Delayed small-intestinal transit in tropical malabsorption

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Summary and conclusions

The time of breath hydrogen appearance (T) after oral lactulose was determined in 98 patients in London who had been to the tropics. Fifty-six controls from three different ethnic groups had no evidence of gastrointestinal disease; 23 had tropical malabsorption, which was severe in 10; and 19 had chronic diarrhoea without malabsorption. Mean T was significantly delayed in patients with tropical malabsorption compared with controls, indicating that their mouth-caecum transit rate was abnormally slow. In six patients with tropical malabsorption who were reinvestigated after treatment a fall in the value for T seemed to parallel clinical improvement. Three patients with diarrhoea due to chronic colonic disease had delayed T. Patients with tropical malabsorption have bacterial colonisation of the small intestine, which is important in the pathogenesis of the disease. Bacterial overgrowth, which sometimes occurs after infective diarrhoea in the tropics and gives rise to tropical sprue, is a result of stasis.

Introduction

The term sprue (of Dutch origin) was originally used by Manson¹ in China for chronic tropical malabsorption. Since then it has embraced many different entities, including the syndrome of postinfective tropical malabsorption, which starts with an acute onset of diarrhoea (sometimes bloody).² Abnormal bacterial colonisation of the jejunum is important in the pathogenesis of this disease.³⁻⁵ Small-intestinal motility is usually increased by the presence of bacteria and is important for maintaining the normal milieu of the intestinal lumen.^{6,7} I have therefore determined the mouth-caecum transit rate for lactulose in patients with tropical malabsorption using the breath hydrogen technique.^{8,9}

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Patients and methods

Ninety-eight patients in the Hospital for Tropical Diseases, London, agreed to investigation after the procedure had been explained (see tables I and II). The 56 who served as controls were admitted with either trivial symptoms or for exclusion of disease after being in the tropics; none had symptoms of malabsorption or clinical evidence of gastrointestinal disease. Thirty-one were English. Eleven of the Africans were from West Africa; two were from Sudan and Egypt respectively. Seven Asians were from the Indian subcontinent; four were from the Middle East, and one was from the Far East. The Africans and Asians had been resident in the UK for means of four (0.3-15) and six (0.1-20) years.

All 23 patients with tropical malabsorption were north Europeans. Acute diarrhoea had started in the tropics, had persisted, and was usually accompanied by weight loss. The 10 patients with severe disease had abnormalities in xylose excretion, 72-hour faecal fat excretion, and the Schilling test; and 13 with mild disease had abnormalities in one or two of these investigations. Total bacterial and enterobacterial concentrations were raised in the jejunal lumen of one patient who was investigated. With one exception (a patient who developed the disease in Oman) all patients with severe disease developed symptoms while in the Indian subcontinent, Nepal, or Afghanistan. Symptoms in the patients with mild disease started in those countries in six, in Africa in five, and in South America in two cases. In both groups the mean length of history was four months and the mean daily stool frequency was four. Estimates of mean weight loss were 6 (0-19) kg in the mild group and 14 (6-19) kg in the severe group, and mean 72-hour stool weights were 534 (154-1137) g and 785 (92-1783) g respectively. Seven patients in each group had been treated with either a broad-spectrum antibiotic or metronidazole, or both. Most had also received diphenoxylate hydrochloride.

The 19 patients with chronic diarrhoea were north Europeans, and symptoms had started in a tropical or subtropical country. Any weight loss was minimal, and none gave a history suggesting malabsorption. Mean length of history was 8 (1-36) months, mean stool frequency three daily, and mean 72-hour stool weight in nine 265 (59-444) g. Twelve had received some medication before admission.

After an overnight fast each patient drank 50 ml Duphalac syrup (33.5 g lactulose) made up to 250 ml with water at room temperature. Serial tests were performed on eight patients, six of them after treatment of tropical malabsorption (see table III). Xylose (25 g dissolved in 250 ml water, followed by 250 ml water), lactose (50 g dissolved in 400 ml water), and glucose (100 g in 400 ml water) drinks were also given after a similar fast on another day to some patients (see table IV). The patients were sitting throughout the tests and smoking was not allowed. Breath hydrogen concentrations were measured in end samples of expired air¹⁰ before and at 10-minute intervals after the sugar was given. Sampling was continued for at least two hours and, if hydrogen had not appeared by then, up to five hours. Hydrogen was measured by gas chromatography (Gow-Mac 69-552, Co Clare, Ireland), argon being used as carrier. Standard

TABLE I—Details of 98 patients investigated (ranges in parentheses)

Group	No of patients	Sex		Mean age (years)	Mean weight (kg)	Mean haemoglobin concentration (g/dl)	Serum protein (g/l)		No with parasites				
		M	F				Albumin	Total globulin	<i>Giardia lamblia</i>	<i>Entamoeba histolytica</i> cysts	Hook-worm	<i>Trichuris trichiura</i>	<i>Strongyloides</i>
Controls (English)	31	25	6	34 (22-59)	65 (45-94)	14.9 (11.8-17.5)*	43 (36-51)†	30 (20-39)†	1	2		1	
Controls (African)	13	8	5	32 (22-45)	62 (48-76)	13.8 (11.8-16.9)	41 (36-47)‡	33 (26-46)‡		2		3	1
Controls (Asian)	12	10	2	39 (24-60)	62 (46-86)	14.9 (12.9-18.0)	41 (35-49)§	35 (28-43)§	1		2	1	
TM (mild)	13	7	6	27 (20-49)	64 (48-83)	13.8 (12.0-16.1)	42 (37-47)	30 (24-39)	5				
TM (severe)	10	7	3	32 (18-57)	58 (41-73)	13.5 (10.5-15.8)	39 (32-45)	26 (21-35)	3				
Chronic diarrhoea	19	13	6	34 (20-52)	66 (49-85)	14.6 (13.0-16.2)	44 (38-53)*¶	30 (24-38)*¶	1	2			

Numbers tested: *28; †25; ‡12; §10; ||11; ¶18.
TM = Tropical malabsorption.

TABLE II—Results of absorption tests (ranges in parentheses) [proportions of patients with abnormal results given in square brackets]

Group	Mean urinary xylose (mmol/5 h)	Mean faecal fat/24 h (mmol)	Mean Schilling test result (%)		Jejunal biopsy	Mean rise in blood glucose (mmol/l)		Mean time of maximum blood glucose (min)		Red-blood-cell folate concentration (μg/l)	Serum vitamin B ₁₂ concentration (ng/l)
			Urinary vitamin B ₁₂ /24 h	Plasma vitamin B ₁₂ /8 h		After 50 g lactose	After 25 g glucose + 25 g galactose	After lactose	After glucose and galactose		
Controls (English)	9.0 (8.6–10.0) [0/4]	11 (8–14) [0/4]	23 (14–30) [0/4]	1.4 (0.8–3.2) [0/4]	[0/3]	1.7 (0.5–2.7) [2/7]	2.7 (1.2–6.6) [0/5]	40 (30–60) [0/7]	40 (30–60) [0/5]	269 (95–440) [1/7]	311 (180–640) [0/7]
Controls (African)	8.1 [0/1]	13 [0/1]	15 [0/1]			0.2 (0–0.8) [7/7]	1.0 [1/1]	45 (0–120) [1/7]	60 [0/1]	269 (150–420) [0/5]	516 (220–700) [0/6]
Controls (Asian)	8.0 [0/1]	16 [0/1]	10 [0/1]	0.6 [0/1]		0.6 (0.1–1.1) [3/4]	4.3 (3.7–4.9) [0/2]	49 (15–60) [0/4]	60 [0/2]	356 (200–650) [0/3]	445 (155–700) [0/4]
TM (mild)	8.5 (4.4–17.3) [6/11]	23 (9–64) [7/11]	11 (3–27) [8/12]	0.6 (0.3–0.8) [4/10]	[7/12]	1.6 (0.1–3.1) [2/10]	1.8 (1.5–2.5) [0/5]	42 (30–60) [0/10]	33 (15–60) [0/5]	340 (120–650) [2/10]	292 (80–700) [3/10]
TM (severe)	2.7 (1.2–6.4) [10/10]	82 (35–129) [10/10]	1 (0–1.2) [10/10]	0.1 (0–0.3) [9/9]	[10/10]	0.8 (0.1–1.9) [4/7]	0.9 (0.8–1.1) [3/7]	32 (15–60) [0/7]	45 (15–60) [0/7]	258 (50–650) [4/9]	275 (25–700) [4/10]
Chronic diarrhoea	9.7 (6.8–14.2) [2/13]	12 (6–18) [0/12]	20 (15–29) [0/11]	1.2 (0.8–2.2) [0/10]	[2/8]	2.0 (0.3–4.6) [2/12]	1.9 (1.5–2.4) [0/6]	37 (15–120) [1/12]	40 (30–60) [0/6]	291 (110–600) [1/11]	289 (125–615) [1/12]
Normal range	8.0–16.0	11–18	>10	>0.6		>1.1	>1.1	<60	<60	150–650	150–700

Conversion: SI to traditional units—Urinary xylose: 1 mmol/5 h ≈ 0.15 g/5 h. Faecal fat: 1 mmol/24 h ≈ 0.3 g/24 h. Blood glucose: 1 mmol/l ≈ 18 mg/100 ml. TM = Tropical malabsorption.

TABLE III—Results of serial measurements of breath hydrogen after lactulose in eight patients

Case No	Group	Time between first (0), second, and third investigations (weeks)	Treatment between investigations	Clinical improvement	T (min)*
1	Control	0	None	—	20
2	Chronic diarrhoea	46			30
3	TM (mild) (<i>G lamblia</i>)	0	None	—	50
4	TM (severe)	1			40
5	TM (severe)	0	Mepacrine	+	90
6	TM (severe)	8			Flat curve
7	TM (severe)	0	Tetracycline + folic acid	+	120
8	TM (severe)	3			80
9	TM (severe)	5	Tetracycline + folic acid	+	50
10	TM (severe)	0			90
11	TM (severe)	5	Tetracycline + folic acid	+	70
12	TM (severe)	0			190
13	TM (severe) (<i>G lamblia</i>)	7	Metronidazole + folic acid	—	100
14	TM (severe) (<i>G lamblia</i>)	0			140
15	TM (severe) (<i>G lamblia</i>)	8	Metronidazole	—	170
16	TM (severe) (<i>G lamblia</i>)	0			100
17	TM (severe) (<i>G lamblia</i>)	8			110

*Time of first hydrogen appearance. (See text.) TM = Tropical malabsorption.

hydrogen curves were constructed before or after each series of determinations from standard hydrogen and air mixtures prepared by the British Oxygen Company (Special Gases), London. The time of first hydrogen appearance (T) was taken as the point nearest the start of hydrogen production. Only the major and sustained appearance of hydrogen, after results had been plotted, was designated T; minor or transient hydrogen peaks were not accepted. The area under the hydrogen curve (parts per million × minutes × 10²) was determined by counting squares on linear graph paper between 0 and 120 minutes. Student's *t* test was used for comparison of means.

Results

In 12 patients the hydrogen curve was flat and T could not be determined. The figure gives the values for T in the remaining 86. The mean T in patients with severe tropical malabsorption was significantly higher than in the English (*t* = 5.43; DF = 35; *P* < 0.001) and combined controls (*t* = 6.20; DF = 57; *P* < 0.001). The mean T in all patients with tropical malabsorption was significantly higher than in the English controls (*t* = 3.85; DF = 46; *P* < 0.001). The mean T in patients with severe tropical malabsorption was significantly higher than in patients with either a mild form of the disease (*t* = 3.59; DF = 19; *P* < 0.01) or chronic diarrhoea (*t* = 2.10; DF = 24; *P* < 0.05). The highest values for T in the controls (120 minutes) occurred in two elderly patients with hyperlipoproteinaemia, both of whom gave diabetic values in glucose tolerance tests. The three highest values for T in the group with chronic diarrhoea occurred in a patient with amoebic dysentery (180 minutes), a patient with non-specific ulcerative colitis (150 minutes), and a cyst carrier of *Entamoeba histolytica* (140 minutes). Three patients had an early hydrogen peak: two had severe tropical malabsorption and were untreated (cases 6 and 7—table III), and one was an English control. Their peaks were at 30, 20, and 30 minutes respectively. The early peak disappeared after treatment in

the two patients with tropical malabsorption. Eight of the 12 patients with flat hydrogen curves had taken broad-spectrum antibiotics in the previous three months.

Times of first hydrogen appearance (T) (minutes) in 86 patients. In remaining 12, hydrogen curve was flat and T could not be determined. Bars represent means ± 1 SE of mean.

Serial measurements (table III) suggested that clinical improvement was associated with a lower value for T in patients with severe tropical malabsorption. In one of the English controls who had had a severe form of the disease four months before and had completely recovered T was 20 minutes. Table IV summarises the values for T after xylose, lactose, and glucose.

When the 12 patients who did not produce hydrogen were excluded, correlation between T and area under the curve was inversely significant ($r = -0.69$; $n = 86$; $P < 0.001$).

TABLE IV—Times of first hydrogen appearance (T) after xylose, lactose, and glucose

	Controls			TM		Chronic diarrhoea
	English	African	Asian	Mild	Severe	
After 25 g xylose						
No studied	6	3	4	5	2	5
No with hydrogen	1	1		2	2	
T (min)	50	50		50 (40–60)	30 (20–40)	
After 50 g lactose						
No studied	5	6	3	1	3	2
No with hydrogen	1	6	3		1	1
T (min)	80	50 (40–70)	26 (20–40)		60	50
After 100 g glucose						
No studied	6		2	1		6
No with hydrogen						

TM = Tropical malabsorption.

Discussion

Mouth-caecum transit rate, as measured by the breath hydrogen technique, was significantly prolonged in the patients with tropical malabsorption. Since the rise in blood glucose after oral carbohydrate was not delayed (table II), this finding presumably represented diminished small-intestinal motility. The passage of barium in the small intestine is often slow in patients with tropical sprue in southern India.¹¹ Three patients with chronic diarrhoea also had delayed transit; they had evidence of colonic disease. In some patients tropical malabsorption begins with bloody diarrhoea; possibly disease of the colon is the initiating factor and is in some way associated with small-intestinal stasis. The mechanism of the altered peristalsis is unknown and is contrary to what would be expected, but it would result in colonisation of the ileum with bacteria, which is particularly severe in classical tropical sprue and tropical malabsorption. Decreased small-intestinal motility would also encourage proliferation of ingested bacteria in the jejunum. Even if stasis does not occur until after bacterial colonisation, stasis and colonisation are likely to create a vicious circle. Motility slowly returned to normal after treatment in the few patients in this series who were tested serially (table III).

No ethnic differences in transit rate were detected. Full details

of treatment before admission to hospital were not known, though several patients had had antibiotics, metronidazole, and diphenoxylate hydrochloride. This last drug depresses small-intestinal peristalsis and may therefore have played a part in the pathogenesis of tropical malabsorption by encouraging stasis and bacterial overgrowth. It is probably an undesirable agent for acute diarrhoea in the tropics. Most patients who did not produce hydrogen had taken antibiotics that had presumably altered the colonic bacterial flora.

Lactulose was of no value in disclosing small-intestinal bacterial overgrowth in tropical malabsorption; the bacterial concentration is presumably much lower than that in the blind-loop syndrome.¹² Xylose, which is absorbed more slowly than glucose,¹³ seems to be a more suitable substrate. Four patients with tropical malabsorption produced hydrogen within one hour after xylose (table IV); probably at least part was produced by bacteria in the small intestine. The high incidence of adult hypolactasia in Africans and Asians¹⁴ is apparent from the production of hydrogen by all those tested with lactose (table IV).

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References

- Manson, P, *Notes on sprue. China. Imperial Customs II—Special series No 2. Medical reports for the half-year ended 31st March, 1880.* Shanghai, Statistical Department of the Inspectorate General, 1880.
- Twining, W, *Clinical Illustrations of the more important Diseases of Bengal with the Result of an Inquiry into their Pathology and Treatment.* Calcutta, Baptist Mission Press, 1835.
- Banwell, J G, and Gorbach, S L, *Gut*, 1969, **10**, 328.
- Klipstein, F A, et al, *Annals of Internal Medicine*, 1973, **79**, 632.
- Tomkins, A M, Drasar, B S, and James, W P T, *Lancet*, 1975, **1**, 59.
- Gorbach, S L, et al, *Gastroenterology*, 1967, **53**, 856.
- Abrams, G D, and Bishop, J E, *Proceedings of the Society for Experimental Biology and Medicine*, 1967, **126**, 301.
- Calloway, D H, and Murphy, E L, *Annals of the New York Academy of Sciences*, 1968, **150**, 82.
- Levitt, M D, *New England Journal of Medicine*, 1969, **281**, 122.
- Metz, G, et al, *Clinical Science and Molecular Medicine*, 1976, **50**, 237.
- Baker, S J, and Mathan, V I, in *Tropical Sprue and Megaloblastic Anaemia*, p 200. Edinburgh and London, Churchill Livingstone, 1971.
- Rhodes, J M, Jewell, D P, and Middleton, P, *Gut*, 1977, **18**, 985.
- Cook, G C, *Scandinavian Journal of Gastroenterology*, 1977, **12**, 733.
- Cook, G C, in *Intestinal Enzyme Deficiencies and their Nutritional Implications*, ed B Borgström, A Dahlqvist, and L Hambræus, p 52. Uppsala, Almqvist and Wiksell, 1973.

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ONE HUNDRED YEARS AGO In most civilised countries, means of pursuing anatomical teaching and study are now legally provided by the supply of subjects under suitable regulation. It appears, however, that in Ohio no such provision exists, and the supply of subjects for dissection is still in the hands of "resurrectionists." The state of things which led to the still unforgotten horrors and crimes of Burke and Hare appears to lead there to similar terrors and "resurrection sensations" of a startling kind. In the *Ohio Clinic* of June 8th, we read that intense excitement prevailed in the city last week over the accidental discovery by a son of the body of his father (the son of an ex-President of the United States) in the dissecting-room. The son was engaged, in company with detective police-officers, in searching the rooms for the body of a friend, when the removal of a cloth over the face of a corpse upon the floor disclosed to the horror-stricken son the face of his father who, had been buried only the day before. A more tragic occurrence was never depicted upon the stage. The newspapers made the most of it on the next day.

Sketches were published of dissecting-rooms, of chutes and hoisting-shafts, with bodies suspended in them from windlasses; imprecations were heaped upon resurrectionists, upon medical colleges and medical men. Crowds of people visited the college, and a constant throng wended its way all day long up the long narrow alley behind the college building to inspect the wooden door of the chute. As the resurrectionist who plundered the grave did not think fit to present himself with a confession of his crime, the janitor of the college was seized as a victim, incarcerated in the county jail, and only released on a bail of five thousand dollars. The authorities in the meanwhile possessed themselves of the keys of the college, and roamed over the house the entire night in search of other bodies. The *Clinic* puts this deplorable circumstance as a landmark in the history of a movement for legalising dissections in the State (as a necessary part of medical training), and of removing the incentives to grave-robbing from the reckless class of persons who now make it a business there, as they did formerly in this country. (*British Medical Journal*, 1878.)