Advances in Diagnosis and Surgical Treatment of Biliary Tract Disease

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Foreword

The therapy of biliary tract disease has undergone remarkable change in the past few years, and more is yet to come. There are few areas of medicine where the rate of accretion of new knowledge and technology has so quickly been translated into innovations in medical practice. This monograph is an attempt to capture at one point in time the excitement and potential value of these advances. It is not a "proceedings"! The contributions, however, derive from a multidisciplinary panel of experts who participated in the Second Postgraduate Course of The Society for Surgery of the Alimentary Tract at Digestive Disease Week, 1982. My co-editors and I are indebted to them for sharing with us their unique contributions to the diagnosis and treatment of gallstones, cancer of the gallbladder, and benign and malignant diseases of the biliary tree. We hope that you enjoy reading this book as much as we have enjoyed putting it together. It is intended to bring the reader up to the level of understanding that is used by the authors in their daily practice. Heed the knowledge contained herein, for when applied wisely, it will bring great benefit to your patients with biliary tract disease.

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Contents

CHAPTER 1

An Internist's View of Surgical Diseases of the Biliary Tract

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THIS paper is directed toward biliary surgeons who are attending a postgraduate course organized by the Society for Surgery of the Alimentary Tract and I write it as an internist who has been honored by election as a Fellow of this prestigious Society. There are many new developments of relevance to all of us in the field of biliary surgery. This paper will review the present situation of several of these developments. New methods of dissolving gallstones in the gallbladder are not proving to be widely applicable, causing this condition to remain a surgical problem in the foreseeable future. However, many traditional surgical tasks such as the draining of intraperitoneal and intrahepatic pus and removing stones from the bile ducts are being taken over by the invasive radiologist, endoscopist, and internist working in cohorts with expert ultrasonographers and nuclear medicine physicians. Techniques are ever-improving. Biliary stents are being introduced into the biliary and pancreatic ducts without surgical assistance.

Dissolving Gallstones

The primary defect in the production of lithogenic "bile," and hence of cholesterol gallstones, is diminished hepatic secretion of bile acids. Cholesterol crystallization is a prerequisite for the formation of cholesterol gallstones, yet many biles show no crystals despite marked supersaturation with cholesterol.[1] A higher HMG-CoA reductase in liver biopsies can be shown; this increases cholesterol synthesis. Biliary glycoproteins also increase.

The gallbladder plays an important role. It acts as a reservoir for stone growth and mixing. It increases the viscosity of bile. It provides the nucleus for gallstone formation, usually in the form of mucus or inflammatory cells. Increased cholesterol in bile may stimulate gallbladder mucus production.[2] The increased incidence of gallstones after truncal vagotomy may be related to increased resistance through the sphincter of Oddi, leading to gallbladder dilatation, bile

stasis, and ultimately to stone formation.[3] Late pregnancy is associated with incomplete gallbladder emptying and retention of cholesterol crystals.[4]

The prevalence increases with age in both sexes, but the sex differential changes with advancing years. There are three times more female than male sufferers below age 40; and over age 80, the ratio of female to male is three to two.

Genetic factors, the relation to obesity, cirrhosis, ileal resection, and drugs such as cholestyramine or clofibrate will not be discussed here.

Some gallstones can be dissolved by the administration of the naturally occurring bile acid, chenodeoxycholic acid (Figs. 1 and 2). The bile acid pool is expanded. The secretion and relative concentration of biliary cholesterol is decreased and the duration and secretion of saturated bile is reduced. The hepatic enzyme HMG-CoA reductase is also reduced, thus inhibiting cholesterol synthesis. The gallstones must be small and radiolucent, lying in a gallbladder which is visualized by cholecystography. However, about 15% of radiolucent stones are composed of pigment. The only way to prevent valueless drug treatment in as

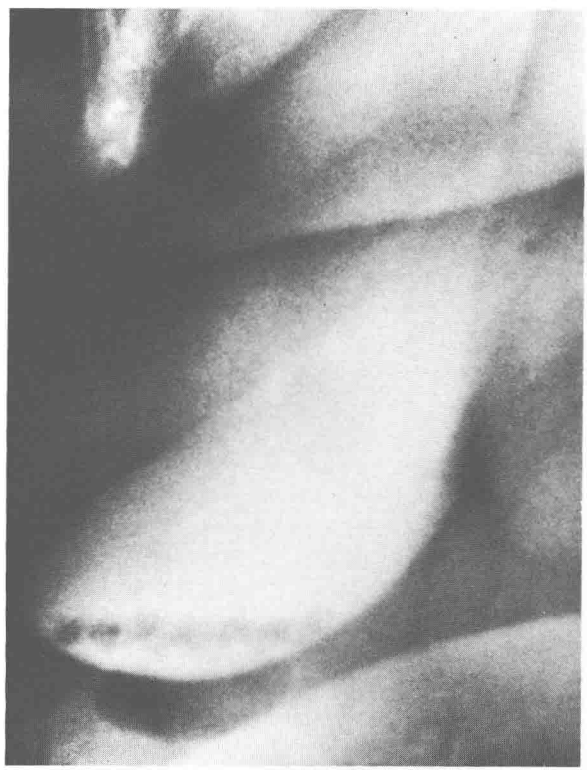

Figure 1. Oral cholecystogram shows multiple small radiolucent stones in a functioning gallbladder.

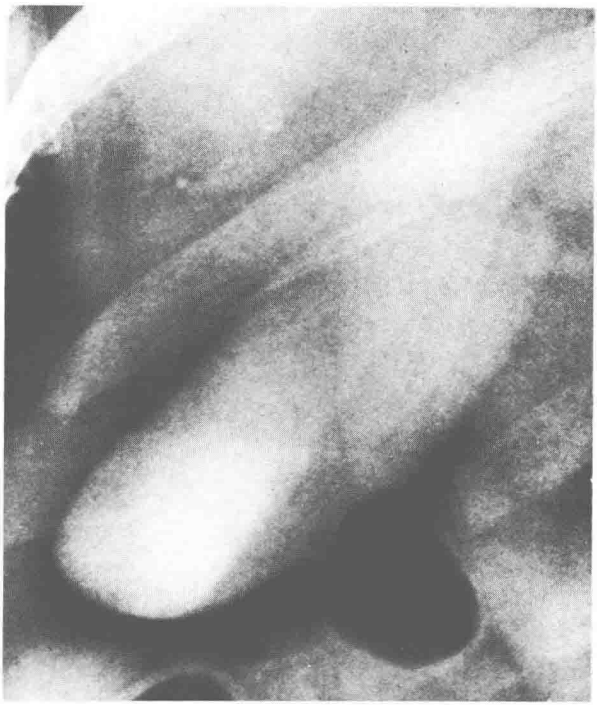

Figure 2. Same patient after taking 750 mg chenodeoxycholic acid daily for 1 year. The gallstones have dissolved.

many as one in six patients is to determine the cholesterol saturation of the bile in every patient. Unsaturated bile almost always indicates pigment stones. A further sample taken during treatment permits ascertainment that bile has been rendered sufficiently unsaturated to enable cholesterol gallstones to return to solution. Unfortunately, bile sampling requires duodenal intubation, and the biochemical techniques for biliary lipid analysis, although simple, are not widely available.

A National Cooperative Gallstone Study costing approximately $11 million has been conducted in the United States.[3] Nine hundred sixteen patients were studied, 15% of whom dropped out. Within 2 years, 14% of the high-dose patients (750 mg/day) and 5% of the low-dose patients (375 mg/day) showed complete dissolution of gallstones as indicated by oral cholecystography (Table 1). There was partial dissolution in 25%, but patients with partially dissolved stones are still left with stones in the gallbladder. Whether simple reduction in size of the stones is of substantial benefit to the patient is unclear.

Results were better in females, in patients who were not obese, and in those with a serum cholesterol value equal to or exceeding 227 mg/100 ml. Symptoms were not reduced. A hepatotoxicity which was clinically significant occurred in

TABLE 1
Chenodeoxycholic Acid Treatment (*National Cooperative Study 1981*)

Regime	No.	Percent Dissolved	Percent Hepatotoxicity
750 mg	305	14	3.0
375 mg	306	5	0.4
Placebo	305	1	0.4

Fifteen percent of patients were dropouts.

3% of patients receiving 750 mg/day, in 0.4% receiving 375 mg/day, and in 0.4% of the placebo group. Changes were always reversible biochemically but in 2.6% led to withdrawal from the trial. There was a 10% elevation of the serum cholesterol and low-density lipoproteins. This might pose an added risk for the patients prone to develop coronary artery disease. Liver biopsies of patients before and during chenodeoxycholic acid treatment have shown changes by both light and electron microscopy.[4] Diarrhea was noted in 40% of patients on the high dose, and in 20% on the placebo or low-dose patients. The prospects of dissolution of the stones can be predicted by the 6-month cholecystogram compared with the control. The greater sensitivity of ultrasound over cholecystography makes this a more suitable method of following the rate of dissolution.[5] The drug should be given in a single bedtime dose.

The reported low rates for dissolution of gallstones can hardly be regarded as satisfactory. In part, they can be related to the dose of chenodeoxycholic acid, which was clearly inadequate—certainly in the obese. The dose necessary is considered to be 14.4 mg/kg/day; this would mean 1000 mg daily in a 70-kg patient.[6]

Follow-ups on possible recurrence are scanty, but it seems likely that 50% of patients will have a recurrence of gallstones within 2 years and up to 75% of patients will have a recurrence at 5 years. This rate might be prevented by a continuous small dose of chenodeoxycholic acid at bedtime. A diet rich in natural fiber might also be used to reduce the cholesterol saturation of bile. Drugs which would increase recurrence, such as sex hormones, cholestyramine, and clofibrate, must be avoided.

Better drugs with fewer side-effects are clearly needed. One of these may be ursodeoxycholic acid derived from the Japanese white-collared bear (Table 2). This is the 7-beta epimer of chenodeoxycholic acid and represents less than 1% of total bile acid in normal bile. It differs from chenodeoxycholic acid only in the position of one hydroxyl group. It definitely dissolves gallbladder stones in a lower dose[7] and it reduces the cholesterol saturation in bile by inhibiting hepatic HMG-CoA reductase. It has several advantages over chenodeoxycholic acid. Smaller doses (10 mg/kg body weight) are required, and dissolution is more rapid. Diarrhea is not a complication since the bile acid does not precipitate in the colon and less is absorbed.[8] Increases in transaminases are absent. However, it is more costly. A small percentage of patients may form calcium rims around their

TABLE 2
Ursodeoxycholic Acid (Tokyo Cooperative Study 1980)

600 mg	29	34%
150 mg	23	17%
Placebo	20	1%

There was no hepatotoxicity or diarrhea.

previously radio-translucent stones while on ursodeoxycholic acid therapy and this will again prevent further stone dissolution.[9] Its efficacy in dissolving gallstones has not been shown to be greater than that of chenodeoxycholic acid.

The conclusion then is that even at an optimistic guess, only 30% gallstone sufferers have stones suitable for dissolution.

Cholecystectomy

For patients in good general health and with symptomatic gallstones demonstrated in the gallbladder, there is no doubt that cholecystectomy offers the best prospect of permanent cure (Table 3). As an elective procedure, cholecystectomy for chronic cholecystitis and cholelithiasis carries an operative mortality of about 0.4% in the best hands.[10] Many series of several hundred have been published without a fatality. In patients over age 50, the mortality is about 0.8%. Complications of cholecystectomy were encountered in 6.9% of 2395 patients,[11] 54% are common to all operations, and 36% are specific to biliary tract surgery. The most serious complication is probably the development of biliary stricture.

The role of either drug or surgical therapy in the patient who is shown to have gallstones in a functioning gallbladder but who is asymptomatic remains controversial (Table 4). Physicians usually believe in leaving well-enough alone. The surgeon, as is usual, is more likely to take a positive attitude toward surgery. Reports on the consequences and natural history of asymptomatic "silent gallstones" are equally divided. One publication states that if the stones are left, there is about a 50% chance that cholecystectomy will be required within 20 years, with about 25% of patients developing serious complications.[12] Another

TABLE 3
Chenodeoxycholic Acid and Surgical Treatment in Gallbladder Stones

	Chenodeoxycholic Acid	Surgery
Patients suitable (%)	?30	?90
Stones removed (%)	14	100
Duration of therapy	2 Years	4 Weeks
Recurrence (%) (5 years)	50–70	? 0 (Duct stones ?)
Approximate cost (dollars)	1300	5–10,000

TABLE 4
Prognosis of Silent Gallstones

Author	Percentage Symptoms	Follow-up
Bell-Blumgart (1982)	50%	20 Years
Grouch et al. (1981)	13%	10–15 Years
Comfort et al. (1948)	15%	10–20 Years

follow-up study states that only a small number of these people—about 15%—develop symptoms and require cholecystectomy.[13] Gallstones are a frequent incidental autopsy finding. Recent reports from the University of Michigan show that when 123 patients with "silent gallstones" were followed from 10 to 15 years, only 16 (13%) developed symptoms of biliary pain and only three of these developed complications.[14] It seems likely, therefore, that only a small percentage of patients with "silent gallstones" will develop symptoms, and when they do the presentation is unlikely to be as an emergency. In young, otherwise fit individuals with demonstrated asymptomatic gallstones, surgery is probably indicated (Table 5). In older people, in particular those over 65, obese, or with other diseases—especially cardiac, respiratory, or hepatic—surgery is contraindicated.

One can conclude that if the patient's general condition permits surgery, symptomatic gallstones are a surgical, and not a medical, problem.[15]

The Effects of Cholecystectomy

Poor results after cholecystectomy can be expected in about one third of patients (Table 6). These poor results may be due to incorrect diagnosis. About 95% of those *with gallstones* are relieved of symptoms or improved postoperatively.[16] Thus, results are good if stones are present, but if none are found the original diagnosis should be in question. The patients may have been suffering from a psychosomatic, or other, disorder. Symptoms may be related to technical difficulties at the time of surgery; these include biliary stricture and residual calculi which will be discussed later.

TABLE 5
Management of Asymptomatic Gallstones

Age of patient and general condition
Other diseases
Psychology
Size of stone(s)
Medical
Diet High-fiber
Low cholesterol
Maintain normal weight

TABLE 6
Effects of Cholecystectomy

If gallstones present, 95% relief
Stricture
Residual calculi
Post cholecystectomy syndrome
Colonic cancer increases
Gallbladder cancer decreases

The postcholecystectomy syndrome is a term applied to the persistence or development of symptoms after cholecystectomy, and biliary dyskinesia has been incriminated. The existence of this syndrome is in some doubt, partly because it has been loosely used to cover persistent symptoms that are probably unrelated to the gallbladder disease.

Cholecystectomy may predispose a patient to the development of colonic cancer. Large bowel cancer has been related to increased colonic content of bacterially degraded bile acids such as deoxycholic acid.[17,18] Dietary fiber tends to protect against this effect. After cholecystectomy, fecal bile acids increase and the incidence of right-sided colonic cancer increases (Fig. 3).[19,20]

Cholecystectomy does seem to have an effect in reducing gallbladder cancer. There are fewer deaths from gallbladder cancer for every 100 cholecystectomies done during the previous year.[21]

Choledocholithiasis

Approximately 15% of patients operated upon for gallstones will have stones in the common bile duct.[22] If the stones are diagnosed before or at elective cholecystectomy, they should clearly be dealt with surgically at that time. Operative cholangiography is essential for their demonstration.

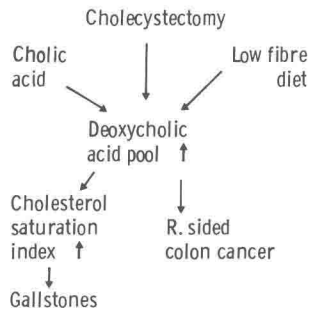

Figure 3. Cholecystectomy leads to an increase in the deoxycholic acid pool and hence increase of bacterially degraded bile acids in the colon, which would predispose to colonic cancer.

More than 1% of those having a cholecystectomy will have a retained common bile duct stone during the immediate postoperative period. Such stones usually result from failure to perform operative cholangiography. Calculi in the hepatic ducts are especially liable to be overlooked. If the T-tube is still in position in the common bile duct, the approach is easy. The T-tube is washed twice out daily for 2–3 days with normal saline and a repeat cholangiogram is taken. The stones may have disappeared. If after clamping the tube for a few days, the stone has still not disappeared, extraction must be performed. This is done through an adequate (greater than the French 12) catheter.[23] The stone may have to be crushed before extraction is possible. A choledochoscopy with direct visualization may be useful.[25] Cholesterol-rich stones may be dissolved by intrabiliary infusions of sodium monooctoate.[26]

If the common duct stone is diagnosed sometime after the cholecystectomy, a decision has to be made between endoscopic papillotomy and open operation as the treatment of choice. Open operation in experienced hands carries an operative mortality of less than 2%. Some surgical results are even better than this. In one series, 69 operations for retained or recurrent bile duct stones resulted in no deaths and only two recurrences.[27] Endoscopic papillotomy with stone extraction in experienced hands carries a mortality of about 1% (Fig. 4).[28] About 7% suffer immediate complications (bleeding, cholangitis, pancreatitis, or perforation) and half of these require surgical intervention. The choice of endoscopy or surgery depends in part on which experienced operators are available in that particular medical institution. Much depends also on the age and general condition of the

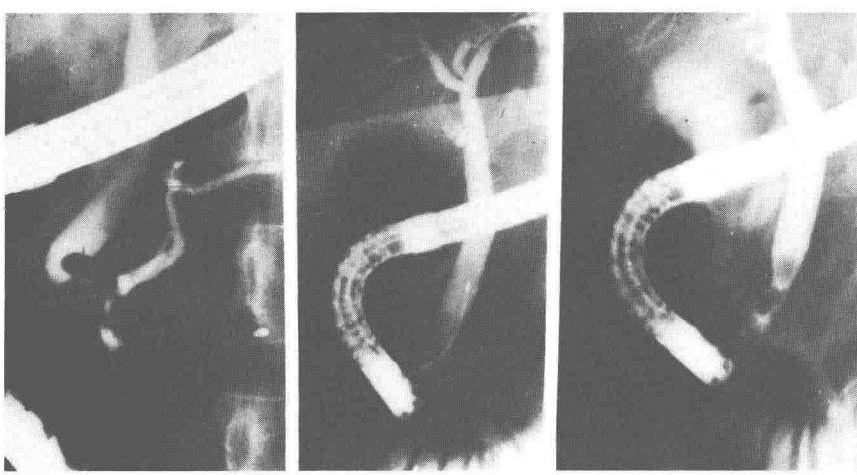

Figure 4. Endoscopic sphincterotomy. Left-hand figure shows a residual gallstone at the lower end of the common bile duct. Central figure shows electrocautery in position at the lower end of the common bile duct. Right-hand figure—post sphincterotomy—shows that the stone has passed. Air bubbles are seen in the common bile duct.

TABLE 7
Duodenoscopic Sphincterotomy for Bile Duct Stones[a]

Age > 70 Years			
Number	Successful	Stones Cleared	Complications
71	69 (92%)	65	9 (13%)

Mean hospital stay was 11 days.
[a]Adapted from Mee et al., *Br Med J* **2:** 521, 1981.

patients. In elderly and frail patients over age 60, common bile duct surgical exploration has a mortality of 5–10%, and endoscopic papillotomy a mortality of 1%. It is in this bad-risk group, therefore, that endoscopic sphincterotomy is particularly valuable (Table 7).[29] The use of endoscopic papillotomy in the young, healthy patient is more controversial and long-term, follow-up studies of papillotomies are eagerly awaited. Common bile duct stones can also be removed transhepatically.[30] The nasobiliary route may be used after prior papillotomy, with or without the need to split the papilla, and a pigtail catheter is placed in the common bile duct. Failures are only 10%.[33] This nasal endoscopic approach is being increasingly used as an emergency procedure in patients who are severely ill with cholangitis or pancreatitis and who still have a gallbladder. A sphincterotomy provides excellent duct drainage and rapid clinical improvement. Where necessary, a pigtailed catheter can also be placed in the pancreatic duct.[34] These procedures are extremely useful preoperatively.

Biliary Drainage by Endoprosthesis

An endoprosthesis may be introduced into the biliary system to allow drainage. Using the transhepatic route, a guide wire is passed through the biliary stricture into the lower common bile duct or duodenum. A tapered dilator is then passed over the guide wire and the endoprosthesis is advanced over both by means of a length of tubing of similar caliber to the prosthesis. Once the endoprosthesis is in position so that it will allow drainage of bile into the lower common bile duct or duodenum, the guide wire and dilator are removed (Figs. 5 and 6).[31,35] In one series, internal biliary drainage was attempted upon 150 patients with obstructive jaundice and was successful in 123, 99 of whom had permanent drainage with the endoprosthesis.[36] The effect upon jaundice was equal to that in 43 patients who underwent surgical operation with palliative surgical bypass.

Biliary drainage can be similarly instituted by placing a catheter endoscopically through the tumor over a guide wire. This catheter can later be replaced by a permanent indwelling prosthesis placed endoscopically through the papilla.[37]