

# Ingested Matter Affects Intestinal Lesions in Crohn's Disease

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**Background:** Environmental factors of the modern Western lifestyle may trigger Crohn's disease (CD) in susceptible individuals. Because such factors could be part of ingested matter, we intended to improve intestinal Crohn's lesions by exclusion thereof.

**Methods:** At first we tested a highly restricted diet (based on spelt bread and red meat, both derived from intensively monitored organic farming) in 5 pilot cases. In a subsequent controlled trial, 18 patients with mild-to-moderate CD were randomly assigned to receive either this active diet or a control diet (low-fiber, low-fat, and high-carbohydrate). Mucosal improvement was assessed by magnetic resonance imaging (MRI) and endoscopy. Secondary endpoints included sonography, the Crohn's Disease Activity Index (CDAI), and the Inflammatory Bowel Disease Questionnaire (IBDQ).

**Results:** Four of 5 pilot patients showed significant improvement within 4 weeks. From 18 patients in the controlled trial, 8 were randomized to the active and 10 to the control group; 4 decided to quit immediately after dietary counseling, 3 in the active and 1 in the control group ( $P = 0.183$ ). At 6 weeks MRI and endoscopy showed improvement of intestinal lesions in 3 of 4 assessable patients of the active group and 1 of 9 patients of the control group ( $P = 0.027$ ). Sonography showed improvement in 4 of 5 patients of the active group and in 1 of 8 assessable patients of the control group ( $P = 0.016$ ). CDAI and IBDQ improved in both groups to a similar extent.

**Conclusions:** Ingested matter as part of the modern Western lifestyle may cause persistence of intestinal Crohn's lesions.

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**Key Words:** Crohn's disease, etiology, environment, nutrition, diet, magnetic resonance imaging

Several lines of evidence suggest that environmental factors such as cigarette smoking play a role in the etiology

of Crohn's disease (CD).<sup>1</sup> It seems that such environmental factors did not always exist but were rather created after industrialization and increased in intensity to the current time. The increase in incidence during the second half of the 20th century<sup>2</sup> and in immigrant populations,<sup>3</sup> the geographic differences within Europe,<sup>4</sup> the urban–rural gradient,<sup>5</sup> and the earlier age at onset in recent years support the hypothesis of growing environmental hazards in populations with a Western lifestyle.<sup>6</sup> As CD is a primary disease of the gut, it is commonly believed that environmental factors are part of ingested matter that is typically found in Western diets.<sup>7</sup> The modern use of fertilizers, pesticides, preservatives, and food additives has introduced a variety of changes to agriculture and food production. Industrialization had a strong influence on farming, food processing, distribution and storage, as well as cooking habits.<sup>8</sup>

The 19th and 20th centuries brought significant changes into human nutrition within a relatively short period of time. Any of such changes manifests a potential culprit in the etiology of CD. Refined carbohydrates,<sup>9,10,11,12</sup> processed dietary fats,<sup>13,14,15</sup> the proportion of fatty acids,<sup>42</sup> omega-3 fatty acids,<sup>17,9</sup> food additives,<sup>18</sup> microparticles,<sup>19,20</sup> or dietary yeast<sup>21</sup> have been studied previously. However, none of these factors have been successfully singled out. Individual exclusion diets have been shown to maintain remission in some trials<sup>22</sup> but showed no or only minor benefits in others.<sup>23,24,25</sup> On the other hand, elemental diet and total parenteral nutrition have demonstrated symptomatic and radiological improvement.<sup>26,27,28</sup> These and other reports have created initial but not generally accepted evidence that nutritional modification benefits the course of CD.

Further evidence that ingested matter may lead to CD came from clinical observations in patients after surgery. When an ileostomy was constructed proximal to the anastomosis, thereby excluding the anastomosis from the fecal stream, recurrence of CD was effectively prevented.<sup>29,30</sup> After the ileostomy was closed and the fecal stream was reintroduced, recurrence of CD occurred within days. These findings clearly link the fecal content to the recurrence of CD. The fecal content is a composite of ingested matter, microbiota, and body fluids, from which ingested matter and/or microbiota are likely part of the environmental disease-promoting factors.

For this study we hypothesized that the adult CD phenotype is expressed in genetically susceptible individuals that

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are continuously exposed to yet unidentified (excepting the known contribution of smoking) environmental factors, which enter the body through the mouth, and to which exposure has increased since the beginning of the 20th century in societies with Western lifestyles. We therefore tested the hypothesis that exclusion of such disease-promoting ingested factors would improve intestinal lesions in mild-to-moderately active CD by providing a highly restricted diet, derived from intensively monitored organic farming. As the organic production of fruits and vegetables is intrinsically difficult, such items were excluded.

## MATERIALS AND METHODS

### Patients

We first tested the exclusion of potential disease-promoting ingested factors in 5 pilot cases with stricturing CD. The disease was located in the neoterminal ileum in 2 cases (A1L3B3 according to the Vienna classification<sup>31</sup>) and in the upper small bowel in the remaining 3 cases (A1L4B2). Clinical improvement was judged by global physician assessment. Bowel wall thickening (BWT) and disease extent were assessed by transabdominal bowel sonography (TABS) before and after 4 to 6 weeks of diet.

In a second, controlled part, patients with mild-to-moderate active CD (Crohn's Disease Activity Index [CDAI] 150–220<sup>32</sup>) with ulceration of the left-sided colon or a significant lesion of the small bowel or right-sided colon that was assessable by means of magnetic resonance imaging (MRI) were included. Patients with signs or symptoms that needed operation within 1 week, obvious lack of compliance with any of the diet regimens (e.g., vegetarians), with a body mass index (BMI) below 18, accidental weight loss of more than 5% in the last 3 months, therapy with prednisone over 25 mg or any dose equal or below that had been adjusted during the previous 4 weeks, budesonide or mesalamine that had been adjusted during the same period, azathioprine or anti-TNF therapy that had been initiated or changed during the previous 3 months, or concomitant antibiotic or probiotic therapy were excluded from the trial. Eighteen patients were randomly assigned to receive either the active or the control diet at a 1:1 ratio. Only the study coordinator (G.B.) and the dietician (I.W.) were aware of the group assignment. The primary study endpoint was an improvement in the MRI (in patients with small bowel or right colonic target lesion) or endoscopy score (in patients with left colonic target lesion) after 6 weeks. Transabdominal bowel sonography (TABS) was used as screening investigation for identifying patients with a potential target lesion and for stratification of patients into either the endoscopy or the MRI subgroup. Improvement in TABS score was also used as a secondary endpoint. Other secondary endpoints included the CDAI, the Inflammatory Bowel Disease Questionnaire (IBDQ), and inflammatory parameters (C-reactive protein [CRP],  $\alpha$ 1-acid glycoprotein,

and erythrocyte sedimentation rate [ESR]). The nutritional status was assessed by BMI. Additionally, serum concentrations of total protein, albumin, cholesterol, triglycerides, ferritin, and transferrin were measured before and after the 6 weeks. After randomization, all patients received a face-to-face dietary counseling by a single dietician (I.W.).

No change in concomitant therapy was made during the study. In case symptoms of CD deteriorated (CDAI increase by more than 70 points from baseline for 2 weeks) or a change in medication was necessary, the patient was withdrawn from the study. The trial was approved by the ethics committee of the Medical University of Vienna and the General Hospital of Vienna.

### Dietary Interventions

Patients in the active group were instructed to keep a highly restricted diet composed of red meat (pork, beef, lamb), certain sourdough bread (produced for the purpose of this study by a single Viennese bakery from freshly ground spelt using a historic recipe without addition of extra yeast), rape oil (for frying the meat), and fresh (nonfrozen) butter (as spread for bread), all of which came from intensively monitored organic farming. Only plain tap water and organic tea were allowed for drinking, and rock salt (halite) was allowed for spicing. Organic farming was defined by avoidance of chemical fertilization, pesticides, genetically manipulated crops, food processing, gamma irradiation, chemical preservation, or industrial food additives, best resembling a situation before the year 1850. As fruits and vegetables are considered difficult to control for such criteria, they were excluded from the diet. For the same reason butter and rape oil were only allowed in small amounts (butter less than 20 g/d, rape oil less than 2 tablespoons/d). Baking soda toothpaste was given for dental care. To ensure the same quality of goods, patients received these goods from a local delivery system. They were also told to avoid the use of a dishwasher, limit dishwashing-soap, and rinse plates with water.

The control group was instructed to eat a low-fat, high-carbohydrate diet that is complete in nutrients, but to avoid fiber-rich fruits and vegetables. In order to provide certain restrictions, the control group was asked not to eat any red meat. To avoid vitamin deficiency, both groups received 3 intramuscular multivitamin injections (vitamin B complex and vitamin C) at weeks 0, 3, and 6. All patients were asked to keep a nutrition and symptom diary throughout the study. Both groups were contacted by the dietician by phone 1 week after the initial counseling and at weeks 3 and 6 by a face-to-face interview. Compliance was evaluated through the patients' nutrition diaries and by asking certain pitfall questions. Patient appointments were separated by group and day for all visits to avoid exchange of information between patients themselves. At the end of the study, nutrition diaries were analyzed for nutritional substrates including protein,

carbohydrates, fat and fiber content by using BKV BLS II.3 software (Aconsoft, PIU-PRINTEX, Vienna, Austria), which is based on the German Nutrient Data Base ([www.bls.nvs2.de](http://www.bls.nvs2.de)) and covers average nutritional values (137 constituent data per food) of  $\approx 10,000$  foods available in the German market (fresh foods, food preparations, dishes, etc.).

During the follow-up period (weeks 6–24), the active group was instructed to stepwise add other food items and drinks, derived from organic farming, such as local fruits and vegetables, dairy products, beer, wine, honey, etc. Refined sugar and ready-made canned or frozen food were not allowed. The control group was instructed to eat also red meat but still to avoid fiber-rich and hard fibrous fruits and vegetables. They had 2 more face-to-face dietary counsels at weeks 12 and 24.

### MRI Examination

Small bowel and right colonic disease was assessed by MRI before and after 6 weeks of the diet. Two hours prior to the exam, patients received ispaghula (dissolved in an aqueous solution with meglumine gadoterate) for small bowel distension. To minimize artifacts from bowel movements, butylscopolamin (20 mg, Buscopan, Boehringer Ingelheim, Germany) was injected intravenously. MR imaging was performed on a 1.5 Tesla unit (Intera, Philips, Best, The Netherlands) using a body phased-array coil in a supine position. Axial and coronal steady-state gradient recalled-echo (GRE), axial fat-suppressed T2-weighted turbo spin-echo (TSE), and axial and coronal T1-weighted GRE fat-suppressed sequences were applied before and after intravenous-contrast injection (0.1 mmol/kg Gd-DTPA-BMA; Omniscan, GE Healthcare, Oslo, Norway). Changes in BWT and in contrast enhancement (CE) of the bowel wall and disease extent were used for the assessment of the most prominent bowel lesion (so-called target lesion; Table 1). For assessing the response to the intervention, the change in longitudinal extent was scored at week 6. Two scores (week 0 and week 6) were established for each patient by a consensus of 2 radiologists

(K.T. and W.S.) who were blinded for the type of intervention. The change in score was rated into 1 of 4 groups: complete healing, improvement, no change, or worsening.

### Endoscopy

Left colonic disease was assessed after enema preparation by endoscopy using Olympus CF-100 colonoscopes. As only parts of the colon were assessed, the most prominent lesion was judged by a modified SES-CD before and at week 6<sup>33</sup> (Table 1). Similar to MRI, the response was evaluated from videos by consensus of 2 endoscopists (A.P., C.G.) who were blinded to the type of intervention.

### Sonography

TABS was performed as previously described.<sup>34</sup> For evaluation of target lesions BWT and the change in longitudinal extent were graded as shown in Table 1 and the response was scored similar to MRI assessment.

### Statistical Analysis

The primary study endpoint was the improvement or healing of endoscopic or MRI-based signs of intestinal inflammation after 6 weeks. The placebo response in CD as measured by endoscopic improvement is considered very low over this period of time (below 5%; Geert D'Haens pers. commun.). The necessary sample size (1-sided) to detect an increase from an assumed success rate of 5% (in the control group) and 50% (in the active group) with a power of 80% and at alpha level of 5% was 15 for each group. The Fisher exact test (2-sided, mid *P*-value corrected) and the paired *t*-test (2-sided) were used for statistical evaluation.

## RESULTS

### Pilot Cases

Five subjects with small bowel CD (3 female, 2 male, median age 36 years [27–29], median duration of disease 7 years [2–8]) were instructed to undergo dietary changes as

**TABLE 1.** Magnetic Resonance Imaging (MRI), Endoscopy, and Sonography Scores

	Score	0	1	2	3	4
MRI	BWT (mm)	<3	3-4.9	5-7.9	$\geq 8$	Fistula, abscess
	CE	Normal	+	++	+++	
	Change in extent <sup>a</sup>	<30%	30-59%	60-89%	$\geq 90\%$	
Endoscopy	Ulcers size (mm)	None	<5	5-19	$\geq 20$	
	Ulcerated area surface <sup>a</sup>	None		10-30%	30%	
Sonography	BWT (mm)	<3	3-4.9	5-7.9	$\geq 8$	Fistula, abscess
	Change in extent <sup>a</sup>	<30%	30-59%	60-89%	$\geq 90\%$	

BWT, bowel wall thickening; CE, contrast enhancement.

<sup>a</sup>Postintervention only (score was either added in case of worsening or deducted in case of improvement).

suggested in the active diet group. All patients had obstructive symptoms due to stricturing CD and were considered for surgery. Two patients had a history of bowel resection 5 years (i.e., subtotal colectomy with ileosigmoid anastomosis) and 7 years earlier (ileocecal and segmental sigmoid resection). Three patients were active smokers. Azathioprine therapy was either absent ( $n = 2$ ) or stable for more than 6 months (100–150 mg/day,  $n = 3$ ). None received steroids or infliximab. Although concomitant therapy was unchanged, all patients showed significant improvement of bowel symptoms within 4 to 6 weeks, which concurred with improvement in BWT and disease extent as measured by TABS in 4. Due to their individual success, 4 patients continued on a broadened organic diet including fruits and vegetables and were successfully avoiding surgery during the following years (mean follow-up period 3.8 years).

### Controlled Study

In January 2004, 780 patients were initially invited by mail to participate in this study. Seventy-three patients (9.4%) responded and received additional information. After this second mailing, 31 of 73 patients agreed to participate and underwent screening. Thirteen of 31 screened patients had either no sufficient target lesion or a CDAI below 150 and were excluded. Eighteen patients were randomized; 8 were allocated to the active and 10 to the control group. Eleven patients were stratified into the MRI assessment, 7 into endoscopy, respectively, based upon location of their lesions. All patients received the same amount of dietary counseling by a single dietician (I.W.). It was explained that the study intended to compare 2 diets for the treatment of CD. Four of 18 patients quit the study without testing the diet for a single day, 3 in the active group because they felt that they could not adhere to the strict diet and 1 in the control group because the diet was considered ineffective ( $P = 0.183$  by Fisher exact test). All other patients finished the study (5 in the active group and 9 in the control group), 8 evaluated by MRI and 6 by endoscopy. Patient characteristics are listed in Table 2.

### Primary Endpoint

One patient in the active group who had been stratified to MRI evaluation (because the patient had had a Rutgeerts i4 lesion both at endoscopy and TABS in the neo-terminal ileum 2 weeks before inclusion into the study<sup>35</sup>) had to be excluded from evaluations as the target lesion could not be identified on either MRI scans at week 0 and 6 (score 0 for both occasions). After 6 weeks, 3 of 4 patients in the active group (Fig. 1) and 1 of 9 patients in the control group showed improvement on either MRI or endoscopy evaluation (75% versus 11%,  $P = 0.027$  by Fisher exact test). The mean imaging score improved from 3.3 to 1.8 ( $P = 0.051$ ) in the active group and remained unchanged (4.9 to 4.9;  $P = 0.5$  by

**TABLE 2.** Patient Characteristics

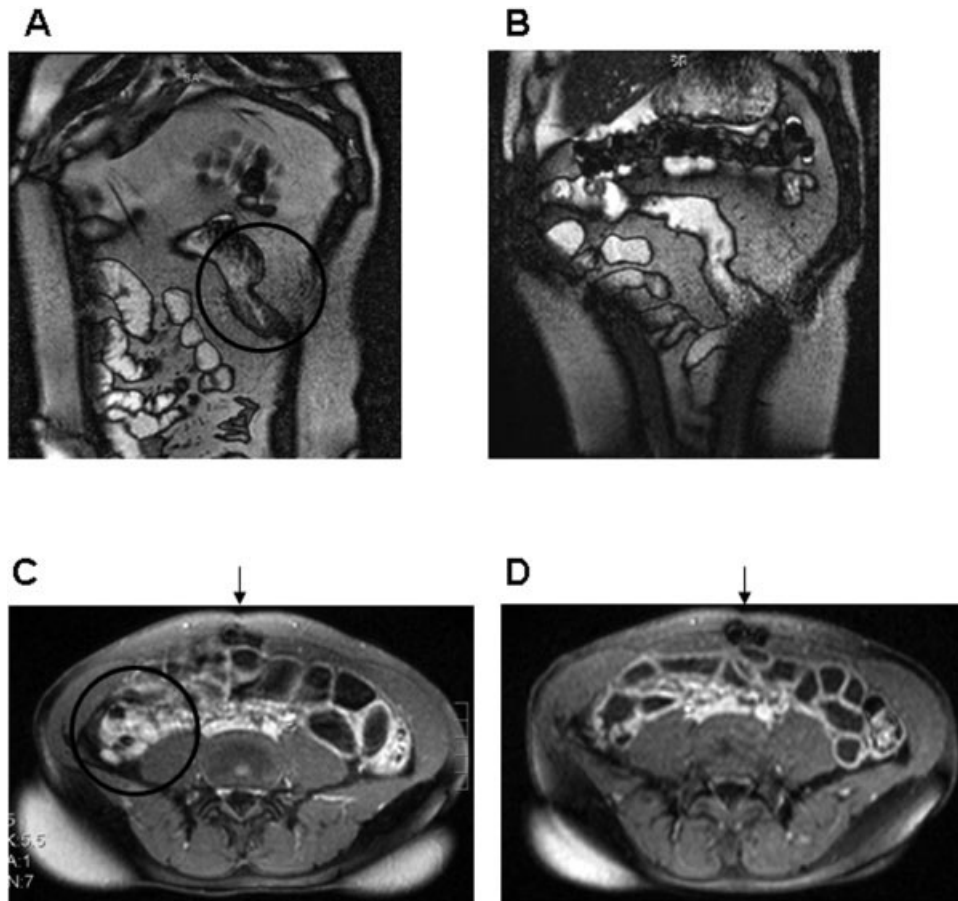
	Measure	Active Group	Control Group
Total	n	5	9
Sex	n (female)	2	3
Age	mean (SD)	48 (19)	48 (13)
CDAI	mean (SD)	169 (15)	171 (31)
IBDQ	mean (SD)	182 (23)	175 (18)
Vienna classification	A(1/2)	3/2	6/3
	L(1/2/3/4)	4/1/0/0	5/2/1/1
	B(1/2/3)	1/3/1	0/4/5
Smoking history	Active (n)	1	1
	Previous (n)	2	5
Therapy			
Azathioprine	n (mean dose; mg)	1 (100)	3 (167)
Budesonide	n (mean dose; mg)	2 (6)	2 (3)
Prednisolon	n (mean dose; mg)	0	1 (5)
Infliximab	n (mean dose; mg/kg)	0	1 (5)
Mesalazine	n (mean dose; g)	2 (2.5)	4 (3)

paired *t*-test) in the control group (Fig. 2). The detailed changes in imaging parameters are shown in Table 3.

### Secondary Endpoints

TABS showed improvement in 4 out of 5 patients in the active and 1 out of 8 in the control group (80% versus 12.5%,  $P = 0.016$  by Fisher exact test). The mean TABS score changed from 1.6 to  $-0.2$  ( $P = 0.052$ ) in the active group and from 1.8 to 2.8 ( $P = 0.78$  by paired *t*-test) in the control group. Single parameter changes are listed in Table 3. In 1 patient of the control group who had been stratified to endoscopy evaluation the target lesion was not assessable by TABS as it was located in the rectum. A good correlation was found between the TABS and MRI/endoscopy scores ( $R^2 = 0.65$ ;  $P < 0.001$ ). At the end of the follow-up period the TABS scores further improved in 1 case and worsened in 2 of the active group (mean score at week 24: 0.4), while it improved in 3 cases (after initializing azathioprine therapy) and worsened in another 3 of the control group (mean score at week 24: 1.4).

At the beginning of the study the mean CDAI was 169 in the active group and 177 in the control group. After 6 weeks the CDAI dropped in both groups (113 in the active and 117 in the control group; Table 4). Four patients in the active (80%) and 7 patients in the control group (78%) were in remission. We could not identify any correlation between the CDAI and any of the imaging studies. Changes in IBDQ, laboratory parameters, and nutritional status were not statistically significant (Table 4). The mean daily energy uptake was 1629 kcal in the active group and 1551 kcal in the control



**FIGURE 1.** A,B: Coronal MRI (GRE sequence) from patient 2 (male) before (A) and after (B) 6 weeks of active diet. The target lesion (circle) is located in the left upper quadrant and corresponds to jejunum. Both an improvement in BWT (7 mm to 4 mm) and disease extent (10 cm to 5 cm) were assessed. C,D: Axial MRI scan (gadolinium-enhanced T1-weighted GRE sequence) from patient 28 (female) before (C) and after (D) 6 weeks of active diet. The target lesion (circle) is located in the right lower quadrant and corresponds to the neoterminal ileum after ileocecal resection. Note the change in contrast enhancement (++ to +) between panel A and B. To better compare these sections, 2 corresponding scans were selected, both of which depict the umbilicus (arrow).

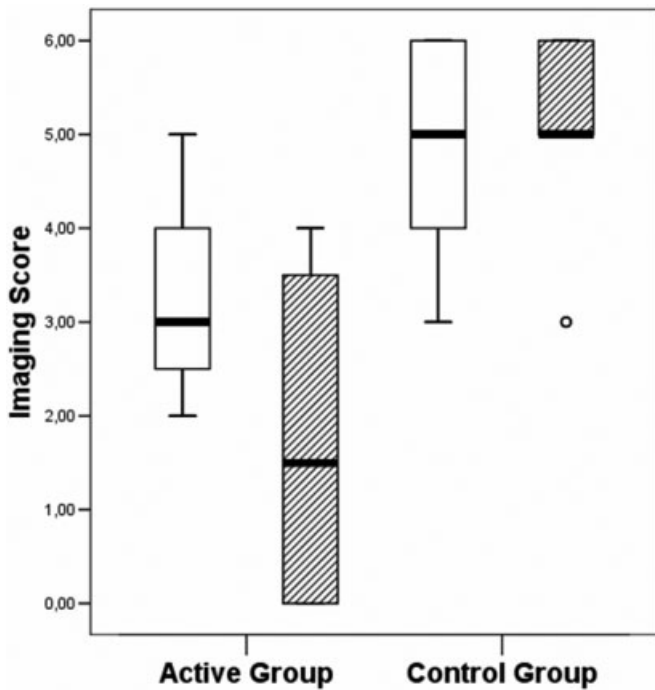
group. This was paralleled by a drop in body weight from 69 to 65 kg in the active group and from 86 to 84 kg in the control group and in the BMI from 23 to 22 and from 28 to 27, respectively. The baseline values for cholesterol, triglycerides, total protein, and albumin were within the normal range throughout the study. Analysis of the consumption of nutritional substrates indicated equal daily intake of carbohydrates and fat, while the active group consumed considerably more fiber and somewhat also protein (Table 5). Compliance testing by pitfall questioning and the evaluation of nutritional diaries exposed 1 case (control group) who did not adhere to the diet.

In the follow-up period, 1 of 5 patients in the active group and 3 of 9 patients in the control group received additional therapy due to worsening of clinical symptoms. After 24 weeks the mean CDAI was 110 in the active group and 130 in the control group. Four patients in the active (80%) and 5 patients in the control group (56%) were still in

remission. TABS evaluation of the 4 responders in the active group revealed unchanged findings or further improvement in 3 and worsening in 1 case. The single responder in the control group had an unchanged TABS evaluation at week 24.

## DISCUSSION

For this study we hypothesized that environmental factors that were introduced during the beginning of the 20th century in societies with a Western lifestyle might cause CD in genetically susceptible individuals. Several lines of evidence suggest that such environmental factors are part of ingested matter. We expected these to be complex nutritional changes rather than a single dietary factor and hypothesized that a certain diet, which best resembles food quality before the industrial revolution, should be able to improve or heal intestinal lesions in CD. To test this hypothesis we excluded potential environmental factors from ingested matter by providing a novel diet based on highly restricted organic food.



**FIGURE 2.** Primary endpoint (MRI and endoscopy). The mean imaging score improved from 3.3 (week 0: open bar) to 1.8 (week 6 hatched bar,  $P = 0.051$ ) in the active group and remained unchanged (4.9 (week 0: open bar) to 4.9 (week 6: hatched bar),  $P = 0.5$  by paired  $t$ -test) in the control group.

Upon TABS evaluation, 4 out of 5 pilot cases and 4 out of 5 patients in the controlled trial showed improvement. Correspondingly, 3 out of 4 patients improved as shown by MRI or endoscopy evaluation in the active diet group while only 1 out of 8 patients did so in the control group. The results of this study support the hypothesis that culprits in the etiology of CD are part of ingested matter in societies with a Western lifestyle. These preliminary data indicate that exclusion of such factors may lead to improvement of intestinal ulcer-

ations and may offer a potential therapy for this chronic disease. An alternative interpretation, of course, could be that there was something beneficial within the active diet that promoted bowel healing. However, as bread and meat were the main sources of food without any supplement this seems quite unlikely.

The presented results are based on a small pilot and an incomplete controlled series and the study was prematurely terminated after 2 years due to slow recruitment. In fact, only 18 patients were randomized (most of them within the first quarter of the trial) and only 5 (out of 15 intended) completed the active diet. Because of the small patient numbers, only a per-protocol analysis was performed. Recruitment difficulties were based on a low response rate to our primary and secondary mailing (indicating that dietary intervention was considered ineffective by the patients), on a high proportion of patients that dropped out of screening, as they did not show any target lesion, and local limitations of the delivery system for providing the diet (Vienna area). Intentions to recruit patients through collaborating IBD clinics or by articles that were published in the patient newsletters failed. Lastly, the high drop-out rate (3/8; 38%) after the initial dietary counseling in the active group reflects the mental difficulty to follow such a strict diet. We consider the small number of patients in this series a major shortcoming and do not believe that such a diet should be recommended as an interventional method in CD at this point in time. However, the data add to our understanding of environmental factors as triggers of CD, which was the primary goal of our study.

It is difficult to relate our results to previous dietary studies in CD as they typically focused on single dietary factors such as sugar or fat<sup>26,36</sup> and did not assess intestinal healing as an endpoint. Similar to us, however, Lomer et al<sup>25</sup> tried to avoid a variety of modern food components, mostly from highly processed sources, but not as rigorously as in the present study. Their initial uncontrolled trial showed good effects on the CDAI. Their larger controlled study was neg-

**TABLE 3.** Changes in Magnetic Resonance Imaging (MRI), Endoscopy, and Sonography Parameters

Score	Active Group (n = 5)		Control Group (n = 9)		
	Week 0	Week 6	Week 0	Week 6	
MRI	BWT (mm)	6	5	8	8
	CE (0-3)	2	1	3	3
	Extent (cm)	15	13	18	18
Endoscopy	Ulcers size (mm)	5	0	13	13
	Ulcerated area (%)	10	0	19	19
Sonography	BWT (mm)	6	4	7	7
	Extent (cm)	14	12	9	9

Data are mean (SD). BWT, bowel wall thickening; CE, contrast enhancement.

**TABLE 4.** Secondary Response Parameters (CDAI, IBDQ, Laboratory Markers) and Nutritional Status Before and After 6 Weeks of Diet

	Active Group (n = 5)			Control Group (n = 9)		
	Week 0	Week 6	P	Week 0	Week 6	P
CDAI	169 (15)	113 (35)	0.006	177 (31)	117 (47)	0.019
IBDQ	182 (23)	196 (20)	0.204	180 (15)	192 (20)	0.071
ESR (1 h)	17 (6)	15 (3)	0.500	26 (13)	20 (15)	0.364
CRP (mg/dL)	1.1 (0.9)	1.1 (1.0)	0.955	0.5 (0)	0.7 (0.4)	0.255
$\alpha$ 1-acid glycoprotein (mg/dL)	79 (28)	78 (16)	0.965	101 (26)	99(34)	0.787
BMI	23 (4)	22 (3)	0.108	28 (6)	27 (5)	0.228
Total protein (g/L)	73.4 (47)	72.6 (46)	0.686	74.3 (67)	73.4 (45)	0.725
Albumin (g/L)	45.4 (49)	42.9 (35)	0.574	43.2 (61)	42.1 (41)	0.681
Transferrin (g/L)	2.88 (0.14)	2.86 (0.53)	0.949	2.88 (0.49)	2.98 (0.63)	0.543
Ferritin ( $\mu$ g/L)	36 (17)	27 (20)	0.422	88 (116)	73 (76)	0.364
Triglycerides (mg/dL)	130 (72)	118 (58)	0.488	146 (78)	135 (75)	0.528
Cholesterol (mg/dL)	164 (26)	146 (22)	0.058	185 (33)	179 (38)	0.535

Data are mean (SD). Statistical evaluation was done by paired *t*-test (2-sided).

ative, as patients received high-dose steroid therapy in parallel, which likely concealed the benefits of the diet.<sup>24</sup> For the interpretation of our results it is important to note that concomitant therapy was unchanged in both the pilot and the controlled series and that our primary endpoint was improvement or healing of intestinal CD lesions, an objective measure. In contrast, the subjective scores (CDAI and IBDQ) improved in both diet groups to a similar degree, likely reflecting a high placebo effect, which is well known for dietary interventions. For those patients who were willing to start the diet, compliance was excellent in both groups. Some of the patients had the intention to lose weight, especially those in the control group (reflected by a higher starting BMI). Intended weight loss may have added to the subjective benefits of the control diet. Since functional bowel symptoms as in irritable bowel syndrome are prevalent in IBD and potentially sensitive to dietary interventions they may explain the divergence of subjective measures and radiologic/endoscopic scores.<sup>33,35</sup> Other objective markers such as ESR or

CRP did not change; however, the pretreatment levels were quite low or even normal.

Mucosal improvement is an accurate endpoint and pathophysiologically meaningful as the intestinal disease is considered the actual manifestation of CD.<sup>37</sup> By using MRI or endoscopy it was possible to perform the study double-blinded, as both patients and judging physicians were uninformed of the type of diet. Previously established quantitative scores for assessment of the various imaging techniques were adjusted for the purpose to better compare the different imaging methods. Changes in BWT and CE of the bowel wall in T1-weighted fat-suppressed images were selected as MRI measures because they had demonstrated the best reproducibility<sup>38,39,40</sup> and had been used previously for estimating therapeutic effect.<sup>41</sup> Because there was a good correlation between MRI/endoscopy and TABS in the controlled series, we may also consider the results from the pilot series informative.

It is generally assumed that there is no placebo response when investigating mucosal improvement by endoscopy or MRI. This could be in conflict with our results in the patient who improved on a control diet. However, besides the dietary intervention, a significant stricture at the ileorectal anastomosis was dilated by a balloon during the first endoscopic investigation (as the scope was not able to pass into the neoterminal ileum for assessment of the target lesion). In retrospect, this endoscopic intervention may have improved the flow of feces, reduced bacterial overgrowth in the target region (neoterminal ileum), which may have added to the reduction in the ulcer size at the second endoscopy. In addition to that, this patient stopped smoking at entry into the

**TABLE 5.** Analysis of Nutritional Substrates

	Active Group (n = 5)	Control Group (n = 9)
Energy (kcal)	1629 (619)	1551 (360)
Protein (g)	91 (34)	68 (12)
Fat (g)	205 (28)	196 (14)
Carbohydrates (g)	48 (103)	51 (58)
Fiber (g)	46 (23)	16 (4)

Data are mean (SD) per day.

study.<sup>1</sup> On the other hand, no patient in the active group received any endoscopic intervention or quit smoking. The results of both series support our hypothesis that ingested matter within a Western lifestyle contributes to CD in genetically susceptible individuals.

This study indicates that ingested matter within a Western lifestyle may contribute to the development of CD and that its avoidance may induce intestinal lesions. How could we have missed identifying disease-causing factors within the Western lifestyle so far? First, as Western nutrition is well tolerated by the majority of individuals, the disease-causing effect is not obvious. Second, a long lag interval (likely to be years) between exposure and disease expression may obstruct a cause–effect relationship. Third, we believe it is a complex combination of factors (rather than a single one) that were introduced little by little and gradually increasing in density. At this point we can only speculate on the nature of such factors. One disease model may involve (qualitative, quantitative, or metabolic) changes of the intestinal microbiota, because both the genetic characteristics and the intestinal microbiota are believed to contribute to the expression of the disease phenotype in murine models of IBD.<sup>42</sup> In humans, higher bacterial concentrations within the mucus layer, reduced diversity of fecal microbiota, and the presence of adherent-invasive *Escherichia coli* have been associated with CD.<sup>43,44,45</sup> It is currently not known whether nutrition can affect the composition of the intestinal microbiota, but it may alter bacterial gene expression, metabolism of substrates, and growth,<sup>46</sup> which all may affect the intestinal milieu. A next step in the search for culprit factors may be a stepwise addition of certain nutritional components in patients who responded to this diet. The ultimate goal, however, is a complete understanding of gene–environment interactions that lead to the expression of the disease phenotype.

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### REFERENCES

- Cosnes J, Beaugerie L, Carbonnel F, et al. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology*. 2001;120:1093–1099.
- Bernstein CN, Blanchard JF. The epidemiology of Crohn's disease. *Gastroenterology*. 1999;116:1503–1504.
- Probert CS, Jayanthi V, Pollock DJ, et al. Crohn's disease in Bangladeshi and Europeans in Britain: an epidemiological comparison in Tower Hamlets. *Postgrad Med J*. 1992;68:914–920.
- Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*. 1996;39:690–697.
- Blanchard JF, Bernstein CN, Wajda A, et al. Small-area variations and sociodemographic correlates for the incidence of Crohn's disease and ulcerative colitis. *Am J Epidemiol*. 2001;154:328–335.
- Ekbom A. The epidemiology of IBD: a lot of data but little knowledge. How shall we proceed? *Inflamm Bowel Dis*. 2004;10(Suppl 1):S32–S34.
- Gibson PR, Shepherd SJ. Personal view: food for thought—Western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment Pharmacol Ther*. 2005;21:1399–1409.
- Hugot JP, Alberti C, Berrebi D, et al. Crohn's disease: the cold chain hypothesis. *Lancet*. 2003;362:2012–2015.
- Lorenz-Meyer H, Bauer P, Nicolay C, et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). *Scand J Gastroenterol*. 1996;31:778–785.
- Martini GA, Brandes JW. Increased consumption of refined carbohydrates in patients with Crohn's disease. *Klin Wochenschr*. 1976;54:367–371.
- Tragnone A, Valpiani D, Miglio F, et al. Dietary habits as risk factors for inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 1995;7:47–51.
- Ritchie JK, Wadsworth J, Lennard-Jones JE, et al. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. *Br Med J (Clin Res Ed)*. 1987;295:517–520.
- Guthy E. [Crohn's disease and nutritional lipids. Hypothesis on etiology of regional enteritis]. *Dtsch Med Wochenschr*. 1982;107:71–73.
- Heckers H, Melcher FW, Kamenisch W, et al. [Chemically prepared fats and Crohn disease. A pilot study of the occurrence of trans-fatty acids in the subcutaneous tissue of Crohn patients in comparison with healthy controls as a parameter of long-term fat intake]. *Z Gastroenterol*. 1988;26:259–264.
- Roediger WE, Giles A, Kaczmar A, et al. Does exclusion of enteral lipid assist remission in Crohn's disease? *J Clin Gastroenterol*. 1993;17:38–41.
- Shoda R, Matsueda K, Yamato S, et al. Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. *Am J Clin Nutr*. 1996;63:741–745.
- Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med*. 1996;334:1557–1560.
- Mahmud N, Weir DG. The urban diet and Crohn's disease: is there a relationship? *Eur J Gastroenterol Hepatol*. 2001;13:93–95.
- Lomer MC, Grainger SL, Ede R, et al. Lack of efficacy of a reduced microparticle diet in a multi-centred trial of patients with active Crohn's disease. *Eur J Gastroenterol Hepatol*. 2005;17:377–384.
- Lomer MC, Harvey RS, Evans SM, et al. Efficacy and tolerability of a low microparticle diet in a double blind, randomized, pilot study in Crohn's disease. *Eur J Gastroenterol Hepatol*. 2001;13:101–106.
- Barclay GR, McKenzie H, Pennington J, et al. The effect of dietary yeast on the activity of stable chronic Crohn's disease. *Scand J Gastroenterol*. 1992;27:196–200.
- Jones VA, Dickinson RJ, Workman E, et al. Crohn's disease: maintenance of remission by diet. *Lancet*. 1985;2:177–180.
- Giaffer MH, Cann P, Holdsworth CD. Long-term effects of elemental and exclusion diets for Crohn's disease. *Aliment Pharmacol Ther*. 1991;5:115–125.
- Persson PG, Ahlbom A, Hellers G. Diet and inflammatory bowel disease: a case-control study. *Epidemiology*. 1992;3:47–52.
- Stange EF, Schmid U, Fleig WE, et al. [Exclusion diet in Crohn disease: a controlled, randomized study]. *Z Gastroenterol*. 1990;28:561–564.
- Allardyce DB. Preoperative parenteral feeding in Crohn's disease: preoperatively, to induce remission, and at home. *Am Surg*. 1978;44:510–516.
- Pfeil AB, Schuster AT, Kemperdick H. Clinical remission and disappearance of radiologic manifestations in Crohn's disease after oligopeptide diet treatment. *J Pediatr Gastroenterol Nutr*. 1988;7:926–930.
- Stenson WF, Alpers DH. Nutritional therapy in inflammatory bowel

- disease: a historical overview. *Curr Opin Gastroenterol*. 1997;13:135–139.
29. D'Haens GR, Geboes K, Peeters M, et al. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology*. 1998;114:262–267.
  30. Rutgeerts P, Geboes K, Peeters M, et al. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet*. 1991;338:771–774.
  31. Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis*. 2000;6:8–15.
  32. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70:439–444.
  33. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004;60:505–512.
  34. Gasche C, Moser G, Turetschek K, et al. Transabdominal bowel sonography for the detection of intestinal complications in Crohn's disease. *Gut*. 1999;44:112–117.
  35. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99:956–963.
  36. Pascu M, Roznowski AB, Muller HP, et al. Clinical relevance of transabdominal ultrasonography and magnetic resonance imaging in patients with inflammatory bowel disease of the terminal ileum and large bowel. *Inflamm Bowel Dis*. 2004;10:373–382.
  37. D'Haens G, Van Deventer S, van Hogezaand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology*. 1999;116:1029–1034.
  38. Koh DM, Miao Y, Chinn RJ, et al. MR imaging evaluation of the activity of Crohn's disease. *AJR Am J Roentgenol*. 2001;177:1325–1332.
  39. Maccioni F, Viscido A, Broglia L, et al. Evaluation of Crohn disease activity with magnetic resonance imaging. *Abdom Imaging*. 2000;25:219–228.
  40. Sempere GA, Martinez S, V, Medina CE, et al. MRI evaluation of inflammatory activity in Crohn's disease. *AJR Am J Roentgenol*. 2005;184:1829–1835.
  41. Madsen SM, Thomsen HS, Schlichting P, et al. Evaluation of treatment response in active Crohn's disease by low-field magnetic resonance imaging. *Abdom Imaging*. 1999;24:232–239.
  42. Elson CO, Cong Y, McCracken VJ, et al. Experimental models of inflammatory bowel disease reveal innate, adaptive, and regulatory mechanisms of host dialogue with the microbiota. *Immunol Rev*. 2005;206:260–276.
  43. Darfeuille-Michaud A, Boudeau J, Bulois P, et al. High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. *Gastroenterology*. 2004;127:412–421.
  44. Manichanh C, Rigottier-Gois L, Bonnaud E, et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut*. 2006;55:205–211.
  45. Swidsinski A, Ladhoff A, Pernthaler A, et al. Mucosal flora in inflammatory bowel disease. *Gastroenterology*. 2002;122:44–54.
  46. Backhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. *Science*. 2005;307:1915–1920.