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Appraisal of the ^{14}C-glycocholate acid test with special reference to the measurement of faecal ^{14}C excretion

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SUMMARY The ^{14}C-glycocholate test, including the measurement of marker corrected faecal ^{14}C, has been assessed in the following groups of subjects: normal controls (18), patients with diarrhoea not attributable to altered bile acid metabolism (21), patients with diverticula of the small intestine (12), patients with previous resection of ileum and often proximal colon (34), and established ileostomists (10). Patients with diverticular disease had increased breath $^{14}CO_2$ excretion, but normal faecal excretion of ^{14}C, and this test was more frequently abnormal than the Schilling test. Ileostomists excreted increased amounts of faecal ^{14}C, even when the ileum was intact and apparently normal. The pattern after resection was complex. Breath ^{14}C output was normal if the ileal resection was less than 25 cm in length, although some of these patients had increased faecal ^{14}C excretion if, in addition, at least 15 cm of proximal colon had been resected or by-passed. Longer ileal resections were associated with increased breath and/or faecal ^{14}C excretion, depending in part on the length of colon resected or by-passed and the 24 hour faecal volume. Fewer than half these patients had both increased breath and faecal excretion of isotope and faecal ^{14}C alone was occasionally normal with an ileal resection of 50 cm or more. The ^{14}C-glycocholate test was more frequently abnormal than the Schilling test in this group. The use of faecal marker correction had only a minor impact on the results. These data suggest that, in patients with ileal resection, faecal ^{14}C, like faecal weight, is determined by the extent of colonic resection as well as by the amount of ileum resected.

The ^{14}C-glycocholic acid (^{14}C-GCA) test (Fromm and Hofmann, 1971; Sherr *et al.*, 1971) detects increased bile acid deconjugation either in the small bowel as a result of bacterial overgrowth or in the large bowel after ileal malabsorption (Fromm, 1973). Simultaneous measurement of breath $^{14}CO_2$ and faecal ^{14}C is said to distinguish these conditions (Fromm and Hofmann, 1971), which may coexist in patients with distal small gut disease or resection. However, faecal measurement prolongs the test and necessitates additional equipment for faecal combustion. Possibly because of these difficulties, several reports involving the ^{14}C-GCA test have not mentioned the measurement of faecal ^{14}C (Parkin *et al.*, 1972; James *et al.*, 1973).

We assessed the test in a series of patients with presumed bacterial overgrowth, ileal resection, ileostomy, non-specific diarrhoea, and normal control subjects. The activity of ^{14}C was measured in both breath and faeces, and the faecal output corrected for non-recovery of a simultaneously administered marker. The value of the additional information gained from faecal ^{14}C estimation is discussed.

Methods

The patients studied comprised four groups in addition to a control series of healthy subjects. Neither patients nor controls were receiving any drug therapy likely to interfere with the test. All symptomatic treatment for diarrhoea was discontinued for at least 24 hours beforehand. The tests were done mainly on a day-case basis and the previous food intake was not controlled. The diagnosis, in each case, was based on the usual clinical, radiological, and laboratory investigations as well as, where relevant, surgical records.

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CONTROL SUBJECTS

This group consisted of 18 subjects (11 males, seven females) with a mean age of 42·6 years (range 19-67 years). None had any history of gastrointestinal symptoms.

PATIENTS WITH MISCELLANEOUS DIARRHOEA (Table 1)

Twenty-one patients were studied (10 males, 11 females) with a mean age of 46·4 years (range 23-68 years). Fifteen had chronic, persistent, diarrhoea unexplained after full investigation (1-15), five had untreated coeliac disease (16-20), and one (21) had steatorrhoea caused by pancreatic insufficiency.

PATIENTS WITH OVERGROWTH OF SMALL INTESTINE (Table 2)

Twelve patients (six males, six females) with a mean age of 70·1 years (range 55-77 years) were studied. All had jejunal or duodenal diverticula and the majority had well-documented evidence of malabsorption. All patients had a history of chronic, continuous, or intermittent bowel symptoms but two were asymptomatic at the time of study (cases 3, 8). The majority had improved with antibiotics in the past.

PATIENTS WITH ILEAL RESECTION (Table 3)

Thirty-four patients (13 males, 21 females) were studied having a mean age of 46·7 years (range 21-75 years). They had undergone resection of the small bowel at least six months previously for a number of conditions, most frequently Crohn's disease. No patient was acutely ill at the time of study and the usual haematological and biochemical measurements were stable.

ILEOSTOMY PATIENTS (Table 4)

Ten patients were studied, seven with ulcerative colitis and three with Crohn's disease. The mean age of the group was 44·6 years (range 30-67 years). All patients had normally functioning ileostomies with the exception of one subject (case 4) who had intermittent ileostomy diarrhoea.

TECHNIQUES

After an overnight fast patients underwent a Schilling test with intrinsic factor (Schilling, 1953) and a ^{14}C-GCA study. Simultaneous estimation of creatinine clearance rate was performed to help interpretation of the Schilling test. No patient had a clearance of less than 50 ml/min. Control subjects and ileostomists did not undergo a Schilling test.

^{14}C-glycocholic acid (5 uCi) (Radiochemical

Table 1 *Patients with miscellaneous diarrhoea*

Diagnosis			*Breath $^{14}CO_2$ (%)**	*Corrected faecal ^{14}C (%)†*	*24 hour faecal weight (g)§*	*Schilling (%)‡*
No.	*Sex*	*Age (yr)*				
Idiopathic diarrhoea						
1	M	48	0·4	1·7	30	22·5
2	M	49	2·0	6·6	90	14·0
3	F	61	2·6	3·5	145	12·1
4	F	35	0·2	—	0	10·3
5	M	53	1·6	0·9	440	19·5
6	F	26	0·8	3·3	155	16·2
7	M	57	0·9	1·9	150	11·1
8	M	30	1·9	—	5	22·6
9	F	23	2·1	10·3	190	21·0
10	F	35	0·3	0·2	75	21·3
11	F	48	2·5	1·1	60	23·5
12	F	68	1·7	4·7	370	9·0
13	M	34	1·8	—	55	14·0
14	M	66	0·3	5·1	160	29·0
15	F	57	4·0	10·3	870	15·2
Coeliac disease						
16	M	42	1·8	7·3	320	25·9
17	M	35	0·5	0·7	115	15·9
18	F	48	1·2	—	80	23·6
19	F	48	0·2	—	35	25·7
20	M	58	0·6	2·6	205	18·0
Pancreatic insufficiency						
21	F	53	1·8	5·5	300	9·1

Normal range: *< 4·0%
†<10·3%
‡> 8·0% of administered dose respectively.
§Single 24 hour faecal collection.

Table 2 *Patients with symptomatic small intestinal diverticulosis*

Diagnosis			Breath $^{14}CO_2$(%)*	Corrected faecal ^{14}C (%)†	24 hour faecal weight (g)§	Schilling (%)‡
No.	Age (yr)	Sex				
Jejunal diverticula						
1	77	F	7·6	0·9	60	4·4
2	55	M	25·1	7·6	220	24·4
3**	66	F	0·6	0·3	170	32·5
4	74	M	9·8	7·4	465	10·9
5	69	F	7·2	—	×	9·0
6	64	F	14·4	0·6	200	0·0
7	65	F	5·7	3·5	90	12·8
8**	55	M	2·9	8·2	100	15·9
Jejunal + duodenal diverticula						
9	67	M	17·4	6·3	190	1·0
10	69	M	8·2	—	0	10·4
Duodenal diverticula						
11	71	F	6·7	1·9	130	13·2
12	60	M	7·0	3·7	260	2·1

Malabsorption was not demonstrated in patients 8, 11, 12.
Key as in Table 1.
**Asymptomatic at time of study.
× Patient unable to co-operate.

Centre, Amersham) and unlabelled glycocholate (0·1 mmol) as carrier (Hofmann and Thomas, 1973), were given orally together with labelled cyanocobalamine (1 μg containing 0·5 uCi of ^{57}Co), a capsule of intrinsic factor (10 mg), and copper thiocyanate (2·5 mmol) as a non-absorbed faecal marker. These were followed by a standard liquid test meal (corn oil 18 g, glucose 40 g, Casilan 15 g, water to 300 ml). Intramuscular vitamin B_{12} (1 mg) was given one hour later.

Expired breath samples were collected over silica gel and trapped in counting vials containing methyl benzethonium hydroxide (1 mmol) in 2 ml ethanol with phenolpthalein (20 g per litre in ethanolic solution) as indicator. Samples were obtained in duplicate each hour for six hours. They were counted for ^{14}C activity (Intertechnique SL 30) and converted to disintegrations per minute by external standardisation.

The total 24 hour stool output was weighed and homogenised with a known volume of water. One aliquot was analysed for copper (Dick, 1969). A further aliquot was oxidised (Packard oxidiser) and the $^{14}CO_2$ trapped in counting vials containing Carbosorb (Packard). Samples were counted for ^{14}C activity and converted to disintegrations per minute *via* external standardisation. Faecal estimations were not measured if the stools were solid and less than 75 g in weight, because recovery of ^{14}C and marker was invariably very low and marker correction produced spuriously high results in some normal individuals.

Urine was collected for 24 hours and an aliquot counted for γ-activity (Scaler-Ratemeter).

All results are expressed as a percentage of the administered dose. The mean hourly breath $^{14}CO_2$ output was calculated as described by Fromm and Hofmann (1971), and the results expressed as the total cumulative output over six hours. Faecal ^{14}C recovery was corrected for non-recovery of the copper marker.

In the statistical assessment of observed differences, both parametric (Student's *t* test) and non-parametric (Wilcoxon's sum of ranks test) methods were used. In all cases identical values for P were obtained.

Results

CONTROL SUBJECTS

The mean cumulative output of $^{14}CO_2$ in the breath over the initial six hours was 1·97% (±0·23 SEM) (range 0·7-4·0%). Only six subjects had a 24 hour faecal collection of more than 75 g and in these the mean corrected faecal ^{14}C recovery was 3·7% (±1·34 SEM) (range 0·2-9·4).

We have defined our normal range as the mean + two standard deviations of our control results. This gives an upper limit for breath $^{14}CO_2$ output of 4·0% and for corrected faecal ^{14}C recovery of 10·3%.

PATIENTS WITH MISCELLANEOUS DIARRHOEA (Table 1)

Breath $^{14}CO_2$ and corrected faecal ^{14}C recovery were all within the normal range. Similarly ^{57}Co recovery was also normal for subjects (> 8.0%).

PATIENTS WITH STASIS OF SMALL INTESTINES (Table 2)

Corrected faecal ^{14}C recovery was normal in every case. Breath $^{14}CO_2$ output was increased in all but

Table 3 *Patients with ileal resection*

Diagnosis			Length of resected bowel (cm)		Breath $^{14}CO_2$ (%)*	Corrected faecal ^{14}C (%)†	Faecal copper (%)	24 hour faecal weight (g)§	Schilling (%)‡
No.	Age (yr)	Sex	Ileum	Colon					
Omental tear									
1	33	M	25	Nil	1·3	5·9	6·9	140	20·1
Benign stricture									
2	62	M	15	Nil	1·9	8·2	4·9	65	—
3	60	F	15	Nil	1·1	6·1	40·1	130	14·3
4	34	F	5	11	0·3	—	—	0	3·2
Crohn's disease									
5	52	M	14	11	3·7	1·6	20·0	145	23·1
Mesenteric thrombosis									
6	49	F	60	Nil	9·6	7·8	0·5	40	6·5
Post-irradiation stricture									
7	68	M	30	Nil	7·5	5·9	39·4	180	17·1
Crohn's disease									
8	53	F	60	10	11·1	—	—	10	7·8
9	41	M	120	15	17·4	2·3	18·2	160	5·6
10	41	M	50	15	15·1	9·2	74·6	290	2·9
11	55	F	40	Nil	6·9	8·8	35·6	115	8·1
12	51	F	35	5	15·6	8·6	44·9	870	0·2
13	53	M	30	NK	11·1	—	—	70	0·6
14	40	F	75	11	8·0	58·3	34·1	370	1·6
15	41	F	35	Nil	4·4	14·1	55·9	375	12·9
16	54	F	50	By-pass	12·9	34·3	82·0	545	1·8
17	49	F	NK	15	16·6	17·9	80·8	490	1·5
18	57	M	50	8	20·3	14·8	13·3	90	2·4
19	69	M	100	12	21·2	24·1	41·3	445	0·4
20	32	M	36	15	5·9	57·9	15·4	275	4·1
21	37	F	45	10	9·8	43·6	80·3	545	15·9
22	33	M	200	22	10·6	17·8	35·0	940	0·7
23	57	F	60	15	13·5	17·7	23·9	105	1·5
24	29	F	35	12	7·5	70·8	25·0	725	1·0
25	26	F	30	15	8·0	22·9	29·9	235	14·5
TB bowel									
26	58	F	17	22	1·5	27·0	81·9	205	8·0
Crohn's disease									
27	21	F	22	15	0·8	16·9	86·9	510	17·4
28	35	M	45	15	1·5	19·8	57·6	250	19·8
29	75	F	35	By-pass	0·8	56·4	97·3	1000	0·9
30	47	F	40	50	0·4	40·3	89·4	530	0·9
31	68	F	5	15	2·0	15·5	94·0	740	1·5
32	44	F	80	15	3·9	56·5	49·9	660	4·9
33	29	F	17	By-pass	1·2	21·9	76·0	470	8·1
34	36	M	30	35	3·3	28·6	91·2	300	15·7

Key as in Table 1.
NK: length unknown.

Table 4 *Ileostomists*

Diagnosis			Duration of ileostomy (yr)	Length of resected ileum (cm)	Breath $^{14}CO_2$ (%)*	Corrected faecal ^{14}C (%)†	24 hour faecal weight (g)§	Faecal copper (%)
No.	Age (yr)	Sex						
Ulcerative colitis								
1	32	F	4	0	0·54	18·5	420	87·2
2	50	F	4	6	0·87	17·3	440	84·6
3	55	M	2	9	0·40	21·6	590	72·7
4	67	F	15	NK	1·61	32·8	1145	100·0
5	38	F	4	6	0·31	16·8	500	90·9
6	54	M	3	15	3·20	9·1	570	92·2
7	35	F	3	0	0·96	10·4	195	87·9
Crohn's disease								
8	30	M	2	35	0·22	67·5	720	96·4
9	33	F	7	50	0·25	52·2	770	82·9
10	52	M	2	45	0·18	56·4	420	47·3

Key as in Table 1.
NK: length unknown.

two patients (cases 3, 8) both of whom were asymptomatic at the time of study. By comparison with the control series breath $^{14}CO_2$ output was significantly raised ($P < 0{\cdot}001$).

^{57}Co recovery was abnormal in four subjects and in all of these breath $^{14}CO_2$ output was high.

PATIENTS WITH ILEAL RESECTION (Table 3)
Corrected faecal ^{14}C recovery was increased in 20 subjects and breath $^{14}CO_2$ was raised in 18. The mean breath $^{14}CO_2$ output was significantly increased ($P < 0{\cdot}001$) when compared with controls. Faecal ^{14}C recovery was also similarly raised ($P < 0{\cdot}02$). Patients 1-5 had normal results and patients 6-14 had increased breath $^{14}CO_2$ but normal faecal ^{14}C. Patients 14-34 had increased faecal ^{14}C.

The Schilling test was normal ($>8{\cdot}0\%$) in 12 subjects and nine of these had increased breath or stool ^{14}C output. Twenty-one patients had an abnormal Schilling test and all but one of these (case 4) had an abnormal ^{14}C-GCA study.

ILEOSTOMY PATIENTS (Table 4)
All patients produced large stool volumes and faecal copper recovery was correspondingly high. Corrected faecal ^{14}C was significantly increased compared with controls ($P < 0{\cdot}01$).

Corrected faecal ^{14}C recovery in the three patients with Crohn's disease was significantly higher than in the patients with ulcerative colitis ($P < 0{\cdot}001$). All patients had normal breath $^{14}CO_2$ excretion.

Discussion

In this series all the subjects with non-specific diarrhoea had normal breath and faecal ^{14}C outputs. These included five subjects whose 24 hour faecal weights were greater than 300 g. It appears that, where ileal function is normal, increased faecal volume alone will not result in bile acid malabsorption. This agrees with other published work (Fromm *et al.*, 1973) but Pedersen *et al.* (1973) did find increased faecal ^{14}C in five patients with unexplained diarrhoea and speculated that they might have a primary defect in ileal anion transport. Two of our patients had faecal ^{14}C recoveries of $10{\cdot}3\%$, which is at the upper limit of our normal range.

All but two of the patients with diverticular disease of the small intestine had increased breath excretion of $^{14}CO_2$, while faecal ^{14}C recovery was normal in all. The two patients with normal tests were asymptomatic at the time of study and had not been taking antibiotics for at least 18 months. Presumably their small gut bacteria were incapable of metabolising ^{14}C-GCA but direct bacteriological confirmation of this was not available. In this group, as a whole, the Schilling test was a less sensitive indicator of bacterial contamination in that only four subjects had an unequivocally low result.

Almost all the patients with ileal resection had either increased breath or faecal excretion of ^{14}C or both. Five patients (1-5, Table 3) had normal tests and all had had resection of 25 cm length or less and the remaining ileum was presumably able to absorb bile acids effectively. Four other patients with equally short resections (26, 27, 31, 33, Table 3) had increased faecal ^{14}C excretion but normal breath outputs. There may have been inaccurate recording of the length of resection or, in those with Crohn's disease, the remaining ileum may have been affected by recurrent disease. Other reports (Fromm *et al.*, 1973; Lenz, 1975) indicate that ileal resections of greater than 50 cm are invariably accompanied by bile acid malabsorption, but do not suggest a limit below which absorption is adequate. Most subjects in the present study with longer ileal resections had increased breath excretion of $^{14}CO_2$ and, in the whole group, there was a significant positive correlation ($P < 0{\cdot}01$) between length of ileal resection and output of $^{14}CO_2$ (Fig. 1).

Eight patients (6-13, Table 3) had increased breath excretion with normal faecal excretion of ^{14}C, the pattern seen typically in patients with bacterial overgrowth of the small gut and not described in previous reports in patients with ileal resection (Fromm and Hofmann, 1971; Fromm *et al.*, 1973; Pedersen *et al.*, 1973; Lenz, 1975). However, they all had more than 25 cm of ileum resected and none had responded to antibiotics (see Scarpello and Sladen, 1977). Surprisingly, they include four patients (6, 8-10, Table 3) with ileal resections of more than 50 cm, and one who had lost 120cm. This

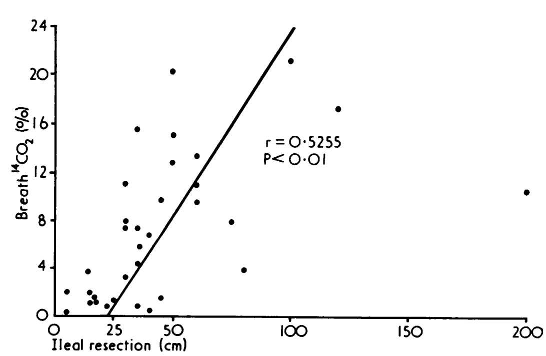

Fig. 1 *Correlation between the cumulative output of breath $^{14}CO_2$ over six hours and length of resected ileum ($P < 0{\cdot}01$).*

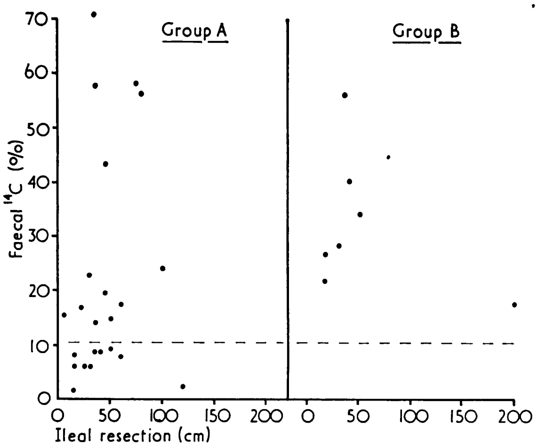

Fig. 2 *Marker-corrected faecal* ^{14}C *related to length of ileal resection. Group A: less than 20 cm of proximal colon resected or by-passed. Group B: more than 20 cm of proximal colon resected or by-passed.*

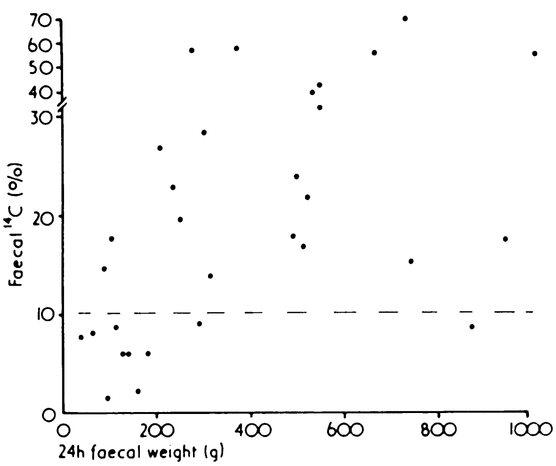

Fig. 3 *Marker-corrected faecal* ^{14}C *plotted against 24 hour faecal weight for ileal resected patients, excluding ileostomists (the dotted line denotes the upper limit of normal).*

implies that faecal ^{14}C is not an infallible test for ileopathy. They had had either no colonic resection or short lengths of colon resected or by-passed and six of these patients produced relatively small volumes of formed stools (180 gm). Colon transit time must have been sufficiently slow to allow malabsorbed bile acid to be deconjugated and the glycine to be absorbed and not appear in the faeces. The observations of Cummings *et al.* (1973) imply that an intact colon can absorb water effectively in patients with ileal resection and presumed bile acid malabsorption, and we have observed this experimentally in the rat (manuscript in preparation).

By contrast 21 patients (14-34, Table 3) had increased faecal ^{14}C excretion and, with two exceptions, all produced more than 200 g of faeces during the study (Fig. 3). In these patients malabsorption of bile acid was probably responsible, at least in part, for the diarrhoea and, in those treated with bile acid binding agents, there was definite improvement in symptoms (see Scarpello and Sladen, 1977). It is noteworthy that nine of these patients (26-34, Table 3) had normal breath outputs of $^{14}CO_2$ and the disorder of bile acid metabolism would not have been detected without faecal analysis. Most of these nine patients excreted more than 75% of the marker in 24 hours and some had very large volume stools (500-1000 g). Presumably colon transit was so rapid that there was insufficient time for bile acid deconjugation and absorption of glycine. This is particularly likely to occur if much of the colon is resected or by-passed. Indeed all patients, in whom more than 20 cm of colon was resected or by-passed, had increased faecal ^{14}C excretion irrespective of the length of ileum resected (Fig. 2). Similarly Lenz (1975) has noted that breath $^{14}CO_2$ output was normal in patients with Crohn's disease subjected to combined resection of ileum and most of the colon.

This interpretation of increased faecal ^{14}C and normal breath $^{14}CO_2$ in patients with combined ileal and colonic resection must be viewed with caution in the light of the finding in ileostomists that faecal ^{14}C is almost always increased and sometimes greatly so. In the subjects with Crohn's disease this implies impaired ileal function caused by resection or disease and is in keeping with other studies which indicate impaired small bowel function in Crohn's ileostomists (Allan *et al.*, 1975). Indeed, faecal ^{14}C output was significantly greater in the Crohn's ileostomists compared with the ulcerative colitis group. In those with ulcerative colitis, only small lengths of ileum had been resected and ileal function was not obviously disturbed, with the possible exception of patient 4 (Table 4) who did have episodes of ileostomy diarrhoea. There are no other reports of the ^{14}C-GCA test in ileostomists for comparison. The simple conclusion that bile acid absorption is impaired in otherwise healthy ileostomists is refuted by direct measurement of faecal bile acid losses in these subjects (Percy-Robb *et al.*, 1971; Miettinen and Peltokallio, 1971). It may be that bile acids are deconjugated excessively in the terminal ileum of ileostomists, perhaps related to increased bacterial activity at this site (Gorbach *et al.*, 1967) and that the ^{14}C-glycine is largely excreted in the effluent. This could occur in other patients with extensive colonic resection and large volume outputs and might invalidate the simple interpretation that high faecal ^{14}C necessarily means bile acid malabsorption.

Returning to the patients with ileal resection, the ^{14}C-GCA test seemed a more sensitive indicator of ileal dysfunction than the Schilling test, although if the Schilling test was combined with breath $^{14}CO_2$ output only two patients (cases 27, 33, Table 3) had normal results with an increased faecal ^{14}C output. The use of a faecal marker was designed to compensate for variable colonic emptying, but does impose additional work on the laboratory. Analysis of our results using uncorrected faecal ^{14}C excretion shows that the interpretation would be changed in only four patients with ileal resection (cases 18, 22, 23, 25, Table 3). Their faecal ^{14}C output would be regarded as normal, but all had a high breath output and in two (18, 23) the faecal collections were possibly incomplete. Where the faecal volume is large, as in ileostomists, marker correction was clearly unimportant. If facilities are not available for the measurement of faecal ^{14}C, the 24 hour faecal volume will give an approximate indication of the severity of bile acid malabsorption (Fig. 3). The present results support other observations (Fromm *et al.*, 1973) that a faecal volume greater than 200 g implies that bile acid absorption is impaired in patients with ileal resection.

In conclusion, whereas increased breath $^{14}CO_2$ provides a satisfactory screening test for bacterial overgrowth in the small intestine, the results can be misleadingly normal in many patients with clinically important ileal dysfunction especially if they have also lost much of their colon. This difficulty is largely overcome by the simultaneous measurement of 24 hour faecal volume and ^{14}C excretion. The interpretation of increased faecal ^{14}C in ileostomists with an apparently intact ileum is difficult, but probably does not imply bile acid malabsorption.

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