

Food intolerance and Crohn's disease

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Abstract

It has been claimed that prolonged remissions of Crohn's disease can be achieved after enteral or parenteral nutrition, by identifying and excluding foods that exacerbate a patient's symptoms. The occurrence of food intolerances were assessed after induction of remission with elemental diet in 42 eligible patients to whom single foods were introduced over five days. Suspect foods were reinvestigated with open and if possible, double blind rechallenge. Fourteen patients (33%) dropped out of the study because of relapse of disease unrelated to food (n=8) or because of difficulties in complying with the regimen (n=6). Twenty (48%) of the patients identified food sensitivities whereas eight (19%) did not. Seventeen of the patients who identified food sensitivities had an open rechallenge with recurrence of symptoms in 10 (24% of total). Food sensitivity was confirmed in three patients on double blind challenge. There was no significant difference in the duration of remission between patients who did or did not identify food sensitivities. During the study three cases of intolerance to the formula diet, and one of severe salicylate sensitivity were encountered. In conclusion food sensitivities are evident after treatment of Crohn's disease with elemental diet but are variable, often do not persist, and are of insufficient importance to warrant putting all patients through elimination diets.

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It has been claimed that food sensitivities occur often in Crohn's disease and that exclusion of foodstuffs after treatment with elemental diet prolongs remission.^{1,2} This is particularly intriguing as it incriminates food in the pathogenesis of Crohn's disease. In support of this theory there is evidence of a close correlation between activity of Crohn's disease and conditions within the intestinal lumen. Thus diversion of faecal stream by split ileostomy may induce remission of resistant Crohn's colitis, and enteral or parenteral nutrition seem to be as effective as corticosteroids in inducing remission whereas both forms of treatment are singularly ineffective in the management of ulcerative colitis.³⁻⁵

The main work on the subject of food intolerance in Crohn's disease by Alun-Jones *et al*^{1,2} has involved the use of elemental diet or total parenteral nutrition to obtain clinical remission from active disease, followed by a daily, single food reintroduction regimen (elimination diets). Two open studies and a controlled trial report on the treatment of a total of 77 patients all of whom had achieved full clinical remission by means of diet (parenteral nutrition (33), enteral nutrition (25), and 19 simply by the use of elimination

diets). Daily food reintroductions were successfully carried out in 64 patients with subsequent exclusion of suspect foods. Life table analysis (of all 77 patients) showed a 32% relapse in the first year then an annual relapse rate of 11%. The controlled trial compared duration of remission on an elimination diet (n=10) with that on an unrefined carbohydrate, fibre rich diet (n=10). This study, however, had to end prematurely, apparently because of the high relapse rate in the fibre rich group.⁶ It was concluded from these studies that elimination diets induce a prolonged remission similar to that achieved by other methods of treatment.⁷ More recently an independent although smaller study has been reported, which again used a daily food reintroduction programme.⁸ In this study only nine of 20 patients identified food sensitivities. The four double blind challenges that were done were negative and only 30% maintained remission for longer than 12 months indicating no influence of elimination diets on the duration of remission. Ginsberg and Albert have described a patient with severe steroid dependent disease who was shown to have milk sensitivity (despite a normal lactose tolerance test) by double blind challenge. A full remission was maintained by avoidance of dairy products but in long term follow up the sensitivity was not persistent.⁹

Hence, the occurrence of food sensitivity in Crohn's disease after elemental diet, its significance regarding the duration of remission achieved, and its value in the routine management of patients treated with elemental diet is uncertain. Our aim was to investigate food intolerances in Crohn's disease after treatment with elemental diet and its importance in the duration remission induced by diet in an attempt to determine how valuable such therapeutic dietary manipulation is.

Patients and methods

Patients were selected from a group of 80 who were admitted to Northwick Park Hospital during a five year period for management of active Crohn's disease with an elemental diet. Thirty eight of these were excluded from this study. Thirteen would have been unable to cope with the elimination regimen for social reasons or because of poor understanding, eight had tight small intestinal strictures, and eight were on high dose steroids (both of which would have made the results difficult to interpret), four refused, two were treated for postoperative fistulas, two were pregnant, and one was treated for extensive pyoderma gangrenosum and had no gastrointestinal symptoms.

Forty two patients (Table I) who had responded satisfactorily to a four to eight week course of elemental diet proceeded to investigation of possible food intolerances. Eight had

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TABLE I Details of the 42 patients studied

Age	Sex	Site of disease	Food intolerance			Duration of remission (months)
			1st	2nd	DB	
65	F	SB	+	+	+/-	53*
14	F	SB	+	-		28†
21	F	SB	+	-		37†
23	F	SB	-	-		10†
15	F	SB	-	-		6†
18	M	I	-	-		19*
30	M	I	-	-		7†
54	M	I	+	-		20*
51	F	I	+	+	ND	6†
31	M	I	+	+	ND	24*
17	F	I	+	+	-	39*
30	F	I	+	+	+	54*
28	M	IC	-	-		9*
21	M	IC	-	-		7†
56	F	IC	-	-		6†
50	M	IC	+	ND		4†
16	M	IC	+	ND		13†
26	M	IC	+	-		23†
20	F	IC	+	-		28†
25	F	IC	+	+	ND	21†
44	M	IC	+	+	ND	10†
20	M	C	-	-		13*
24	F	C	+	-		46*
34	M	C	+	-		11†
18	F	C	+	-		28†
24	F	C	+	+	+	22†
18	M	All	+	+	ND	7*
33	M	All	+	+	+	6*
16	M	SB	DC			
25	F	SB	ER			
21	F	I	DC			
42	F	I	ER			
13	M	I	DC			
15	M	I	DC			
28	F	I	ER			
23	M	I	ER			
28	M	I	ER			
23	M	IC	ER			
27	F	IC	ER			
22	M	IC	DC			
33	M	C	DC			
20	F	C	ER			

+ = Positive challenge; - = negative challenge; † = time of relapse; * = still in remission; ND = not done; 1st = first food introduction; 2nd = open food rechallenge; DB = double blind challenge; SB = small bowel; I = ileal; IC = ileocolonic; C = colonic; All = all sites involved; DC = did not comply; ER = early relapse.

evidence of stricturing on barium radiographs but none had a history suggestive of obstructive episodes. All patients gave fully informed consent for these studies that were approved by the Harrow Health Authority ethics committee.

Remission from active disease was achieved with elemental diet (Elemental 028 Scientific Hospital Supplies, Liverpool, UK or Vivonex from Norwich Eaton, Surrey, UK) as the sole source of nutrition for four to eight weeks as previously described.¹⁰ In the final week of treatment, when remission had been achieved, the patient's normal diet was discussed paying particular attention to any personally suspected food intolerances. Then an individualised reintroduction programme was designed for each patient, usually starting with rice or potato and lamb or chicken on the first week. Each food was introduced over five days with suspect foods being left until all other reintroductions were complete. During the early phase of reintroductions patients continued with elemental diet as a nutritional supplement. Figure 1 shows the method used for the dietary diagnosis of food intolerances in these patients. Each patient kept a daily diary to record and score symptoms (nausea, flatulence, pain, bowel openings, etc) and to note other life occurrences (family or work stress, coincidental illness such as flu, menstrual period, etc). Patients were reviewed every week for the first month and every other week until

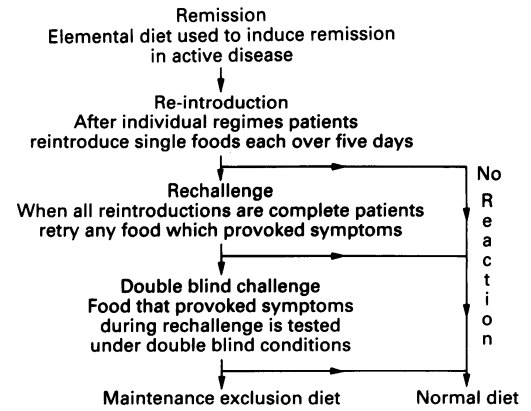


Figure 1: Method used for dietary diagnosis of food intolerance in Crohn's disease.

food reintroductions were completed. If symptoms of disease occurred during any five day reintroduction then that particular food was said to be suspect and was temporarily omitted from the diet. The patient returned to eating only foods that had been shown to be safe. When symptoms resolved further reintroductions were commenced.

Suspect foods were tried again in an open reintroduction and if symptoms recurred the patient was offered a double blind challenge all of which were done as inpatient studies. Suspect food was masked in a meal in which all other constituents were known to be safe. All challenge and placebo meals were assessed by five volunteers for smell, taste, and texture to determine if the challenge food could be detected. Meals were checked when fresh, after freezing and thawing, and when appropriate after heating. When an acceptable formula was found to conceal the suspect food, the test and challenge meals were made up, labelled, and frozen by a person not involved in the study. Patients received the challenge or placebo for five days with a two week interval between.

At each review particular watch was kept for the development of inappropriate obsession with food or an excessive tendency to limit diet and reintroductions. Patients developing such features (n=6) were excluded from the study and gradually weaned onto a normal unrestricted diet. When all reintroductions and challenges were complete the maintenance diet was reviewed in detail to ensure that it was nutritionally adequate.

During the study period three patients were found to be sensitive to the elemental diet formula used to induce remission and a further patient proved to have profound salicylate sensitivity. The cases of these particular patients are reported in detail.

STATISTICAL ANALYSIS

The long term outcome of groups of patients was compared with log rank significance testing.¹¹

Results

EXCLUSION AND CHALLENGE

Figure 2 shows the results of the reintroduc-

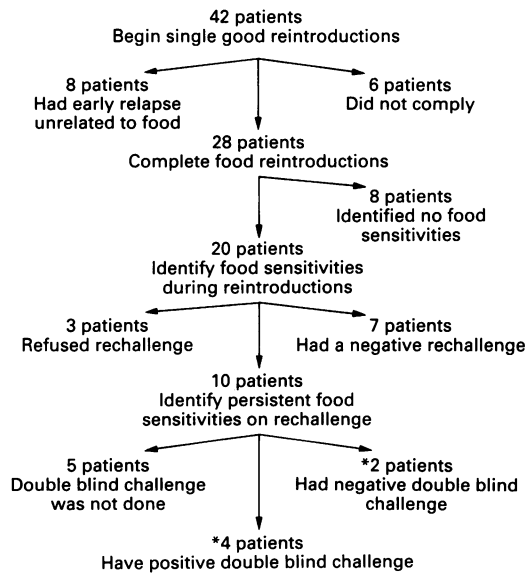


Figure 2: Results of single food reintroduction in patients with diet induced remission from active Crohn's disease. ★ One patient had two double blind challenges of which one was positive and the other negative.

tion regimen. Of the 42 patients who began individual food reintroductions 28 completed the regimen. Eight failed to do so because of a recurrence of their disease that could not be attributed to any particular food constituent. A further six patients were withdrawn because they could not tolerate the restrictions of the regimen (three of these were teenagers).

During the reintroductions phase, eight (of 28) patients remained symptom free. Table II shows the foods that the remaining 20 patients identified as causing symptoms. Figure 3 shows that the highest frequency of intolerances seem to occur in the first eight weeks after completing the course of elemental diet.

TABLE II Foods identified as causing symptoms on reintroduction, on rechallenge, and on double blind challenge

Food sensitivities identified on reintroduction	Food sensitivities identified on rechallenge	Food sensitivities identified on double blind challenge
Milk (5)	Milk (4)	Milk (1)
Peanuts (5)	Peanuts (2)	Peanuts (1)
Citrus fruits (3)	Citrus fruits (1)	Wheat (1)
Wheat (2)	Wheat (1)	Salicylate } (1)
Eggs (2)	Eggs (1)	Aspirin }
Fish (2)	Haricot beans (1)	
Haricot beans (2)	Aspirin (1)	
Apple (2)	Alcohol† (1)	
Coca Cola (2)	Chicken (1)	
Aspirin (1)	Plums (1)	
Alcohol (1)	Beetroot (1)	
Cockles (1)		
Pork (1)		
Beef (1)		
Chicken (1)		
Oats (1)		
Rye (1)		
Corn (1)		
Chocolate (1)		
Ice-cream (1)		
Sausages (1)		
Plums (1)		
Blackcurrants (1)		
Mushrooms (1)		
Cabbage (1)		
Spinach (1)		
Lettuce (1)		
Beetroot (1)		

Numbers of patients identifying the specific food sensitivity in parentheses.
 †All alcoholic beverages caused diarrhoea; an open trial of pure ethanol also caused diarrhoea.

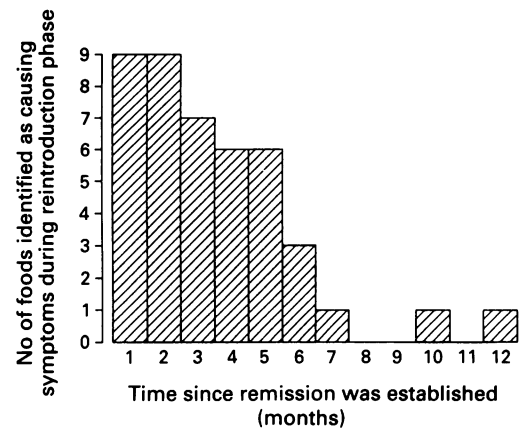


Figure 3: Frequency of identifying food intolerances related to time since diet induced remission in patients with Crohn's disease undergoing single food reintroduction.

Of the twenty patients eligible for phase 2, three refused to try the suspect foods arguing that they were not important in their diets (mushroom, apple, and peanuts) and they did not wish to risk a recurrence of symptoms. Seven patients had negative food rechallenges and were instructed on healthy eating habits.

Ten patients consistently identified the same foods as causing their symptoms. Of these three identified one food only, one identified two foods, two identified three foods, two identified four foods, one identified five foods, and one (salicylate sensitivity) identified multiple foods. Five patients who consistently identified particular foods as causing symptoms did not have double blind challenges. Three of these had recurrence of their disease despite being on exclusion diet (milk, peanuts, and plums) and rechallenge was inappropriate. One patient had identified milk as causing symptoms but his lactose tolerance test was positive and he remains well on a lactose free diet. One patient had identified alcohol to cause diarrhoea. It was not possible to construct a satisfactory double blind challenge to pure ethanol. Two patients had negative double blind challenges (chicken and haricot beans), four patients (one of the group of five had one positive and one negative double blind challenge) had positive double blind challenge with wheat, milk (lactose tolerance test was normal), peanuts, and salicylate.

The 16 patients who did not identify foods as causing symptoms have been followed up for between nine and 46 months. Figure 4 shows the duration of remission. Twelve patients completed the food exclusion arm of the study and continued to avoid the foods that had caused symptoms. Figure 4 shows that their follow up time has ranged from seven to 55 months and the duration of their remission did not differ significantly ($p=0.1$) from patients who did not have food sensitivity.

SPECIAL CASES

Formula intolerance

There were three cases of formula intolerance. A 24 year old woman had been diagnosed five years

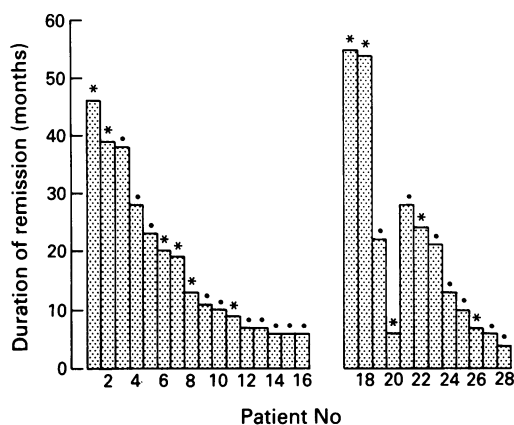


Figure 4: Duration of remission from active Crohn's disease in patients who had a negative (1-16) or positive (17-28) food reintroduction process. ★ Patients who were still in remission when the study was completed. ● Patients who had relapsed during the study period.

previously and had persistent abdominal pain, diarrhoea, and ill health despite repeated courses of steroids. She started on $\frac{1}{3}$ strength Vivonex (the carbohydrate source is glucose solids of maize origin and the fat source is safflower oil) orally but her diarrhoea became worse and she began to vomit. Nasogastric tube feeding was started but symptoms persisted over the next 24 hours. Intravenous steroids were given but there was no improvement over 48 hours. Her nasogastric feed was then changed to a modular feed in which the carbohydrate was potato based. Her improvement was dramatic and within 24 hours. One week later a double blind challenge with Vivonex resulted in recurrence of vomiting and diarrhoea that resolved immediately when her feed was changed. As she progressed through elimination diet both wheat and corn caused diarrhoea on first reintroduction but not later. Four years later she is symptom free and on a normal diet.

A 24 year old man was admitted for treatment for newly diagnosed ileocolonic Crohn's disease. He started to take oral Elemental 028 (the carbohydrate source is glucose of maize origin and the fat source is arachis oil). His symptoms worsened over three days and he began to vomit. Nasogastric feeding was started with $\frac{1}{3}$ strength feed but he continued to deteriorate and developed persistent vomiting. A change to a modular formula diet, as in the previous case, resulted in an immediate loss of symptoms and a 24 month complete remission. As he progressed through food reintroductions he did not identify anything that caused symptoms.

A 26 year old man was admitted for treatment of newly diagnosed stricturing ileal Crohn's disease associated clinically with an ileovesical fistula. To improve his nutritional state and get him into clinical remission before surgery he was given Elemental 028 but immediately became systemically unwell and developed diarrhoea and vomiting. Nasogastric feeding exacerbated matters but his symptoms settled as soon as he was changed to a modular feed. Elective surgery was carried out six weeks later and he did not therefore proceed through food reintroductions. He remains well three years later.

Salicylate sensitivity

A man had small bowel Crohn's disease with multiple strictures diagnosed in 1976 at age 18 years. High dose corticosteroids were unhelpful and he underwent ileal resection with a 12 month remission. An obstructive episode was treated with bypass enteroenteric anastomosis and maintenance prednisolone and he remained in remission for five years. Obstructive symptoms then resulted in a further small bowel resection but he did not achieve remission despite prednisolone. He was referred in 1984 and had a full clinical remission with elemental diet and began single food reintroductions. Severe reactions were encountered on two occasions to citrus fruits (high in salicylate) but further progress was hampered by obstruction at the old anastomosis that had to be refashioned in 1986. For the next four years he was symptom free only while on elemental diet despite at least 12 week trials of prednisolone, azathioprine, and methotrexate. The ileocolic anastomosis required a stricturoplasty without remission. After a prolonged course of elemental diet an elimination diet was repeated and it became evident that he was profoundly sensitive to salicylate. Four months after beginning a low salicylate diet a fistula at the site of the stricturoplasty required resection. He is now (two years later) in complete remission, remains on a strict low salicylate diet, and is on no medication apart from supplements. Both his double blind challenge and two inadvertent home challenges with salicylate were characterised by violent vomiting and diarrhoea.

Discussion

Out of a group of 80 patients with Crohn's disease treated with elemental diet 48% were judged to be unsuitable for the food exclusion study. Twenty (47%) of the remaining 42 patients studied were able to identify foods that caused symptoms. These apparent food sensitivities were often not persistent and only 24% of patients identified the same food on rechallenge, and 15% of patients had positive double blind challenge. There was only the occasional dramatic response to food exclusion, as shown by the patient with salicylate sensitivity and overall avoidance of suspect foods did not prolong remission. Formula sensitivity to elemental diet in Crohn's disease has not previously been reported but should be considered when symptoms are exacerbated early in the treatment phase especially if associated with vomiting.

Our findings are similar to those of Gaffer *et al*⁸ but contrast sharply with those of the Cambridge group who found a higher occurrence (83%) of food related symptoms in their patients and a longer remission in those identifying food intolerances.^{1,2} Both studies, however, are not strictly comparable as we used elemental diet for at least four weeks and had five day introduction cycles with reintroduction of once only identified foods whereas Alun-Jones *et al* used diet to symptomatic remission only, had a daily introduction programme without repeat exposure to suspect foods, and in one study used a high fibre diet in the control group.²

Contrary to previous claims, when food

related symptoms are identified after an exclusion diet, this does not seem to prolong remission in most patients. The reason for this is not clear but it is worth noting that McCamman *et al* noted that 'explosive diarrhoea, gas, cramps, sweating, and feeling light headed were common complaints' after healthy volunteers finished an elemental regimen and started to eat food.¹² This suggests that some symptoms in patients with Crohn's disease may stem from motility disturbance and such food related symptoms would be unlikely to influence the duration of remission.

There are, however, other possible mechanisms by which food sensitivities are mediated. The most interesting case was reported by Ginsberg and Albert. He was a patient with well documented milk sensitivity that was not persistent and may have been related to activity of disease.⁹ It would seem, however, that the occasional patients with such sensitivities (as in our patient with salicylate sensitivity) come to light clinically because of chronic persistent disease activity rather than the more usual relapsing and remitting disease and it is for these patients that the elimination diets may be more appropriate.

Reintroduction of food after elemental regimens must nevertheless be undertaken with the greatest of care irrespective of whether or not elimination diets are used. Eight patients have required emergency surgery coinciding with the unrestricted reintroduction of food after remission induced by diet.^{2,8,13} In two of the studies the details of the individual patients are not reported. Our own experience (two patients) and that of Morin *et al*¹³ has been that such acute relapses only occur in patients who have strictures or fistulas.

In summary food intolerance occurs in Crohn's disease but is not as frequent as claimed by some previous studies and its occurrence and intensity are variable. Our study suggests that food sensitivity is of insufficient importance to warrant putting all patients through elimination diets.

- 1 Workman EM, Alun-Jones V, Wilson AJ, Hunter JO. Diet in the management of Crohn's disease. *Human Nutrition Applied Nutrition* 1984; **38**: 469-73.
- 2 Alun-Jones V, Workman E, Freeman AH, Dickinson RJ, Wilson AJ, Hunter JO. Crohn's disease: maintenance of remission by diet. *Lancet* 1985; *i*: 177-80.
- 3 Jewell DP, Kettlewell MGW. Split ileostomy for Crohn's colitis. In: Bayless TM, ed. *Current Management of inflammatory bowel disease*. Toronto: B C Decker, 1989: 294-6.
- 4 O'Morain C, Segal AW, Levi AJ. Elemental diet as a primary treatment of acute Crohn's disease: a controlled trial. *BMJ* 1984; **288**: 1859-62.
- 5 Alun-Jones V. Comparison of total parenteral nutrition and elemental diet in induction of remission of Crohn's disease. *Dig Dis Sci* 1987; **32S**: 100-7.
- 6 Hunter JO. Crohn's disease - dietary management. In: Hunter JO, Alun-Jones V, eds *Food and the gut*. London: Baillière Tindall, 1985: 221-37.
- 7 Summers RW, Switz DM, Sessions JT, Beckett JM, Best WR, Kern F, *et al*. National co-operative Crohn's disease study: results of drug treatment. *Gastroenterology* 1979; **77**: 847-69.
- 8 Gjaffer MH, Cann P, Holdsworth CD. Longterm effects of elemental and exclusion diets for Crohn's disease. *Aliment Pharmacology and Therapeutics* 1991; **5**: 115-25.
- 9 Ginsberg AL, Albert MB. Treatment of a patient with severe steroid dependent Crohn's disease with non-elemental formula diet. Possible aetiologic dietary factor. *Dig Dis Sci* 1989; **34**: 1624-8.
- 10 Teahon K, Bjarnason I, Pearson M, Levi AJ. Ten years experience with elemental diet in the management of Crohn's disease. *Gut* 1990; **31**: 1133-7.
- 11 Peto R, Pike MC, Breslow NE, Cox DR, Howard SV, Mantel N, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977; **35**: 1-39.
- 12 McCammon S, Beyer PL, Rhodes JB. A comparison of three defined formula diets in volunteers. *Am J Clin Nutr* 1977; **30**: 1655-60.
- 13 Morin CL, Roulet M, Ry CC, Weber A. Continuous elemental enteral alimentation in children with Crohn's disease and growth failure. *Gastroenterology* 1980; **79**: 1205-10.