non-alcoholic beverages (for which a reasonable fit was obtained once a non-linear term for intake was included in the model).

DISCUSSION

In this prospective cohort study, it was confirmed that preceding increased disease activity is associated with an increased risk of relapse. Importantly, potentially modifiable dietary factors were also identified that were associated with an increased risk of relapse of UC. The strongest relationship between a dietary factor and an increased risk of relapse observed in this study was for a high intake of meat, particularly of red meat and processed meat. This is a novel finding. Consumption of large amounts of sulphur and sulphate were also associated with an increased risk of relapse, and although they may have been spurious findings due to the number of statistical tests performed, these components of food may offer an explanation for the increased risk seen with meat. Red meat, for instance, is stated as a food to be avoided on a low sulphur amino acid diet[28] and processed foods contain large amounts of sulphate as a food additive.[23] Similarly, a high alcohol intake was associated with an increased risk of relapse and many alcoholic drinks contain large amounts of sulphates as additives.[23] A high sulphur diet, either from sulphur amino

acids or sulphate additives, results in the generation of hydrogen sulphide[26 27] and mucosal damage in the colon.

Contrary to beliefs commonly held by patients, no association was detected between increased intake of milk or dairy products and relapse, and no apparent protective effect of an increased intake of dietary fibre.

The strengths of this study are that the study design removed the possibility of recall bias and minimised misclassification bias by being a prospective study; a dietary assessment tool (FFQ plus a validated food photograph atlas) and a validated disease activity index were used to assess baseline habitual dietary intake and disease outcome; there was a very low dropout rate and the statistical analysis controlled for non-dietary differences between patients who did and did not relapse.

There are some potential criticisms of the dietary assessment tool. It has been suggested that FFQs overestimate habitual energy intake[52 53] and on initial inspection this would appear to be the case in this study as more patients overestimated than underestimated energy intake based on PAL. However, this may have been a reflection of their true requirements because subjects had a higher than expected energy expenditure related to subclinical disease activity or previous weight loss and subsequent catch-up from earlier relapses. Habitual diet was assessed at only one time point for each individual and therefore recall of the immediate diet by participants was prone to reflect small seasonal differences or recent special occasions. However, the global market has made foods previously considered to be seasonal available most of the year and studies to determine the effect of season on intake have shown little impact on nutrient intake.[54] Also, as a prospective cohort study there is no reason to consider that errors in reporting of diet would be more common among either relapsers or those who remained in remission.

A further potential criticism of the study is that sigmoidoscopy was not performed to confirm relapses nor were stool samples analysed to exclude an infective agent. However, the activity index used had been shown in a separate cohort to accurately predict a relapse of UC, which was defined by a clinician and included examination of the rectal mucosa in some cases. It would be impossible to exclude a small number of cases being misclassified using this (or any other non-invasive) method but for a population the method of defining relapse has been validated, in much the same way as the Crohn's disease activity index does not use endoscopic confirmation.[55] Furthermore, examination of the rectal mucosa can also give false negative results as up to one

third of patients with proximal inflammation of the colon have a non-inflamed rectal mucosa,[56] particularly with the use of rectal treatments.

The main weakness of the study relates to data for sulphur and sulphate content of the diet rather than data for meat, protein, and alcohol content of foods, which are robust. Although data on the sulphur content of foods in the food tables are reliable, they are incomplete, with the majority of foods consumed by participants not having a sulphur content listed. Only foods or dishes containing fruit or nuts are allocated a sulphur content.[41] However, as the sulphur composition of meat, which is known to be high, was missing from the food tables, and relapse was associated with a high consumption of meat and meat products, more complete food tables for sulphur would be expected to increase the differences in sulphur consumption between participants who did or did not relapse.

Similarly, there are limitations with the data on sulphate content of foods as they are based on one method of sulphate analysis, reported in one paper. This showed wide variation in sulphate content for certain foods (for instance, bread) depending on whether it was homemade or processed. Therefore, mean values for sulphate content of foods were used. Sulphate data, unlike sulphur data, were complete for virtually all foods consumed by the study subjects but their accuracy has not been independently validated. Sulphasalazine is also a potential source of ''dietary'' sulphate but as a sulphate ester it is unlikely that anionic sulphate is liberated because acid hydrolysis, comparative with the effect of gastric acid, does not release sulphate from sulphate esters.[57] Furthermore, decreased levels of hydrogen sulphide production have been noted in patients taking 5-aminosalicylic acid drugs, including sulphasalazine,[20] and few patients were taking sulphasalazine.

In summary, despite the inherent difficulties in the assessment and validation of nutritional intake, results from this observational cohort study suggest that certain dietary factors influence whether or not a patient with UC in remission is at increased risk of relapse. Dietary factors are less important statistically than measures of prior disease activity in determining the risk of relapse but clinically much more important because nutrient intake is potentially modifiable. A high meat, protein, or alcohol intake is associated with an increased risk of relapse which may well occur because these foods are rich sources of sulphur and sulphate which increase the concentration of faecal hydrogen sulphide that is toxic to the colonocyte. More comprehensive data on sulphur and sulphate contents of foods is required in order to gain further insights into the potential role of these nutrients in the aetiology of relapses of UC. In addition, an intervention study is needed before it could be concluded that sulphur and sulphate rich foods definitely increase the risk of relapse, and that a low meat and sulphur or sulphate diet negates that risk without significant side effects.

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EDITOR'S QUIZ: GI SNAPSHOT ....

Robin Spiller, *Editor*

Late complication of blunt abdominal trauma

Clinical presentation

A 34 year old man was evaluated in the emergency department for a two day history of abdominal pain, nausea, vomiting, dyspnoea, and breathlessness. He had a history of blunt abdominal trauma 13 years ago with recurrent symptoms of bowel obstruction resolving spontaneously. The patient reported having had bowel movements the morning of his presentation but no subsequent passing of flatus. His temperature was 37.3℃ with slight sinus tachycardia (108/mn) and blood pressure of 100/60 mm Hg. He was lethargic but normally oriented. Physical examination revealed mild tenderness in the mid abdomen with absent bowel sounds. No breath sounds were heard in the left lower thorax. Laboratory work demonstrated elevated white blood cell count. Plain chest films obviated an elevated diaphragm bilaterally, more pronounced on the left side. A thoracoabdominal computed tomography scan study was undertaken (fig 1).

Question

How can the left hemithorax content be related to the patient's complaints?

See page 1498 for answer

This case is submitted by:

Figure 1   Thoracoabdominal computed tomography scan.

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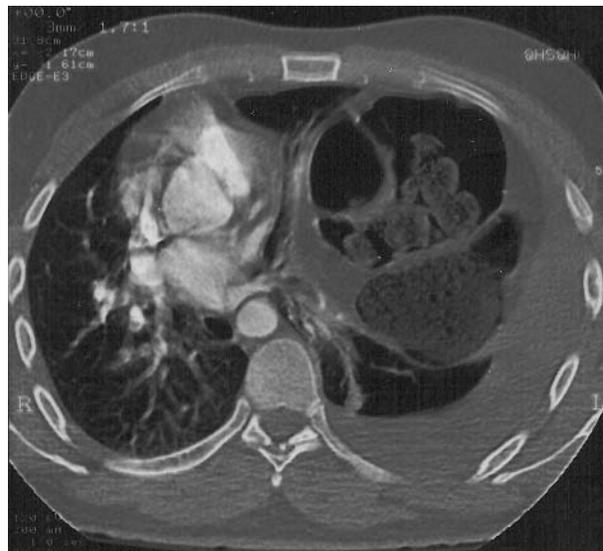
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PostScript ....

LETTERS

ITPA genotyping test does not improve detection of Crohn's disease patients at risk of azathioprine/6-mercaptopurine induced myelosuppression

The thiopurine drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective for the treatment of inflammatory bowel disease (IBD) and their prescription is increasing. Haematotoxicity, which can lead to potentially life threatening bone marrow suppression, represents the most serious side effect of thiopurine therapy. It has been attributed to the accumulation of active cytotoxic metabolites of AZA/6-MP, collectively called 6-thioguanine nucleotides, resulting from a deficiency in thiopurine catabolism specifically catalysed by the thiopurine S-methyltransferase (TPMT) enzyme. Genotyping tests are now available to identify deficient and intermediate methylators who are, respectively, homozygous and heterozygous for non-functional alleles of the TPMT gene. As pointed out by Lennard in the leading article (Gut 2002;**51**:143–6), it is clear that myelosuppression may be caused by other factors in addition to variable TPMT.

Since the identification of the molecular basis of inosine triphosphate pyrophosphatase (ITPAse) deficiency,[1] a clinically benign condition characterised by abnormal accumulation of inosine triphosphate in erythrocytes, the possibility of a correlation between thiopurine toxicity and ITPAse deficiency has been raised. Complete ITPase deficiency was found to be associated with a homozygous missense 94C>A mutation that encodes a Pro^{32}Thr exchange, whereas an intronic IVS2+21A>C polymorphism was shown to have a less severe effect, homozygotes retaining 60% ITPAse activity. It was then postulated that in ITPAse deficient patients treated with thiopurine drugs, a 6-thio-ITP metabolite could accumulate resulting in toxicity.[1] A recent study in 62 patients with inflammatory bowel disease reported a significant association between the ITPA 94C>A polymorphism and AZA related adverse effects, specifically flu-like symptoms, rash, and pancreatitis.[2] No correlation was observed with occurrence of neutropenia but only 11 patients were studied. We previously reported TPMT genotype analysis in 41 Crohn's disease (CD) patients who had experienced leucopenia during AZA/6-MP therapy.[3] Even though this study confirmed the efficiency of TPMT genotyping in identifying patients at risk of developing myelosuppression, it also highlighted its limitations, as only 27% of patients carried mutant alleles of the TPMT gene that were associated with enzyme deficiency. This prompted us to investigate the occurrence of ITPA mutations in this series of patients in order to evaluate whether genotyping of the ITPAse gene could improve the detection rate of patients at risk of thiopurine myelotoxicity.

Our population comprising 41 patients with CD has been described in detail previously.[3] Briefly, all patients had either leucopenia (white blood cell count <3000/mm³; n = 24) or thrombocytopenia (platelets <100 000/mm³; n = 30), or both (n = 14), leading either to discontinuation of treatment or reduction of dose by 50% or more during AZA (n = 33) or 6-MP (n = 8) treatment. Patients were genotyped for the ITPA 94C>A and IVS2+21A>C mutations according to a previously described procedure based on endonuclease digestion of polymerase chain reaction products.[1] Distribution of the 41 patients according to their ITPA genotype is presented in table 1 and compared with that of a previously published control population of 100 healthy Caucasians.[1] Allele frequencies in the CD population were 0.085 for the 94C>A mutation and 0.12 for the IVS2+21A>C mutation, similar to frequencies observed in the control population (0.06 and 0.13, respectively). There was no significant difference in the genotypes distribution between the two populations, which confirmed the lack of association between ITPAse deficiency and myelosuppression during thiopurine therapy. Due to the retrospective nature of the study, no correlation with other side effects could be investigated.

In conclusion, application of ITPA genotyping tests does not seem to improve the identification of patients at risk of myelosuppression with AZA/6-MP therapy. Although we believe that conventional TPMT genotyping tests should still be applied before the initiation of thiopurine treatment, further work is needed on the role of other candidate genes that may be involved in thiopurine haematotoxicity.

Acknowledgements

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Small bowel malignancy at diagnosis of coeliac disease

We were very interested in the paper by Rampertab et al (Gut 2003;**52**:121–14) and the correspondence by Hawdle et al (Gut 2004;**53**:470). Their data are quite similar to ours, from the Italian Registry of Complications of Coeliac Disease.

We collected information on 1968 patients over 18 years of age (mean age at diagnosis: 36.7 years; female/male ratio 3:1), diagnosed with coeliac diseases between January 1982 and December 2002 at 20 Italian clinical centres specialised in gastrointestinal disease. The diagnosis was made according to revised ESPGHAN criteria.[1] We found five (0.25%) patients with a small bowel malignancy at the time of diagnosis of coeliac disease. Age range was 49–69 years (mean 59 years) with a predominance of females (4:1). Survival rate was very poor as three patients died within 36 months of diagnosis.

These results indicate that there is an increased risk of developing small bowel malignancy in patients with coeliac disease. This correlation was confirmed by the female/male ratio. In fact, while small bowel neoplasms are usually more frequent in males, in our population four of five cases were female. Moreover, mean age at diagnosis of these cases was higher than that of patients overall, emphasising that the risk of a neoplasm increases with longstanding coeliac disease.

Table 1 Distribution of ITPA genotypes in 41 Crohn's disease (CD) patients and 100 healthy Caucasians

ITPA genotype	CD patients (n = 41)	Control population† (n = 100)
Wt/Wt	26 (0.63)*	64 (0.64)
Wt/94C>A	6 (0.15)	10 (0.10)
Wt/IVS2+21A>C	7 (0.17)	24 (0.24)
94C>A/94C>A	0 (0.00)	0 (0.00)
IVS2+21A>C/IVS2+21A>C	1 (0.02)	0 (0.00)
94C>A/IVS2+21A>C	1 (0.02)	2 (0.02)

*Values in parentheses represent genotype frequencies.
†The control population comprised 100 healthy Caucasians who were genotyped in a previous study.[1]

In conclusion, early diagnosis of coeliac disease should be made to prevent small bowel neoplasms from developing, and screening for this cancer should be carried out at diagnosis of coeliac disease, especially in patients diagnosed during adulthood.

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Reference

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Hypergastrinaemia in patients infected with *Helicobacter pylori* treated with proton pump inhibitors

We read with interest the commentary by McColl on *Helicobacter pylori* infection and long term proton pump inhibitor (PPI) therapy (*Gut* 2004;**53**:5–7).

It is remarkable that he did not mention gastrin although hypergastrinaemia is a result of reduced gastric acidity[1] as well as *Helicobacter pylori* infection,[2] and that patients with H pylori infection treated with PPI have additive hypergastrinaemia.[3] Hypergastrinaemia predisposes to gastric carcinoids in animals[4 5] and humans[6 7] as well as to malignant ECL cell derived tumours (gastric carcinomas) in animals[8] and humans.[9 10]

Interestingly, the carcinogenic effect of H pylori infection may be completely explained by its hypergastrinaemic effect,[11] a work where McColl was one of the authors. Furthermore, the increased gastric cancer frequency in moderate hypergastrinaemic INS-GAS mice concomitantly infected by H pylori infection[12] may also be caused by increased hypergastrinaemia in infected mice.[13]

To conclude, it is odd that gastrin was not taken into consideration when discussing the risk of gastric cancer following treatment with PPI in patients infected with H pylori. Animal as well as human studies linking gastrin to gastric cancer give support for a strategy where H pylori is eradicated in patients on long term PPI treatment.

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Terminal ileal biopsies should not be used to document extent of colonoscopic examination

We commend the British Society of Gastroenterology and the authors for the excellent publication of guidelines for the management of inflammatory bowel disease in adults (*Gut* 2004;**53**(suppl V):vi–16). However, we feel that their recommendation for routine terminal ileal biopsying is inappropriate. Although it is important to biopsy the terminal ileum if there is macroscopic evidence of an abnormality, their statement that ''a terminal ileal biopsy performed at colonoscopy documents the extent of examination'' is not recommended practice, due to the potential risk of variant Creutzfeld-Jacob disease transmission from prion proteins which are prevalent in the lymphoid tissue of Peyer's patches in the ileum. Although the use of disposable forceps may reduce the risk of transmission, there could still be contamination of the intubation channel of the colonoscope and prion protein is resistant to the standard endoscopic cleaning process.[1] If the extent of examination needs to be documented, then a photograph of the ileocaecal valve or ileal mucosa is preferable.

It is worth emphasising that prion protein may be present in any part of the gastrointestinal tract[2] and random biopsy of gastrointestinal mucosa for reasons other than confirming an endoscopic abnormality or excluding microscopic colitis is not accepta-

ble. Similarly, for surveillance colonoscopy where multiple biopsy is recommended, the risk benefit ratio of this policy must be supported by the clinical indications.

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IgG food antibodies should be studied in similarly treated groups

The recent paper by Atkinson and colleagues (*Gut* 2004;**53**:1459–1464) regarding IgG food antibodies and irritable bowel syndrome (IBS) fails to compare like with like. Regardless of the IgG results, the treatment group excluded significantly different foods to the control group, particularly those foods which appear to exacerbate symptoms of IBS. Of particular concern is the ''yeast exclusion'' diet. A low yeast diet is not a recognised diet in standard textbooks of dietetics and nutrition. However, alternative practitioners offering such a ''yeast exclusion diet'' sometimes recommend exclusion of a wide range of foods, such as: bakery products, alcoholic beverages, many other beverages including commercial fruit juices, cereals, condiments, dairy produce, fungi, meat products (hamburgers, sausages, and cooked meats made with bread or breadcrumbs), yeast extracts (Bisto, Marmite, Oxo, Bovril, Vegemite, gravy browning, and all similar extracts), all B vitamin preparations, and sometimes, most worryingly, ''sugar foods'' (sugar, sucrose, fructose, maltose, lactose, glycogen, glucose milk, sweets, chocolate, sweet biscuits, cakes, candies, cookies, puddings, desserts, canned food, packaged food, hamburgers, honey, mannitol, sorbitol, galactose, monosaccharides, polysaccharides, date sugar, turbinado sugar, molasses, maple syrup, most bottled juices, all soft drinks, tonic water, milkshakes, raisins, dried apricots, dates, prunes, dried figs, and other dried fruit).

Therefore, regardless of IgG antibody status, the dietary restrictions in one group are not controlled for by the other group, and hence the conclusion may not be valid.

It would also be helpful to know if any of the patients with IgG antibodies to a particular antigen also had IgE antibodies to the same antigen.

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IgG antibodies to foods in IBS

We read with interest the article by Atkinson *et al* (*Gut* 2004;**53**:1459–64). The authors describe an important advance in our understanding of the putative role of inflammation in irritable bowel syndrome (IBS). However, we wonder whether their conclusion that assay of IgG antibodies may have a role in identifying candidate foods for elimination to treat patients with IBS may be a step too far. The four foods to which the patients most commonly formed antibodies and hence the four foods most commonly eliminated from the "true diet" were yeast (86.7%), milk (84.3%), whole egg (58.3%), and wheat (49.3%). The "sham diet" involved eliminating foods to which the patients had not formed antibodies and, therefore, in the sham group the exclusion rates for yeast, milk, whole egg, and wheat were very low (0%, 1.3%, 26.7%, and 8% respectively). It is therefore difficult to assess whether a diet excluding these foods would have led to symptomatic improvement in all patients, regardless of their antibody status.

Furthermore, the foods to which the study group commonly formed antibodies were similar to those already identified as leading to symptomatic benefit in patients with IBS when excluded from their diet. In a review cited by Atkinson and colleagues,[1] it was noted that in eight trials of exclusion diets in IBS, seven identified dairy products and five identified wheat as worsening symptoms. It is not clear whether the difference in improvement in symptoms seen in the current study between true and sham groups can be explained simply by the omission of these foods. This could in practice eliminate the need for antibody testing.

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Reference

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Influence of dietary factors on the clinical course of inflammatory bowel disease

Jowett *et al* reported in their elegant study on the role of diet in maintaining remission in patients with ulcerative colitis (*Gut* 2004;**53**:1479–84). Surely the effect of diet has an essential, but often forgotten, role in altering the course of disease in all types of inflammatory bowel diseases. This role does not necessarily act by maintaining patients in remission clinically, but perhaps more importantly by minimising the activities of the disease and rendering it quiescent.

We have recently reported a case of active stricturing Crohn's disease in an adult female patient with high stoma output.[1] She was treated solely with casein base formula (Modulen IBD-Nestle, Vevey, Switzerland) for three weeks. Her stoma output was reduced from 2800 ml to 400 ml per day by day 10. Serum albumin and serum protein significantly increased also. She subjectively felt better and pain free and stopped her opiate and non-opiate formula. The casein based formula is a nutritionally complete formulation containing a natural anti-inflammatory growth factor, transforming growth factor α2. The mechanism for inducing remission in our patient was possibly inhibition of expression of MHC class II protein in downregulating the inflammatory response.[2]

Previous studies have shown that there is a decrease in plasma antioxidant defences in all types of inflammatory bowel disease.[3] This is mirrored by an increase in free radical peripheral leucocyte DNA damage. It is therefore possible that the casein based formula acts as an antioxidant to minimise the oxidative stress that occurs in patients with active Crohn's disease. Another possible mechanism is that this formula may have a role as a prebiotic by stimulating the activity of bacteria which are already present in the gut.

Remission induced in our case study highlights the part played by a casein based formula in the management of adult Crohn's disease. The encouraging result demonstrates the need to treat similar cases with dietary measures first. This opportunity should not be missed as it may well obviate the need for surgical intervention or administration of potent pharmacotherapeutic agents which carries the risk of several comorbidities.

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Identification of ferroportin disease in the Indian subcontinent

Haemochromatosis is a common inherited disorder of iron metabolism, characterised by excessive iron absorption and deposition in tissues. The majority of cases are associated with mutations in the *HFE* gene and inherited in an autosomal recessive manner.[1] Autosomal dominant forms of haemochromatosis have been reported, mainly associated with mutations in the *ferroportin 1* gene.[2] This syndrome, termed type 4 haemochromatosis or more recently ferroportin disease,[3] is usually characterised by an early increase in serum ferritin with normal transferrin saturation. Iron accumulation is most prominent in Kupffer cells and other macrophages, in addition to hepatocytes. Some patients do not tolerate venesection therapy well and can develop anaemia. Hereditary iron overload disorders appear to be uncommon in Asia. Secondary iron overload due to beta thalassaemia is relatively common in the Indian subcontinent. However, primary iron overload disorders and *HFE* mutations appear to be rare and cases have not been well characterised in this region.[4 5] We identified a patient from the Indian subcontinent with features typical of ferroportin disease.

A 36 year old female of Sri Lankan origin presented for a routine medical examination in December 2003. She was found to have an elevated serum ferritin of 3145 µg/l. Her serum iron (17.1 µmol/l) and transferrin saturation (29%) were normal. Liver functions tests, blood glucose, and thyroid studies were all normal. Physical examination was normal and she had no significant past medical history or risk factors for iron overload.

C282Y, H63D, and S65C *HFE* gene mutations were all negative and she had no family history of iron overload. Her mother and three siblings all had normal serum ferritin levels. Her father died of ischaemic heart disease aged 48 years.

A magnetic resonance imaging scan showed hepatic iron overload. Liver biopsy showed grade 3–4 iron deposition within hepatocytes and Kupffer cells; no fibrosis or cirrhosis was evident (fig 1). The hepatic iron concentration was 17 700 µg/g dry weight and hepatic iron index was 9.1.

Venesection therapy was initially poorly tolerated with the development of anaemia following the first two 500 ml venesections. Her haemoglobin is now stable on a programme of 300–500 ml venesections every three weeks.

The features of ferroportin disease in this patient led us to sequence the *ferroportin 1* gene, as previously described.[6] Analysis of the DNA sequence revealed a heterozygous three base pair deletion (TTG) in exon 5. This is the same deletion, V162del, described by us and others in haemochromatosis patients from Australia, the UK, Italy, and Greece.[6–9]

This is the first report to identify V162del or indeed any *ferroportin 1* mutation in an individual from the Indian subcontinent. Identification of V162del in an Asian patient confirms that this mutation is likely to be the most common mutation of *ferroportin 1* and the most common cause of non-*HFE* associated haemochromatosis. The wide geographical distribution of this mutation suggests that it is a recurrent mutation that has repeatedly arisen in distinct populations, probably by slippage mispairing.

Iron overload in this patient was typical of ferroportin disease. At the time of diagnosis she was asymptomatic and had no fibrosis on liver biopsy. Whether fibrosis or clinical complications will develop with age if iron stores are not depleted is unclear.

In conclusion, we have identified the V162del mutation of *ferroportin 1* in a fifth geographical location, emphasising that this mutation is the most common and widely distributed mutation which causes non-*HFE* haemochromatosis. We have identified V162del in a region where iron overload disorders have not been well characterised. Analysis of this and other *ferroportin 1* mutations may be useful in the study of iron overload disorders in this region and may be the basis of hitherto unexplained cases of iron overload.
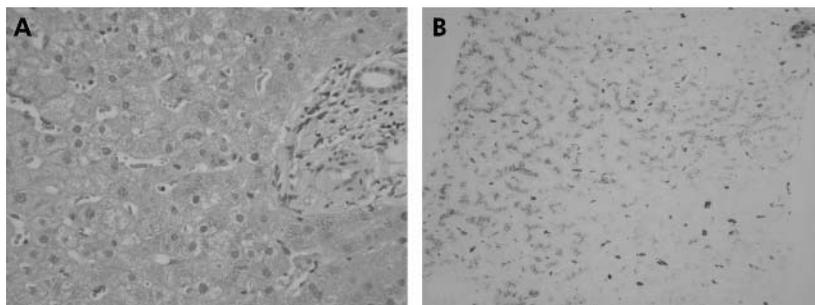
Figure 1 Liver biopsy sections from our patient stained with (A) haematoxylin and eosin and (B) Perls' Prussian blue (magnification 100×). Grade 3–4 iron is prominent in hepatocytes and Kupffer cells.

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BOOK REVIEW

Morson and Dawson's Gastrointestinal Pathology, 4th edn

Edited by D W Day, J R Jass, A B Price, et al. Massachusetts: Blackwell Publishing, 2003, £175.00, pp 692. ISBN 0-632-04204-4

Why do people buy s book such as this, which involves a not inconsiderable financial outlay (even if you box clever and make it tax deductible)? I think for two main reasons—firstly, for use as a bench book, and secondly, for information on the pathological basis of gastrointestinal disease for interest, teaching, or indeed research purposes.

On the first criterion, this book succeeds, usually quite brilliantly. As a *vade mecum* on gastrointestinal pathology it should be on the shelf of every pathologist who engages in the reporting of such material. In my view, the book is more user friendly than the competition—Fenoglio-Preiser and Goldman to name but two—and is certainly more readable. I would therefore extol its virtues unreservedly in this respect.

On the second criterion, as a source book, I suppose the correct word is patchy. Some sections, for example that on colorectal tumours, is admirable in this respect, whereas other sections are more limited in scope and even cursory in their treatment of the pathobiology. There is also the problem of the unavoidable intrinsic delay in producing such a book, resulting in reference lists which are some years away from the publication date. I am aware however that my personal outlook is not that of most individuals who will purchase this volume so I am probably being over critical. It is, after all, quintessentially a bench book, and excellent at that.

However, I do have one real beef. In any multiauthor work there is bound to be variation, but here we are not told which one of the stellar caste were responsible for which section or chapter. Of course we can make informed guesses about the Barrett's or colorectal carcinoma sections, but who did the GIST bit? Because of some (minor) errors in the criteria for the diagnosis of malignancy, I have tried to berate a number of authors who have all denied responsibility, and blamed someone else—usually the author(s) absent at the time. Not good enough.

I have to concede however that the authors have succeeded in producing perhaps *the text* in gastrointestinal pathology, which is a credit to both themselves and the discipline in the UK. I congratulate them.

N A Wright

CORRECTIONS

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In the January 2005 issue of *Gut*, one of the author's names of the paper entitled Human peripheral and gastric lymphocyte responses to *Helicobacter pylori* NapA and AphC differ in infected and uninfected individuals (H J Windle, Y S Ang, V A Morales, R McManus, and D Kelleher. *Gut* 2005;**54**:25–32) was cited incorrectly. V A Morales should read V Athie-Morales. The journal apologises for this mistake.

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In the December issue of *Gut* fig 1 in the paper by AJG Bell *et al* (Human lymphocyte stimulation with pouchitis flora is greater than with flora from a healthy pouch but is suppressed by metronidazole. *Gut* 2004;**53**:1801–1805) is incorrect. The labels for fig 1C are inverted; the squares should have been labelled HetNon and the triangles HetPM. The legend is also incorrect because the label for flora grown on agar without metronidazole is HetNon, not HetP as stated.