Gut, 1979, **20**, 312-317

Clinical trial

Rowachol — a possible treatment for cholesterol gallstones[1]

J. DORAN, M. R. B. KEIGHLEY, AND G. D. BELL

From the University Department of Therapeutics, City Hospital, Nottingham, and the University Department of Surgery, General Hospital, Birmingham

SUMMARY It has been claimed that Rowachol, a proprietary choleretic, is occasionally successful in the treatment of gallstones. In gallstone patients we have examined its effect on the lipid composition of (1) samples of fasting gall bladder bile obtained at the time of cholecystectomy, and (2) T-tube bile on the tenth post-operative day. In a dose of two capsules, three times a day for only 48 hours, Rowachol significantly lowered the cholesterol solubility of both gall bladder ($P < 0.001$) and T-tube bile ($P < 0.05$). Rowachol in a dose of one capsule three times a day for 48 hours did not alter bile composition, while four capsules four times a day for a similar period caused a significant ($P < 0.05$) deterioration in biliary lipid composition. The possible mechanisms of action of Rowachol and their therapeutic implications are discussed.

The bile of patients with cholesterol gallstones is frequently saturated with cholesterol (Admirand and Small, 1968). It has been shown that chenodeoxycholic acid (CDCA) enhances the cholesterol solubility of human bile and in suitable patients promotes dissolution of cholesterol gallstones (Bell *et al.*, 1972; Danzinger *et al.*, 1972; Thistle and Hofmann, 1973; Iser *et al.*, 1975; Thistle *et al.*, 1978). One of the major disadvantages of CDCA therapy is the fact that the patient with large gallstones (greater than 1 cm in diameter) may need to take the drug for several years before successful dissolution is observed radiologically (Dowling, 1977). Several possible adjuncts to CDCA therapy have been suggested including phenobarbitone (Coyne *et al.*, 1975), β sitosterol (Gerolami and Sarles, 1975; Maudgal *et al.*, 1977; Begemann *et al.*, 1978; Thistle *et al.*, 1978), choline (Thistle *et al.*, 1978), and a low cholesterol diet (Maudgal *et al.*, 1977). None of these 'adjuvants' has yet been shown actually to accelerate the speed of gallstone dissolution (Thistle *et al.*, 1978) and so the search for safe and effective alternatives and/or adjuvants to CDCA continues.

Rowachol[2] is a proprietary choleretic consisting of six cyclic monoterpenes (Fig. 1), all derived from purified plant essential oils—for example, l-menthol from *Mentha piperidis*, the peppermint plant or l-cineol from eucalyptus leaves. This particular combination of terpenes was chosen by the manufacturer because, in the rat, it was shown to have a larger and more sustained choleretic effect than equimolar quantities of any of its individual constituents (Mörsdorf, 1966). This agent has been extensively marketed in Europe for over 25 years, and is freely available on prescription in the United Kingdom. There have been a number of papers in the German (Blumenberg, 1957), Japanese (Kameda, 1960; Okabe, 1960; Noda *et al.*, 1965), and English (Hordinsky, 1971, 1973) literature reporting that prolonged courses of Rowachol treatment have resulted in successful dissolution of patients' gallstones. In the above papers the only reported side-effect was of a peppermint or camphor taste after eructation. Since this preparation seemed, therefore, to be substantially free from side-effects, we felt that any claims of efficacy deserved careful consideration. Several of the terpenes in Rowachol—for example, menthol, menthone, pinene—have long been shown to be excellent cholesterol solvents *in vitro*, and indeed the structurally related terpene, d-limonene, has recently been advocated as an agent for dissolving retained common duct stones (Igimi *et al.*, 1976). However, it is unlikely that significant amounts of these compounds appear in bile because of their relatively low molecular weight (Smith, 1973). Previous studies in the rat (Mörsdorf and Wolf, 1966; Kodama *et al.*, 1976) and dog (Kodama

[1]Presented in part at the York Meeting of the British Society of Gastroenterology, September 1977 (*Gut* (1977) **18**, A.977).

[2]Rowa Ltd, Bantry, Co. Cork, Eire.

Received for publication 2 November 1978

Gut: first published as 10.1136/gut.20.4.312 on 1 April 1979. Downloaded from http://gut.bmj.com/ on 19 April 2018 by guest. Protected by copyright.

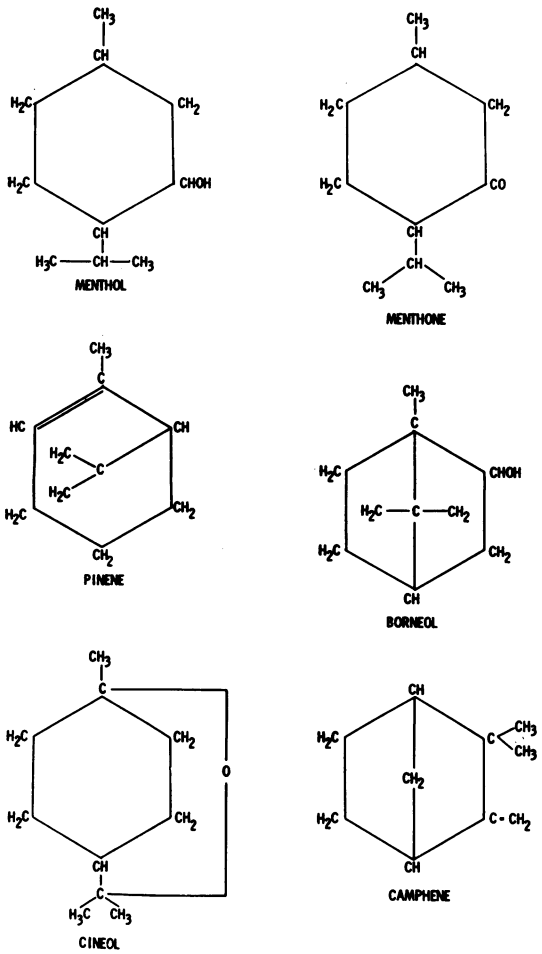

Fig. 1 *Chemical formulae of terpenes in Rowachol—menthol 32%, menthone 6%, pinene 17%, borneol 5%, cineol 2%, camphene 5%, made up to 100% with olive oil. Each capsule contains 0·1 ml of liquid.*

et al., 1976) have shown that a number of cyclical monoterpenes and their metabolites can affect bile flow and biliary lipid composition. We argued that any cholelitholytic effect that Rowachol might have in man was also likely to be mediated by induced alterations in the lipid composition of bile. We therefore studied the effect of orally administered Rowachol on bile salt, phospholipids, and cholesterol output in T-tube bile and the resultant changes in the cholesterol solubilising capacity of gall bladder bile.

Methods

EFFECT OF ROWACHOL ON BILIARY LIPID SECRETION

Nineteen patients were studied. All had undergone cholecystectomy and exploration of the common bile duct for gallstones with insertion of a T-tube. Between the sixth and eighth postoperative days a T-tube cholangiogram was performed and found to be normal before the T-tube was clamped to restore the enterohepatic circulation of bile salts. Eight patients (age 51·4 years ± SEM 4·9; range 22-66 years; weighing 61·3 kg ± 2·0, range 53-70 kg) then received Rowachol by mouth at a dose of two capsules tds (each capsule contains 32 mg menthol, 17 mg pinene, 6 mg menthone, 5 mg each of borneol and camphene and 2 mg cineole). The other 11 patients (age 50·1 years ± 5·5, range 25-70 years; weight 61·0 kg ± 2·5, range 46-71 kg) acted as controls. In all cases the patients' gallstones appeared to be of predominantly cholesterol type, but chemical analysis was not performed. After 48 hours the T-tube was unclamped and bile collected by gravity drainage. Bile was collected into graduated tubes at 10-minute intervals for 140 minutes, bile flow was recorded and the samples were stored at −20°C for later analysis of biliary lipid content. We decided to collect bile for a total of 140 minutes in the present study so that we could compare the results obtained with those previously reported when ioglycamide was infused intravenously for 120 minutes after a 20 minute baseline period of observation (Bell *et al.*, 1978a).

EFFECT OF ROWACHOL ON GALL BLADDER BILE COMPOSITION

Forty-nine patients undergoing elective cholecystectomy were studied. All had radiolucent stones in functioning gall bladders. Twenty received no medication before surgery and acted as controls, while the other 29 were given Rowachol for 48 hours before operation. Three different doses of Rowachol were used--one capsule tds (nine patients); two capsules tds (12 patients); and four capsules qds (eight patients). The groups were not formally matched, but were comparable for age, weight, and sex distribution. Gall bladder bile was obtained by needle aspiration at the time of operation.

ANALYSIS OF BILE SAMPLES

Biliary bile acid concentration was measured enzymatically using 3αhydroxysteroid dehydrogenase (Talalay, 1960). Phospholipids were determined using the method of Bartlett (1959), while cholesterol was assayed using a modification of the method of Carr and Drekter (1956) after lipid

Gut: first published as 10.1136/gut.20.4.312 on 1 April 1979. Downloaded from http://gut.bmj.com/ on 19 April 2018 by guest. Protected by copyright.

extraction with chloroform:methanol (2:1 V/V). The cholesterol saturation index (CSI) was calculated using the equation devised by Thomas and Hofmann (1973) based on the limits of cholesterol solubility as defined by Hegardt and Dam (1971).

STATISTICAL ANALYSIS

The statistical significance of differences between the results was assessed using Student's unpaired *t* test.

Results

EFFECT OF ROWACHOL ON BILIARY LIPID SECRETION

Rowachol in a dose of two capsules tds for 48 hours did not influence bile flow (Table). The rates of secretion of bile salts. phospholipids, and cholesterol in the T-tube patients on and off Rowachol is shown in the Table. Numerically, bile salt and phospholipid secretion were enhanced, while cholesterol output was slightly depressed, but the difference between the treated and control groups was not statistically significant.

The mean cholesterol saturation index of T-tube bile in the two groups is plotted graphically in Fig. 2. During the first hour of collection the bile from the treated patients was significantly less saturated with cholesterol than was the bile from the controls. After 60 minutes the bile from both groups began to be more saturated, as the bile salt pool was being depleted, and the differences between the groups were no longer as marked.

EFFECT OF ROWACHOL ON COMPOSITION OF GALL BLADDER BILE

Figure 3 shows that the effect of Rowachol on the composition of gall bladder bile varies with the dose given. The mean cholesterol saturation index (± SEM) for the controls was 1·313 ± 0·080 and for patients receiving the lowest dose of Rowachol was 1·426 ± 0·105 (P = NS). However, in patients

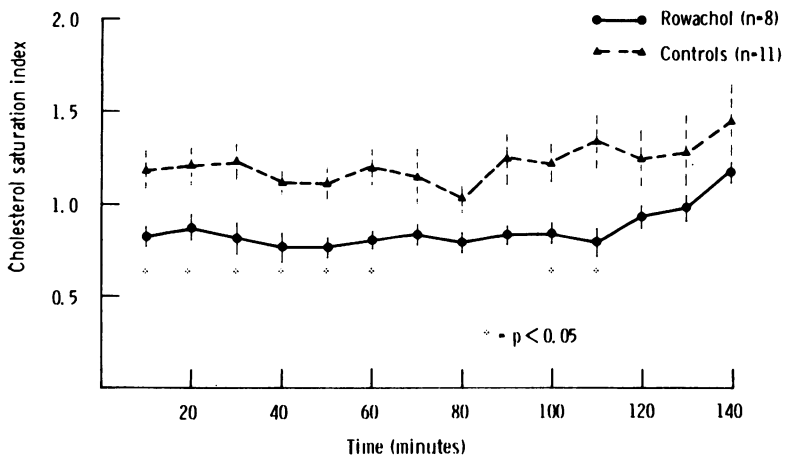

Fig. 2 *Effect of Rowachol on the cholesterol saturation index of T-tube bile during 140 minutes' drainage.*

Table *Bile flow (ml/min) and biliary excretion of bile salts, phospholipids, and cholesterol (μmol/min ± SEM) in control patients and those receiving Rowachol*

Time (min)	Controls (n = 11)				Rowachol (n = 8)			
	Bile flow	BS	PL	Ch	Bile flow	BS	PL	Ch
0- 10	0·81 ± 0·09	24·7 ± 4·4	9·3 ± 1·4	2·7 ± 0·4	0·81 ± 0·06	34·5 ± 5·0	10·8 ± 0·5	2·5 ± 0·2
10- 20	0·72 ± 0·08	22·2 ± 4·0	7·9 ± 1·1	2·6 ± 0·4	0·73 ± 0·09	31·9 ± 3·0	9·9 ± 1·0	2·3 ± 0·3
20- 30	0·76 ± 0·07	24·1 ± 4·9	8·6 ± 1·3	2·7 ± 0·3	0·75 ± 0·08	33·5 ± 5·6	10·1 ± 0·7	2·3 ± 0·2
30- 40	0·87 ± 0·09	28·6 ± 5·4	10·0 ± 1·4	3·1 ± 0·4	0·79 ± 0·09	38·0 ± 6·9	10·8 ± 0·7	2·4 ± 0·2
40- 50	0·78 ± 0·07	27·0 ± 5·1	8·9 ± 1·3	2·7 ± 0·3	0·79 ± 0·09	38·7 ± 7·3	11·5 ± 0·9	2·6 ± 0·3
50- 60	0·81 ± 0·07	28·0 ± 5·7	8·8 ± 1·1	2·8 ± 0·3	0·84 ± 0·09	37·6 ± 8·9	11·3 ± 0·9	2·5 ± 0·2
60- 70	0·86 ± 0·06	28·4 ± 5·3	9·0 ± 0·9	2·7 ± 0·3	0·79 ± 0·10	33·9 ± 9·1	10·0 ± 0·8	2·5 ± 0·2
70- 80	0·78 ± 0·08	28·4 ± 5·7	8·7 ± 1·1	2·4 ± 0·3	0·78 ± 0·10	32·6 ± 8·9	10·5 ± 1·1	2·4 ± 0·2
80- 90	0·78 ± 0·09	27·2 ± 5·5	8·7 ± 1·0	2·5 ± 0·2	0·76 ± 0·12	32·7 ± 7·9	10·6 ± 1·2	2·4 ± 0·3
90-100	0·67 ± 0·07	22·2 ± 5·5	7·4 ± 1·0	2·2 ± 0·2	0·74 ± 0·07	30·3 ± 4·9	10·3 ± 0·9	2·4 ± 0·2
100-110	0·67 ± 0·08	24·8 ± 4·5	7·1 ± 1·0	2·4 ± 0·3	0·66 ± 0·07	26·8 ± 5·9	9·5 ± 1·2	2·1 ± 0·3
110-120	0·58 ± 0·05	18·7 ± 4·2	6·4 ± 1·0	2·2 ± 0·2	0·57 ± 0·07	18·8 ± 2·8	8·0 ± 0·9	1·8 ± 0·2
120-130	0·58 ± 0·07	15·4 ± 4·0	5·6 ± 0·8	2·1 ± 0·2	0·52 ± 0·05	13·9 ± 1·4	7·1 ± 0·7	1·8 ± 0·1
130-140	0·62 ± 0·12	12·3 ± 3·0	5·5 ± 1·0	2·1 ± 0·3	0·56 ± 0·04	14·1 ± 2·5	7·6 ± 1·0	2·1 ± 0·2

Gut: first published as 10.1136/gut.20.4.312 on 1 April 1979. Downloaded from http://gut.bmj.com/ on 19 April 2018 by guest. Protected by copyright.

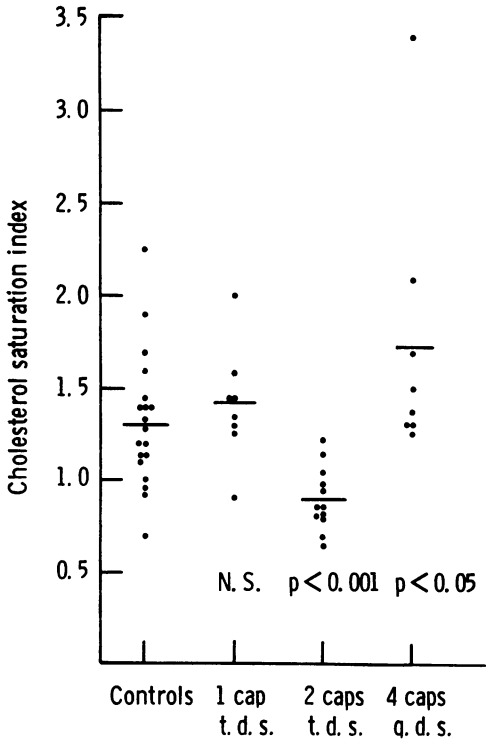

Fig. 3 *Cholesterol saturation index of gall bladder bile from controls and from patients given Rowachol for 48 hours before surgery.*

receiving a dose of two capsules tds the cholesterol saturation index was 0·900 ± 0·51, which is significantly lower than the controls (P < 0·001). Nine of the 12 patients in this group had bile that was less than saturated with cholesterol. In contrast, the cholesterol saturation index of 1·743 ± 0·262 found in the patients given the largest dose was significantly higher than that of the controls (P < 0·05).

Discussion

The results of this study show that Rowachol, in a dose of two capsules three times a day for 48 hours, significantly enhances the cholesterol solubility of human T-tube and gall bladder bile. In most previous series, gallstone patients treated with Rowachol (Blumenberg, 1957; Kameda, 1960; Okabe, 1960; Noda *et al.*, 1965; Hordinsky, 1971, 1973) received the preparation in liquid form in daily doses equivalent to only two to four of the enteric-coated capsules employed in the present study. It can be seen from our own study that one capsule of Rowachol three times a day for 48 hours failed to alter bile composition. It is possible therefore that the low gallstone dissolution rates reported in some series (Hordinsky, 1971) may simply reflect the fact that the dose employed was too small.

D-limonene (p-mentha-1,8-diene) occurs as a major component of the essential oils of citrus fruits. It is a monoterpene structurally similar to several of the terpenes in Rowachol. Kodama *et al.* (1976) have recently shown that in the rat d-limonene decreased the ratio of biliary bile salts and phospholipids to cholesterol, while, on the other hand, one of its major metabolites, p-menth-1-ene-8,9-diol, significantly increased the same ratio. It is possible that some of the terpenes in Rowachol (or their metabolites) favourably influence biliary lipid composition, while others, like d-limonene itself, cause a deterioration. This could possibly explain why the largest dose of Rowachol (four capsules qds) caused an increase in the cholesterol saturation of bile, while the lower dose decreased it.

Measurement of the rate limiting enzymes of hepatic cholesterol (HMGCoA Reductase) and bile acid synthesis (cholesterol 7αhydroxylase) in the microsomal fraction of liver from patients with cholesterol gallstones has shown increased HMGCoA reductase activity and diminished 7αhydroxylase activity (Nicolau *et al.*, 1974a, 1974b; Salen *et al.*, 1975). It has recently been shown that cholesterol secretion into bile is correlated with HMGCoA reductase levels in the liver (Key *et al.*, 1977). CDCA and the structurally related bile acid ursodeoxycholic acid enhance the cholesterol solubility of human bile and promote cholesterol gallstone dissolution by depressing hepatic HMGCoA reductase (Coyne *et al.*, 1976; Maton *et al.*, 1977). In our T-tube patients Rowachol increased bile salt and slightly decreased cholesterol output. Similar findings have previously been reported in the rat (Mörsdorf and Wolf, 1966). We have shown that this terpene preparation significantly depressed hepatic HMGCoA reductase levels in the rat (Bell *et al.*, 1978b). We are currently investigating all the individual terpene constituents of Rowachol to determine, in the rat, how much each one contributes to this effect. Having determined the 'active' ingredient(s) of this terpene preparation in the rat, we then intend to carry out a formal dose response study in man.

Despite its complex composition we chose to use Rowachol in the present pilot study because it was (1) readily available in the United Kingdom; (2) known to be safe when given for prolonged periods, and (3) had previously been shown occasionally to dissolve patients' gallstones (Blumenberg, 1957; Kameda, 1960; Okabe, 1960; Noda *et al.*, 1965; Hordinsky, 1971, 1973). We ourselves have now treated 27 patients with radiolucent gallstones for

Gut: first published as 10.1136/gut.20.4.312 on 1 April 1979. Downloaded from http://gut.bmj.com/ on 19 April 2018 by guest. Protected by copyright.

periods of six to 12 months. We already have radiological evidence of gallstone dissolution/disappearance in seven of the patients taking the terpene preparation. The drug was well tolerated by the patients and no evidence of hepatotoxicity emerged (Bell *et al.*, 1978b).

It is known that certain terpenes such as cineol (eucalyptol) and α pinene are potent hepatic microsomal enzyme inducers (Jori *et al.*, 1972). It is perhaps not surprising therefore to find that Rowachol itself significantly ($P < 0.01$) increased urinary D-glucaric acid excretion when given to patients in a dose of two capsules tds for six weeks (Bell *et al.*, 1978c). We are currently investigating the effect of this terpene preparation on a series of hepatic microsomal enzymes including cholesterol 7α-hydroxylase, as at the present time we have no good explanation for the increased bile salt secretion observed either in our own study or the previous one of Mörsdorf and Wolf (1966).

Previous studies in the rat (Traissac *et al.*, 1963; Mörsdorf, 1966; Mörsdorf and Wolf, 1966) and in man (Traissac, *et al.*, 1963; Hordinsky, 1973) have shown Rowachol to be a potent choleretic. Mörsdorf (1966) showed that menthol and borneol were the most potent choleretics in Rowachol. The choleresis produced by these terpenes and also others such as d-limonene (Kodama *et al.*, 1976) is dose-related. In the present study no obvious choleretic effect was noted. This may be because (1) the last dose was at least 12 hours before the start of the experiment, and (2) the dose used (in mg/kg body weight) was relatively small.

We conclude that the terpene preparation, Rowachol, its individual constituents, and possibly other related compounds merit further investigation as possible cholelitholytic agents.

The authors are grateful to Rowa Ltd, who kindly supplied the Rowachol capsules, and also had English translations made of the papers quoted from the Japanese literature; One of us (J.D.) was in receipt of a grant from Schering Chemicals Ltd.

References

Admirand, W. H., and Small, D. M. (1968). The physicochemical basis of cholesterol gallstone formation in man. *Journal of Clinical Investigation*, **47**, 1043-1052.

Bartlett, G. R. (1959). Phosphorus assay in column chromatography. *Journal of Biological Chemistry*, **234**, 466-468.

Begemann, F., Bandomer, G., and Herget, H. J. (1978). The influence of β-sitosterol on biliary cholesterol saturation and bile acid kinetics in man. *Scandinavian Journal of Gastroenterology*, **13**, 57-63.

Bell, G. D., Doran, J., Fayadh, M., Murphy, G., and Dowling, R. H. (1978a). Effect of ioglycamide (Biligram) on bile flow and biliary lipid secretion in man. *Gut*, **19**, 300-307.

Bell, G. D., Doran, J., Middleton, A., Middleton, B., Richmond, C. R., and White, D. A. (1978b). Rowachol, a proprietary essential oil preparation, lowers hepatic microsomal HMGCoA. reductase and dissolves cholesterol gallstones (Abstract). *Gut*, **19**, A972.

Bell, G. D., Doran, J., Middleton, A., Middleton, B., Richmond, C. R., and White, D. A. (1978c). Rowachol, a proprietary terpene preparation, dissolves cholesterol gallstones (Abstract). *British Journal of Clinical Pharmacology*, **6**, 454P.

Bell, G. D., Whitney, B., and Dowling, R. H. (1972). Gallstone dissolution in man using chenodeoxycholic acid. *Lancet*, **2**, 1213-1216.

Blumenberg, F. W. (1957). Therapie von Cholepathien mit einer Terpenkombination. *Medizinische*, 726-728.

Carr, J. J., and Drekter, I. J. (1956). Simplified rapid technique for extraction and determination of serum cholesterol without saponification. *Clinical Chemistry*, **2**, 353-368.

Coyne, M. J., Bonorris, G. G., Chung, A., Goldstein, L. I., Lahana, D., and Schoenfield, L. J. (1975). Treatment of gallstones with chenodeoxycholic acid and phenobarbital. *New England Journal of Medicine*, **292**, 604-607.

Coyne, M. J., Bonorris, G. G., Goldstein, L. I., and Schoenfield, L. J. (1976). Effect of chenodeoxycholic acid and pentobarbital on the rate-limiting enzymes of hepatic cholesterol and bile acid synthesis in patients with gallstones. *Journal of Laboratory and Clinical Medicine*, **87**, 281-291.

Danzinger, R. G., Hofmann, A. F., Schoenfield, L. J., and Thistle, J. L. (1972). Dissolution of cholesterol gallstones by chenodeoxycholic acid. *New England Journal of Medicine*, **286**, 1-8.

Dowling, R. H. (1977). Chenodeoxycholic acid therapy of gallstones. *Clinics in Gastroenterology*, **6**, 141-163.

Gerolami, A., and Sarles, H. (1975). β sitosterol and chenodeoxycholic acid in the treatment of cholesterol gallstones (Letter). *Lancet*, **2**, 721.

Hegardt, F. G., and Dam, H. (1971). The solubility of cholesterol in aqueous solutions of bile salts and lecithin. *Zeitschrift für Ernährungswissenschaft*, **10**, 223-233.

Hordinsky, B. Z. (1971). Terpenes in the treatment of gallstones. *Minnesota Medicine*, **54**, 649-652.

Hordinsky, B. Z. (1973). Dissolution of gallstones. *Proceedings of the Shevchenko Scientific Society*, **7**, 1-7.

Igimi, H., Hisatsugu, T., and Nishimura, M. (1976). The use of d-limonene preparation as a dissolving agent of gallstones. *American Journal of Digestive Diseases*, **21**, 926-935.

Iser, J. H. Dowling, R. H., Mok, H. Y. I., and Bell, G. D. (1975). Chenodeoxycholic acid treatment of gallstones—a follow-up report and analysis of factors influencing response to therapy. *New England Journal of Medicine*, **293**, 378-383.

Jori, A., Di Salle, E., and Pescador, R. (1972). On the inducing activity of Eucalyptol. *Journal of Pharmacy and Pharmacology*, **24**, 464-469.

Kameda, H. (1960). *Clinical Investigations of Disease of the Gall Bladder and the Biliary Tract, in Particular of the Results of Infra-red Spectrophotometric Examination.* From translation of lecture given at the 46th General Meeting of the Japanese Society of Gastroenterology at Osaka, June 1960.

Key, P. H., Bonorris, G. G., Coyne, M. J., Taub, M., and Schonfield, L. J. (1977). Hepatic cholesterol synthesis: a determinant of cholesterol secretion in gallstone patients. (Abstract). *Gastroenterology*, **72**, 1182.

Kodama, R., Inoue, H., Noda, K., and Ide, H. (1976). Effect of d-limonene and related compounds on bile flow biliary lipid composition in rats and dogs. *Life Sciences*, **19**, 1559-1567.

Maton, P. N., Murphy, G. M., and Dowling, R. H. (1977).

Gut: first published as 10.1136/gut.20.4.312 on 1 April 1979. Downloaded from http://gut.bmj.com/ on 19 April 2018 by guest. Protected by copyright.

Ursodeoxycholic acid treatment of gallstones. *Lancet*, **2**, 1297-1301.

Maudgal, D. P., Bird, R., Enyobi, V. O., Blackwood, W. S., and Northfield, T. C. (1977). Chenic acid in gallstone patients: effect of low cholesterol and high plant sterol diets. *Gut*, **18**, A419.

Mörsdorf, K. (1966). Les terpènes cycliques et leur action cholérétique. *Extrait du Bulletin de Chimie Therapeutique*, No. 4, pp. 442-444.

Mörsdorf, K., and Wolf, G. (1966). Untersuchungen zur Wirkungspotenz einiger Choleretika. *Deutsches Medizinisches Journal*, **7**, 303-306.

Nicolau, G., Shefer, S., Salen, G., and Mosbach, E. H. (1974a). Determination of hepatic 3-hydroxy-3 methylglutaryl CoA reductase activity in man. *Journal of Lipid Research*, **15**, 94-98.

Nicolau, G., Shefer, S., Salen, G., and Mosbach, E. H. (1974b). Determination of hepatic cholesterol 7 α-hydroxylase activity in man. *Journal of Lipid Research*, **15**, 146-151.

Noda, H., Kuriyama, S., and Tokuda, A. (1965). Clinicopathological studies on cholelithiasis. II. Medical treatment of cholelithiasis—experience with terebene oil preparation (Japanese). *Naika Hokan* (*Japanese Archives of Internal Medicine*), **12**, 505-511.

Okabe, H. (1960). Clinical experience with terpene preparation (Rowachol) in treatment of disease of the gall bladder and cystic duct. *Shokakibyo No Rinsho*, **12**, 12-17.

Salen, G., Nicolau, G., Shefer, S., and Mosbach, E. H. (1975). Hepatic cholesterol metabolism in patients with gallstones. *Gastroenterology*, **69**, 676-684.

Smith, R. L. (1973). *The Excretory Function of Bile. The Elimination of Drugs and Toxic Substances in Bile*, p. 16. Chapman and Hall: London.

Talalay, P. (1960). Enzymatic analysis of steroid hormones *Methods of Biochemical Analysis*, **8**, 119-143.

Thistle, J. L., and Hofmann, A. F. (1973). Efficacy and specificity of chenodeoxycholic acid therapy for dissolving gallstones. *New England Journal of Medicine*, **289**, 655-659.

Thistle, J. L., Hofmann, A. F., Ott, B. J., and Stephens, D. H. (1978). Chenotherapy for gallstone dissolution. I. Efficacy and safety. *Journal of the American Medical Association*, **239**, 1041-1046.

Thomas, P. J., and Hofmann, A. F. (1973). A simple calculation of the lithogenic index of bile: expressing biliary lipid composition on rectangular co-ordinates. (Letter) *Gastroenterology*, **65**, 698-700.

Traissac, F. J., Savini, E., Romani, J'D., Charbonnier, A., Perissat, J., and Keller, A. (1963). Effet choléretique d'un complexe terpenique. *Extrait de l'information thérapeutique*, No. 1. pp. 23-25.

Gut: first published as 10.1136/gut.20.4.312 on 1 April 1979. Downloaded from http://gut.bmj.com/ on 19 April 2018 by guest. Protected by copyright.