The Effect of Elemental Diet on Intestinal Permeability and Inflammation in Crohn's Disease

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This study examines whether treatment of acute Crohn's disease with an elemental diet improves intestinal integrity and inflammation as assessed by a ^{51}Cr-labeled ethylenediaminetetraacetatic acid (EDTA) permeability test and the fecal excretion of ^{111}In-labeled autologous leukocytes, respectively. Thirty-four patients with active Crohn's disease completed a 4-week treatment course with an elemental diet. Active disease was characterized by increased intestinal permeability [24-hour urine excretion of orally administered ^{51}Cr-EDTA, 6.4% ± 0.6% (mean ± SE); normal, <3.0%] and by high fecal excretion of ^{111}In-labeled leukocytes (14.2% ± 1.1%; normal, <1.0%). Twenty-seven (80%) went into clinical remission, usually within a week of starting treatment. After 4 weeks of treatment, there was a significant decrease in both the urine excretion of ^{51}Cr-EDTA (to 3.4% ± 0.5%; $P < 0.01$) and the fecal excretion of ^{111}In (to 5.7% ± 1.0%; $P < 0.001$), indicating that such treatment is not just symptomatic. A framework for the mechanism by which elemental diet works, centering around the importance of the integrity of the intestinal barrier function, is proposed, and also appears to provide a logical explanation for some relapses of the disease.

The management of acute Crohn's disease is straightforward in the majority cases, involving the judicious use of sulphasalazine, corticosteroids, a wide range of antibiotics, and immunosuppressants (1–7). However, the universal problem with these treatments is the frequency and severity of side effects of long-term administration (2,8). An alternative approach to treatment has been to use chemically defined diets such as an elemental diet, in which the sole form of nutrition and calories is provided by oligosaccharides, amino acids, and short-chain fatty acid and no normal food is included (9–11). Recent controlled trials have shown an efficacy similar to total parentral nutrition and corticosteroids (11,12). A retrospective study at this hospital showed that 96 of 113 patients (85%) treated with elemental diet went into clinical remission with no serious side effects and, upon discontinuation of treatment, maintained remission for at least as long as those treated with corticosteroids only (13).

Despite its efficacy and lack of serious side effects, elemental diet is not widely used for treatment of active Crohn's disease, in part because of its poor palatability and to the considerable effort required of patients, dietitians, and physicians (14,15). Skepticism has also been flamed by the lack of understanding of the mechanisms by which elemental diet works, and the conventional explanation of allergy, bowel rest, and antigen exclusion have no proven basis (16). Most importantly, perhaps, there is little direct experimental evidence that elemental diet is anything more than a symptomatic treatment for the disease (17). Using a ^{51}Cr-labeled ethylenediaminetetraacetatic acid (EDTA) permeability test and ^{111}In-labeled leukocytes, we show objectively that treatment with elemental diet reduces intestinal permeability and inflammation in patients with Crohn's disease.

Subjects and Methods

Patients and Clinical Assessment

Of 38 consecutive patients with active Crohn's disease attending Northwick Park Hospital and requiring urgent medical treatment, as opposed to surgery, 34 com-

0016-5085/91/$3.00

pleted the studies. The 4 patients who did not complete these studies were either intolerant to the diet (2 patients) or refused dietary treatment (2 patients). These were 19 men and 15 women, mean age 37 ± 3 years (mean ± SE; range, 16–77 years). Eight had small intestinal, 12 ileal, 9 ileocolonic, and 5 colonic involvement of Crohn's disease. Five had undergone previous surgery. The mean duration of disease was 5.5 ± 6.9 years (range, 0–24 years), and 13 cases were newly diagnosed. Four patients were being treated with prednisolone (10 mg/day) and 6 with sulphasalazine (2–4 g/day), and these treatments were continued at an unchanged dose.

All patients were admitted to a metabolic research ward. Blood samples were obtained for routine hematological and biochemical tests as well as erythrocyte sedimentation rates, and C-reactive protein and disease activity was assessed clinically by the method of Harvey and Bradshaw (18) on the day before treatment with elemental diet was begun. Clinical remission was defined subjectively as a return to prerelapse well-being (13).

These studies were approved by the Harrow Health Authority Ethical Committee, and all patients gave informed consent.

Permeability Estimations

The test solution consisted of 100 μCi (3.7 MBq) ^{51}Cr-EDTA (Amersham International, Amersham, Buckinghamshire, England) in 10 mL water (19). After an overnight fast, subjects drank the test solution at 8 AM, then drank approximately 300 mL water. Normal food and fluid was allowed 2 hours later. Urine was collected for 24 hours, placed in polythene bottles, and counted in a high-resolution bulk sample counter at a final volume of 2 L. Urine was counted for 60 seconds, which allows measurement of $<0.005\%$ of the ingested dose with a statistical accuracy of ±4%. The normal upper limit of ^{51}Cr-EDTA urine excretion in 24 hours is 3.0% of the orally administered dose (19).

The ^{51}Cr-EDTA permeability test was performed upon completion of the ^{111}In studies, and the urine activity data were corrected for any ^{111}In spillage. The estimated radiation dose received during the test is 0.1 mSv.

^{111}In Leukocyte Imaging and Fecal Excretion

On the day of admission, patients underwent ^{111}In labeling of neutrophils (20,21). An indwelling catheter is placed into an anticubital vein, and 60 mL of blood is drawn into a syringe containing 11 mL of acid citrate dextrose (National Institute of Health formula A), dispensed into two sterile polythene tubes, and allowed to sediment for 1 hour at room temperature. The supernatant is removed and centrifuged at 100*g* for 5 minutes. The supernatant is removed and respun at 300*g* for 10 minutes to yield cell-free plasma. The pellet from the 100*g* centrifugation is resuspended and incubated for 10 minutes in 0.1 mL HEPES saline buffer (pH 7.4) containing 20 mmol/L HEPES in 0.8% (vol/vol) sodium chloride, 4.4 mmol/L tropolone, and $^{111}InCl_3$ (Amersham International). Five milliliters of cell-free plasma is added to the cell suspension and centrifuged at 100*g* for 5 minutes. The supernatant containing unlabeled ^{111}In is poured off and the cells resuspended in 6 mL of cell-free plasma. Five milliliters is injected IV and the rest used for standards. The labeling efficiency averaged 87% (range, 69%–96%). The leukocytes are not activated and maintain their integrity and function during the isolation and labeling procedure (22).

Following reinjection of the labeled leukocytes, abdominal scintigrams are obtained with an IGE 400 AT camera (International General Electric) with a star computer at 1–4 hours and 20 hours for localization of disease. Individual fecal excretions were collected over a 4-day period and counted in a high-resolution bulk sample counter. Standards (2% of the injected dose) were made up to 200 mL with water and distributed over a fixed amount of filter paper in a plastic container. Each sample was counted for 20 seconds, which enables the measurement of 0.01% of the injected dose with a statistical accuracy of ±4%.

The activity of ^{111}In given to the patients varied. The standard dose is 300 μCi (11 MBq). In patients studied on more than two occasions, the second and subsequent dose was reduced to 40–60 μCi to avoid excessive radiation. This affects the quality of scintigrams but the accuracy of fecal counts is only minimally affected. Assuming a 300-μCi (11 MBq) dose of ^{111}In, the radiation received is 6.5 mSv.

Treatment

After these baseline studies, all normal food intake was stopped and treatment with an elemental diet (Vivonex, Norwich-Eaton, Newcastle upon Tyne, or EO28, Scientific Hospital Suppliers, Liverpool, England) started. The aim of treatment was to provide a daily intake of nitrogen of 0.17–0.30 g/kg body weight, depending on the degree of nitrogen depletion, and 2–3000 kcal. A starter regime was used beginning at one-third strength and gradually increasing the osmolality to full strength ($\approx$550 mOsm/L) over 3 days, and the volume was increased thereafter as necessary to meet the above-mentioned aims. Oral intake was encouraged. Failing this, the elemental diet was administered through a fine-bore nasogastric tube (3 of 34 patients).

Patients were kept in the hospital until compliance was ensured, and thereafter treatment was continued at home. The tests were repeated at 4 weeks while the patients remained on the diet. Fifteen patients were also studied at 2 weeks to assess the rapidity of response.

Statistics

Student's paired *t* test was used on sequential data for statistical analyses.

Results

Clinical Response

The patients admitted to this study were unwell enough to warrant hospital admission. During

Table 1. Laboratory Indices and Clinical Disease Activity

	Elemental diet	
	Pretreatment	Posttreatment
Hemoglobin [g/L (g/dL)]	121 ± 22 (12.1 ± 2.2)	121 ± 18 (12.1 ± 1.8)
Erythrocyte sedimentation rate (mm/h)	38 ± 31	25 ± 25[a]
C-Reactive protein [g/L (mg/dL)]	0.56 ± 0.48 (5.6 ± 4.8)	0.30 ± 0.46 (3.0 ± 4.6)[a]
Albumin [g/L (g/dL)]	31 ± 7 (3.1 ± 0.7)	33 ± 6 (3.3 ± 0.6)
Crohn's Disease Activity Index (18)	8 ± 4	4 ± 3[a]

NOTE. Values are means ± SD. Normal values: hemoglobin, 120–170 g/L (12–17 g/dL); erythrocyte sedimentation rate, <8 mm/h; C = reactive protein, <0.01 g/L (<1.0 mg/dL); albumin, 30–50 g/L (3.0–5.0 g/dL).
[a]Differ significantly ($P < 0.05$) from pretreatment values.

their 1-week pretreatment investigation, there was minimal or no clinical improvement.

The typical symptomatic response from the elemental diet was that patients felt a sense of well-being with loss of nausea on the fourth day. This was followed by reduced frequency and quantity of stool and loss of abdominal pain within a week. Seven patients had a marginal or no clinical response to the diet; the remaining 27 had a clinical remission. Most lost weight in the early phase of treatment which was regained as the calorie and nitrogen intake was increased. There were no significant differences in pretreatment and posttreatment weights (56 ± 11 kg vs. 55 ± 9 kg; $P > 0.5$).

The pretreatment and posttreatment values for hemoglobin, erythrocyte sedimentation rate, C-reactive protein, albumin, and clinical disease activity are shown in Table 1. All improved significantly apart from hemoglobin and albumen.

Permeability Studies

Twenty patients underwent permeability testing before and after 4 weeks of treatment. Table 2 shows the results. Pretreatment 24-hour urine excretion values of ^{51}Cr-EDTA were 6.4% ± 0.6% (mean ± SE), which did not correlate significantly with any of the nonspecific laboratory parameters of inflammatory activity. After treatment there was a significant decrease in the urine excretion of ^{51}Cr-EDTA to 3.4% ± 0.5% ($P < 0.01$), and 12 of 20 had values within the normal range.

^{111}In Leukocyte Studies

An improvement in the abdominal scintigraph was noted in most patients studied and Figure 1 shows representative pretreatment and posttreatment scintigrams. However, these cannot be quantitated accurately; hence the need for fecal ^{111}In estimation.

Pretreatment excretion of ^{111}In (14.2% ± 1.1%) did not correlate significantly with the nonspecific laboratory parameters of inflammatory activity or intestinal permeability.

Table 2 shows the pretreatment and posttreatment values of the fecal excretion of ^{111}In. Overall there was a significant decrease in the ^{111}In excretion from 14.2% ± 1.1% to 5.7% ± 1.0% (normal, <1%; $P < 0.001$). Eleven patients underwent ^{111}In leukocyte studies before and after 2 and 4 weeks of treatment. The pretreatment excretion was 15.0% ± 1.5%. At 2 weeks there was a significant decrease ($P < 0.01$) in the excretion to 7.9% ± 2.2%. At 4 weeks the excretion (8.4% ± 2.0%) differed significantly from pretreatment values but not from the 2-week data. The alterations in intestinal inflammation did not correlate significantly with changes in the nonspecific laboratory indices of inflammation, clinical disease activity, or intestinal permeability.

Discussion

This study assessed the symptomatic response and the nonspecific laboratory response to elemental diet in patients with acute Crohn's disease; in keeping with previous reports, there is a rapid and significant improvement in both parameters (10–12,23–26). We

Table 2. Changes in Disease Activity and Permeability During Treatment With Elemental Diet

		Crohn's Disease Activity Index		24-hour urine excretion of ^{51}Cr-EDTA (% of dose)[a]		4-day fecal excretion of ^{111}In (% of dose)[b]	
Patient no.	Disease location	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
1–8	Small intestinal	7 ± 3	4 ± 4	5.8 ± 1.5	2.7 ± 1.2 (n = 7)	17.8 ± 5.9	4.3 ± 4.9
9–20	Ileal	7 ± 2	4 ± 2	7.8 ± 2.2	3.6 ± 1.0 (n = 5)	15.6 ± 6.1	7.1 ± 4.6
21–29	Ileocolonic	7 ± 3	4 ± 2	6.9 ± 4.3	4.2 ± 3.7 (n = 6)	10.3 ± 4.9	4.3 ± 5.5
30–34	Colonic	14 ± 14	4 ± 4	4.5 ± 0.7	2.8 ± 0.4 (n = 2)	11.4 ± 4.8	2.6 ± 1.7

NOTE. Values represent means ± SE.
[a]Normal, <3.0%.
[b]Normal, <1.0%.

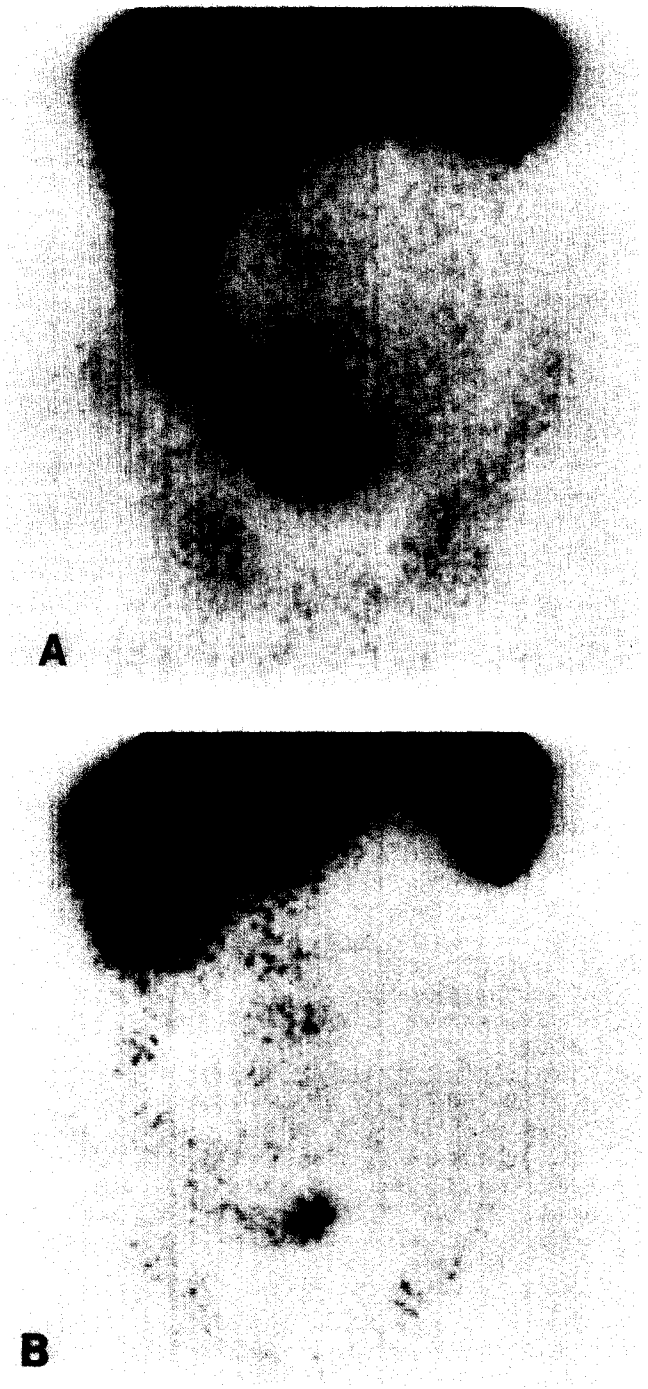

Figure 1. *A.* Pretreatment abdominal scrintigraph of a patient with active Crohn's disease showing intense activity in the right iliac fossa representing ileocecal inflammation.

B. The same patient after 4 weeks of elemental diet showing normal uptake into liver, spleen, vertebra, and pelvic bones with no significant activity in the right iliac fossa.

have now extended these studies and shown that intestinal integrity, as assessed by the ^{51}Cr-EDTA permeability test, is often restored by such treatment and, moreover, that intestinal inflammation is significantly reduced. Thus, in patients with Crohn's disease there is an interesting interaction between symptoms, the mucosal barrier function as reflected by permeability changes, and neutrophil flux to the intestine.

The usual duration of treatment with elemental diet is empirically determined to be 4 weeks but depends on the aim and expectation of the treatment. Thus 7 days appears sufficient for a symptomatic response, 2 weeks for the acute inflammation to subside, 4 weeks to maintain remission periods comparable to those of steroid-treated patients, and intermittent treatment by itself or as supplement to food to achieve a growth spurt in children (13,24–27).

The etiology of Crohn's disease is unknown, but it is suggested that the disease may represent an inappropriate immunologic response to an exogenous agent (28,29). Warren and Sommers (30) argued that a prerequisite for such a response was an underlying, primary abnormality of intestinal permeability. Morphological studies are in keeping with such a mechanism (31,32) but, more importantly, functional studies have shown a high prevalence ($> 90\%$) of increased intestinal permeability in patients with small intestinal involvement irrespective of disease activity (33–35). However, extrapolation of data obtained in individuals with diseases to etiological events, as opposed to pathogenesis, is fraught with difficulties (36,37). This is particularly so in Crohn's disease, in which the intestinal damage may be associated with irreversible structural and functional changes. However, Hollander et al. (38) reported a high prevalence ($\approx 50\%$) of increased intestinal permeability to polyethylene glycol 400 in apparently unaffected first-degree relatives of patients with Crohn's disease, suggesting that abnormal intestinal permeability may be a primary underlying abnormality in Crohn's disease (37–39). Similar studies using lactulose/L-rhamnose and ^{51}Cr-EDTA have been normal (40,41), perhaps reflecting the different permeation pathways that the probes use (42–44). Our results suggest that increased intestinal permeability to ^{51}Cr-EDTA in Crohn's disease relates to the acute inflammation and hence to disease activity. A similar conclusion was reached by Sanderson et al. (45), who observed a significant improvement in the differential urine excretion of lactulose/L-rhamnose in children treated with an elemental diet.

The 4-day fecal excretion of ^{111}In leukocytes is currently the technique of choice to quantitate intestinal inflammation, especially in a patchy disease such as Crohn's disease, in which it gives information unobtainable by other means (20–22,46–48). The unchecked accumulation of neutrophils in acute Crohn's disease undoubtedly contributes directly to tissue damage by lysosomal release and superoxide radical generation (49,50), but the precise site and nature of the neutrophil chemoattractant is unknown.

The current study shows for the first time that treatment with elemental diet alone reduces the acute inflammation in patients with Crohn's disease, showing that the treatment is not just symptomatic. The mechanism is unknown, but it is likely to be caused by several interacting factors rather than a single event (14,15). In a general context, and by analogy with the proposed pathogenesis of peptic ulceration in the gastroduodenal mucosa, small intestinal integrity is maintained by a balance between luminal aggressive factors (bile acids, pancreatic juices, bacteria, ingested foodstuffs, etc.) and mucosal defense, in which the intercellular junctions of adjacent enterocytes appear to be the most important for limiting macromolecular absorption (37,42–44,51,52). Relapse of Crohn's disease is characterized by severe disruption of the intercellular junctions (45), which may allow mucosal exposure of neutrophil chemoattractants. Elemental diet may alter luminal aggressive factors (15,17) to the extent that repair of the intestinal barrier function is possible. The central importance of the barrier function in Crohn's disease relapse is in keeping with observations that relapses are often heralded by heavy alcohol binges, gastrointestinal infection, and nonsteroidal antiinflammatory drug (19,53–57).

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Received May 15, 1990. Accepted November 25, 1990.

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The authors thank R. I. Copeland for obtaining scintigrams and Sister Tobin and the staff of Haldane Ward for excellent work.