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Idiopathic bile acid catharsis

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SUMMARY In the course of extensive routine screening for bile acid malabsorption a few patients were detected in whom chronic diarrhoea was apparently induced by excess bile acid loss which was neither associated with demonstrable conventional ileopathy nor with any other disorder allied to diarrhoea. In three patients subjected to scrutiny the results obtained were in harmony with a concept of idiopathic bile acid catharsis. Ingestion of cholestyramine was followed by immediate relief, but the diarrhoea recurred whenever this treatment was withdrawn. It is suggested that idiopathic bile acid catharsis should be suspected in patients with unexplained chronic diarrhoea and especially in those with a diagnosis of irritable colon with diarrhoea.

The distal ileum has the only intestinal active transport system for bile acid anions. Regardless of passive uptake of some bile acids from other parts of the gut, the ileal mechanism is critical for the intestinal bile acid reabsorption. The capacity of this system is quite large, but, even so, a minor fraction of the detergent molecules escapes normally into the colon where the dihydroxy bile acids in solution, and especially their free acids, inhibit absorption of sodium and water. If ileal absorption fails high concentrations of such bile acids may flood the colon to induce here net secretion of fluid and watery diarrhoea containing excess amounts of the detergent.

Until recently bile acid catharsis or cholerhoeic enteropathy has been described only as a sequel to ileal surgery or inflammatory disease. Lately, however, we have proposed that a similar syndrome may originate also from a functional ileal disorder (Thaysen and Pedersen, 1973; Thaysen and Pedersen, 1975). Presumptive evidence of the existence of that phenomenon was achieved upon the introduction of the ^{14}C cholylglycine breath test as a screening procedure for bile acid malabsorption (Fromm and Hofmann, 1971; Pedersen *et al.*, 1973). By now the assay combining measurement of breath and stool ^{14}C radioactivity has been applied to some 300 patients with gastrointestinal complaints and in particular to those with diarrhoea and/or steatorrhoea. In a few of them with chronic obscure diarrhoea the assay indicated bile acid malabsorption which was apparently not associated with any conventional ileopathy. As no other cause of the diarrhoea could be detected, primary bile acid catharsis was suspected, a view supported by the finding that the diarrhoea was abolished by long-term treatment with cholestyramine.

After our preliminary report on five patients with possible idiopathic bile acid malabsorption about 10 additional cases have added further presumptive evidence for the existence of that disorder. Even if this question is still in the balance, the application of this concept of an idiopathic bile acid catharsis has apparently been of benefit to some of our patients with seemingly incurable chronic diarrhoea. Consequently we have deemed it timely to draw attention again to this syndrome. In order, however, to make as strong a case as possible the present discussion will be restricted to the three most thoroughly examined patients.

Methods

For this study (Table 1) three patients (two women and one man) were selected according to the following criteria: chronic persistent monosymptomatic diarrhoea, bile acid malabsorption indicated by two different methods, no conventional ileopathy detected, relief from diarrhoea upon bile acid sequestration, recurrence of diarrhoea after discontinuance of this treatment, and on repeated examination rediscovery of bile acid malabsorption.

The examinations performed in each patient comprised a complete haemogram, sedimentation rate, determination of serum concentrations of creatinine, carbamide, electrolytes (including mag-

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Table 1 *Some data in three patients with chronic diarrhoea*

Patient	*Sex*	*Age (yr)*	*Weight (kg)*	*Duration of diarrhoea (yr)*	*Remarks*
LM	F	57	52	35	Migraine, ureterolithotomy performed (1949), eventually addicted to analgesics.
EH	M	35	89	15	Disabled for about five years, 3 m in mental hospital for diarrhoea, slight gastric hypochlorhydria, small intestinal transit ~60 min
IC	F	49	48	49	Urticaria, hay fever, migraine, small intestinal transit ~30 min

Table 2 *^{14}C cholylglycine tests and Schilling tests in patients studied*

Patient	*Cholestyramine ingestion (months follow up)*	*Breath maximal concentration of $^{14}CO_2$ (% $^{14}CO_2$/mmol CO_2)*	*Faeces 24hr ^{14}C excretion (% dose)*	*Schilling test (%)*
LM		0·21	19	15
	31*	0·82	12	
EH		0·30	18	22
	12	0·14	18	
IC		0·86	8	16
	6	0·76	13	
Reference values		<0·1	<8	⩾10

*The reexaminations were performed during cholestyramine withdrawal.

nesium and calcium), thyroxine, alkaline phosphatases, glutamic-pyruvic transaminase, prothrombin, serum protein electrophoresis, a Schilling test, oral tolerance tests with glucose, lactose, and D-xylose, measurements of gastric peak acid output, and of the pancreatic amylase and lipase output upon meal stimulation, a Widal test, examination of serum for antibodies against *Yersinia enterocolitica*, investigation of duodenal aspirates for *Giardia lamblia* parasites and bacterial overgrowth, of the stools for enteric pathogens, ova, blood, and daily fat excretion, and of the urine for 5 hydroxyindole acetic acid. Proctoscopy was performed. Rectal and duodenal mucosal biopsies were examined by light microscopy, and in the same specimens the pattern of the immunoglobulin-containing cells was evaluated (courtesy of Dr Jan Søltoft (Søltoft, 1973)). Furthermore, all the disaccharidases were measured in separate small gut biopsies (courtesy of Dr E. Gudmand-Høyer). The radiological examinations included a complete gastrointestinal series with special emphasis upon the terminal ileum, and a cholecystogram.

Screening for bile acid malabsorption was performed by means of the ^{14}C cholylglycine breath test as described by Fromm and Hofmann (1971) with minor modifications (Pedersen *et al.*, 1973). In the breath part of the assay the results were expressed as the individual maximum percentage of the administered dose exhaled as $^{14}CO_2$ at either two, four, or six hours after ingestion of the tracer. Similarly, the 24 hour faecal ^{14}C radioactivity was recorded in percentages of the dose administered (Table 2).

Kinetics and pool size of chenodeoxycholic acid were assessed by the isotope dilution technique as described previously by Pedersen and Arnfred (1975) (Table 3).

In one patient the faecal bile acid excretion was measured chemically by Miettinen (1973).

Table 3 *Kinetics of chenodeoxycholic acid (CDC) in the three patients studied*

Patient	*CDC half life (days)*	*CDC synthesis rate (mmol/24 h)*
LM	0·8	1·7
EH	1·1	1·6
IC	0·8	6·8
Controls (n = 10) Mean ± SD	3·0 ± 0·8	0·4 ± 0·2

CASE LM

She was a 57-year-old housewife, born 1915, with a history of almost continuous, usually watery diarrhoea over some 35 years. Since 1949 she had had frequent headaches diagnosed as migraine. In the same year an uncomplicated ureterolithotomy was performed. Between 1960 and 1968 she was admitted to hospital on several occasions, mainly for diarrhoea and abdominal discomfort. Thorough examinations revealed no specific cause of the diarrhoea and a diagnosis of irritable colon was made. The symptoms were refractory, however, to a number of anticholinergics, constipating drugs, sedatives, and various dietary regimens. In the ensuing years she professed to experience more severe abdominal colic associated with nausea, occasional vomiting, and frequent headaches. She became addicted to analgesics and at least twice each week

her doctor was summoned to administer injections of pethidine.

Upon admission to our unit in 1973 all medication was withdrawn. The diarrhoea continued as before. Transiently she developed rather severe symptoms of abstinence. Apart from this, her general physical condition was satisfactory. With some difficulty the extensive diagnostic programme was completed. The bile acid studies revealed an excess detergent loss (Tables 2 and 3), whereas the results of the many other investigations were normal. A tentative diagnosis of idiopathic bile acid catharsis was made and upon ingestion of cholestyramine the diarrhoea subsided overnight.

The next two years her bowel habits were normal under long-term treatment with 4 g questrane three times daily. Whenever the dose was reduced the diarrhoea reappeared within a couple of days. Apart from the bile sequestering agent she took no medicine. All her earlier complaints had vanished as had her neurosis. At the same time she managed single-handed to nurse her husband who had become severely disabled by rheumatoid arthritis. The patient was studied again when treatment had been discontinued for one week. Within a couple of days the watery diarrhoea recurred, but otherwise she was in excellent health. At the end of the week a ^{14}C cholylglycine test indicated bile acid malabsorption as before (Table 2), whereas the results of the routine laboratory examinations were within normal limits.

CASE EH

A 35-year-old male former butchery employee, born in 1938, had had a history of increasingly severe watery diarrhoea and abdominal colic over some 15 years. Between 1969 and 1971 these complaints resulted in three admissions to a medical department. Thorough examinations were negative and a diagnosis of colonic neurosis was made. Anticholinergics, constipating drugs including opiates, and an imposing array of sedatives were of no avail, however. He was discharged from his job at the butchery because of the diarrhoea that was often imperative and associated with incontinence. For the same reason he was unfit to continue his hobby as a fisherman. To all appearances he developed a severe neurosis and in 1972 he spent three months in a mental hospital on group therapy without achieving any relief. Nevertheless, on his discharge he was referred for outpatient psychotherapy. In addition, the medication continued as outlined above with some 20 tablets daily.

In 1974 he was admitted to our unit. All medication was withdrawn, but still he passed between eight and 12 watery stools per day. His physical condition was excellent, but he was emotional with deficient capacity to concentrate. Apart from slight hypochlorhydria (PAO: 8·5 mEq H^+/h) and a relatively rapid small intestinal transit time (a barium meal entered the caecum in 60 minutes) the conventional examinations disclosed no abnormality. On the other hand the bile acid studies revealed an excessive detergent loss (Tables 2 and 3). As a result of these investigations, idiopathic bile acid catharsis was suspected, and the diarrhoea and abdominal colic subsided promptly upon cholestyramine ingestion.

In the ensuing year he passed one solid stool each day on 4 g questrane three times daily. Almost immediately upon his discharge he had obtained employment in a machine factory where soon he became foreman for his colleagues. In his spare time he resumed fishing, and, apparently to make up for lost time in previous years, he often assisted as a bricklayer and a carpenter in the local community. At any rate he had a working day of some 16 hours.

After one year he was studied again when questrane medication had been discontinued for seven days. The watery diarrhoea had recurred within a few days. Apart from this, he was sound in mind and body. A ^{14}C cholylglycine test indicated bile acid waste, while the results of the routine laboratory examinations were satisfactory. Radiographic examination demonstrated a slightly slower small intestinal transit of a barium meal, which now entered the caecum after 120 minutes.

CASE IC

IC was a 49-year-old typist, born in 1925, who had a life-long history of watery diarrhoea. She had a family history of hypersensitivity disorders and in the patient this disposition had manifested itself in recurrent urticaria from early childhood, and in hay fever from puberty. In her 20s she developed migraine. As regards the diarrhoea her parents recalled that it was almost impossible to take the child out in a pram because of the vast numbers of napkins required. According to the patient she had continuously passed between eight and 15 watery stools daily. During infancy she was hospitalised once and in 1963 she was referred to our unit. On both occasions trials with elimination diets failed to improve her bowel habits. The cause of the diarrhoea was not revealed and treatment with constipating drugs and anticholinergics was unsuccessful.

In 1974 she was readmitted to our unit. She had never experienced any specific alimentary intolerance. She was in perfect health, except for the distressing diarrhoea and occasional migraine. Ergotamine and analgesic tablets were taken infre-

quently. Her general physical condition was excellent. Among the conventional examinations a few may be pertinent. A slight blood eosinophilia was demonstrated. The duodenal biopsy contained a few eosinophils, whereas none was found in the rectal biopsies. The pattern of the immuno-globulin-containing cells was normal in the intestinal mucosal specimens. On radiographic examination a barium meal had entered the descending colon within 30 minutes. The stools became discoloured four hours after ingestion of carmine.

The ^{14}C cholylglycine test was associated with a marked pathological breath $^{14}CO_2$, whereas the 24 h ^{14}C faecal radioactivity was within normal limits (Table 2). However, a direct measurement of the faecal bile acids over three days (by courtesy of Professor T. Miettinen) demonstrated an excess bile acid loss of 791 mg per day (normally 238 mg $\pm$ 25 mg/24 h (Miettinen, 1973)). In addition, the bile acid waste was substantiated by means of the isotope dilution technique (Table 3). Upon cholestyramine ingestion her bowel habits became normal for the first time in her life.

The patient was reexamined about six months later. On 2 g questrane three times daily she had two to three soft stools in the morning. She had no faecal incontinence and her abdominal discomfort had vanished. Her allergic disorders and the migraine were unchanged. Bile acid sequestration was discontinued for one week. In a few days the diarrhoea recurred and at the end of the week a ^{14}C cholylglycine test indicated bile acid malabsorption (Table 2). During cholestyramine treatment repeated radiography revealed an unchanged rapid small gut transit of a barium meal, whereas the colonic transit rate was markedly reduced.

Discussion

In the three patients with chronic diarrhoea the results that were achieved suggest bile acid malabsorption in the absence of conventional ileopathy. Of course, these findings must be assessed carefully before the concept of idiopathic bile acid catharsis can be considered and, furthermore, it is almost equally important to eliminate other possible causes of the diarrhoea.

EXPLORATION OF THE CAUSE OF THE DIARRHOEA

This would be an even more formidable task were it not for the facts that the diarrhoea was monosymptomatic, that the watery evacuations indicated osmotic or secretory diarrhoea, and that the outcome of the majority of the investigations that were carried out was normal.

As regards osmotic diarrhoea the disaccharidase deficiencies, glucose-galactose malabsorption, and the local and general immune deficiency states could be ruled out. The usual parasitic diseases occurring in Scandinavia were not detected. Intestinal histopathological lesions were neither visualised radiographically nor registered in the biopsies obtained.

As to secretory diarrhoea the examinations suggest bile acid malabsorption. Congenital chloridorrhoea, another ileal anion transport defect, was ruled out by the demonstration of normal urinary chloride excretion. Enteric infections can be disregarded as can the contaminated small bowel syndrome. The examinations did not visualise villous adenomas which may result in secretory diarrhoea when located in the distal colon.

Regardless of its cause, the diarrhoea associated with endocrine dysfunction is often watery. No endocrinopathy was detected, however, and specifically gastrinoma and carcinoidosis can be disregarded. Strong circumstantial evidence suggests that the same applies to vipoma and medullary carcinoma of the thyroid gland.

Reference should be made to the examinations listed in the Methods section, as most of them have not been discussed specifically in this brief survey. If anything, the above discussion may help to focus attention on colonic bile acid overloading and the terminal ileum.

DEMONSTRATION OF BILE ACID MALABSORPTION

In the ^{14}C cholylglycine test applied as a screening procedure the label is in the carboxyl carbon of the glycine moiety. The test is essentially an assay of bile acid deconjugation, as the labelled glycine upon liberation will be oxidised to $^{14}CO_2$ that can be measured in breath. Increased breath radioactivity means increased exposure to deconjugating bacteria which, in turn, indicates either bacterial proliferation in the small gut or bile acid malabsorption. By itself the breath test gives no information on the intestinal site of deconjugation. This problem can be solved by a simultaneous assessment of faecal ^{14}C radioactivity as an increased loss of the label in the stool features bile acid malabsorption exclusively. In two of the three patients from the present study the ^{14}C cholylglycine test indicated bile acid malabsorption, whereas in the third patient (IC) the outcome of the test was ambiguous with an abnormal breath and a normal stool radioactivity (Table 2). This result was probably caused by insufficient stool collection. At any rate, she had an excess faecal loss of ^{14}C when examined again some six months later and, more important, a chemical examination demonstrated an increased faecal bile

acid excretion during her first admission. In our experience the ^{14}C cholylglycine test is a specific, though perhaps not very sensitive, assay of bile acid malabsorption (Pedersen *et al.*, 1973). As it is a relatively new test we have chosen additionally to assess indirectly the efficiency of bile acid absorption by means of the isotope dilution technique. In all three patients this method disclosed a decreased half-life and an enhanced rate of synthesis of the bile acid investigated indicating a rather substantial bile acid loss (Table 3). We therefore think that in our three patients the occurrence of bile acid malabsorption has been established beyond reasonable doubt.

TERMINAL ILEUM

According to strong circumstantial evidence a conventional ileopathy can be disregarded in the three patients. In particular, it seems impossible to reconcile a diagnosis of chronic inflammatory involvement of the ileum with the maintenance of perfect physical condition throughout at least 15 years, with the radiographic visualisation of a regular intestinal mucosal pattern, and to some extent with the preservation of a normal vitamin B_{12} absorption (Schilling test).

In the absence of overt ileal disease the cause of the bile acid malabsorption is a matter of conjecture. Bile acids can escape ileal absorption when either precipitated or adsorbed to bacteria, dietary residue, or sequestrants, but in this situation they will at most display a rather mild laxative action in the colon. Consequently, the actual catharsis must be due to gross malabsorption of bile acids in solution and, as far as can be seen, this leaves for consideration two main factors: the possibility of contact between bile acids and the absorptive epithelium and the properties of the absorptive mechanism itself.

It is still disputed whether the intestinal transit rate can be a limiting factor in bile acid absorption. The problem has been approached by Meihoff and Kern (1968) who observed bile acid loss in healthy volunteers with mannitol-induced diarrhoea. Later Thaysen (1977) registered a similar detergent waste in two out of eight patients with lactose malabsorption. Even if patient I.C. had no osmotic diarrhoea it is quite conceivable that her extremely rapid small gut transit prevented the bile acids from being absorbed properly. The same cannot apply, however, to patient L.M. who had a completely normal transit. This finding may even exclude in her the presence of ileocaecal sphincter incompetence—an elusive phenomenon which has been thought to allow too rapid transit through the terminal ileum and so lead to bile acid malabsorption.

It must be underlined that the cells possessing the ability to transport bile acid anions have not been identified and that our knowledge of their function is almost non-existent. Nevertheless, it may be mentioned that the hypothesis of a relative lack of ileal transport sites for bile acid anions has been advanced by Small *et al.* (1974) as a possible cause of bile acid malabsorption. Furthermore, support for this theory may be derived from actual experience gained in association with the attempts to dissolve gallstones by oral ingestion of highly purified chenodeoxycholic acid. Some patients develop diarrhoea on 0·5 g of this compound daily, whereas others tolerate 4 g or more per day. If the onset of diarrhoea reflects the maximum absorptive capacity of the ileum, this property is apparently subject to wide individual variation. In this respect our patients might then represent a negative selection.

It should be emphasised not only that bile acid sequestration is helpful, but also that the original symptoms recur whenever the medication is withdrawn.

In our unit, which serves a population of about 200 000, we have diagnosed idiopathic bile acid catharsis in 12 more patients over the last three years. They were detected among 68 patients referred to us for irritable colon, colonic neurosis, or suspected allergic diarrhoea. Earlier, but without examining the faecal bile acids, Schapiro *et al.* (1970) have obtained relief from chronic non-specific diarrhoea by cholestyramine therapy in five out of 12 patients.

Since cholestyramine is not quite innocuous and since it may be a matter of lifelong treatment we think this agent should be given only to those patients in whom bile acid malabsorption is confirmed.

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