Intestinal streaming patterns in cholerrhoeic enteropathy and diverticular disease

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SUMMARY Streaming of gastrointestinal contents depends on the demonstration of differential rates of recovery of equal doses of two synchronously fed markers. There was no significant difference in the rate of throughput of polyethylene glycol (a liquid phase marker) and chromium sesquioxide (a solid phase marker) in healthy volunteers ($n = 7$) and hospital inpatients ($n = 5$) with normal bowel habit, so that streaming does not usually occur. In cholerrhoeic enteropathy ($n = 5$), however, the rate of throughput of polyethylene glycol was increased. In colonic diverticular disease ($n = 7$) the rate of throughput of polyethylene glycol was significantly lower. In cholerrhoeic enteropathy the liquid phase marker was excreted 1.5 times faster than the solid phase, but in the diverticular disease group the liquid phase was excreted 0.75 times more slowly than the solid phase marker. This may reflect the effects of colonic hypersegmentation on the relative distribution of the liquid and solid phases.

Whitby and Lang (1960) suggested the possibility that streaming might occur in the gastrointestinal tract, and this suggestion was further examined by Wilkinson (1971). Proof of streaming of solid and liquid phases depends on the demonstration of differential rates of recovery of synchronously fed markers of the solid and liquid phases. A satisfactory solid phase marker is one that is insoluble and unabsorbed; a marker of the aqueous phase needs to be water soluble and unabsorbed.

Chromium sesquioxide (Cr_2O_3) satisfies these criteria for a marker of the solid phase. It has been used since 1947 (Kreula) and its usefulness has been commented on by Whitby and Lang (1960) and Davignon, Simmons, and Ahrens (1968). Polyethylene glycol 4000 (PEG) is water-soluble and is a suitable marker of the water phase of the gastrointestinal contents (Wilkinson, 1971). It has been shown to be unabsorbed in both healthy and diseased bowel (Shields, Harris, and Davies, 1968). This marker has been in use since 1956 (Hyden) and was first used in man by Beeken (1967).

The aim of the present study was to investigate

the rates of recovery of marker of the solid and the liquid phase in a variety of clinical situations.

Clinical Material and Methods

Streaming of intestinal contents was investigated in two clinical situations. In the first experiment streaming patterns in subjects with formed stools and those with diarrhoea were investigated. In the second experiment streaming patterns of normal subjects were compared with those from a group of patients with colonic diverticular disease. These two abnormal groups represented two apparent extremes of disturbance of gastrointestinal physiology.

The clinical details of all those studied are given in table I.

The first study involved 14 individuals, five patients with chronic diarrhoea (1-5), four normal subjects (11-14), and five patients (6-10) with a variety of disorders, all of whom had formed stools. The diarrhoeal patients had frequent (more than four) watery stools that were capable of separation into a pellet and supernatant on centrifugation (Findlay, Eastwood, and Mitchell, 1973). Their faecal bile

Subject Group	No.	Age	Sex	Study (Days)	Stool Weight ¹ (g)	Clinical Details
Diarrhoeal patients	1	70	F	7	581	Strangulated small bowel; total ileal resection; jejunocolic anastomosis
	2	58	F	8	505	Infarcted bowel; resection 90 cm of small bowel (jejunum and ileum)
	3	62	M	4	485	Crohn's disease; resection 50 cm distal ileum; half of ascending colon resected
	4	37	F	7	395	Crohn's disease; resection 100 cm distal ileum, plus excision of ascending and transverse colon; former pelvic colectomy
Non-diarrhoeal patients	5	46	M	7	363	Pyloroplasty and vagotomy
	6	55	M	5	83	Morbidly obese patient—losing weight in hospital
	7	32	M	6	142	Crohn's disease; ileo-ileal fistula
	8	51	F	7	56	Thyrotoxicosis before therapy
	9	41	M	4	430	Crohn's disease; resection of 50 cm distal ileum; on hydrophilic colloid (Isogel)
Healthy volunteers	10	71	F	11	107	Infarction of lower 2/3rd ileum, caecum midtransverse colon; jejunotransverse colon anastomosis
	11	37	M	7	193	Normal
	12	35	M	7	154	Normal
	13	34	F	7	79	Normal
	14	36	M	7	93	Normal
	15	29	M	7	185	Normal
	16	28	M	7	92	Normal
Colonic diverticula	17	28	M	7	125	Normal
	18	75	F	7	63	Diverticula in sigmoid colon
	19	60	F	7	150	Extensive diverticular disease in distal colon
	20	80	M	7	89	Extensive diverticular disease in sigmoid colon
	21	73	M	7	82	Marked diverticular disease of distal descending colon and sigmoid colon
	22	82	M	7	57	Well marked muscular thickening with early diverticular disease high up in the pelvic colon
	23	51	F	7	107	Sigmoid and descending colonic diverticular disease
	24	31	F	7	50	Sigmoid diverticula

Table I Clinical details of four groups of subjects studied

¹Mean daily

acid excretion exceeded 2 g per day, suggesting cholerrhoeic enteropathy (Hofmann, 1967). Normal faecal bile acid excretion in our laboratory is less than 700 mg per day. Patients 6-10 had stools that did not separate into pellet and supernatant on centrifugation.

The second study involved 13 individuals, six normal subjects (12-17), and seven patients with uncomplicated diverticular disease (18-24). All the individuals were studied at home; none of them were taking any aperient or had diarrhoea during the study.

All of those studied were on their habitual diet. No individual was taking any preparation containing either Cr₂O₃ or PEG.

During the period of study each individual took 500 mg of PEG (two capsules of PEG 4000 Sandoz) and 500 mg of chromium sesquioxide (two capsules of chromium Sandoz) thrice daily synchronously. Stools were collected individually in plastic bags, using the technique of Hinton, Lennard-Jones, and Young (1952). PEG and Cr₂O₃ were estimated in duplicate from aliquots taken from pooled 24-hour collections. Cr₂O₃ was estimated using the method of Bolin, King, and Klosterman (1952). PEG 4000 was estimated using the method of Malawer and

Powell (1967) using 9 mg of acacia per litre. The amount of each marker was expressed in terms of output per 24 hours.

The data were studied by regression analysis. This technique finds the line of best fit of a variable y on a variable x , ie, estimates the values of a and b in the relation

$$y = a + bx$$

The variable y increases more or less rapidly than the variable x according as the slope b is greater than or less than unity.

RECOVERIES OF MARKERS (ADDED TO FAECES)

PEG : 101% ± 5% (n = 10)

Cr₂O₃ : 97% ± 5% (n = 10)

COEFFICIENT OF VARIATION BETWEEN ASSAYS OF A 10 MG STANDARD

PEG 4.6% (n = 21)

Cr₂O₃ 3.4% (n = 20)

Results

Tables II and III show estimated values of b , regression slope, for the groups of subjects studied. It will be seen that, for the two groups of normal

Subjects	Degrees of Freedom	Polyethylene Glycol on Chromium	Polyethylene Glycol on Dose	Chromium on Dose
Four healthy normal subjects	17	0.99 $\pm$ 0.048	1.08 $\pm$ 0.14	1.07 $\pm$ 0.14
Five non-diarrhoeal patients	23	1.12 $\pm$ 0.070	0.25 $\pm$ 0.099 ¹	0.31 $\pm$ 0.072 ¹
Five diarrhoeal patients	31	1.55 $\pm$ 0.14 ¹	1.31 $\pm$ 0.056 ¹	0.73 $\pm$ 0.046 ¹
Groups I and II pooled	42	1.016 $\pm$ 0.036	—	—

Table II Regression slopes for those with formed stools and diarrhoeal patients

¹Indicates a slope significantly different from unity at the 0.1% level

Subjects	Degrees of Freedom	Polyethylene Glycol on Chromium	Polyethylene Glycol on Dose	Chromium on Dose
Seven healthy normal subjects	24	0.97 $\pm$ 0.041	1.09 $\pm$ 0.069	1.08 $\pm$ 0.076
Seven colonic diverticular patients	34	0.78 $\pm$ 0.038 ¹	0.57 $\pm$ 0.098 ¹	0.78 $\pm$ 0.11

Table III Regression slopes for six normal subjects and seven patients with diverticular disease of the colon

¹Indicates a slope significantly different from unity at the 0.1% level

subjects and the non-diarrhoeal patients there is no evidence of a differential rate of throughput of polyethylene glycol and chromium. For both groups of healthy normals, a comparison of polyethylene glycol and chromium output with intake, ie, the slopes of cumulative polyethylene glycol and chromium regressed on cumulative dose, do not differ significantly from unity. This indicates a rapid attainment of equilibrium in which output matches input for both markers. For the non-diarrhoeal subjects, the outputs are considerably depressed and variable indicating that these subjects had not all reached equilibrium. Nevertheless, the polyethylene glycol and chromium throughputs are consistent and the pooled slope for the four normal and non-diarrhoeal subjects (6-14) is 1.016 ± 0.036 .

For the diarrhoeal subjects, the slope of polyethylene glycol on chromium is significantly elevated to 1.55 ($P < 0.001$) indicating that the polyethylene glycol throughput is about one and a half times that of chromium during the period studied. This appears to be due to elevated throughput of polyethylene glycol and depressed throughput of chromium.

The seven colonic diverticular patients have a low throughput of polyethylene glycol in relation to chromium (which is passed at a rate consistent with the dose) indicating a lag in the liquid phase.

Discussion

In this study we have attempted to investigate differences in the throughput of two markers, PEG 4000 and Cr_2O_3 . For this reason we did not attempt to study patients who had achieved equilibrium.

In the proximal part of the colon there is a high

proportion of water which decreases as the contents move distally. Water in the proximal part of the colon is in three phases: (1) molecular or gel water, ie, water bound to the dietary residue and which is inherently part of the residue (Manners and Kidder, 1968); (2) interstitial water, ie, water that lies in the interstices of the dietary residue and cannot be expressed from formed stools, even if the stool is centrifuged at 14 000 *g* (Findlay *et al*, 1973); (3) free water, ie, water which lies freely in the bowel and which is not particularly associated with the dietary residue. It is this free water that makes a stool diarrhoeal. Free water can be expressed on centrifugation at 14 000 *g*, but no free water can be expressed from a formed stool on centrifugation (Findlay *et al*, 1973).

It can be seen from the data (tables II and III) that in both experiment I and experiment II the groups of normal subjects behaved identically. A typical example of a normal excretion pattern of PEG and Cr_2O_3 is shown in figure 1a. Two conclusions can be drawn from the results of these normal subjects. First, as the regression coefficients of PEG on Cr_2O_3 do not differ significantly from unity (table II) it can be deduced that an equal rate of throughput of solid and liquid markers exists, ie, no streaming. This conclusion differs from the observations of Wilkinson (1971) who found that by the end of one week 12 subjects excreted more PEG than Cr_2O_3 indicating streaming with the liquid phase moving faster than the solid phase. Wilkinson's patients, however, were inpatients in a metabolic ward, and no information was given regarding their clinical state or their bowel habit. Our normal subjects were individuals taking their

FIG 1 Cumulative inputs and outputs of three subjects: (a) normal, (b) cholerrhoeic enteropathy, (c) diverticular disease.

Vertical axis, input (g) and output of markers Cr_2O_3 and PEG 4000

Horizontal axis duration of experiment in days.

Solid line synchronous input of both markers (cumulative).

Interrupted lines, outputs of the two markers (cumulative).

habitual and varied diets and pursuing their normal activities. Our conclusion regarding no evidence of streaming in normal people was based on 45 observations in seven subjects, as a result of measuring daily PEG and Cr_2O_3 output, whereas Wilkinson's observations were based on single measurements of these markers from aliquots taken from a week's collection. In addition, if one includes the data of the patients with formed stools and without diverticular disease our conclusions are unaltered and based on 70 observations.

The second conclusion to be drawn from the results for the normal subjects (tables II and III) is that PEG on dose (1.08 ± 0.14 and 1.09 ± 0.069) and Cr_2O_3 on dose (1.07 ± 0.14 and 1.08 ± 0.076) (table II) indicates that output of marker equalled input of marker, ie, equilibrium had been reached. The rapid attainment of equilibrium by our normal volunteers is of interest and differs from the findings of Davignon *et al* (1968), Whitby and Lang (1960), and Beeken (1967) where more than 20% of patients failed to attain a steady state. This difference possibly reflects the difference between inpatients, especially those on liquid formula diets used as controls, and truly healthy subjects studied under their normal environmental conditions. However, it should be noted that our non-diarrhoeal patients had not achieved equilibrium by the end of the study. Although this group did not stream PEG or Cr_2O_3 (slope 1.12 ± 0.070) they were far from being in equilibrium (PEG on dose being 0.25 ± 0.099 and Cr_2O_3 on dose being 0.23 ± 0.072). These observations would indicate that their medical condition was associated with a modified handling of these gastrointestinal markers of solid and liquid phases.

Patients with cholerrhoeic enteropathy were chosen because they have continuous, frequent diarrhoeal stools and yet they remain well enough to be studied. Excessive amounts of bile acids are known to modify water and electrolyte absorption in the small and large bowel (Forth, Rummel, and Glasner, 1966; Mekhjian and Phillips, 1970; Mekhjian, Phillips, and Hofmann, 1971; Teem and Phillips, 1972) and also to cause secretion of water (Mekhjian, Phillips and Hofmann, 1968). These actions thus combine to cause an increased quantity of water in the gastrointestinal tract.

The water in the colon is therefore able to flow onwards to the rectum unimpeded by the haustra, and, normal segmental activity being much diminished, a 'conduit' situation exists (Connell, 1962). It is not surprising, therefore, that in patients with cholerrhoeic enteropathy streaming occurs with liquid marker travelling faster than solid marker (1.55 ± 0.14) (see table II). An example of a typical diarrhoeal streaming pattern is shown in figure 1b.

This streaming pattern is achieved partly as a result of an increased throughput of PEG (1.31 ± 0.056) and partly as a result of a reduction in the rate of throughput of chromium (0.73 ± 0.046). These values differ significantly ($P < 0.001$) from the values obtained in normal subjects (table II). A possible explanation for the retarded rate of solid marker may be that patients with cholerrhoeic enteropathy are advised to eat small quantities of fruit and vegetables (Barany, 1971; Dyer, 1972). This diminished intake of plant material may simply retard the effective transit rate of the solid phase. It must be stressed, however, that it is not reasonable to assume that the streaming pattern demonstrated in these patients with cholerrhoeic enteropathy will be typical of all diarrhoeal subjects, nor of the entire cholerrhoeic group.

Streaming also occurs in diverticular disease, the slope for PEG on Cr_2O_3 being 0.78 ± 0.038 , differing at the 0.1% level, from normal subjects (table III). The streaming pattern is opposite in direction to that seen in the diarrhoeal patients referred to above, ie, the solid phase passes through more quickly than the liquid phase (figure 1c). The data in table III indicate that this streaming pattern occurs as a result of a relative diminution in the rate of throughput of PEG (0.57 ± 0.098) compared with the throughput of chromium (0.78 ± 0.11). This may be due to the increased colonic segmentation found in diverticular disease exerting an intraluminal pressure so that more than the usual quantity of interstitial water is expressed from the stool. As distal colonic activity is higher than proximal colonic activity, the interstitial water thus expressed and marked by PEG might be retropulsed (Misiewicz *et al*, 1966). This would cause the excreted faeces to be depleted in PEG. Evidence of retropulsion in the colon has been observed radiologically (Ritchie, Truelove, and Ardran, 1968). Although the figure for the regression coefficient of chromium on dose in the diverticular disease (0.078 ± 0.11) (table III) is not significantly different from the values found in either group of normal subjects (1.07 ± 0.14 and 1.08 ± 0.076) (tables II and III) it is lower, and it is possible that a study of a larger number of patients might establish a significant difference. Such findings would be compatible with the slower than normal transit times of patients with diverticular disease (Painter, 1972). It is important to realize that when transit times are measured using a marker of only one phase the time indicated does not necessarily represent the time of all phases of intestinal content. This is well illustrated by the different flow rates described.

The techniques described indicate the overall streaming effect that is taking place down the

gastrointestinal tract. Nevertheless, the conclusions drawn from the streaming patterns we have described confirm current views on the intestinal dysfunction in the two abnormal groups studied. Streaming patterns may therefore be regarded as indicators of highly complex intestinal dysfunction.

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References

- Bárány, F. (1971). Medical management. In *Regional Enteritis (Crohn's Disease)* (5th Skandia International Symposium), edited by A. Engel and T. Larsson, pp. 155-165. Nordiska Bokhandeln, Stockholm.
- Beeken, W. L. (1967). Clearance of circulating radiochromated albumin and erythrocytes by the gastro-intestinal tract of normal subjects. *Gastroenterology*, **52**, 35-41.
- Bolin, D. W., King, P., and Klosterman, E. W. (1952). A simplified method for the determination of chromic oxide (Cr_2O_3) when used as an index substance. *Science*, **116**, 634-635.
- Connell, A. M. (1962). The motility of the pelvic colon II. Paradoxical motility in diarrhoea and constipation. *Gut*, **3**, 342-348.
- Davignon, J., Simmonds, W. J., and Ahrens, E. H., Jr. (1968). Usefulness of chromic oxide as an internal standard for balance studies in formula-fed patients and for assessment of colonic function. *J. clin. Invest.*, **47**, 127-138.
- Dyer, N. H. (1972). Medical management of Crohn's disease. *Clin. Gastroent.*, **1**, 449-467.
- Findlay, J. M., Eastwood, M. A., and Mitchell, W. D. (1973). The physical state of bile acids in the diarrhoeal stool of ileal dysfunction. *Gut*, **14**, 319-323.
- Forth, W., Rummel, W., and Glasner, H. (1966). Zur resorptionshemmenden Wirkung von Gallensäuren. *Naunyn-Schmiedeberg's Arch. Pharm. exp. Path.*, **254**, 364-380.
- Hinton, J. M., Lennard-Jones, J. E., and Young, A. C. (1969). A new method for studying gut transit times using radioopaque markers. *Gut*, **10**, 842-847.
- Hofmann, A. F. (1967). The syndrome of ileal disease and the broken enterohepatic circulation: choleraic enteropathy. *Gastroenterology*, **52**, 752-757.
- Hyden, S. (1956). The recovery of polyethylene glycol after passage through the digestive tract. *K. LantbrHögsk. Annlr.*, **22**, 411-422.
- Kreula, M. S. (1947). Absorption of carotene from carrots in man and the use of the quantitative chromic oxide indicator method in the absorption experiments. *Biochem. J.*, **41**, 269-273.
- Malawer, S. J., and Powell, D. W. (1967). An improved turbidimetric analysis of polyethylene glycol utilising an emulsifier. *Gastroenterology*, **53**, 250-256.
- Manners, M. J., and Kidder, D. E. (1968). Polyethylene glycol as marker in piglet diets with a high dry-matter content. *Brit. J. Nutr.*, **22**, 515-526.
- Mekhjian, H. S., and Phillips, S. F. (1970). Perfusion of the canine colon with unconjugated bile acids. *Gastroenterology*, **59**, 120-129.
- Mekhjian, H. S., Phillips, S. F., and Hofmann, A. F. (1968). Conjugated bile salts block water and electrolyte transport by the human colon. (Abstr.). *Gastroenterology*, **54**, 1256.
- Mekhjian, H. S., and Phillips, S. F., and Hofmann, A. F. (1971). Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. *J. clin. Invest.*, **50**, 1569-1577.
- Misiewicz, J. J., Connell, A. M., and Pontes, F. (1966). Comparison of the effect of meals and prostigmine on the proximal and distal colon in patients with and without diarrhoea. *Gut*, **7**, 468-473.
- Painter, N. S., and Truelove, S. C. (1964). The intraluminal pressure patterns in diverticulosis of colon. *Gut*, **5**, 201-213.
- Ritchie, J. A., Truelove, S. C., and Ardran, G. M. (1968). Propulsion and retropulsion in the human colon demonstrated by time-lapse cinefluorography. (Abstr.). *Gut*, **9**, 735-736.
- Shields, R., Harris, J., and Davies, M. W. (1968). Suitability of polyethylene glycol as a dilution indicator in the human colon. *Gastroenterology*, **54**, 331-333.
- Teem, M. V., and Phillips, S. F. (1972). Perfusion of the hamster jejunum with conjugated and unconjugated bile acids: inhibition of water absorption and effects on morphology. *Gastroenterology*, **62**, 261-267.
- Whitby, L. G., and Lang, D. (1960). Experience with the chromic oxide method of fecal marking in metabolic balance investigations on humans. *J. clin. Invest.*, **39**, 854-863.
- Wilkinson, R. (1971). Polyethylene glycol 4000 as a continuously administered non-absorbable faecal marker for metabolic balance studies in human subjects. *Gut*, **12**, 654-660.