

Ten years' experience with an elemental diet in the management of Crohn's disease

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Abstract

The immediate and longterm outcome of treating patients with acute Crohn's disease with an elemental diet was studied retrospectively. Successful diet induced remission was achieved in 96 of 113 patients (85%) regardless of age, sex, site or severity of disease, or associated complications of strictures, fistula, or perianal disease. Treatment was unsuccessful in 17 patients (15%), but there were no features at the outset of treatment that distinguished these patients from those who had successful remission. The longterm outcome of treatment was assessed over a five year period by analysis of life tables and survival curves. Twenty two per cent of the patients relapsed within six months of treatment and thereafter the annual relapse rate was 8-10%. Patients with disease complicated by fistula or perianal involvement had early relapse, approaching 100% for the latter. A further retrospective comparison of long-term outcome of diet *v* steroid induced remissions showed no significant difference in the relapse rates between the two groups at one, three, and five years.

It is now generally accepted from two large clinical studies^{1,2} that steroids are beneficial in obtaining remission from acute Crohn's disease and that sulphasalazine is effective in mild to moderately active Crohn's colitis. There have been encouraging reports on the value of cyclosporine^{3,4} and quadruple chemotherapy⁵ as used in tuberculosis, but like immunostimulation and immunosuppression their role is not firmly established. Once remission is achieved, there are no concrete guidelines on how to prolong it.^{1,2,6,7}

The universal problem with all these conventional treatments is the frequency and severity of their side effects and their toxicity when given long term.^{2,8} An alternative approach to treatment has been to use chemically defined diets or total parenteral nutrition for the induction of remission. The physiological aspects of these diets were detailed by Winitz *et al.*⁹ Initial use was largely confined to the short bowel syndrome, gastrointestinal fistula, and nutritional support of debilitated patients, many of whom had Crohn's disease.¹⁰⁻¹² Observation of improvement not only in nutritional state but also in disease activity led Voitk *et al.*¹³ and Fisher *et al.*¹⁴ to propose dietary manipulation for use as a primary treatment for inflammatory bowel disease. Several reports attest to the value of such treatment.^{15,16} Furthermore, trials comparing elemental diets, steroids, and total parenteral nutrition^{17,18} show all treatments to be equally

effective. Dietary manipulation appears to be of particular value in paediatric patients with Crohn's disease^{19,20} where the treatment may reverse growth failure.

Most studies to date have been small and short term. There is now the need to assess the overall effectiveness of elemental diet in a large number of patients with Crohn's disease, the effect of site and severity of the disease on the success of treatment, and the longterm outcome after diet induced remission. This study is a retrospective analysis of our experience with elemental diets in 113 patients with Crohn's disease which addresses these questions.

Patients and methods

Between 1977 and 1988, 113 patients with Crohn's disease²¹ were treated with an elemental diet at Northwick Park Hospital. Their medical records were reviewed. We also reviewed the records of 37 patients who were treated during this time with steroids only and who had not undergone intestinal resection previously.

Note was made of the patient's age, sex, details of diagnosis, the site of disease, past history of the illness, symptoms, weight, haemoglobin concentration, erythrocyte sedimentation rate, and serum albumin concentration before and after treatment. The Crohn's disease activity index as described by Harvey and Bradshaw²² was calculated where possible.

The treatment phase analysed was the first treatment recorded at our unit for active Crohn's disease with prednisolone or elemental diet, or both. Treatment with steroid or elemental diet has followed a standardised protocol. Prednisolone has been given in a high dose oral pulse of 0.75 mg/kg/day which is then gradually reduced.

Elemental diet (Vivonex, Norwich Eaton, Surrey, UK), used either as the sole treatment of active Crohn's disease or as part of a treatment programme, has been given as the only source of nutrition for periods averaging four weeks (range 2-12 weeks). Nitrogen was given at 0.17-0.3 g/kg/day depending on the extent of nitrogen depletion and energy at 8.4-12.6 MJ. Starter regimens were used beginning the feed at 1/3 strength and 1800 ml. Over a three day period the osmolality was increased to full strength (550 mmol/l) and subsequently as extra energy and nutrition are required the volume is increased. The poor palatability of the diet was in part overcome by flavouring, cooling, and drinking from a straw. Failing this the diet was administered via a fine bore nasogastric tube.

The response to treatment was deduced from both the patient's and the physician's assessment and a remission was said to have occurred when both noted a return to prerenal well being.

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Failure of treatment was said to have occurred if the patient was no better at the end of treatment or if the treatment plan had to be changed either because the patient's clinical state deteriorated or because he or she could not tolerate the proposed regimen.

A relapse was defined as the reappearance of clinical features of disease requiring a change in management.

STATISTICS

Sequential data were analysed by the paired Student's *t* test. The longterm outcome of treatment was analysed using lifetable and survival curve analysis. Comparison between the long-term outcome of groups with different treatment regimens or different anatomic location of disease was made using lifetable and survival curve analysis and logrank significance levels. For these analyses 'censoring' of patients refers to those patients who had been lost to follow up or had not yet reached the time point being analysed.²³⁻²⁵

Results

In the group of 113 patients who were treated with an elemental diet there were 56 women and 57 men. Ninety six took the diet orally and 17 required nasogastric feeding. Their average age was (mean (SD)) 32 (15) years. Thirty patients were newly diagnosed and 83 had been diagnosed six years (2 months to 24 years) previously (median and range). Twelve patients had associated perianal disease and five had extraintestinal manifestations of disease.

IMMEDIATE OUTCOME

Table I shows the site of disease and indication for treatment in the 113 patients treated with an elemental diet. Ninety six (85%) obtained remission, of whom 72 were treated with an elemental diet only and 24 continued the maintenance dose of prednisolone on which they had relapsed. Sulphasalazine had been continued if it had previously been of benefit. Figure 1 shows that the site of disease does not appreciably affect the chances of obtaining a remission. The details of remission are shown in Figure 2. The modified Crohn's disease activity index could be calculated for 67 patients. There was a significant improvement from pretreatment values of (mean (SD)) 8.3 (3.5) to 2.8 (1.9) after treatment ($p < 0.001$). There were similar improvements in the erythrocyte sedimentation rate ($n = 67$) and

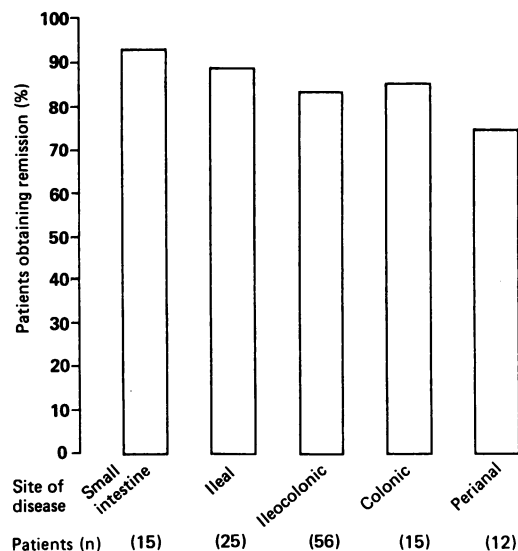


Figure 1: The success rate of obtaining remission v site of disease in patients treated for active Crohn's disease with elemental diet. (Ten patients with perianal disease have been grouped in more than one group).

albumin ($n = 64$): 42 (27) mm in the 1st h to 18 (14) mm in the 1st h ($p < 0.001$) and 34 (8) g/dl to 38 (5) g/dl ($p < 0.001$) before and after treatment respectively. Body weight increased significantly ($n = 55$) by 1.8 kg ($p < 0.001$), but ranged from a loss of 9 kg to a gain of 16 kg. Haemoglobin concentrations did not change significantly during treatment.

Seventeen patients failed to obtain remission with the elemental diet and of these, seven patients could not tolerate the diet. Table I and Figure 1 show that treatment failure was not related to the site of disease. There were no features (sex, age, site of disease, and disease activity) that distinguished this group at the onset of their exacerbation from those successfully treated. Altogether, 17% (five of 30) of newly diagnosed patients and 14% (12 of 83) of patients with an established diagnosis of Crohn's disease failed to obtain remission.

LONGTERM OUTCOME

The longterm outcome after successful treat-

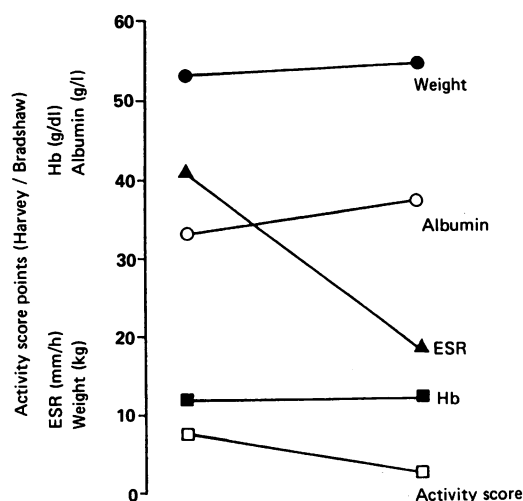


Figure 2: The changes in activity score, haemoglobin, erythrocyte sedimentation rate, albumin, and weight occurring during dietary treatment.

TABLE I Anatomic location of disease, complications, and results of treatment in 113 patients treated with elemental diet

Disease	Total No of patients	No of patients with symptomatic strictures	No of patients with fistula	No of patients who had surgery while on diet and in remission	Failure to obtain remission
Small intestinal	15	9	1	3	1
Terminal ileal	25	15	2	3	3
Ileocolonic	56	11	6	9	9
Colonic	15	0	1	1	2
Perianal	12*				3*
Extraintestinal	5*				

*Ten of those with perianal disease and those with extraintestinal disease have been classified in more than one group.

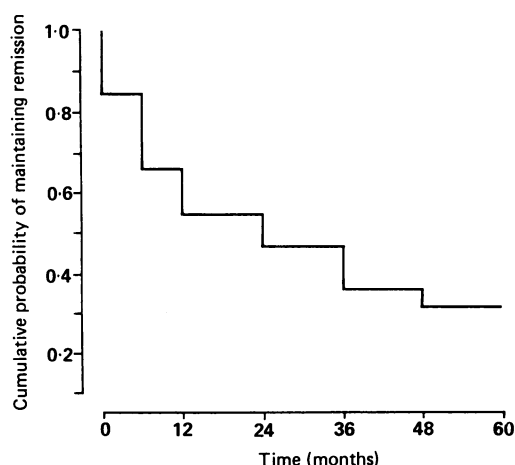


Figure 3: Survival probability curve showing the cumulative probability of maintaining remission for the 113 patients who were started on an elemental diet as treatment for active Crohn's disease. This curve is drawn from the lifetable data in Table II.

ment with the elemental diet was analysed in the following groups of patients.

Group 1

This group includes all 96 patients who had a successful response to treatment with the elemental diet including 16 patients (nine from diet only group and seven from diet plus maintenance prednisolone group) who proceeded in remission directly to surgery. To allow for the possibility that a maintenance dose of prednisolone might influence the outcome of treatment we calculated separate life tables for the group treated with diet alone ($n=87$) and for those who continued the maintenance dose steroid on which they had relapsed ($n=26$). Using the log-rank significance test there was no significant difference between the two groups ($p>0.05$). Both these groups were therefore combined in calculating the survival curve in Figure 3 and the life table in Table II. Altogether, 22% of patients relapsed in the first six months; thereafter the relapse rate was predicted at 8–10% per year. The probability of maintaining remission at three years was 38%.

This group was analysed to determine the influence of the site of disease on the longterm outcome (Fig 4). There was no significant difference between the four subgroups with regard to sex distribution, mean age, or duration of disease. In small intestinal disease relapse occurred early and the probability of maintaining remission for three years was 59%. In ileal

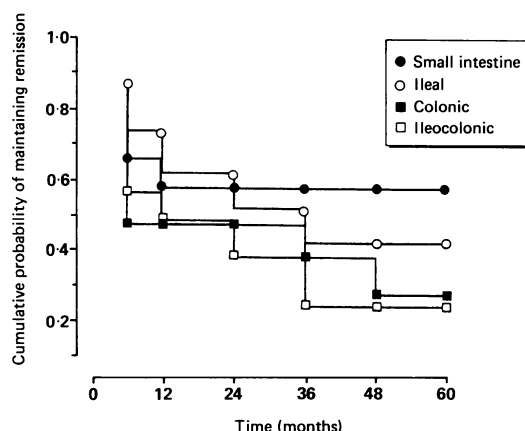


Figure 4: Survival probability curves, classified according to site of disease, predicting cumulative probability of maintaining remission in a group of 111 patients treated for active Crohn's disease with elemental diet.

disease early relapse was not a feature and once remission was obtained relapse was predicted at a rate averaging 12% per year and the probability of maintaining remission for three years was 54%. Early relapse was evident in colonic and ileocolonic disease. Altogether, 37% of those with colonic disease, who had obtained remission, relapsed within the first six months. After this period the relapse rate of colonic and ileocolonic disease averaged 10% per year and at three years 26% of patients with ileocolonic and 39% with colonic disease were still in remission. At the time points shown in Figure 4, there was no significant difference in the relapse rate of disease for the different anatomic locations.

Group 2

In this analysis a comparison was made between those patients treated with diet alone ($n=52$) and those who had been treated with prednisolone only ($n=37$). In an attempt to make the groups comparable all patients who had previous surgery were excluded from analysis. The clinical details of the groups are summarised in Table III. There were no significant differences between the two groups for age, sex, or duration of disease; however, most of the 37 patients in the steroid group were treated before 1984 when the unit was gaining experience with the elemental diet and steroids were still the mainstay of treatment for acute Crohn's disease. The life tables and survival probability curves for these patients are shown in Tables IV and V and Figure 5. Of note from the life tables is that fewer of the group treated with prednisolone were 'censored' during the five year period of analysis. It seems from the survival curves that the patients treated with diet fared better at most time points than those treated with prednisolone. When the number of relapses occurring at each time point were compared, however, there was no significant difference between the two groups.

COMPLICATED DISEASE

Thirty three of 35 patients with symptomatic strictures achieved remission. Twelve had elective surgery while in remission at the end of

TABLE II Lifetable analysis on 113 patients who were treated with an elemental diet for an acute exacerbation of Crohn's disease

Time (months)	No at start	Censored during this time*	No at risk	No who relapsed	Probability of maintaining remission	Cumulative probability of maintaining remission
0	113	—	113	17	0.85	0.85
6	96	3	94.5	24	0.7461	0.6341
12	69	17	60.5	8	0.8676	0.5502
24	44	13	37.5	5	0.8667	0.4768
36	26	3	24.5	5	0.796	0.3795
48	18	4	16	2	0.875	0.3320
60	12	3	10.5	0	1	0.3320

*Patients lost to follow up or not reaching time point being analysed.

TABLE III Clinical details of patients treated for active Crohn's disease with either elemental diet or prednisolone. Survival curves, predicting cumulative probability of maintaining remission for these patients, are shown in Figure 5

Treatment	Elemental diet (n=52)	Prednisolone (n=37)
Age (mean (SD), years)	31.2 (15.5)	29.8 (16.2)
Sex	29 M 23 F	16 M 21 F
Duration of illness:		
New diagnosis	24	22
Length of history	3.5 (6 months–18 years)	1.5 (6 months–12 years) (median and range)
Previous treatment	13 sulphasalazine 2 prednisolone No resections	17 sulphasalazine 5 prednisolone No resections
Site of disease:		
Small intestinal	9	0
Ileal	15	9
Ileocolonic	15	13
Colonic	12	15
Perianal	7*	1*

*Some patients are classified in more than one group.

TABLE IV Lifetable analysis on 37 patients who were treated with prednisolone for an acute exacerbation of Crohn's disease

Time (months)	No at start	Censored during this time*	No at risk	No who relapsed	Probability of maintaining remission	Cumulative probability of maintaining remission
6	37		37	9	0.7568	0.7568
12	28		28	10	0.6429	0.4865
24	18		18	5	0.7223	0.3513
36	13		13	4	0.6924	0.2432
48	9	2	8	0	1	0.2432
60	7		7	0	1	0.2432

*See footnote to Table II.

TABLE V Lifetable analysis on 52 patients who were treated with an elemental diet for an acute exacerbation of Crohn's disease and who had not previously had surgery

Time (months)	No at start	Censored during this time*	No at risk	No who relapsed	Probability of maintaining remission	Cumulative probability of maintaining remission
6	52	3	50.5	10	0.8020	0.8020
12	39	8	35	6	0.829	0.6648
24	25	10	20	2	0.9	0.5976
36	13	2	12	3	0.75	0.4482
48	8	1	7.5	0	1	0.4482
60	7	2	6	0	1	0.4482

*See footnote to Table II.

dietary treatment. Of the 21 patients who went onto a diet of normal food, 13 have maintained remission (mean (SD) 22 (29) months, range 1–108 months) and eight have relapsed with a mean (SD) time to relapse of 22 (29) months (range 1–96 months).

Eight of 10 patients with fistula achieved remission. Four patients had elective surgery while on the diet. The four patients who went onto a diet of normal food all relapsed within one month.

Twelve patients were treated for associated perianal disease and three failed to obtain a remission. In the remaining eight patients the intestinal symptoms responded within a week of beginning treatment but the perianal disease often required prolonged treatment. All but one patient with perianal disease who had a remission relapsed within eight weeks of going back on to normal food.

Discussion

Crohn's disease with its protean manifestations and spontaneously variable course demands longterm follow up of a large number of patients

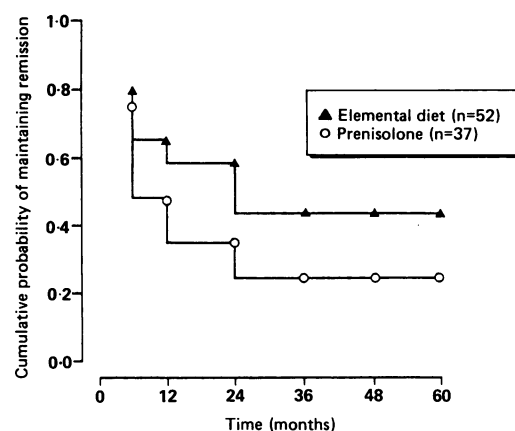


Figure 5: Survival probability curves, predicting cumulative probability of maintaining remission for patients treated for active Crohn's disease with prednisolone alone (n=37) or elemental diet alone (n=52). These curves are drawn from data in Tables IV and V. There is no significant difference between the outcome at the different time points at p values of 0.01 (logrank significance test).

for the complete assessment of any type of treatment. In a disease where weight loss, nutritional depletion, and gastrointestinal tract dysfunction are permanent features dietary manipulation and nutritional support have been used with encouraging results.^{19 20 26 27} The trials to date, however, have been too small to assess fully the value of the diets in acute disease and information on the longterm outcome after such treatment is totally lacking. The population of patients in this study is largely unselected and represents patients attending a district general hospital for the management of Crohn's disease. Altogether, 85% of patients obtained a remission and the longterm follow up indicates that patients with uncomplicated Crohn's disease do as well as patients treated with steroids, but the patients with strictures, fistula, or perianal disease may require further treatment after diet induced remission.

A major difficulty in all treatment studies of patients with Crohn's disease is the definition of relapse and remission. Some studies define remission arbitrarily as a Crohn's Disease Activity Index below 150, thus facilitating comparison between studies, but this is not possible in a retrospective study. Much reliance was therefore put on less stringent clinical and subjective assessments of the patient's well being which nevertheless correlated with laboratory indexes and the Harvey and Bradshaw Clinical Activity index. The definition of a relapse is also controversial, but as treatment changes are not taken lightly by either patients or physicians and are nearly always documented in the notes it was thought that this would be the most representative and objective measure of a relapse.

By the above criteria 85% of patients with acute Crohn's disease achieved a remission when treated with an elemental diet, which compares favourably with that reported for steroids and total parenteral nutrition.^{1 18} Included in this analysis were 26 (23%) patients taking a maintenance dose of steroids, because such patients often constitute a large proportion of any population with Crohn's disease. There was, however, no significant difference between these patients and those treated with an elemental diet only

with regard to the length of remission obtained. Remission in the whole group was unrelated to age, sex, length of history, or whether there were associated complications of strictures, fistula, or perianal disease. Nevertheless, the clinical impression is that patients with small intestinal and ileal disease have a more rapid and complete symptomatic response to treatment with elemental diet than those with ileocolonic, colonic, or perianal disease.²⁸ Whether this reflects a different course of the disease or a true difference in response to treatment is not clear.

Our remission rate with the elemental diet, though comparable with that in most studies,^{17 18 29} is higher than in some other published work.^{29 30} The reason for this is not clear. The possible explanations for poorer results in some studies^{30 31} include less experience in the practicalities of using an elemental diet, less use of hospitalisation and nasogastric tubes in early stages of treatment which could result in early withdrawal, and allowing normal food as well as an elemental diet during treatment. The importance of the diet formula used in treatment has not been investigated. We have used elemental diets only. Some groups may have used other chemically defined diets,^{29 30} and what influence this may have had on outcome is not known. In our study 15% failed to obtain remission or did not tolerate the diet. This figure may underestimate slightly the intolerance to an elemental diet since a failed attempt to start the diet may not have been noted in the medical records.

On resumption of normal food after a diet induced remission there was a tendency for distal gut disease to relapse more frequently, although this was not statistically significant. Moreover, when the outcome of steroid and diet induced remissions was compared there was no significant difference in the number of relapses between the two groups at any time. Patients with symptomatic strictures do particularly well on an elemental diet but many tend to relapse when food is introduced. In particular, patients with fistula and perianal disease require further treatment to maintain a diet induced remission.

Elemental diet seems to be a safe and successful treatment for acute Crohn's disease with remission rates comparable to those achieved with steroids. The success of treatment is unrelated to the site or the severity of disease. Most patients with fistula or perianal disease and many patients with strictures will require a more definitive form of treatment to maintain diet induced remissions.

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