Ileal function in patients with untreated adult coeliac disease

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SUMMARY A double-lumen perfusion technique has been used to investigate jejunal and ileal absorption of glucose, water, and electrolytes in a group of patients with untreated adult coeliac disease. Correct positioning of the tube was confirmed by measuring the differential jejunal and ileal handling of bicarbonate. Eight control subjects and eight patients with coeliac disease were perfused with an isotonic electrolyte solution containing 50 mM glucose and 25 mM bicarbonate.

The group of coeliac patients had impaired jejunal absorption of glucose ($P < 0.001$), water ($P < 0.01$), sodium ($P < 0.02$), and chloride ($P < 0.05$) compared with the control group. In contrast the group of coeliac patients had normal ileal glucose and water absorption and increased ileal sodium ($P < 0.01$) and chloride ($P < 0.05$) absorption compared with the controls. Evidence for ileal adaptation was found in three individual patients who had absorptive values outside 2SD of the normal mean.

The results indicate that the distal small intestine in coeliac disease has the ability to adapt to the damage and loss of absorptive capacity in the proximal small intestine.

After jejunal resection and experimental jejunal bypass in the rat the remaining ileal mucosa becomes hypertrophied (Loran and Althausen, 1958; Booth, Evans, Menzies, and Street, 1959; Tilson and Wright, 1970; Weser and Hernandez, 1971; Bury, 1972; Gleeson, Dowling, and Peters, 1972). Studies of ileal function following jejunal resection or bypass showed enhanced absorption of glucose, water, and electrolytes (Dowling and Booth, 1967; Bury, 1972; Perry, 1973), maltose (Bury, 1972), bile salts (Perry, 1973), and vitamin B₁₂ (MacKinnon, 1972). Untreated adult coeliac disease might be compared to this experimental animal model because the mucosal lesion is more marked in the jejunum than in the ileum (Stewart, Pollock, Hoffbrand, Mollin, and Booth, 1967) and some patients absorb vitamin B₁₂ to a greater extent than normal subjects (Elias, MacKinnon, Short, and Dowling, 1973). Recent perfusion studies indicate that many patients with coeliac disease secrete fluid and electrolytes into the lumen of the upper jejunum (Fordtran, Rector, Locklear, and Ewton, 1967; Schmid, Phillips, and Summerskill, 1969; Russell, Allan, Gerskowitch,

and Robertson, 1972; Silk, Kumar, Perrett, Clark, and Dawson, 1974a; Kumar, Silk, Rousseau, Pagaltsos, Clark, Dawson, and Marks, 1974). Despite these findings not all of these patients complained of either severe symptoms or diarrhoea (Silk *et al*, 1974a; Kumar *et al*, 1974). One explanation for this may be that ileal function is enhanced in patients with coeliac disease.

The present study was undertaken to explore this possibility; ileal function has been assessed in eight patients with untreated adult coeliac disease by studying absorption during ileal perfusion of an isoosmotic electrolyte solution containing 50 mM glucose and 25 mM bicarbonate. A direct comparison between ileal and jejunal function has been made by perfusing the same test solution through the jejunum of each subject studied. An ileal biopsy was obtained from each patient but owing to technical difficulties it was not always possible to correlate ileal morphology directly with function as a number of the perfusion experiments were carried out distal to the biopsy site. One of the problems that occurs when carrying out ileal perfusions is that one cannot always be sure that the test segment is correctly positioned. Initial studies

carried out in normal subjects (Silk, Webb, Lane, Clark, and Dawson, 1974b) indicated that correct ileal positioning of the perfusion tube could be confirmed by using as a functional marker the differential handling of bicarbonate by the jejunum and ileum (Phillips and Summerskill, 1967), because, compared with in the jejunum, no significant absorption or even net secretion occurred in the ileum. The same criteria were used to confirm correct positioning of the perfusion tube during the ileal studies in coeliac patients.

Materials and Methods

SUBJECTS

Eight patients with untreated adult coeliac disease with a mean age of 38 years (range 18-57 years) were studied. The diagnosis of coeliac disease was established by history, physical examination, the usual laboratory criteria of malabsorption, and the typical histological appearance of the jejunal biopsy. All these patients subsequently showed clinical and morphological improvement when gluten was withdrawn from the diet. Relevant clinical details of the patients studied are shown in table I. We have no explanation for the low incidence of biochemical steatorrhoea in this group of random coeliac patients. It is of note, however, that the diagnosis was suspected mainly on haematological grounds in four cases.

Eight normal adult volunteers without evidence of gastrointestinal disease with a mean age of 40 years (range 22-47 years) acted as controls. The full purpose and nature of the study was explained to

all subjects and informed consent to the study was given in each case.

BIOPSY TECHNIQUE

Intestinal mucosal biopsies were obtained from the patients with untreated adult coeliac disease using the biopsy capsule of Crosby and Kugler (1957). Jejunal biopsies were taken under fluoroscopic control from a 10-cm segment of upper jejunum beyond the duodenal-jejunal flexure and ileal biopsies were taken when the biopsy capsule was situated 140-200 cm from the mouth of each subject.

The biopsies were graded as normal, partial villous atrophy (PVA), or subtotal villous atrophy (SVA). Values in the coeliac patients were compared with the normal control data of Stewart *et al* (1967).

Morphological Procedure

Each biopsy was orientated on a ground glass slide and fixed in a 10% formaldehyde saline solution. They were then examined under a dissecting microscope and photographed. The histology was classified according to the criteria of Stewart *et al* (1967) with particular reference to villous height, mucosal thickness, and epithelial surface.

EXPERIMENTAL TECHNIQUES

The patients and normal control subjects were intubated with a double-lumen perfusion tube incorporating a proximal occlusive balloon as previously described (Silk *et al*, 1974b). The tube was allowed to pass until the infusion orifice was distal to the duodenal-jejunal flexure and the final

Patient	Age (yr) and Sex	Status at Diagnosis			
		Diarrhoea	Faecal Fat (g/24 hours)	Radiograph of Small Intestine	Jejunal Biopsy
F.A.	25 F	Severe Bowels open 10-15/day	3.2	Thickened mucosal folds with flocculation	SVA
R.B.	46 M	Occasionally only	1.0	—	SVA
P.F.	43 M	Watery Bowels open 2-3/day	—	Normal	SVA
M.H.	30 F	Severe Bowels open 4-5/day	4.7	Thickened mucosal folds	SVA
E.K.	57 F	Diarrhoea in past, constipated at time of diagnosis	—	Dilatation	SVA
J.Mc.M.	54 F	Mild, Bowels open 2-3/day	16.7	Carcinoma of ampulla of Vater, small bowel normal	SVA
E.S.	18 F	None	2.1	Normal	SVA
C.F.	28 F	Intermittent diarrhoea, Bowels open 4-6/day	4.7	Dilated jejunum with thickened mucosal folds, clumping of barium	SVA

Table I Clinical details of patients with untreated adult coeliac disease

position checked radiologically so that the 15 cm perfusion segment was positioned in the upper jejunum. The test solution was infused at 20 ml/min and after a 30-min equilibration period three 10-min samples were collected from the distal collecting orifice by simple syphonage. After the jejunal perfusion experiments had been completed each subject was permitted oral fluids and a light diet until midnight. During this period the perfusion tube was allowed to pass distally through the small intestine. The ileal perfusion experiments were carried out the following morning at which time the mercury bag was situated 180-210 cm from the mouth of each subject. The final position of the tube was checked radiologically to confirm that the infusion orifice appeared to lie in the distal small intestine.

PERFUSION SOLUTION

The jejunum and ileum of each subject was perfused with an isotonic electrolyte solution containing 50 mM glucose, 25 mM bicarbonate, 117 mM sodium, 5 mM potassium, and 96 mM chloride. The solution contained a non-absorbable marker, polyethylene glycol (PEG), labelled with 1 μ Ci (14 C) PEG/1 (Wingate, Sandberg, and Phillips, 1972; Silk, 1974).

LABORATORY MEASUREMENTS

The glucose and bicarbonate contents of the perfusion solution and intestinal aspirates were analysed in a routine laboratory by standard methods. The glucose content was measured using a Technicon analyser (AA2) by a modification of the neocuproine method of Brown (1961). The bicarbonate content was measured using a Technicon 6/60 analyser (Skeggs and Hochstrasser, 1964). The (14 C) PEG content of the perfusion solutions and aspiration samples were measured as previously described (Silk, Perrett, Webb, and Clark, 1974c).

Calculations and statistics

Absorption rates were calculated from previously described formulae (Holdsworth and Dawson, 1964). The statistical significance of differences in absorption rates between the two groups of subjects was evaluated by the unpaired t test (Langley, 1968).

Results

JEJUNAL MORPHOLOGY

All patients with untreated adult coeliac disease had subtotal villous atrophy of the jejunal mucosa. The villous height and surface cell heights were markedly reduced and mucosal thickness markedly increased compared with normal subjects (table II).

JEJUNAL FUNCTION

1 Bicarbonate absorption

The rates of bicarbonate absorption are shown in figure 1a. Although there was no significant difference between the rates of bicarbonate absorption by the group of normal subjects (4.2 ± 2.9) compared with the group of patients with coeliac disease (1.7 ± 6.0), three of the coeliac patients exhibited net secretion into the lumen of the jejunum. Values are the mean absorption rates expressed as m-equiv $\text{hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$.

2 Glucose absorption

The rates of glucose absorption are shown in figure 2a. There was severe impairment of glucose absorption by the group of coeliac patients (6.6 ± 12.4) compared with the normal controls (27.3 ± 13.7 ; $P < 0.001$). Values are the mean absorption rates expressed as m mol $\text{hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$. Each individual patient with coeliac disease had a glucose absorption value below 2SD of the normal mean.

3 Water and electrolyte absorption

The rates of water absorption are shown in fig 3a

Patient	Site of Ileal Biopsy (cm) ¹	Villous Height (μ)		Mucosal Thickness (μ)		Surface Cell Height (μ)	
		Jejunum	Ileum	Jejunum	Ileum	Jejunum	Ileum
F.A.	150	83	280	313	—	17.2	23.6
R.B.	180	0	306	366	226	20.6	31.8
P.F.	170	65.6	106	347	308	17.2	23.0
M.H.	150	0	0	506	270	15.3	17.3
E.K.	140	31.0	172	296	150	17.2	22.8
J.Mc.M.	150	0	224	241	119	14.2	28.4
E.S.	200	0	569	330	106	15.0	26.7
C.F.	165	0	87	319	285	14.0	20.0
Normal range ²		330-636	372-691	65-170	73-132	29.3-36.8	30.3-36.4

Table II Microscopic appearances of small intestinal mucosa

¹Cm from mouth of each subject.

²Normal data taken from Stewart *et al* (1967); n = 10.

Fig 1 Absorption of bicarbonate from the jejunum (a) and the ileum (b). Negative sign indicates net secretion into the lumen of the intestine.

Fig 2 Glucose absorption from the jejunum (a) and from the ileum (b). Negative sign indicates net secretion into the lumen of the intestine.

and the rates of sodium and chloride absorption are shown in fig 4a and fig 5a respectively. There was severe impairment of water absorption by the group of coeliac patients (-2.3 ± 254.8) compared with the group of normal controls (183.7 ± 140.5 ; $p < 0.01$). The values are the mean absorption rates expressed as $\text{ml hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$. Five patients exhibited net water secretion (values below 2SD of the normal mean). There was impairment of sodium absorption by the group of coeliac patients (-2.7 ± 32.0) compared with the group of

normal controls (15.2 ± 19.0 ; $p < 0.02$; fig 4a). The values are the mean absorption rates expressed as $\text{mEq hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$. The three patients who secreted bicarbonate into the lumen of the jejunum also exhibited net secretion of sodium into the lumen of the jejunum (values below 2SD of the normal mean). There was also impairment of chloride

Fig 3 Water absorption from the jejunum (a) and from the ileum (b). Negative sign indicates net secretion into the lumen of the intestine.

Fig 4 Sodium absorption from the jejunum (a) and from the ileum (b). Negative sign indicates net secretion into the lumen of the small intestine.

Fig 5 Chloride absorption from the jejunum (a) and from the ileum (b). Negative sign indicates net secretion into the lumen of the small intestine.

absorption by the group of patients with coeliac disease (-4.3 ± 31.4) compared with the group of normal controls (11.5 ± 15.8 ; $P < 0.05$; fig 5a). Values are the mean absorptive rates expressed as $\text{m-equiv hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$. The same three patients who secreted bicarbonate and sodium also secreted chloride into the lumen of the jejunum (values below 2SD of the normal mean).

ILEAL MORPHOLOGY

In contrast to the findings in the jejunum, the ileum was less severely involved (table II). Ileal biopsies from three patients however, M.H., P.F., and C.F., were grossly abnormal, having severe abnormalities of villous height, mucosal thickness, and surface cell height. None of the other five biopsies were normal according to the criteria of Stewart *et al* (1967). Four had reduced villous height ($172\text{--}306 \mu$) compared with the normal subjects. It was not possible to measure the mucosal thickness of F.A.'s ileal biopsy.

ILEAL FUNCTION

1 Bicarbonate absorption

The rates of bicarbonate absorption in the ileum are shown in figure 1b. The normal subjects absorbed bicarbonate very poorly in the ileum (-0.4 ± 2.5 ; values are the mean absorptive rates expressed as $\text{m-equiv hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$) compared with the jejunum (fig 1a). Four subjects exhibited net secretion of bicarbonate ions into the lumen of the ileum.

These findings indicate that in functional terms the test segment was positioned correctly in the ileum of each normal subject studied. Six out of the eight patients with coeliac disease handled bicarbonate ions in a similar way to the normal subjects (values within 2SD of normal mean) indicating that in these subjects the ileal test segment was correctly positioned. Significant absorption of bicarbonate was seen during 'ileal' perfusion of two coeliac patients ($2.6, 2.7 \text{ m-equiv hr}^{-1} \pm 15 \text{ cm}^{-1}$; values greater than 2SD of the normal mean). The results of the ileal perfusions carried out in these two patients are therefore not included in the present study because one likely explanation for the high absorptive values is that the perfusion tube was wrongly positioned in a more proximal area of the small intestine. Recent experimental evidence suggests that this is a valid assumption because a further group of coeliac patients were found to have either normal or increased ileal luminal pH compared with normal subjects as measured using a radio telemetry capsule (Fairclough, Silk, Perry, Hicks, Clark, and Dawson, 1975; Meldrum, Watson, Riddle, Bown, and Sladen, 1972).

2 Glucose absorption

The rates of glucose absorption are shown in fig 2b. In contrast to glucose absorption in the jejunum (fig 2a) the group of coeliac patients absorbed glucose normally in the ileum (16.9 ± 13.8) compared with the control group (12.5 ± 10.6 ; values are the mean absorptive rates expressed as $\text{mmol hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$). Two patients (E.S. and R.B.) had absorption values above the normal range (one value greater than 2SD of the normal mean).

3 Water absorption and electrolyte absorption

The rates of water absorption in the ileum are shown in fig 3b and the rates of sodium and chloride absorption are shown in figs 4b and 5b respectively. There was no significant difference between the rates of ileal water absorption during perfusion of the group of coeliac patients (95.3 ± 82.1) compared with the group of normal controls (51.2 ± 72.0 ; $t = 2.14$, $P > 0.05$; fig 3b). Two patients (J.Mc.M. and R.B.) had absorption values greater than 2SD of the normal mean. The group of coeliac patients absorbed sodium faster (10.2 ± 10.1) than the normal control group (1.1 ± 10.2 ; $P < 0.01$; fig 4b); values are the mean absorptive rates expressed as $\text{m-equiv hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$. Two coeliac patients (J.Mc.M. and R.B.) had absorption values greater than 2SD of the normal mean. Similarly the group of coeliac patients absorbed chloride faster (6.8 ± 9.0) than the

normal control group (1.8 ± 7.2 ; $P < 0.02$; fig 5b); values are the mean absorption rates expressed as $m\text{-equiv hr}^{-1} 15 \text{ cm}^{-1} \pm 2\text{SD}$. Two patients (J.Mc.M. and E.S.) had absorption values greater than 2SD of the normal mean.

Discussion

The results of the jejunal perfusion experiments showed that not only was absorption of glucose, water, and electrolytes severely impaired in the group of patients with coeliac disease, but that net secretion occurred into the gut lumen during perfusion of a number of individual patients. These findings are in general agreement with all the recent perfusion studies carried out to investigate jejunal function in coeliac disease (Schedl and Clifton, 1963; Holdsworth and Dawson, 1965; Fordtran *et al*, 1967; Schmid *et al*, 1969; Russell *et al*, 1972; Silk *et al*, 1974a; Kumar *et al*, 1974). We have previously reported (Kumar *et al*, 1974) that three out of nine patients with untreated coeliac disease absorbed glucose normally from the jejunum. We believe that the discrepancy between those results and the present findings is due to differences in experimental technique rather than differences in patient selection. Sladen (1970) showed that luminal glucose concentrations along a 45 cm-segment fell in an exponential fashion during perfusion of a glucose saline solution. Thus it would be easier to highlight defects in absorption using a 15-cm segment rather than a 30-cm segment which was used in the study of Kumar *et al* (1974).

In contrast to the results of the jejunal perfusions, the ileal perfusion studies show that the coeliac patients have the same or greater capacity to absorb glucose, water, and electrolytes compared with normal subjects. Indeed every patient (including P.F. and M.H. whose results are excluded) had absorptive values for water, sodium, and chloride that were greater than normal mean values. Elias *et al* (1973) showed that two out of nine patients with coeliac disease absorbed vitamin B₁₂ to a greater extent than normal controls. Schedl, Pierce, Rider, and Clifton (1968) showed that two patients with coeliac disease absorbed methionine faster from the ileum than four normal control subjects. These latter findings taken in conjunction with the results presented in this paper substantiate the original suggestion of Schedl and Clifton (1963) that the distal small intestine in coeliac disease has the ability to adapt to the damage and loss of absorptive capacity in the proximal small intestine.

The absorptive capacity of the terminal ileum of patients four months after ileostomy is greatly enhanced compared with that of the normal terminal

ileum (Wright, Cleveland, Tilson, and Herskovic, 1969). Similarly, the absorptive capacity of the jejunum of patients after small bowel resection is enhanced compared with controls (Dowling and Booth, 1966; Weinstein, Shoemaker, Hersh, and Wright, 1969). Detailed histological studies indicate that the increased absorptive capacity is due to mucosal cell hyperplasia (Porus, 1965; Wright *et al*, 1969), an explanation which is adequately supported by experimental studies recently carried out in the rat (Gleeson *et al*, 1972). The present histological studies have not proved helpful in providing an explanation as to why ileal function is enhanced in some coeliac patients. It was not always possible to obtain peroral biopsies from the distal ileum, and apart from attaching the biopsy capsule to the test segment of the perfusion tube, there would appear to be no way of ensuring that ileal biopsy and perfusion are carried out at the same site. All but one (patient E.S.) of the ileal biopsies were undoubtedly taken proximal to the perfusion site, and all showed minor to severe (patients M.H. and P.F.) morphological abnormalities indicating a degree of proximal or midileal involvement in coeliac disease. It is of note, however, that the coeliac patients (J.Mc.M., E.S., and R.B.), who showed evidence of ileal adaptation (absorption values greater than 2SD of normal mean), had greater ileal surface cell heights than the other coeliac patients and there was a trend for these same three patients to have taller villi than the remaining coeliacs. It is most likely that the enhanced ileal function in coeliac disease is due to distal ileal mucosal cell hyperplasia occurring in response to the jejunal mucosal lesion. In support of this explanation, vitamin B₁₂ absorption, normally limited by the availability of receptor sites (Donaldson, Robins, Small, and Mathan, 1971), is enhanced in some patients with coeliac disease (Elias *et al*, 1973). A much more detailed study of ileal morphology in coeliac disease is needed before firmer conclusions can be drawn.

There was no consistent correlation between ileal function and severity of symptoms. It is interesting though that none of the patients who had evidence of enhanced ileal function presented with severe diarrhoea (table I). Phillips and Giller (1973) recently showed that a patient with coeliac disease had enhanced colonic function with respect to water and electrolyte absorption. The present study indicates that patients with coeliac disease may have enhanced ileal function. Two previous studies have shown that occasionally jejunal function may be normal in coeliac disease (Silk *et al*, 1974a; Kumar *et al*, 1974). There are thus three reasons why patients with untreated

adult coeliac disease do not always present with severe diarrhoea.

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