We propose that the susceptibility to nephropathy in insulin dependent diabetics is linked with the liability to raised arterial pressure. This predisposition, as manifested in the parents, is likely to be transmitted genetically, though mediation through familial sharing of environmental factors cannot totally be excluded. Interestingly, comparatively low blood pressure is an almost universal feature among long term survivors of uncomplicated diabetics.

We thank Mr T Murrell and Mr R F House for statistical advice, Mrs J Gray for secretarial help, and the British Diabetic Association for research group support.

References

Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn’s disease

JEAN K RITCHIE, JANE WADSWORTH, J E LENNARD-JONES, ELIZABETH ROGERS

Abstract
Between 1 September 1980 and 31 August 1983, 352 patients with inactive or mildly active Crohn’s disease but not taking drug treatment apart from sulphasalazine were entered from 40 hospitals into a prospective trial to assess the effects of two different diets on disease activity over two years. One hundred and sixty two patients were randomly allocated to take a diet unrestricted in sugar and low in fibre and 190 to a diet with little or no sugar and high in unrefined carbohydrate.

No clear difference in clinical course was detected among patients who accepted the two different types of dietary advice.

Introduction
One of the most difficult features of Crohn’s disease is its chronicity and tendency to recur after resection. A harmless treatment which decreased the relapse rate after medical or surgical treatment would represent real progress. Many studies have shown that patients with Crohn’s disease tend to eat more sugar, and one study also showed less raw fruit and vegetables, than healthy control subjects. A retrospective comparison suggested that the clinical course of 32 patients treated with a diet low in refined carbohydrate and high in unrefined cereals, vegetables, and fruit was more favourable than that of a matched group of patients treated without dietary modification.

We report the results of a randomised prospective single blind trial over two years of two types of dietary advice given to patients with Crohn’s disease who were well despite the presence of diseased intestine or after resection. One group of patients was advised to avoid refined carbohydrate and to replace it with unrefined carbohydrate. This change resulted in increased dietary fibre but a fibre supplement was not advised. The other group was advised to avoid unrefined cereal foods but was given no advice to alter the consumption of refined carbohydrate.

Patients and methods
Selection of patients—Criteria for the diagnosis of Crohn’s disease were based on a typical clinical history with characteristic appearances in radiographs or at laparotomy and whenever possible confirmed by biopsy or...
a resection specimen. Patients with a stoma and those with disease limited to the stomach or duodenum, or both, were excluded, as were patients with anal disease only. From among patients attending their outpatient clinics participating clinicians were asked to identify patients with Crohn’s disease who were well, either with known structural disease or after resection of all apparently diseased intestine, and who were receiving no treatment other than nutritional supplements, antidiarrhoeal drugs, or maintenance sulphasalazine. Clinicians were asked to invite such patients to enter a trial of two types of diet to assess whether recurrence of disease activity was affected by the type of food eaten.

Assessment of outcome—The object of the trial was to assess the proportion of patients in each trial group who had a relapse of their disease. Clinical deterioration was defined in order of decreasing importance as the need for surgical or medical treatment in hospital; need for corticosteroid, sulphasalazine (if not already being taken), antibiotic, or immunosuppressive drug treatment for intestinal disease as an outpatient; or as a worsening of symptoms attributable to the disease and severe enough to warrant withdrawal from the trial. Each of these events constituted an "end point" and was regarded as failure of dietary advice to prevent deterioration of disease. Some patients also left the trial because they did not wish to continue one or other of the diets advised, either because they did not like it or because they considered that it caused symptoms. These patients were distinguished from those who left the trial for unrelated or unknown reasons. Patients who completed two years in the trial were those in whom there was no evident clinical deterioration. Their wellbeing at the beginning and end of the trial was assessed in terms of symptoms, body weight, and laboratory findings.

Power of trial—At the outset we estimated that about 40% of patients with Crohn’s disease who are well develop recurrent symptoms requiring treatment within two years. To detect a halving of this rate in nine out of 10 trials 260 patients should be studied for up to two years. In the event, clinicians from 40 hospitals collaborated to enable 352 patients to be included.

Randomisation and "blindness"—Eligible patients were invited to enter the trial after full explanation by the clinician. Those who accepted were referred to the dietitian, who held the randomisation code as a consecutive series of sealed envelopes. A further explanation of the principles of each diet was given by the dietitian, and if the patient agreed to accept whichever of the two diets was allocated the next envelope was opened and the trial diet disclosed. The clinician was not informed of the diet allocated and, as far as possible, remained blind to the advice given.

Dietary advice—Patients in dietary group A were advised to eat carbohydrate in its refined form using white flour and rice and to avoid unrefined carbohydrate foods; sugar intake was unrestricted. Patients in dietary group B were advised to eat carbohydrate in its natural unrefined state only, avoiding all products containing sugar or white flour; this diet was the same as that advocated in the Bristol study. Both types of advice were accompanied by a booklet, modelled on that used in Bristol, which explained the principles of the diet and gave a list of "acceptable" and "unacceptable" foods. At every visit the dietitian reviewed the patient’s diet and strongly reinforced the advice given.

Dietary assessment—At entry to the trial and every six months thereafter the patient’s sugar and fibre intake was assessed by the dietitian using a standard form and a special list of common foods and household measures based on the tables of McCance and Widdowson, supplemented by manufacturers’ data. Assessment was by the recall method. Patients were encouraged to keep a diary of food eaten on one weekday and one day at the weekend using prepared forms as examples of their diet.

| TABLE I—State and comparability of treatment groups at entry to trial. Except where stated otherwise values are medians (ranges in parentheses) |
|-----------------|-----------------|
| **Dietary group A** | **Dietary group B** |
| **Sex**: | | |
| No (%), male | 60 (37-0) | 70 (36-8) |
| No (%), female | 102 (63-0) | 120 (63-2) |
| **Age (years)** | | |
| Median | 35-6 (17-5-68-6) | 35-2 (14-4-77-7) |
| **Weight (kg)** | | |
| Median | 60 (39-94) | 60 (41-102) |
| **Haeoglobin (g/l)** | | |
| Median | 133 (91-169) | 133 (84-171) |
| **Erythrocyte sedimentation rate (mm in first hour)** | | |
| Median | 10 (1-63) | 12 (1-148) |
| **No (%) taking sulphasalazine at entry** | | |
| Median | 35 (21-6) | 29 (15-3) |
| **No (%) with structural disease present** | | |
| Median | 104 (64-2) | 110 (60-9) |
| **No with previous resection, recurrence** | | |
| Median | 31 | 27 |
| **No with no previous resection** | | |
| Median | 73 | 87 |
| **Site** | | |
| Small bowel | 31 | 37 |
| Small and large bowels | 24 | 31 |
| Large bowel | 19 | 24 |
| **No (%) with no macroscopic disease after resection** | | |
| Median | 58 (35-8) | 76 (40-0) |

Clinical assessment—A detailed form giving the previous history, diagnostic criteria, symptoms, body weight, height, and laboratory data was completed at entry. Thereafter a clinical assessment form was completed every three months to give changes in treatment, the data needed to calculate a simple clinical index, and laboratory findings.

Administration—All clinical and dietary assessment forms were sent to St Mark’s Hospital and checked by the administrative (JKR) and a dietitian (ER) respectively. Queries were dealt with by letter.

Statistical analysis—Non-parametric statistics were used throughout. Results for continuously distributed variables were expressed as median and interquartile range—that is, the range of values lying between the 25th and 75th centiles—and the significance of differences between patients in dietary groups A and B assessed by the Mann-Whitney U test. Other results were expressed as proportions and the log rank test used to compare survival curves of subjects taking the two diets remaining in the trial. For clarity in the figures only the final standard errors (SE) of surviving proportions are shown.

Results

Three hundred and fifty two patients were entered into the trial; 162 were randomised to dietary group A and 190 to dietary group B. It was not possible to define the total populations of eligible patients from whom the sample was drawn. At entry the patients assigned to the two dietary groups were very similar with regard to age, sex, and clinical state (table I).

The median sugar intake in the two study groups at entry was 689 g/week (range 85-2180 g) in group A and 614 g/week (25-2072 g) in group B. For patients who completed the trial the figures were 644 g/week (group A) and 63 g/week (group B). The median fibre consumption at entry was 120 g/week (range 38-304 g) for patients in group A and 127 g/week (44-518 g) for those in group B. At the end of two years the figures were 110 g/week and 195 g/week respectively. Figure 1 shows the median and interquartile ranges.
for sugar and fibre consumption based on all available dietary assessments; there was good compliance with the two diets.

The trial was designed to last two years and 178 patients completed it. The remaining 174 patients required treatment or withdrew for various reasons. Table II summarises the results based on the intention to treat. Twenty-one patients were treated surgically during the trial, 14 in dietary group A and seven in dietary group B. The operations were right hemicolectomy in 11 patients (group A six, group B five), resection of anastomosis in seven (A five, B two), stricturoplasty in one (A), and ileostomy in two (A). Though operative treatment was more common in patients in group A, the difference was of marginal significance ($\chi^2=2.998, 0.10>p>0.05$).

**TABLE II—Clinical outcome in the two treatment groups. Figures are numbers (percentages) of patients**

<table>
<thead>
<tr>
<th>End points:</th>
<th>Dietary group A (n=162)</th>
<th>Dietary group B (n=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal surgery</td>
<td>14 (8-6)</td>
<td>7 (3-7)*</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>21 (13-1)</td>
<td>9 (4-8)</td>
</tr>
<tr>
<td>Withdrawal, more symptoms</td>
<td>2 (1-2)</td>
<td>20 (10-5)</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>15 (9-3)</td>
<td>21 (11-1)</td>
</tr>
<tr>
<td>Total</td>
<td>52 (32-1)</td>
<td>66 (34-7)</td>
</tr>
</tbody>
</table>

Other withdrawals:
- Non-compliance: 4 (2-5) vs 20 (10-5)
- Unknown: 8 (4-9) vs 6 (3-2)
- Unrelated: 8 (4-9) vs 10 (5-3)

Total: 20 (12-8) vs 36 (18-9)

Two years in trial:
- Score worse: 24 (14-8) vs 28 (14-7)
- Score unchanged: 11 (6-9) vs 1 (0-5)
- Score improved: 55 (34-9) vs 59 (31-1)

Total: 90 (55-6) vs 88 (46-5)

* $\chi^2=2.998, p>0.05$.

Thirty nine patients were admitted to hospital during the two years, 21 in group A and 18 in group B. Reasons for admission were acute relapse in seven cases (group A three, group B four), abdominal pain or small bowel obstruction in 18 (A 13, B five), complications of Crohn’s disease in five (A one, B four), investigation or assessment in two (A), and anal operations in seven (A two, B five). Two patients allocated to diet A withdrew, as they considered that the diet led to increased diarrhoea. Twenty patients taking diet B reported an increase in symptoms (nine diarrhoea, seven loss of weight, four abdominal pain) and withdrew from the trial. Twenty other patients taking diet B and four taking diet A failed to attend for follow up. Other outcomes showed little difference between the diets.

Life table analysis was used to compare the progress of patients taking the two diets. Figure 2 shows the cumulative proportion of patients remaining in the trial without deterioration of the disease resulting in one of the end points listed in table II. The proportions at two years were 64% (SE 4%) in group A and 59% (4%) in group B. The log rank test showed no significant difference between the diets. A similar method of analysis (fig 3) applied to patients withdrawing from the trial for any reason other than worsening symptoms (see table II) showed a significant difference ($p<0.03$) between the diets at two years (8% (SE 4%) for diet A, 29% (4%) for diet B), with an excess of withdrawals from diet B at the beginning of the trial.

**FIG 2—Percentage cumulative probability of deterioration of disease shown by reaching one of end points listed in table II during trial.**

Patients who completed two years in the trial remained well. The clinical score, stool count, and body weight showed no significant change with either diet (table II).

Within the two dietary groups there was a wide variation in consumption of fibre and sugar. When the analysis was restricted to those patients who after six months of diet A reported sugar consumption above the upper quartile (765 g/week) and fibre consumption below the lower quartile (100 g/week) and to those taking diet B who reported sugar consumption below the lower quartile (60 g/week) and fibre consumption above the upper quartile (205 g/week) the comparisons then referred to patients who complied very well with their dietary advice. When the analysis was restricted to these 24 patients taking diet A and 38 taking diet B there were no evident differences in outcome.

**FIG 3—Percentage cumulative probability of withdrawal from trial for reasons other than deterioration of disease.**

Discussion

Studies in Britain, Germany, Israel, and Sweden have all shown that patients with Crohn’s disease tend to eat more sugar than do matched healthy controls. Such unanalyzed dietary factors have been considered one of the few clues about the aetiology or pathogenesis of the disease. All but one of these investigations used a method of dietary assessment based on interviews or postal questionnaires; in the only survey in which all items of diet over five days were weighed no significant differences were found, but there was a trend towards more added sugar among the patients than the controls. One controlled study estimated the preillness diet soon after diagnosis of Crohn’s disease and another recorded both the diet reported by patients during the illness and their recall of what they had consumed in health.2 Comparison between sugar intake within six months of diagnosis in one group with the intake seven to 36 months after diagnosis in another showed that the intake of sugar tended to be greater with the longer history of disease and suggested that the increased intake of sugar was a secondary phenomenon.

In this study the initial dietary assessments showed a median consumption of about 90 g sugar daily, similar to the median of 80 g in another study of Crohn’s disease.3 These figures are lower than the published mean daily intakes of 115-200 g in patients with Crohn’s disease in other published studies and of the same order as the 91 g in men and 57 g in women measured by weighing among healthy Cambridgeshire villagers.17

The median fibre intake of 17-18 g daily found in the preliminary questionnaire in this trial was similar to that estimated by Thornton et al among patients with Crohn’s disease before the onset of symptoms.4 Their dietary surveys naturally led to the suggestion that a modification in diet might affect the clinical course of Crohn’s disease. A retrospective study based on comparing the course of the disease among patients attending two different clinics, one of which advocated a low refined, high unrefined carbohydrate diet, suggested that this diet might be beneficial. Though efforts were made to match the groups, differences in selection and in other aspects of management may have affected the results. The only other prospective controlled trial of a low refined carbohydrate diet compared with a normal diet was limited to 20 patients but did suggest that reducing added sugar was helpful.16 An Italian trial found no difference in outcome between a low fibre (residue) diet and an unrestricted (normal fibre) diet.19

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Note: The above text is a transcription of the document content and does not include any editorial comments or analysis.
Our trial was planned in 1979; the first patient was entered in 1980 and the last patient completed the trial in 1985. Forty-five clinicians from 40 hospitals collaborated. One hospital contributed 68 patients, 13 hospitals between 10 and 21 patients, and 26 hospitals fewer than 10 patients. It might be suggested that the dietary assessment method used was unreliable, particularly because patients who wish to show their compliance with the advice given are likely to report higher intakes of fibre in their diet as advised. Even though the trial inevitably tested the advice given rather than known conformity to the diet, this is the situation in practice.

It soon became apparent that some patients did not wish to continue the low refined, high unrefined carbohydrate diet. Some said that it made their symptoms worse, some that it caused weight loss, and others did not like it. About 10% of patients allocated to this diet withdrew for one of these reasons. Furthermore, a similar additional proportion of patients in this dietary group failed to attend for follow up, suggesting that more patients allocated to this diet than the other found the trial unacceptable in practice.

Conversely, a few patients who normally took a high fibre diet but were allocated to take the diet low in fibre found this change difficult to tolerate.

The failure of this trial to show any convincing difference in the clinical course of the disease in the two treatment groups is disappointing. It might be argued that a therapeutic response would have been more likely among patients with active disease. The trial was not conducted among such patients because the response would be difficult to evaluate when drugs were being taken and because there is a real need to find a treatment which decreases the long term relapse rate in those with inactive disease. The cumulative probability of deterioration of the disease was similar to the 40% expected when planning the trial, but the actual proportion of patients who deteriorated resulting in the end points listed in table II was smaller (group A 32%, group B 35%). The difference between the groups was smaller than that judged clinically important when planning the trial. Even among the small group of patients who complied best with the advice given no difference was discernible; it seems unlikely that patients will alter their intake of sugar or dietary fibre, or both, to a greater extent than achieved by this group.

A high proportion of patients in whom all macroscopic disease is resected develop aphthoid ulcers at the anastomotic site within one year of operation. Hence most of the 134 patients in this group (table I) probably had occult disease during the two years of the trial. The results suggest that both the course of mildly active Crohn's disease and deterioration after resection are unaffected by advising replacement of refined by unrefined carbohydrate in the diet. Whether a reduction in sugar intake without a concurrent increase in fibre intake would be beneficial cannot be determined from our study. Other reports have suggested that different dietary approaches may be beneficial, but the results of large trials of these diets are awaited.

The following clinicians collaborated in the trial and we are very grateful both to them and to all the dietitians who took part: Dr R N Allan, General Hospital, Birmingham; Dr A T R Axon, Leeds General Infirmary; Dr R E Barry, Bristol Royal Infirmary; Dr R J Bennett, Hull Royal Infirmary; Professor I A D Boucher, Ninehills Hospital, Dundee; Dr H Brady, Southampton and District Grimsby Hospital, West Bromwich, Oldchurch Hospital, Romford; Dr A R Davidson, Kettering General Hospital, Dr E Elias, Queen Elizabeth Hospital, Birmingham; Professor I E Gillespie, Manchester Royal Infirmary; Dr S R Gould, Epsom District Hospital; Dr R F Harvey, Frenchay Hospital, Bristol; Mr R P Hawley, Mr C V Mann, Dr R J Nicholls, Mr J M A Northover, Mr J P Thomson, and Mr I P Todd, St Mark's Hospital, London; Dr D J Holdstock, Ashford Hospital, Middlesex; Dr C L Hadol, Royal Hallamshire Hospital, Sheffield; Dr J Howell Jones, Walsgrave Hospital, Coventry; Dr J Hywel Jones, Singleton Hospital, Swansea; Dr G D Kerr, Royal Shrewsbury Hospital, Dr J D Kinloch, Chase Farm Hospital, Farnborough, Mr C M Lane, Royal Hampshire County Hospital, Winchester; Professor M J S Langman, City Hospital, Nottingham; Surgeon Commander R J Leicester, Royal Naval Hospital, Haslar; Dr A J Levi, Northwick Park Hospital, Harrow; Mr C G Marks, Royal Surrey County Hospital Guildford; Dr D W Rees and Professor L A Turnberg, Hope Hospital, Salford; Dr R J Russell and Dr D A Farah, Royal Infirmary, Glasgow; Dr K P R Schiller, St Peter's District General Hospital, Chertsey; Dr W Sircus, Western General Hospital, Edinburgh; Dr E T Sawyer, New Cross Hospital, Wolverhampton; Mr C W Venables, Freeman Hospital, Newcastle upon Tyne; Professor D G Weir, Sir Patrick Dun's Hospital, Dublin; Surgeon Commander J G Williams, Royal Naval Hospitals, Plymouth and Haslar; Dr C P Willoughby, Basildon Hospital, Essex; Dr J M T Willoughby, Lister Hospital, Stevenage; Professor R Wright, Southampton General Hospital; Dr G R Youngs, Chester Royal Infirmary; Dr R Zeegen, Westminster Hospital, London.

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Copies of the complete protocol and of the clinical and dietary assessment forms used in the trial may be obtained from JKR.

References

(Accepted 23 June 1987)

How much energy does the breast fed infant consume and expend?

An error occurred in the table in this paper by A Lucas and others (11 July, p 75). Some of the 95% confidence intervals for differences were given in kcal not MJ; these should have read, respectively, 6-8 to 1-8, -0.06 to -0.02, 0.05 to 0.15, -0.10 to 0.13, -0.04 to 0.04, 0.13 to 0.65, 0.04 to 0.67, 0.10 to 0.72, -0.14 to 0.13, 30 to 172, and -0.02 to 0.05.

Radiological progression and lung function in silicosis: a ten year follow up study

Two errors occurred in this paper by Ng Tze-Pin and others (18 July, p 164). In table V the regression coefficients for average silica concentration (mg/m³) should both have had negative signs, reading -36 (17) for forced expiratory volume in one second and -40 (19) for forced vital capacity. In paragraph 5, line 12, of the discussion the figure should read 0.10 mg/m³ and not 0.010 mg/m³.

Corrections