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TREATMENT OF PRURITUS OF OBSTRUCTIVE JAUNDICE WITH CHOLESTYRAMINE

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Retained bile salts have for long been incriminated as the cause of the severe itching suffered by patients with obstructive jaundice. However, even using modern biochemical methods, a good correlation has not been shown between blood bile-salt levels and pruritus (Carey, 1958 ; Osborn *et al.*, 1959). In 1947 Varco noted that pruritus could be relieved in patients with partial biliary obstruction by intermittent external biliary drainage. This effect was presumably by preventing the little bile that could be excreted from being reabsorbed ; the enterohepatic circulation was thus broken. The resin cholestyramine is said to bind bile salts in the intestine, so eliminating them in the faeces (Fig. 1) (Carey, 1960 ; Carey and Williams, 1961 ; Van Itallie *et al.*, 1961), and has been shown to stop the itching of obstructive jaundice (Carey and Williams, 1961). The present work reports the use of this material in 10 patients with pruritus due to obstructive jaundice ; in addition to serum lipid fractions, faecal fat has been estimated.

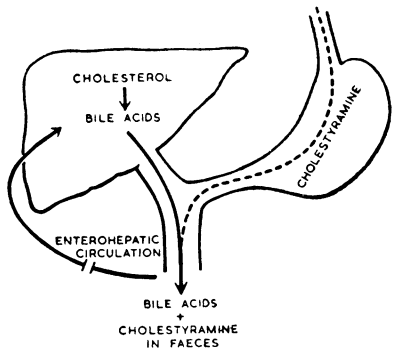

FIG. 1.—Diagram showing the postulated mechanism by which cholestyramine removes bile acid in faeces, so blocking their enterohepatic circulation.

Material and Methods

The 10 patients treated were suffering from chronic obstructive jaundice (nine from primary biliary cirrhosis and one from congenital intrahepatic atresia) of at least one and half years' duration and were in a steady clinical state. All the patients were spontaneously complaining of itching, and scratch marks were present on the skin. The itching was graded clinically as mild, moderate, or severe. During the study the patients received a constant dietary intake of fat, carbohydrate, and protein.

Blood samples were obtained fasting and analyses were done in duplicate. Serum was analysed by the following methods: bile acids (Carey, 1958), cholesterol (Sperry and Webb, 1950), phospholipid (Allen, 1940), total lipids (Albrink, 1959). Triglycerides were calculated by subtracting phospholipids and cholesterol esters from the total lipids. Serum bilirubin and other routine liver-

function tests were determined by standard procedures (King and Wootton, 1959).

Faeces were analysed by the following methods: fat (Van de Kamer *et al.*, 1949), neutral sterols (Abell *et al.*, 1952), and bile acids (Lewis, 1957).

Procedure.—A placebo of 10 g. of bland potato powder flavoured with lemon or orange juice was given daily in three doses for one to four weeks and then, without the patient's knowledge, replaced by cholestyramine powder flavoured similarly in a dose of 10 g. daily (eight patients) or 6.6 g. daily (two patients). A dose of 1.7 g./day was tried for 11 days in Case 3. Cases 3 and 7 received 3 g./day in the form of tablets each containing 750 mg. In Cases 1, 3, 4, and 5 the resin was again replaced by the placebo, and then after 15 to 41 days the resin was reintroduced. In Cases 1–9 the resin was continued for 3 to 20 weeks. All the patients received regular intramuscular injections of vitamins A, D, and K.

General Effects

In Cases 1–8 (Table I) relief of itching started after four to seven days of resin treatment and was complete in 4 to 11 days. These patients were relieved for as long as the resin was continued. This was for three to seven weeks in Cases 1, 2, 7, and 8; 9 to 14 weeks in Cases 4, 5, and 6; and 20 weeks in Case 3. In Cases 9 and 10 itching was not relieved. One patient (Case 10) complained of abdominal discomfort, anorexia, and choking in the throat and refused to continue the resin powder after the first day's treatment. One patient (Case 9) was treated with 10 g. daily for 47 days, but itching was not relieved; she complained of difficulty in swallowing the material and of nausea afterwards. This patient was deeply jaundiced and stercobilinogen was not present in two three-day specimens of faeces; itching was then relieved within seven days by norethandrolone ("nilevar") (30 mg. daily) although jaundice deepened.

In the child patient (Case 3) an attempt was made to determine the minimum effective dose of resin: 1.7 g. daily proved too small, but 3.3 g. daily controlled pruritus for 20 weeks.

In Cases 1–5 the resin was again replaced by a placebo and pruritus reappeared in 7 to 11 days.

In addition to Cases 9 and 10, gastro-intestinal disturbances were complained of by three others (Cases 2, 3, and 6). Diarrhoea was experienced by two patients (Cases 2 and 3) who received 6.6 g. resin daily. One patient (Case 6) complained of constipation. Minor degrees of nausea and reluctance to take the medicine were in fact noticed by most of the patients. One patient (Case 2) complained particularly of difficulty in swallowing the powder.

Biochemical Changes

Serum bile-acid levels fell (Table II) in Cases 1, 2, and 3 within two to seven days of starting therapy. The fall preceded relief of itching. The decrease in Cases 2 and 3 was mainly in trihydroxy bile acids, and in Case 1 the dihydroxy bile acids mainly decreased. These changes resulted in a fall of the ratio of trihydroxy to dihydroxy bile acids in Cases 2 and 3 and a rise in Case 1. In Case 4, after 45 days, the serum total bile-acid level rose slightly and the ratio increased. In Case 9 the itching was not relieved, and serum bile acids did not change. In Case 1 the serum total bile acid rose to pretreatment levels when the resin was stopped, falling again when the material was again administered.

Serum bilirubin level showed a rise of more than 2 mg./100 ml. in two, a fall of more than 2 mg./100 ml. in two, and in the others there was no significant change.

Total serum lipid (Table II) fell significantly in Cases 1 and 3 and showed no significant change in Case 2.

Phospholipids fell significantly in Cases 1 and 2 and showed insignificant changes in Case 3.

Serum triglycerides fell in Cases 1 and 3 and rose in Case 2.

Serum total cholesterol level (Table I) showed a variable change; in Case 1 the value fell 24.7%, while the fall in Cases 2, 3, and 7 was 20%. In Cases 4, 5, 6, and 8 the fall was less than 15% and probably insignificant; in Case 9 a rise was noted. Where a fall occurred it was usually in the free value; the cholesterol esters

TABLE I.—*Clinical and Biochemical Data in* 10 *Patients with Chronic Intrahepatic Obstructive Jaundice*

Case No.	Age and Sex	Duration of Itching (Years)	Cholestyramine (g./Day)	Days to Relief of Itching	Serum Bilirubin* (mg./100 ml.)		Serum Cholesterol* (mg./100 ml.)					
							Total		Free		Esters	
					Initial	During Therapy	Initial	During Therapy	Initial	During Therapy	Initial	During Therapy
1	55 F	7	6·6–10	10	13·7	15·3	450	339	355	251	95	88
2	79 F	7	6·6	8	19·0	22·9	621	497	496	404	125	93
3	9 M	7	1·7–6·6	10	3·1	3·2	309	249	122	78	187	171
4	50 F	14	10	4	33·3	19·2	754	723	560	535	194	188
5	42 F	2	10	9	35·1	36·1	802	726	687	582	115	144
6	70 F	6	10	5	14·8	16·4	547	473	424	367	123	106
7	53 F	3	10	6	5·2	5·2	391	314	164	123	227	191
8	39 F	1¼	10	11	8·5	11·7	1,791	1,582	1,608	1,369	183	213
9	41 F	1½	10	0	20·9	18·9	1,478	1,643	1,347	1,478	131	165
10	54 F	8	10	0	36·7	—		—	—	—	—	—

* Mean of 3–9 values during control period of 7–30 days and mean of 3–13 values during resin therapy of 15–60 days.

TABLE II.—*Changes in Serum Bile Acid and Lipids During Cholestyramine Therapy*

Case No.	Serum Bile Acids* (μg./ml.)								Total Lipids† (mg./100 ml.)		Phospholipid† (mg./100 ml.)		Triglycerides† (mg./100 ml.)	
	Trihydroxy		Dihydroxy		Total		Ratio							
	Before	During Therapy	Before	During Therapy	Before	During Therapy	Before	During Therapy	Before	During Therapy	Before	During Therapy	Before	During Therapy
1	24·2	16·2	16·5	5·2	40·7	21·4	1·5	3·1	1,027	752	550·3	488·9	380·7	161·6
2	57·0	21·6	15·9	17·0	72·9	38·6	3·6	1·3	1,041	1,011	690	585	192	336
3	13·9	5·3	6·9	4·7	20·8	10·0	2·0	1·1	1,409	1,208	470	438	761	608
4	10·1	14·8	22·8	19·2	32·9	34·0	0·44	0·77	—	—	—	—	—	—
9	35·2	36·1	8·5	9·6	43·7	45·7	4·1	3·9	—	—	—	—	—	—

* Mean of 2–3 values during control period of 7–16 days and mean of 3–7 values during resin therapy of 15–50 days.
† Mean of 3–4 values during control period of 7–16 days and mean of 4 values during resin therapy of 15–50 days.

showed a variable change. When the drug was continued the cholesterol lowering was maintained in Cases 1, 2, 3, 6, 7, and 8. In Cases 4 and 5 the administration was associated with an initial fall followed by a rise to the pre-treatment levels as the drug was continued in spite of relief of itching.

Faecal bile-acid output measured in one patient (Case 3) rose from a mean of 81 mg./day during the 10-day control period to 364 mg./day during 54 days of resin therapy.

Faecal neutral sterol was estimated in Case 3 and showed a rise from the mean control value of 236 mg./day to 498 mg./day during resin therapy.

Faecal fat analysis was done in Cases 1 to 5 (Table III). During the control period Cases 1, 3, 4, and 5 had mild steatorrhoea and in Case 2 the steatorrhoea was severe. Cases 1, 4, and 5 showed only slight elevations of faecal fat, but in Cases 2 and 3, including the one with the pretreatment gross steatorrhoea, the increase during treatment was marked. These two patients complained of severe diarrhoea. When the resin was withheld faecal fat decreased towards control values.

TABLE III.—*Effect of Cholestyramine on Daily Mean Faecal Fat Excretion in Five Subjects Maintained on Constant Fat Intake*

Case No.	Dose g./Day	Before*	During†	After‡
1	10	8·9	10·7	7·4
2	6·6	19·7	33·4	20·9
3	6·6	10·4	17·8	—
4	10	8·5	9·3	7·0
5	10	8·9	9·9	7·0

* Mean of 6–27 days before therapy. † Mean of 15–49 days during resin therapy. ‡ Mean of 6–9 days after resin therapy.

Case Reports

Case 1.—A 55-year-old housewife with primary biliary cirrhosis had suffered intolerable itching for seven years. Examination showed jaundice, scratch marks, xanthelasma, and hepatosplenomegaly. A 10-g. placebo was given for eight days and itching was unchanged. This was followed by cholestyramine 10 g. daily, and within 10 days pruritus had ceased (Fig. 2). Serum total bile acids, lipids, triglycerides, and total and free cholesterol levels fell. Serum phospholipids fell slightly; cholesterol esters and bilirubin did not change appreciably. Total faecal fat output showed a slight increase. After 16 days' treatment the placebo was again given and itching returned in 10 days. Serum bile acids and total lipids rose; the cholesterol fraction did not change. The resin has been continued for four weeks with maintenance of relief of pruritus.

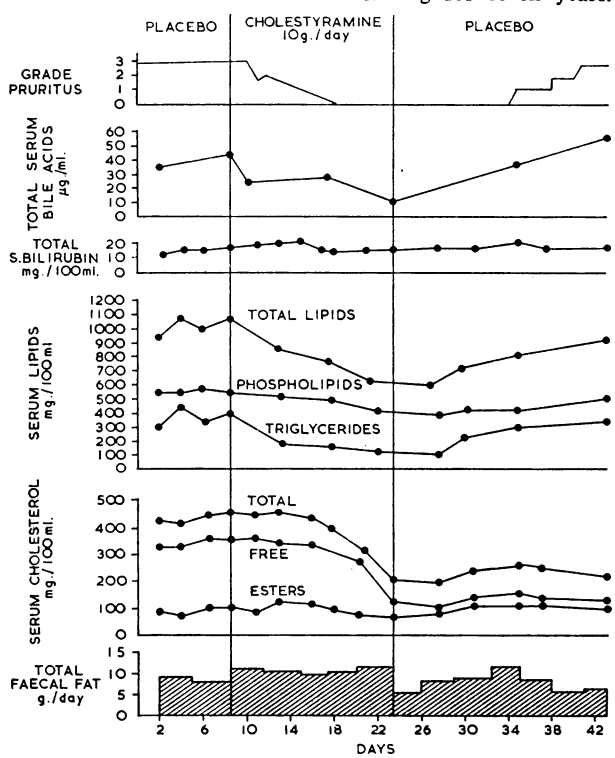

FIG. 2.—Effect of cholestyramine in Case 1, showing fall in serum bile acids and lipid levels; serum cholesterol ester values did not change. Patient was relieved of pruritus in 10 days. Withdrawal of resin resulted in return of pruritus and rise in serum bile acid level.

Case 2.—A 9-year-old boy with chronic intrahepatic biliary atresia was admitted to hospital for relief of pruritus, which had made him miserable since he was 18 months of age. Examination showed a child of average build, scratch marks on the body, and hepatomegaly. The urine showed urobilinogen and the faeces contained stercobilinogen. The placebo was given for 12 days with no relief of itching. Cholestyramine 6.6 g./day was then given, and by the fifth day itching had lessened, totally disappearing by the tenth day of therapy (Fig. 3). His general health improved and the skin became softer. Resin administration resulted in a fall in total serum bile acids, lipids, triglycerides, and total and free cholesterol levels. Serum total bilirubin, phospholipids, and ester cholesterol were virtually unchanged. Faecal bile acids and neutral sterols increased. Steatorrhoea increased after about 10 days' therapy. An attempt was made to find the minimum dose of resin required to relieve itching. Pruritus returned on a dose of 1.7 g./day but again disappeared when the dose was increased to 3.3 g./day. After 54 days' therapy the placebo was substituted for the resin and itching returned within 11 days. Serum bile acids,

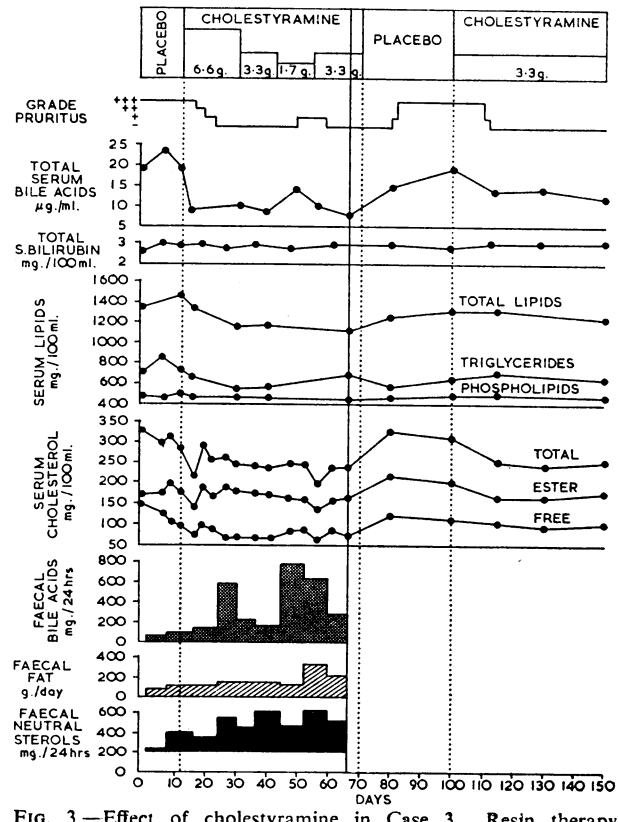

FIG. 3.—Effect of cholestyramine in Case 3. Resin therapy resulted in a fall in total serum bile acid lipids, triglycerides, and total and free cholesterol levels, and increase in faecal bile acid, neutral sterol, and fat excretion. Patient was relieved of pruritus in 10 days. Withdrawal of resin resulted in return of pruritus and exacerbation of hyperlipidaemia and bile-acid retention. Refeeding the resin tended to repeat the previous change. Patient was maintained free of pruritus for 20 weeks by 3.3 g. of resin a day.

lipids, and total, ester, and free cholesterol rose. He was again given the resin in a dose of 3.3 g./day, and has been maintained free of pruritus for 20 weeks.

Discussion

Cholestyramine provided effective control of itching in 8 out of 10 patients with chronic obstructive jaundice. In one of the failures the patient did not take the drug for a sufficient length of time. The other was very deeply jaundiced and the absence of stercobilinogen in the faeces suggests that biliary obstruction is complete. Failures have previously been reported in patients in whom no bile reaches the intestine (Carey and Williams, 1961). The effective maintenance dose seems to be about 6 g. daily, against the 10–15 g. previously employed (Van Itallie *et al.*, 1961; Carey and Williams, 1961), although 10 g. may be necessary initially in the severe case. The powder is not easy to take even when heavily flavoured. Patients will, however, usually accept the discomfort in return for the remarkable relief from the distressing itching. The introduction of chocolate-flavoured tablets should obviate this difficulty, although, as each tablet contains only 750 mg., at least eight will have to be taken daily for a therapeutic dose.

Hitherto the most effective treatment of itching in obstructive jaundice has been either methyltestosterone (Lloyd-Thomas and Sherlock, 1952) or norethandrolone (Sherlock, 1959). These drugs constantly deepen obstructive jaundice and cause bromsulphthalein retention and occasionally icterus in normal subjects (Foss and Simpson, 1959; Kory *et al.*, 1959). Cholestyramine has the advantage of not increasing jaundice by this undesirable cholestatic effect.

Cholestyramine is a strongly basic anion-exchange resin which forms an unabsorbable complex with bile acid in the intestine. The enterohepatic circulation is broken and we have confirmed that it increases the faecal bile-acid output (Carey, 1960; Carey and Williams, 1961; Van Itallie *et al.*, 1961). Serum bile-acid levels would be expected to fall (Tennent *et al.*, 1960; Carey and Williams, 1961), and this was usually the case, the decrease being more pronounced in the trihydroxy (cholic) acid level. As might be expected, the patient with no relief of itching showed no change in serum bile-acid levels, for presumably no bile acids were reaching the intestine. It was surprising that in one other patient, who was relieved, serum bile acids also did not alter. This is unexplained, but serum levels only were being measured, the total bile acid content of the body being unknown. It must be emphasized that methods of estimating bile acids in serum and faeces are difficult and the results reported reflect trends rather than absolute amounts.

Bile acids are final products of cholesterol degradation and their rate of formation is governed in part by reabsorption of bile acids from the small intestine (Bergström and Danielsson, 1958). Cholestyramine might be expected to increase bile-acid turnover, but this has not yet been measured. A cholesterol-lowering effect was anticipated and seen in some cases, but this was not constant. In two patients the effect on serum cholesterol seemed to "escape" as the drug was continued.

The results reported might be used as strong evidence that bile-salt retention is responsible for the pruritus of obstructive jaundice. However, the resin might well act in some way other than by removing bile acids. Serum lipids usually fall (Visintine *et al.*, 1961) and the faecal steroid output increases. The relief of pruritus might be an indirect effect of the changes in bile-acid metabolism. Another substance, possibly of steroid nature and capable of causing pruritus, might also be removed from the body.

Bile acids are used for the emulsification and absorption of dietary fat, and the increased losses of faecal fat are therefore not surprising. This has previously been reported even in normal subjects given cholestyramine (Hashim *et al.*, 1961). The dose should therefore be the smallest that controls pruritus.

Hypoprothrombinaemia, due to failure to absorb vitamin K (Visintine *et al.*, 1961), has been noted. The fat-soluble vitamins A, D, and K should therefore be given by intramuscular injections at two-weekly intervals while the resin is being administered.

Summary

In 8 out of 10 patients with chronic obstructive jaundice pruritus was relieved in 4 to 11 days by 6.6–10 g. of cholestyramine, a resin which binds bile salts in the intestine. One patient who was unrelieved took the drug for too short a time; the other probably had total biliary obstruction. Depth of jaundice was not constantly affected.

In six patients the drug was continued and relief was maintained for 9 to 20 weeks.

Serum bile acids usually fell. In one patient who was relieved of itching and one with total biliary obstruction who was not, the serum bile-acid levels rose slightly. Faecal bile-acid output increased in one patient. Serum cholesterol values showed variable changes, usually falling but sometimes returning to the original level even though treatment was continued.

Output of faecal fat increased, especially in those who initially showed severe steatorrhoea.

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