The ileal brake – inhibition of jejunal motility after ileal fat perfusion in man

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SUMMARY The possibility that malabsorbed fat passing through the human ileum exerts an inhibitory feedback control on jejunal motility has been investigated in 24 normal subjects by perfusing the ileum with a fat containing solution designed to produce ileal luminal fat concentrations similar to those in steatorrhoea (30–40 mg/ml). Mean transit times through a 30 cm saline perfused jejunal segment were measured by a dye dilution technique. Thirty minutes after ileal fat perfusion, mean transit times rose markedly to 18.9 ± 2.5 minutes from a control value of 7.5 ± 0.9 minutes ($n=5$; $p<0.05$). This was associated with an increase in volume of the perfused segment which rose to 175.1 ± 22.9 ml (control 97.6 ± 10.3 ml, $n=5$; $p<0.05$). Transit times and segmental volumes had returned towards basal values 90 minutes after completing the fat perfusion. Further studies showed that ileal fat perfusion produced a pronounced inhibition of jejunal pressure wave activity, percentage duration of activity falling from a control level of $40.3 \pm 5.0\%$ to $14.9 \pm 2.8\%$ in the hour after ileal perfusion ($p<0.01$). Ileal fat perfusion was associated with marked rises in plasma enteroglucagon and neurotensin, the peak values (218 ± 37 and 68 ± 13.1 pmol/l) being comparable with those observed postprandially in coeliac disease. These observations show the existence in man of an inhibitory intestinal control mechanism, whereby ileal fat perfusion inhibits jejunal motility and delays caudal transit of jejunal contents.

It is now nearly 50 years since Snell and Camp¹ first described the association between steatorrhoea and small bowel hypomotility. Although others have subsequently confirmed these findings using radiological,^{2,3} manometric,⁴ and breath hydrogen techniques,⁵ the physiological basis of the motility changes remains obscure. One obvious difference between patients with steatorrhoea and normal subjects is that in health most ingested fat is absorbed proximal to the ileum⁶ whereas in steatorrhoea a considerable amount of fat passes further distally. This difference led us to postulate that malabsorbed fat reaching the ileum and colon inhibits jejunal motility thereby delaying subsequent caudal transit of jejunal contents. The present study was designed to test the above hypothesis by using an ileal infusion of partially digested triglyceride to simulate steatorrhoea in normal subjects. The response has been assessed initially by measuring

jejunal transit times and segmental volumes, and in subsequent studies by recording jejunal motor activity. Plasma concentrations of the gut hormones enteroglucagon and neurotensin, both of which are known to be released by luminal fat,^{7,8} have been serially measured to assess their possible role in the observed responses.

Methods

PROCEDURES

Experiments 1–15: jejunal transit and absorption studies

After an overnight fast, 15 healthy volunteers (seven men and eight women, aged 21–40 years) were intubated with a purpose built 5 lumen radio opaque tube (external diameter 6.5 mm). The tube was positioned under fluoroscopic control so that the jejunal perfusion port A lay 10 cm beyond the duodeno-jejunal flexure, while the ileal perfusion port C, lay a further 70 cm distally, approximately 175 cm from the mouth (Fig. 1a). Passage of the

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Fig. 1 (a) Perfusion tube assembly in position, jejunal perfusion port A lies 10 cm beyond the duodeno-jejunal flexure with ileal perfusion port C 70 cm distal to A. The segment AB is 30 cm.

tube assembly through the small intestine was speeded by means of a deflatable terminal balloon. Intestinal fluid was sampled *via* port B, rapid aspiration being aided by an air bleed. Throughout the study the jejunum was perfused *via* port A at 10 ml/min with an isotonic solution containing NaCl 155 mM, xylose 5 mM, and 1 μ Ci of 14 C-labelled polyethylene glycol (PEG, mol wt 4000), using a Watson-Marlow H R Flow Inducer (Watson-Marlow, Falmouth, England). Once jejunal perfusion had been established for 15 minutes, the ileum was perfused for 30 minutes *via* port C with one of four ileal perfusion solutions, one control and three test. Port B was stoppered for 10 minutes before and throughout the period of ileal perfusion in an attempt to minimise proximal reflux of the ileal perfusate, as preliminary studies using phenol red labelled ileal perfusate showed that this manoeuvre

prevented dye appearing *via* port B when sampling was subsequently recommenced. The effect of each ileal perfusion was assessed at 30 and 90 minutes after its completion by measuring mean transit time through the 30 cm jejunal segment AB, using a 50 mg bolus of bromosulphthalein as described by Dillard *et al.*⁹ Between these transit time determinations, which each took 30 minutes, three 10 minute collections of jejunal fluid were made by syphonage *via* port B for analysis for bilirubin, amylase, PEG, Na⁺, and K⁺. Blood samples for hormone assay were obtained before starting and 30 and 90 minutes after completing ileal perfusion. At the end of each experiment the tube position was rechecked and a barium contrast medium was instilled *via* the distal port to confirm that the tip had not inadvertently entered the caecum as we observed it to do in preliminary experiments when 220 cm of tube was passed. Evidently the intestine concertinas over the tube to a considerable extent during the passage of the peristaltic balloon, so in subsequent studies we did not pass more than 175 cm, relying on the caudad flow of saline from the jejunum to propel the infusate further distally. Once the peristaltic balloon was deflated the tube did not appear to alter its position as judged by fluoroscopy performed at the beginning and end of each study.

Experiments 16–24: jejunal manometric studies

Nine further healthy volunteers (six men and three women, aged 21–25 years) were intubated with a purpose built 6 lumen radio opaque tube (external diameter 6.5 mm) incorporating a terminal balloon as before (Fig. 1b). As shown, there were three side opening jejunal pressure recording ports, J1, J2, and J3, and two perfusion ports, one jejunal, P1, and one ileal, P2. The tube was positioned under fluoroscopic control so that P1 lay 10 cm beyond the duodeno-jejunal flexure with J1, J2, and J3 being 15, 25, and 35 cm distal to P1. The port P2, 70 cm from P1, then lay approximately 175 cm from the mouth.

Jejunal pressure waves were recorded on external pressure transducers (Consolidated Electrodynamics, England) coupled to a Devices polygraph (Devices, England), paper speed 1 cm/min, pen deflection 4 mm per 10 mm Hg pressure change. The side opening pressure recording ports were each perfused at 0.1 ml/min with isotonic NaCl throughout the study using an hydraulic capillary infusion system (Model D1P3, Mui Scientific, Mississauga, Canada). The response to end-occlusion of the pressure ports was 16 mm Hg/sec.

CHEMICALS

Unless otherwise stated all chemicals were of Analar

Fig. 1 (b) Tube assembly for manometric studies. P1 lies 10 cm beyond the duodeno-jejunal flexure with J1, J2 and J3, 15, 25 and 35 cm beyond P1. P2 is 70 cm from P1.

grade and were purchased from BDH, Poole, England. Bromosulphthalein and pancreatin Grade VI were obtained from Sigma Chemical Co, Poole, England, and ^{14}C PEG from Amersham International, Amersham, England. The fat source used for ileal stimulation was Lipofundin 10% (B Braun, Melsungen, W Germany). One hundred millilitres of Lipofundin 10% contains soya bean fat 10 g, emulsified with soya phospholipid 1.5 g and glycerol 2.5 g. The fatty acid composition of soya bean triglyceride is 55% linoleic (C_{18} di-unsaturated) and 30% oleic acid (C_{18} mono-unsaturated).

EXPERIMENTAL DESIGN
Experiments 1–15

These experiments were divided into two parts, each of two and a half hours, allowing two ileal perfusion solutions to be tested in each subject (Fig. 2). In part I of each experiment the ileum was perfused with the control solution, saline I (NaCl 155 mM, 150 ml over 30 minutes), and during part II one of the three test solutions was perfused as shown (Table 1).

Fig. 2 Sequence of ileal perfusion and jejunal transit time measurements (experiments 1–15). Arrows indicate bolus injections of the dye BSP for measurement of jejunal transit times.

Experiments 1–5: Effect of bile salts and pancreatic enzymes

This part of the study was designed to identify possible motility effects of the bile salts and pancreatic enzymes needed to prepare the fat containing test solutions. An isotonic saline solution (saline II) containing NaCl 150 mM, Na taurocholate 5 mM, and pancreatin 5 g/l was perfused into the ileum at 5 ml/min over 30 minutes at the beginning of part II of the experiments.

Experiments 6–10: effect of partially digested fat

The first fat containing solution contained 10 g fat and was prepared by incubating 100 ml of Lipofundin 10% for two hours at 37°C in the presence of Na taurocholate 5 mM, NaCl 37 mM and pancreatin 5 g/l. This hydrolysed about one third of the triglyceride and yielded a final measured free fatty acid concentration of 50–60 mM. The resulting stable emulsion was diluted with distilled water to achieve isotonicity before perfusion (150 ml over 30 minutes).

Table 1 Sequence of solutions perfused into the ileum, each over 30 minutes

Experiment (no)	Ileal perfusion solutions	
	Part I Control solution	Part II Test solutions
1–5	Saline I*	Saline II†
6–10	Saline I	Fat solution‡
11–15	Saline I	Fat + glucose solution§

* 155 mM NaCl , 150 ml; † 150 mM NaCl , 150 ml; ‡ 10 g fat (Lipofundin), 150 ml; § 10 g fat (Lipofundin) + 20 g glucose, 250 ml. Solutions ‡§ were incubated at 37°C for two hours with Na taurocholate 5 mM and pancreatin 5 g/l. NaCl was added to the fat solutions to activate the pancreatin.

Experiments 11–15: effect of partially digested fat and glucose

The second fat containing solution tested was similar to the first, but contained in addition 100 ml of 20% glucose, the final volume being 250 ml, osmolality 610 mosmol.

EXPERIMENTS 16–24: JEJUNAL MANOMETRIC STUDIES

Experiments 16, 17: effect of partially digested fat

Throughout these experiments the jejunum was perfused as before at 10 ml/min *via* P1 with the xylose saline solution already described. After a one hour control period saline I was perfused into the ileum and jejunal pressure wave activity was recorded for one hour. The ileum was then perfused with a fat solution of the same composition as that used in experiments 6–10 and jejunal activity recorded for two hours. While these two studies showed that ileal fat clearly inhibited jejunal activity, the relevance of these findings to post-prandial small bowel motility was open to doubt as no nutrients were present in the jejunum. In the subsequent experiments (18–24) therefore the jejunum was perfused with a mixed nutrient solution throughout the study.

Experiments 18–24: effect of partially digested ileal fat in the presence of jejunal nutrients

The saline control and fat containing test solutions used in these experiments were of identical composition to those used in experiments 6–10 and were perfused in random order while the jejunum was perfused throughout at 2 ml/min *via* P1, with a fat free nutrient solution (0.5 cal/ml). This contained partially hydrolysed corn starch, 87 g/l (Caloreen, Roussel, UK) milk protein 40 g/l (Casilan, Farley Health Products, England) and was rendered isotonic (290 mosmol) with NaCl 122 mM. Proximal reflux of the ileal perfusate was prevented by a saline perfusion at 5 ml/min *via* port J3, commencing 10 minutes before, and lasting throughout the ileal perfusion *via* P2.

All subjects gave informed consent to the procedures which were approved by the Brent Health District Ethical Committee.

ANALYSIS AND CALCULATIONS

Intestinal fluid was collected over ice and stored at -20°C before assay for Na^{+} , K^{+} , bilirubin,¹⁰ amylase,¹¹ PEG,¹² and BSP,⁹ using standard methods. Free fatty acids in the fat emulsion were assayed by titration with 0.1N NaOH after acidification and ether extraction. Intestinal flow was calculated from the infusion rate and changes in

PEG concentrations using standard steady state formulae,¹³ and segmental volumes were calculated from the dye dilution curves as described by Zierler.¹⁴ The coefficient of variation of four repeated measurements averaged 15.9% for transit times and 15.3% for segmental volumes in the five control subjects. This variability reflects not only measurement errors but also the spontaneous variability of intestinal motor activity. Osmolality was measured by freezing point depression using an Advanced Osmometer (Advanced Instruments, USA).

HORMONE ASSAY

Blood was taken *via* an indwelling intravenous cannula into chilled heparinised tubes to which 4000 Kallikrein Inactivating Units of Aprotinin (Trasylol, Bayer, West Germany) had been added to prevent proteolysis. Plasma was then rapidly separated by centrifugation and stored at -20°C before assay in a single batch.

Enteroglucagon and neurotensin were measured using previously described radioimmunoassays^{15–17} with the following modification to the neurotensin assay. The neurotensin antiserum was obtained from a rabbit immunised with synthetic bovine neurotensin, conjugated with bidiazotised benzidine to bovine serum albumin, and injected in Freund's adjuvant. The antiserum was directed to the C-terminal region of the molecule and was used in a final titre of 1:80 000. ^{125}I -neurotensin label was prepared by the chloramine T method¹⁸ and purified by ion exchange chromatography.¹⁹ The specific activity of the ^{125}I -neurotensin was 65 Bq/fmol and the detection limit of the assay was 0.4 fmol/tube.

ANALYSIS OF PRESSURE RECORDS

The percentage duration of pressure activity was measured manually by two independent observers, one of whom was unaware of the solution being tested. Isolated pressure spikes and those of <10 cm water pressure were ignored. Interscorer correlation was excellent ($n=54$, $r=0.97$) and the coefficient of variation of repeated measurement was 6.0% ($n=54$). Results are expressed as the percentage of time that activity was recorded in the hour after ileal infusion of each solution. Migrating motor complexes (MMCs) were observed on average once per seven hour study. They were of short duration (5–10 minutes) and were followed by a similar period of quiescence before resuming the normal fed pattern. Migrating motor complexes were unrelated to the test infusion, so their effect was merely a slight increase in variability and their infrequent occurrence did not systematically bias the results.

STATISTICAL METHODS

Results in the text are expressed as mean $\pm$ SEM and the significance of differences assessed using the non-parametric randomisation test for matched pairs,²⁰ except where numbers were large when the paired Student's *t* test was used after confirming the normality of distribution of the values using rankit plots.²¹

Results

JEJUNAL TRANSIT TIMES AND SEGMENTAL VOLUMES (Tables 2 and 3; Figs 3a,b)

Experiments 1–5 established that during the five hour period of perfusion, mean transit time and segmental volume of the jejunal segment AB was stable and unaffected by simultaneous perfusion of the ileum with saline containing bile salts and pancreatic enzymes. By contrast, when partially digested triglyceride was perfused into the ileum (experiments 6–10) mean jejunal transit times rose significantly to 18.9 ± 2.5 min 30 minutes after the fat perfusion (Fig. 3a; Table 2) (control 7.5 ± 0.9 min after ileal saline, $n=5$; $p<0.05$). Transit times were still raised at 90 minutes (13.2 ± 2.9 min, $n=5$; $p<0.05$) though this value was significantly less than the 30 minute value ($n=5$; $p<0.05$). The delay in transit was associated with an increase in volume of the jejunal segment at 30 minutes which declined towards basal values by 90 minutes (Table 3). Addition of glucose 20 g to the fat solution did not significantly alter its effect when perfused into the ileum, transit times being significantly increased at 30 minutes, returning towards normal at 90 minutes (Fig. 3b; Table 2). Associated segmental volumes again rose significantly at 30 minutes but by 90 minutes the differences from control were no longer significant (Table 3).

Intestinal flow calculated from PEG dilution was stable in experiments 1–5, nor did it change significantly in experiments 6–15, being 11.2 ± 0.9 ml/min after ileal fat, compared with a control value of

Fig. 3 (a) Mean transit times through the jejunal segment AB, 30 and 90 minutes after completing ileal perfusion of saline (columns 1 and 2 respectively) compared with transit times after the fat solution (columns 3 and 4 respectively). (b) Similar data showing effect of ileal perfusion with fat plus glucose solution.

12.5 ± 0.8 ml/min after ileal saline ($n=10$; NS). Output of bilirubin and amylase was low during control periods and unaltered by ileal fat infusion.

JEJUNAL MANOMETRIC STUDIES

Striking inhibition of pressure wave activity was recorded in experiments 18–24, 15–30 minutes after the ileal fat perfusion began. The percentage duration of activity fell from $40.3 \pm 5.0\%$ in the hour after ileal perfusion with saline I to $14.9 \pm 2.8\%$ in the hour after ileal perfusion with the fat solution ($n=7$; $p<0.01$). Figure 4 illustrates the marked inhibition of motility after ileal fat perfusion with a gradual return to normal activity after $1\frac{1}{2}$ –2 hours. This inhibition of motor activity was independent of jejunal luminal contents being quite obvious in experiments 16 and 17 in which the jejunum was perfused with saline (10 ml/min) instead of the fat free mixed nutrient solution. In these two experiments percentage activity after ileal fat perfusion was 5.6% and 14.1% compared with control values after ileal saline of 51.3% and 28.2% respectively.

Table 2 Mean transit times (mean $\pm$ SEM) for jejunal segment AB at 30 minutes and 90 minutes after ileal perfusion with the solutions shown (experiments 1–15).

Experiment (no)	Ileal perfusion solution	Mean transit times (min)			
		Transit time at 30 min	Significance of difference	Transit time at 90 min	Significance of difference
1–5	Saline I	5.6 ± 1.7	NS	9.2 ± 1.2	NS
	Saline II	8.2 ± 1.5		10.1 ± 2.2	
6–10	Saline I	7.5 ± 0.9	$p<0.05$	5.2 ± 0.7	$p<0.05$
	Fat solution	18.9 ± 2.5		13.2 ± 2.9	
11–15	Saline I	7.9 ± 1.8	$p<0.05$	7.3 ± 0.9	$p<0.05$
	Fat and glucose solution	13.2 ± 1.9		11.5 ± 1.3	

Table 3 Segmental volumes (mean $\pm$ SEM) for 30 cm jejunal segment AB at 30 minutes and 90 minutes after ileal perfusion (experiments 1–15).

Experiment (no)	Ileal perfusion solution	Segmental volumes (ml)			
		Segmental volume at 30 min	Significance of difference	Segmental volume at 90 min	Significance of difference
1–5	Saline I	122.6 $\pm$ 13.3	NS	106.0 $\pm$ 13.8	NS
	Saline II	108.1 $\pm$ 10.2		129.5 $\pm$ 13.7	
6–10	Saline I	97.6 $\pm$ 13.7	p<0.05	55.2 $\pm$ 10.2	p<0.05
	Fat solution	175.1 $\pm$ 22.9		124.7 $\pm$ 21.6	
11–15	Saline I	80.2 $\pm$ 15.5	p<0.05	87.4 $\pm$ 10.1	NS
	Fat and glucose solution	113.0 $\pm$ 12.0		100.0 $\pm$ 7.5	

PLASMA ENTEROGLUCAGON AND NEUROTENSIN
Ileal saline perfusion did not significantly alter either enteroglucagon or neurotensin concentrations which were 48.9 ± 7.2 and 15.5 ± 1.9 pmol/l before, and 48.9 ± 5.0 and 17.2 ± 2.0 pmol/l after ileal saline (NS, paired *t* test, *n*=24). After ileal perfusion with partially digested fat however, enteroglucagon and neurotensin plasma concentrations both rose significantly (Fig. 5). The addition of 20 g of glucose to the ileal perfusion solution did not significantly alter the enteroglucagon and neurotensin response, plasma levels at one hour being 277.6 ± 37.0 and 36.8 ± 8.3 pmol/l respectively after ileal fat and glucose (*n*=5) compared with 191.9 ± 23.5 and 48.0 ± 3.5 after ileal fat alone (*n*=14; NS, unpaired *t* test). The results of experiments 6–24 have therefore been analysed together. Plasma neurotensin concentrations rose rapidly once the fat perfusion began from a fasting basal value of 17.8 ± 2.1 pmol/l peaking at 68.0 ± 13.9 pmol/l at 30 minutes and falling slowly thereafter, still being significantly raised at two hours. Plasma enteroglucagon rose more slowly, reaching a plateau of 218 ± 37 pmol/l at one hour (basal 40 ± 9 pmol/l) and remaining raised for up to three hours. The

peak hormone responses for each subject were closely correlated ($r=0.78$; *n*=19; *p*<0.01, direct *t* test).

Discussion

The present results show that when fat was infused into the normal ileum there was inhibition of jejunal pressure wave activity, dilatation of the jejunal lumen and delay in the caudad transit of jejunal contents. These motility changes appeared independent of jejunal contents, being found during perfusion of the jejunum with either a nutrient solution or with normal saline.

Inhibition of motility was produced with an ileal perfusate containing fat at a concentration of 10 g in 150 ml. Taking into account dilution by the 200 ml of saline perfused more proximally, the estimated ileal luminal fat concentration lay between 30 and 40 mg/ml depending on the rate of water absorption by the 35 cm segment BC. The assumption that no water was absorbed yields an estimated ileal luminal fat concentration of 30 mg/ml. On the other hand, 40 mg/ml corresponds to absorption of 100 ml per 30

Fig. 4 Manometric tracing illustrating inhibition of pressure wave activity after ileal fat perfusion in experiment 24. Vertical bar represents 50 mm Hg. Recording ports J1, J2, J3 are 25, 35 and 45 cm from the duodeno-jejunal flexure. The jejunum is perfused throughout with a fat free nutrient solution at 1 cal/min. Pressure recording from J3 is interrupted during ileal fat perfusion as saline 5 ml/min was perfused via this port to prevent proximal reflux of the fat solution.

Fig. 5 Plasma enteroglucagon and neurotensin response (mean $\pm$ SD) after ileal fat perfusion starting at time 0 (experiments 6–24). ** $p < 0.001$ raised compared with basal values; $n = 18$, paired t test.

min per 35 cm – that is, 5.6 ml/h/cm which is approximately three times the average absorption rate found by Whalen²² for this part of the intestine. The intraluminal ileal fat concentration attained in this study should be compared with postprandial values of 5–10 mg/ml in normals²³ and 20–30 mg/ml postprandially after vagotomy and gastro-enterostomy,²⁴ a condition known to be associated with modest steatorrhoea (10–20 g fat/24 h).²⁵ Thus our stimulus approximates to the postprandial ileal fat concentration in moderate to severe steatorrhoea. This conclusion is supported by the experimentally observed rises in the fat sensitive ileal hormones enteroglucagon and neurotensin which were similar to those seen postprandially in untreated coeliac disease.²⁶

These data therefore confirm the existence in man of a braking mechanism which is responsive to partially digested triglyceride in the ileum at concentrations which could occur in malabsorption, a phenomenon which we have called the ileal brake.²⁷

By analogy with the duodenal brake²⁸ it is likely that a number of different stimuli^{29–31} can activate this inhibitory reflex and its full characterisation will require further studies using ileal perfusates containing the products of digestion of both protein and carbohydrate as well as fat.

Our stimulus contained not only triglyceride but also products of its hydrolysis including free fatty acids, mono and triglycerides, glycerol, and phospholipid, as well as bile salts and pancreatic enzymes. We cannot deduce from our data which of these components is responsible for eliciting the reflex though our control studies show that both bile

salts and pancreatic enzymes are without effect. We found no additional effect when glucose was added to the fat solution even at a concentration of 440 mM, which must greatly exceed the maximal ileal luminal concentration found postprandially. It may be that a maximal effect had already been achieved by the fat stimulus thus masking any possible glucose effect, further studies will be necessary to clarify this point.

While marked distension of an intestinal segment is known to produce inhibition of motility in the remainder of the intestine, the so called 'intestino-intestinal inhibitory reflex'^{32, 33} is unlikely to be the basis of our data for two reasons. Firstly, the volume perfused, 150 ml over 30 minutes, should be easily accommodated within the gut without appreciable intestinal distension. This is confirmed by the observation that in the manometric studies basal luminal pressure was not altered by ileal perfusion. Secondly, ileal saline perfusion at the same rate produced no inhibition and neither did the isotonic amino acid and carbohydrate solutions which we have perfused in subsequent studies.³⁴

The ileal perfusion rate of 150 ml over 30 minutes somewhat exceeds previous estimates of normal postprandial terminal ileal flow (200 ml over two hours),³⁵ an unquantifiable portion of the fat perfused could therefore have entered the caecum, a stimulus which has recently been shown to initiate inhibition of both pancreatic³⁶ and gastric³⁷ secretions. The timing of onset of the inhibitory effect we have observed is compatible with either ileal or caecal receptors and our experimental technique does not permit us to decide on their relative importance.

Details of the receptor and effector pathways of this brake are at present unknown but it is likely that in common with other entero-enteric reflexes, both neural³⁸ and hormonal³⁹ effects are important. While the location^{40, 41} and fat sensitivity^{42, 43} of the ileal enteroglucagon and neurotensin producing cells seems to provide strong circumstantial support for their role in the brake, there are discrepant features. Although onset of the inhibitory effect 30 minutes after fat perfusion is compatible with both neural and hormonal mediation, the subsequent recovery of jejunal motility after 1½–2 hours while plasma enteroglucagon and neurotensin concentrations remain raised does throw doubt on their possible causative role. Furthermore, other authors⁴⁴ using totally different techniques have shown an inhibitory effect on gastric emptying and small bowel transit by an ileal infusion of undigested fat at a rate (0.1 g/min) which does not alter plasma levels of either enteroglucagon or neurotensin. Although the experimental techniques are totally

different and comparisons with our data must be cautious, these findings do suggest that at least some of the inhibitory effects of ileal fat are independent of these two hormones. Our fat infusion was more effective in releasing enteroglucagon and neurotensin than that of McFarlane *et al* for two reasons: firstly because our fat was partially digested and it is known that free fatty acids are more potent than neutral fat in releasing neurotensin,⁴⁵ and probably enteroglucagon also; and secondly because our faster infusion rate (5 ml/min) probably results in stimulation of a much larger surface area of ileum and hence a larger number of hormone containing cells. Intravenous infusion studies using synthetic neurotensin have shown an inhibitory effect on gastric emptying in both man⁴⁶ and animals but the effects on small bowel motility have been inconsistent.⁴⁷⁻⁴⁸ Enteroglucagon by contrast has yet to be studied owing to lack of sufficient pure hormone for infusion studies in man. Circumstantial evidence does, however, suggest that enteroglucagon could in the long term play a part in inhibiting jejunal motility since in numerous chronic experimental⁴⁹ and clinical situations⁵⁰ its release is associated with delayed small bowel transit.

Although neural effects have not been investigated in this study, their potential importance cannot be ignored. Others have shown in the rat vagus⁵¹ afferent nerves which are highly sensitive to luminal nutrients while stimulation experiments in the anaesthetised cat⁵² show that sympathetic efferents can profoundly influence intestinal motor activity.

Extrapolation from our experimental data to the pathophysiology of patients with malabsorption obviously requires caution. The inhibitory effect observed has been produced with a stimulus which produces an ileal fat concentration similar to that found in patients with steatorrhoea, however, in conditions of chronic fat malabsorption such as coeliac disease or the short bowel syndrome, longer term adaptive effects⁵³ including ileal mucosal hypertrophy⁵⁴ may be at least as important as any acute effects similar to those we have shown. Nevertheless, this braking mechanism could account for the sluggish small intestinal transit and jejunal hypomotility characteristic of untreated coeliac disease as well as the adaptive prolongation of small bowel transit following proximal small bowel resection.⁵⁵ Destruction of the ileal brake by ileal resection may account for the lack of adaptive lengthening of small bowel transit after such resections and thus may in part account for the poor toleration of distal compared with proximal small bowel resections.⁵⁶

If prolongation of transit time results, as others

have documented,⁵⁷⁻⁵⁸ in an increase in small bowel absorptive capacity then this may explain why despite severe jejunal mucosal damage, not all patients with untreated coeliac disease have severe nutrient malabsorption or fluid diarrhoea.⁵⁹⁻⁶⁰

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