

## PAPERS AND SHORT REPORTS

## Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention

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### Abstract

The cause of intractable chronic diarrhoea was found to be malabsorption of bile acid in five out of 42 patients thought to have the irritable bowel syndrome, six out of 29 patients with persistent diarrhoea after surgery for peptic ulcer, 23 who had undergone small bowel resection, and two others. Specific treatment brought symptomatic relief. The diagnosis was established by measuring the proportion of SeHCAT, a synthetic bile salt, retained one week after oral administration of a tracer dose of less than 100  $\mu\text{g}$  of the compound labelled with 40 kBq (1  $\mu\text{Ci}$ ) of selenium-75.

These results indicate that malabsorption of bile acid is a more common cause of chronic diarrhoea than is generally appreciated. Measurement of retention of SeHCAT is a simple, accurate, and acceptable means of establishing the diagnosis of this debilitating but treatable condition.

### Introduction

The bile acids are a closely related group of naturally occurring detergents that play an essential part in the absorption of fats and fat soluble compounds and are largely reabsorbed unchanged before reaching the caecum. Certain bile acids have a direct effect on the colonic mucosa, controlling the rate of sodium absorption and water secretion. When in abnormally high concentration in the colon they cause diarrhoea, and deficiency results in constipation.<sup>1</sup>

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In healthy subjects the bile acids in the lumen of the small intestine are conjugated with glycine or taurine. Free acids are not present. The conjugates are absorbed by active transport across the mucosa of the terminal ileum.<sup>2</sup> Anaerobic bacteria in the large bowel, or, under pathological conditions, in the small bowel, cause deconjugation with the release of free bile acids, which can be absorbed by passive diffusion from both large and small bowel.<sup>3,4</sup> There is relatively little passive diffusion of glycine conjugates and virtually none of taurine conjugates. Absorption of taurocholate is thus a marker of the functional integrity of the terminal ileum.

Three types of malabsorption of bile acid are recognised. The first (type 1) follows resection or destruction of the ileal mucosa.<sup>5,6</sup> The second (type 2), primary idiopathic malabsorption,<sup>7</sup> is thought to be rare; the third (type 3) is associated with cholecystectomy, vagotomy, and certain drugs<sup>8,9</sup>; its pathogenesis is uncertain. In all the diarrhoea can usually be controlled by bile acid binding agents such as cholestyramine or aluminium hydroxide.

SeHCAT is the taurine conjugate of a synthetic bile acid containing the  $\gamma$  emitting isotope selenium-75. We have previously shown that it behaves in man like other taurine conjugated bile salts.<sup>10-12</sup> Because of the  $\gamma$  emitting label it can easily be measured by either whole body counting<sup>13</sup> or counting of unprocessed sealed containers of stool.<sup>14</sup>

We report here a prospective study in 106 patients and 63 controls of the value of measuring absorption of SeHCAT as a test for the presence of bile acid malabsorption. Our results suggest that bile acid malabsorption types 2 and 3 are more common than is generally recognised.

### Subjects and methods

We examined four groups of subjects (see table I). All gave their informed consent to the investigation, which had previously been approved by ARSAC and the North Lothian District ethical committee. The first consisted of 63 normal controls (seven men, 56 women), including 20 subjects described previously.<sup>12</sup> The mean (range) age was 52 (24-72) years. None had symptoms that could be associated with the gastrointestinal tract. The second group consisted

of 26 patients who had previously undergone small bowel resection (see table II), the third of 29 patients with persistent diarrhoea after previous vagotomy or surgery for peptic ulcer (see table III), and the fourth of 51 patients with chronic diarrhoea of non-inflammatory origin—namely, the irritable bowel syndrome in 43, coeliac disease in two, small bowel ischaemia in two, and other miscellaneous conditions in four.

Diagnoses were based on the combination of clinical history, haematological findings, biochemistry, and, when appropriate, barium follow through, barium enema, and biopsy of the colon or small bowel and were verified on follow up of at least one year. In patients who had undergone vagotomy the concentration of hydrogen in the breath was measured at half hour intervals after oral administration of 50 g glucose. A positive test, suggesting colonisation, was one in which the concentration of hydrogen in the breath remained raised at more than 20 parts per million.<sup>15</sup> This, and whole body retention of vitamin B<sub>12</sub>, which was measured in all patients, were used to exclude or confirm colonisation of the small bowel. The methods of measuring retention of SeHCAT and vitamin B<sub>12</sub> have been described elsewhere.<sup>6, 12</sup> A tracer dose of less than 100 µg SeHCAT was administered labelled with 40 kBq (1 µCi) selenium-75.

## Results

More than 15% of the administered selenium radioactivity was retained in all normal subjects after one week (median retention 31%, range 16-92%) (table I). The 18 patients with diarrhoea after vagotomy who were asymptomatic at the time of the test showed retention greater than 15% after seven days. After one year all were still free of small bowel disease and could be regarded as true negatives. None of the 31 patients with irritable bowel disease who retained more than 15% at seven days showed any evidence of small bowel disease, and none appeared during a follow up of at least 12, and in some up to 24 months. Simple conservative treatment resolved or eased most symptoms.

Thirty seven patients retained less than 8% at one week; 23 of these had undergone resection of the ileum, identified in 17 as varying in length from 20 cm to "the entire ileum" (table II). They thus had type 1 bile acid malabsorption. In others the excised specimen had been so distorted that its length could not be assessed. There was no simple correlation between the extent of the resection and the proportion of SeHCAT retained (table II). The mean (SD) proportion retained after ileal resection was 1.4 (1)% (range 0.5-2%). Two patients who had undergone jejunal resection had, as expected, values in the normal range (both 81%) and did not suffer from diarrhoea.

Nineteen of the 26 patients who had undergone ileal resection obtained symptomatic relief from cholestyramine or aluminium hydroxide; two refused cholestyramine; two others were unable to tolerate a dose large enough to control the diarrhoea, although they did obtain partial relief. One patient, whose diarrhoea after resection of 31 cm of terminal ileum and 7 cm of ascending colon for Crohn's disease was controlled initially by cholestyramine and subsequently by codeine phosphate and loperamide, retained 29% SeHCAT one year after operation at a time when she was receiving no drugs and had normal regular bowel actions. For the purpose of analysis she has been regarded as a false negative, but it is probably more accurate to consider this to be evidence of adaptation.

Six of the 29 patients who had undergone vagotomy or surgery for peptic ulcer retained less than 8% SeHCAT, suggesting type 3 malabsorption (table III). One, however, may have had type 2 malabsorption as diarrhoea preceded the vagotomy. Four obtained

TABLE II—Details of patients who had undergone resection of small bowel

Case No	Sex	Age (years)	Extent of resection	Indication	Proportion of SeHCAT retained after 7 days (%)
1	M	43	20 cm terminal ileum	Crohn's disease	0.9
2	F	44	25 cm terminal ileum and total colectomy	Crohn's disease	0
3	F	21	27 cm terminal ileum and 16 cm ascending colon	Volvulus	1
4	F	53	30 cm terminal ileum	Crohn's disease	0.6
5	F	29	31 cm terminal ileum and 7 cm ascending colon	Crohn's disease	29.1
6	F	70	35 cm terminal ileum and 10 cm jejunum	Adenocarcinoma of small bowel	0
7	F	23	40 cm terminal ileum, ascending colon	Crohn's disease	2.7
8	M	65	45 cm terminal ileum and ascending and transverse colon	Crohn's disease	0
9	F	63	42 cm terminal ileum and right hemicolectomy	Crohn's disease	0
10	M	17	60 cm terminal ileum	Crohn's disease	0.4
11	F	29	60 cm ileum and right hemicolectomy	Crohn's disease	< 1
12	M	50	60 cm terminal ileum and ascending colon	Crohn's disease	0
13	M	40	75 cm proximal ileum	Crohn's disease	4.7
14	F	56	90 cm ileum	Gangrene	4
15	F	28	Entire ileum	Crohn's disease	0.6
16	M	66	1.2 m bowel left	Crohn's disease	5.2
17	F	56	Not known	Radiation damage	2.6
18	F	58	Not known	Radiation damage	0
19	M	31	1 m ileum left	Volvulus	81
20	F	42	Not known	Crohn's disease	2
21	F	65	Not known	Gangrene	3.3
22	M	74	"Extensive"	Not known	2
23	M	65	Not known	Trauma	< 1
24	F	42	Not known	Crohn's disease	< 1
25	M	70	Jejunum only	Jejunal diverticulas	80.5
26	F	58	Not known	Radiation damage	1.2

symptomatic relief with cholestyramine, although one was unable to tolerate a dose adequate to relieve his symptoms completely. Bile salt adsorbing agents were not tried in the two others.

Retention of less than 8% SeHCAT was found in eight other patients. One with chronic pancreatic insufficiency (retention 3%) obtained symptomatic relief with Nutrizym (bromelains and pancreatin), suggesting that bile acid malabsorption was secondary to steatorrhoea.<sup>9</sup> In one with coeliac disease (retention 0) normal bowel action was restored with a gluten free diet, suggesting that bile acid malabsorption was secondary to a widespread mucosal abnormality. The SeHCAT test was not repeated in these treated patients. In the six other patients retention ranged from 0 to 6.5%. They had been thought to be suffering from the irritable bowel syndrome. Cholestyramine gave symptomatic relief in four, suggesting that bile acid malabsorption was the cause of their diarrhoea. Extensive investigations in these patients showed no other pathological condition. The fifth patient defaulted from follow up, and the sixth was a false positive owing to inadvertent administration of aluminium hydroxide, an efficient bile salt sequestering agent, throughout the period of measurement; 3% was retained, although a separate measurement of daily faecal bile acid excretion was within the normal range.

The 17 patients whose whole body retention of SeHCAT was between 8% and 15% (equivocal result) at one week included: five with diarrhoea after vagotomy (table III); one with diarrhoea after cholecystectomy (retention 10.5%); two with immunological abnormalities (one with idiopathic allergy (retention 10%) and one with coeliac disease (retention 13%)); one with hypolactasia (retention

TABLE I—Results of SeHCAT retention test in three groups of patients and one group of healthy controls. Figures indicate numbers of patients

Group No	n	True positive (< 8%)		False positive (< 8%)	Equivocal (8%-15%)			True negative (> 15%)	False negative (> 15%)
		Response to cholestyramine	Cholestyramine not tried		Response to cholestyramine	No response to cholestyramine	Cholestyramine not tried		
1	Controls	63						63	
2	Small bowel resection	26	21	2				2	1
3	Diarrhoea after vagotomy	29	4	2	1		4	18	
4	Chronic diarrhoea due to:								
	Irritable bowel syndrome	43	4	1	2	2	2	31	
	Coeliac disease	2		1			1		
	Small bowel ischaemia	2					2		
	Others	4		1			3		
	Total	169	29	7	1	3	2	114	1

13%); two with ischaemia of the small bowel (retention in both 14%); and five whose diarrhoea was of unknown aetiology (retention 11%, 12%, 13%, 13%, 13%), one of whom subsequently developed an apparently distal colitis. The diarrhoea was intermittent in all and of variable severity. Two of these patients with an equivocal result were investigated on two occasions about one year apart. There was little change (retention 16% and 13%) in the patient with arthrogryposis multiplex; he had nocturnal diarrhoea of many years' duration, normal excretion of faecal bile acids (0.35 mmol (133 mg)/24 h), and no response to cholestyramine. The other patient, who had developed diarrhoea after vagotomy, retained 27% and 13% SeHCAT.

Colonisation, as measured by a positive hydrogen breath test, was associated with malabsorption of bile acid in only one of the patients who had undergone surgery for peptic ulcer (table III). None of the patients with the irritable bowel syndrome showed malabsorption of vitamin B<sub>12</sub>.

TABLE III—Details of patients with diarrhoea after undergoing surgery for peptic ulcer

Case No	Sex	Age (years)	Operation	Symptoms	SeHCAT (% retained at 7 days)
27	M	30	HSV	Intermittent	26
28	M	28	TV, G	Intermittent	65
29	M	72	V, P	Moderately severe	6.3
30	M	43	V, P	Intermittent	33.9
31	M	54	TV, G	Intermittent	15
32	F	72	TV, G, C	Moderately severe	42
33	F	68	TV, G	Intermittent	6†
34	M	62	SV, P	Intermittent	25†
35	F	57	SV, P	Intermittent	27‡ 13‡
36	M	52	TV, P	Moderately severe	0
37	M	50	SV, G	Intermittent	23†
38	M	66	Po	Intermittent	49
39	F	60	TV, P	Intermittent	20
40	M	28	TV, P	Intermittent	51
41	M	54	SV, G	Intermittent	30
42	M	62	TV, G	Intermittent	40
43	M	48	TV, G, C	Moderately severe	26
44	F	42	TV, V > G	Intermittent	41†
45	M	57	TV, G, C	Intermittent	13
46	M	48	TV, P, C	Moderately severe	7
47	F	70	TV, P	Intermittent	14
48	F	57	TV, G	Moderately severe	55
49	M	44	Po	High faecal fat, no diarrhoea	77
50	F	44	V, PG	Intermittent	42
51	F	65	V, P	Moderately severe	17†
52	F	54	V, P	Moderately severe	32
53	M	57	PG	Moderately severe	4
54	M	36	Other*	Intermittent	11
55	M	48	TV, Po, C	Moderately severe	5

HSV = highly selective vagotomy; TV = truncal vagotomy; G = gastroenterostomy; V = vagotomy; P = pyloroplasty; C = cholecystectomy; SV = selective vagotomy; Po = Polya partial gastrectomy; PG = partial gastrectomy, unspecified.

\*Five operations for hiatus hernia.

†Abnormal hydrogen concentration in breath.

‡First test 30 July 1982; second test 23 April 1984.

## Discussion

The principal symptom of bile acid malabsorption, diarrhoea, is debilitating but treatable; cholestyramine is, however, unpalatable and accepted only reluctantly by many patients. The correct dose for a particular patient cannot easily be predicted, and perseverance is required to find the optimum regimen. There are therefore good clinical grounds for requiring a definite diagnosis before attempting a therapeutic trial. Established methods of diagnosing bile acid malabsorption leave a great deal to be desired. The definitive tests, the measurement of total faecal bile acids using chemical techniques and the recovery from the stool of a tracer dose of a bile acid labelled with carbon-14, both require stool collection over three days followed by expensive and time consuming manipulation of the sample. Collection is difficult in patients with severe diarrhoea, and the subsequent manipulations are time consuming and unpopular with laboratory staff. Neither test has ever achieved widespread acceptance in routine clinical practice. Measurement of exhaled carbon-14 dioxide after the administration of carbon-14 glycocholate has been advocated but is unreliable unless supplemented by faecal measurement.<sup>16</sup>

A number of centres have reported encouraging preliminary results using SeHCAT as a test of ileal function,<sup>12 17 18</sup> but the diagnosis had already been established in most of the patients

reported on. It is not yet clear what place, if any, SeHCAT has in the routine investigation of patients with unexplained diarrhoea, although much useful information about absorption of bile acid can be obtained. Absorption of vitamin B<sub>12</sub> has hitherto been used to assess ileal function in the absence of any clinically available test of absorption of bile acid. It is, however, well established that absorption of vitamin B<sub>12</sub> is less sensitive than absorption of bile acid,<sup>19</sup> and absorption of vitamin B<sub>12</sub> may be normal despite extensive resection or disease of the ileum. In the present series absorption of vitamin B<sub>12</sub> was reduced in all patients with ileal resection but was normal in all the others.

For any test there is an inverse relation between sensitivity and specificity. When using the seven day retention of SeHCAT to assess bile acid malabsorption a lower limit of 15% gave a specificity of 0.99 and an upper limit of 8% was associated with a sensitivity of 0.97. But for an identified and avoidable error sensitivity would have been unity. The accuracy in the population studied was 88%, mainly because of the number of cases falling in the equivocal range. As an indicator of ileal or ileocaecal dysfunction a single cut off at 15% is associated with an accuracy of 99%, but the specificity of the test as a measure of bile acid malabsorption is less, probably about 80%. A precise figure cannot be given because of the ambiguity resulting from the intermittent nature of type 3 bile acid malabsorption.

Using these criteria bile acid malabsorption was present in 10 (34%) of 29 patients with diarrhoea after vagotomy, being severe in 6 (21%). It was the principal cause of symptoms in five (12%) of 43 patients diagnosed as suffering from the irritable bowel syndrome. The four who accepted cholestyramine responded. All the patients in the present series had been selected for study on the grounds that they had been referred to a specialist gastroenterological unit and all previous investigations had failed to find a cause for their diarrhoea. The finding of 10 new cases of symptomatic bile acid malabsorption over a period of two years suggests that the condition is substantially more common than is generally believed. An accurate estimate of its prevalence or incidence cannot be obtained from our figures, but our findings imply an incidence greater than one per 100 000 of the adult population.

The difference in retention of SeHCAT on the two occasions on which it was measured in a patient with diarrhoea after vagotomy was consistent with the variation in faecal excretion of bile acids observed in this condition.<sup>20</sup> One of the patients with diarrhoea after vagotomy, in whom the proportion retained fell between the definitely normal (>15%) and definitely abnormal (<8%) limits, and two with idiopathic diarrhoea improved symptomatically with cholestyramine, but it proved impossible to achieve an acceptable balance between diarrhoea and constipation. Another patient with idiopathic diarrhoea, whose retention of SeHCAT was in the equivocal range, subsequently showed evidence of inflammatory bowel disease; two others, who did not respond to cholestyramine or Aludrox, had normal faecal bile acids. It is therefore likely that more than one factor is operating in such patients. There is some evidence that the efficiency with which bile acids are reabsorbed is influenced by the small intestinal transit time.

An isolated failure of the mucosal mechanism for transporting bile acids,<sup>7</sup> whether congenital or acquired, is probably the cause of malabsorption in a further subgroup. In other patients there may be some mucosal damage resulting in modest impairment of absorption. The bile salts undergo an enterohepatic circulation roughly five times each day, with at least a 95% probability of being reabsorbed on each recirculation. A decrease in the efficiency of recovery from 95% to 93% reduces the whole body retention at seven days by more than 50%, from 19% to 7%. The effect of recirculation is therefore to amplify small differences in the efficiency of recovery.

Hitherto the diagnosis of bile acid malabsorption has been difficult to establish. The SeHCAT retention test is simple to perform with readily available equipment,<sup>21 22</sup> is acceptable to both patients and staff, and gives a radiation dose comparable

with a single chest radiograph.<sup>23</sup> Bile acid malabsorption is a more common cause of important morbidity than is generally appreciated. It can be diagnosed easily and reliably by measuring the whole body retention of SeHCAT. Preliminary results in northern Sweden, where the diet has a higher fibre content than in Scotland, suggest that normal subjects there may retain less than 15% at seven days (Nyhlén, personal communication). The actual retention values are thus likely to vary in different populations and should be determined for each centre. We recommend that retention of SeHCAT should be measured routinely in patients with troublesome chronic diarrhoea for which no cause has been found.

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# Older women's attitudes towards breast disease, self examination, and screening facilities: implications for communication

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## Abstract

Qualitative research techniques were used in two studies in Edinburgh to explore older women's attitudes and motivations towards breast disease, self examination, and screening, with a view to identifying appropriate strategies for communication. The results indicated that knowledge of breast disease and screening facilities was poor and that many psychological and emotional issues inhibited self examination.

Increasing information about self examination and clinics is unlikely to influence uptake unless it is presented together with emotional support rather than through

conventional mass media channels. Such support may best be provided by setting breast screening within general health screening rather than emphasising the single disease.

## Introduction

Several studies have suggested that those women who do not take up opportunities for screening may be older and poorer than those who attend clinics offering screening services.<sup>1-3</sup> The same may be true for acceptance of self examination of the breasts, but uptake of screening or the practice of self examination seems likely also to depend on a woman's underlying motivations and attitudes towards breast disease. Most studies on these aspects have been carried out in women who already have some problem with their breasts.<sup>4,5</sup> We therefore thought that the relation between women's motivations and attitudes to breast disease, self examination, and screening facilities required further study, especially in relation to social class.

In exploring women's attitudes to topics as sensitive as breast cancer we thought that a qualitative research approach using group discussions might be most useful.<sup>6</sup> The technique derives from market research, doctors being either unfamiliar with it or sceptical about its relevance in medicine. It is now, however, well established in health education research, especially in Scotland,

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