Prolonged Secretion of Lithogenic Bile After Cholecystectomy

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Hepatic bile samples were obtained from 8 subjects 1½ to 23 years after cholecystectomy for presumed cholesterol gallstones. The content of cholesterol, bile acids and lecithin was determined for each bile sample and compared to the values found in gallbladder bile in 15 control subjects undergoing cholecystectomy for pure and mixed cholesterol stones. Plot of the data on triangular coordinates and subsequent determination of lithogenic index showed that bile was supersaturated with cholesterol in both groups of patients. The cholesterol content of bile remained at supersaturated levels following cholecystectomy and showed no tendency to return toward normal levels with the passage of time.

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RECENT INVESTIGATIONS into the chemical dissolution of cholesterol gallstones[5,15] have focused attention on the length of time a lithogenic bile is secreted by the liver in patients who develop such stones. This time period is critical to the present medical treatment of gallstones because if a bile supersaturated with cholesterol is secreted indefinitely then medical treatment may have to be a lifelong one and the chance of failure due to the patient not taking the medication (chenodeoxycholic acid, CDCA) increases. If the effect of medical treatment is only to delay definitive surgery from age 25 to age 65, for example, then such treatment is of dubious value.

The purpose of this study is to determine whether or not a lithogenic bile is secreted following cholecystectomy for cholesterol gallstones, and if so for how long. To accomplish this we have determined the hepatic bile content of cholesterol, lecithin and bile acids on 8 patients 1½ to 23 years after cholecystectomy for presumed cholesterol gallstones. The hepatic bile composition of these eight patients was compared to the gallbladder bile composition of 15 patients undergoing cholecystectomy for cholesterol gallstones.

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Materials and Methods

Hepatic bile samples were obtained from 5 women and three men ages 28 to 71 who had undergone cholecystectomy 1½ to 23 years previously for gallstones. The bile acid, cholesterol and lecithin content of the bile samples was determined. Former operative and pathology records were obtained in these patients and in each case suggested that the gallstones were pure or mixed cholesterol stones.[10] Bile was obtained by needle or T-tube aspiration of the common bile duct at the time of laparotomy in 6 patients, by duodenal catheter aspiration intra-operatively in one patient, and via a gastrostomy tube postoperatively in one patient. Only bile samples containing 3-25% total solids and sterile to aerobic and anaerobic culture were included in the study. None of the subjects was jaundiced at the time the bile sample was taken, but mild elevations of serum glutamic oxaloacetic transaminase (SGOT) and/or serum alkaline phosphatase were present in three patients, and one patient had a common duct stone (Table 1). The hepatic bile composition in these 8 subjects was compared to gallbladder bile content of bile acids, cholesterol and lecithin of 10 women and 5 men ages 24-70 currently undergoing cholecystectomy for pure and mixed cholesterol gallstones in a radiologically functioning gallbladder. Bile was obtained by needle aspiration of the gallbladder at the time of cholecystectomy. The cholesterol content of the gallstones present was determined in 13 of these subjects after the stones were dried and weighed.

TABLE 1. *Clinical and Laboratory Data on Eight Subjects Who Previously Underwent Cholecystectomy for Gallstones*

Patient No.	Age, Sex (Yrs)	Time Since Cholecystectomy (Yrs)	Serum Bilirubin (mg%)	SGOT IU/L	Serum Alkaline Phosphatase IU/L	How Bile Sample Obtained	Present Diagnosis
1. R.F.	56,F	15	0.5	33	88	Aspiration of common duct	Benign stricture
2. N.T.	46,F	7	0.7	44	140	Aspiration of duodenum	Reflux esophagitis
3. W.F.	44,M	5	0.3	89	217	Aspiration of common duct	Common duct stone
4. M.J.	45,F	23	0.3	42	158	Aspiration of common duct	Neuroma common bile duct
5. I.G.	28,F	3	0.2	29	77	T-tube in common duct	Pancreatitis
6. J.M.	64,M	10	0.4	47	89	Aspiration of common duct	Pancreatitis
7. S.M.	31,F	1.5	0.5	31	51	Aspiration of duodenum	Duodenal ulcer Hiatus hernia
8. G.K.	71,M	8	0.5	20	65	Gastrostomy tube	Duodenal ulcer

The method of analysis for total bile salts was that of Engert and Turner[6] using the 3-α-hydroxysteroid dehydrogenase extracted from *Pseudomonas testosteroni*. Biliary lecithin was estimated following an extraction with chloroform-methanol, and an aliquot of the chloroform extract was evaporated and digested with sulphuric acid and hydrogen peroxide. Phosphorus was then estimated with the standard acid molybdate with subsequent reduction by aminonaphthol-sulfonic to form the characteristic blue color. This method follows that outlined by Bragden.[4] The cholesterol content of bile was estimated by the classical method described by Abell,[1] using the Liebermann Burchard reaction following saponification of the cholesterol esters with alcoholic potassium hydroxide and extraction of the free cholesterol into petroleum ether.

The data for each sample was then plotted on the triangular coordinates of Admirand and Small.[2] From this plot the lithogenic index for each sample was determined as described by Metzger et al.[8] wherein a bile unsaturated with cholesterol as determined by Admirand and Small has an index less than 1.0 and a saturated or supersaturated bile an index of 1.0 or greater.

Results

The hepatic bile samples from 8 subjects who had undergone cholecystectomy 1½ to 23 years previously were saturated or supersaturated with cholesterol in all instances (Table 2). The mean lithogenic index for this group was 1.31 (S.D. ± 0.11). The group of 15 subjects currently undergoing cholecystectomy for pure and mixed cholesterol gallstones had bile samples supersaturated with cholesterol in all but 3 instances (Table 3). The mean lithogenic index for this group was 1.41 (S.D. ± 0.48).

The molar percentages of biliary cholesterol for the current cholecystectomy group (15 subjects) and previous cholecystectomy group (8 subjects) are shown in Fig. 1. The mean value of molar per cent cholesterol for the cuttent cholecystectomy group is 14.0 (S.D. ± 5.2) and

TABLE 2. *Composition of Hepatic Bile and Lithogenic Index in Eight Subjects Who Previously Underwent Cholecystectomy for Gallstones*

Patient	mM per Liter			% of Total mM			Lithogenic
	Bile Acids	Lecithin	Cholesterol	Bile Acids	Lecithin	Cholesterol	Index
1. R.F.	44.3	15.2	6.6	67	23	10	1.00
2. N.T.	23.0	5.1	4.1	72	15	13	1.44
3. W.F.	62.0	16.2	9.5	71	18	11	1.11
4. M.J.	28.1	11.1	4.9	64	25	11	1.09
5. I.G.	42.2	11.2	6.4	70	18	12	1.22
6. J.M.	33.5	13.1	6.3	63	25	12	1.18
7. S.M.	17.5	7.1	4.0	61	25	14	1.36
8. G.K.	14.0	2.9	3.9	67	14	19	2.06
Mean				67	25	12.7	1.31
S.D.				3.9	4.7	2.8	0.11

TABLE 3. *Composition of Gallbladder Bile and Lithogenic Index in 15 Subjects (Gallstones Present)*

Patient	mM Per Liter			% of Total mM			Lithogenic Index	% Cholesterol in stones (dry wt)
	Bile Acids	Lecithin	Cholesterol	Bile Acids	Lecithin	Cholesterol		
1. S.H.	125.0	44.6	15.5	69	22	9	0.92	99
2. L.H.	105.0	36.9	30.6	62	21	17	1.70	95
3. R.K.	153.0	43.6	19.8	71	20	9	0.92	93
4. C.W.	177.0	64.6	35.5	64	23	13	1.29	88
5. H.T.	71.9	33.6	12.5	63	27	10	0.97	86
6. J.M.	117.0	40.3	21.4	66	22	12	1.20	—
7. J.W.	52.0	16.5	9.5	67	21	12	1.21	81
8. P.H.	54.0	18.7	10.9	65	22	13	1.29	68
9. I.B.	31.7	10.5	5.3	67	22	11	1.10	66
10. E.A.	30.0	12.6	5.1	63	26	11	1.07	79
11. Z.M.	58.0	18.1	21.4	60	19	21	2.10	—
12. R.D.	29.0	4.3	5.2	75	11	14	1.46	94
13. E.S.	23.9	10.6	13.7	50	22	28	2.70	73
14. R.A.	98.0	56.0	18.0	56	33	11	1.18	78
15. S.S.	46.0	27.7	16.9	51	30	19	2.06	65
Mean				63	23	14	1.41	
S.D.				6.7	5.0	5.2	0.48	

for the previous cholecystectomy group is 12.7 (S.D. ± 2.8).

The molar per cent of cholesterol in the bile samples in 8 previously cholecystectomized subjects is plotted against time since cholecystectomy in Fig. 2. The graph indicates that bile supersaturated with cholesterol in these subjects does not become less saturated with the passage of time. If one extrapolates this plot the inference is that bile in these patients remains supersaturated with cholesterol indefinitely.

Discussion

In this study we have sampled gallbladder bile in one group of subjects, hepatic bile in the other. It has been shown that gallbladder and hepatic biles from the same subject are similar in their molar per cent composition of cholesterol, bile acids and lecithin; although concentration of these substances is greater in gallbladder bile.[13,16] For this reason it may be permissible to compare gallbladder and hepatic bile composition in different subjects as we have done, but the possibility of introducing error by such comparison cannot be completely dismissed.

Bile samples obtained in this study were all taken from fasting subjects as was the case in the original studies of Admirand and Small.[2] Metzger et al.[9] have shown that fasting hepatic bile is more lithogenic than gallbladder or hepatic bile obtained during feeding. These facts may explain why the plots of our data on triangular coordinates (Fig. 1) relate more closely to the cholesterol solubility line of Admirand and Small than to the line defined by Holzbach et al.[7]

In this study we have elected to examine the bile of patients who have previously undergone cholecystectomy in order to determine how long a lithogenic bile is secreted. One might argue that a study of patients who have had known gallstones present for a long time would yield similar information. However in such a group of patients the effect of the gallstones themselves on bile

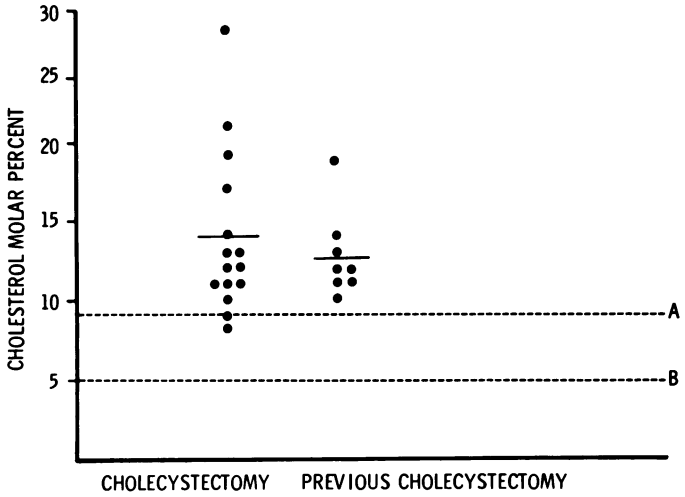

FIG. 1. Cholesterol molar per cent in bile in A) 15 subjects currently undergoing cholecystectomy and B) 8 subjects who previously underwent cholecystectomy. Line A represents the approximate limits of cholesterol solubility in bile reported by Admirand and Small[2] and Line B the linits found by Holzbach et al.[7]

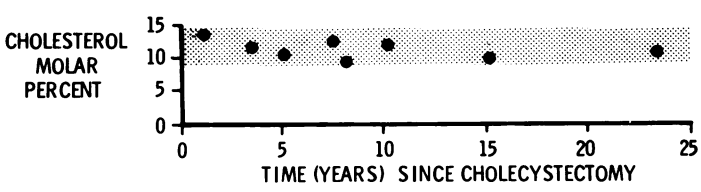

FIG. 2. Molar per cent cholesterol in 8 subjects who previously underwent cholecystectomy for gallstones, plotted against time since cholecystectomy.

composition must be taken into consideration as the bile cholesterol is in equilibrium with stone cholesterol if the gallbladder is "functioning." If the gallbladder in such patients is "non-functioning" they are little different from our cholecystectomized patient group.

Other investigators have reported that hepatic bile remains lithogenic following cholecystectomy for pure and mixed gallstones[3] although not all investigators agree on this point.[11,12] The subjects reported in this study possibly represent the longest followup study of bile composition after cholecystectomy. The data on these subjects up to 23 years after cholecystectomy confirm the reports that bile remains lithogenic and suggests that it does so indefinitely, as no trend toward decreasing cholesterol supersaturation was noted with the passage of time after cholecystectomy. These data support the concept that the production of a lithogenic bile by the liver is a lifelong phenomenon once begun, and has important implications for the future of dissolution of gallstones with the oral administration of CDCA. The observation that gallstones reappear after therapy with CDCA[14] is stopped is not surprising when it is appreciated that the liver continues to elaborate a bile supersaturated with cholesterol.

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