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NONSURGICAL TREATMENT OF GALLSTONES: CURRENT STATUS AND FUTURE PROSPECTS

LYMAN E. BILHARTZ, M.D.

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

MEDICAL GRAND ROUNDS

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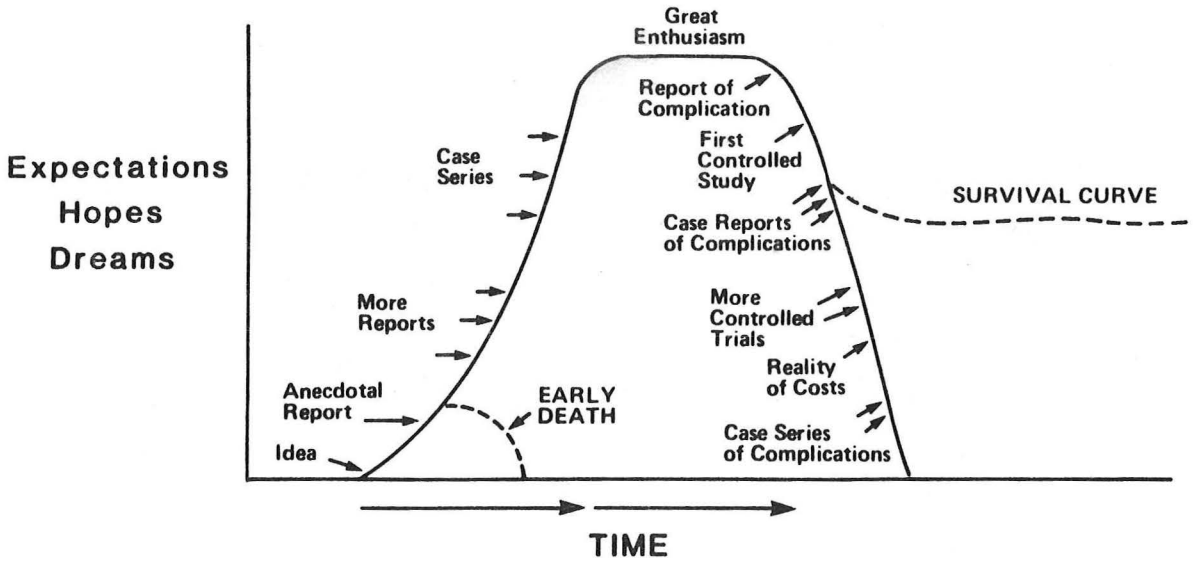

NONSURGICAL TREATMENT OF GALLSTONES

Lyman E. Bilhartz, M.D.
Assistant Professor of Medicine
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In Western societies, the formation of gallstones is a very common occurrence that results in substantial morbidity and enormous economic cost. Over their lifetime, between 10 and 20 percent of all Americans will develop gallstones. This translates into an annual incidence of one million new cases each year. Of these, 500,000 will undergo cholecystectomy, the direct medical cost of which is a staggering four billion dollars per year. Clearly then, the magnitude of this problem in terms of both its morbidity and economic cost necessitates the development of new ways of treating and perhaps even preventing gallstone formation.

I. EPIDEMIOLOGY

Gallstones can be broadly classified into two main categories: cholesterol stones and pigment stones. The pathophysiology of cholesterol stone formation is different from that of pigment stone formation, and thus the epidemiologies of the two diseases are distinct despite similar clinical manifestations. A clear understanding of the epidemiological distinctions is of more than mere academic interest; in many instances epidemiological considerations are the only way to predict a stone's composition and hence the probability of responding to medical therapy.

TABLE 1. RISK FACTORS FOR PIGMENT GALLSTONE FORMATION

1. Chronic hemolysis
2. Alcoholic cirrhosis
3. Biliary infection
4. Age
5. Demographic characteristics: Far East more than the West, rural more than urban

The established risk factors for pigment stone formation are listed in Table 1. Any condition that gives rise to a shortened lifespan of the red blood cells will predispose to pigment stone formation. Thus, autoimmune hemolytic anemias, sphenocytosis, sickle cell anemia, prosthetic heart valves, and malaria all place patients at risk for pigment stones. Patients with alcoholic cirrhosis are known to be at an increased risk, though the mechanism is obscure. When the bile is chronically infected (as may occur in conjunction with parasitic infestations of the bile ducts or as a result of prior bile duct surgery) the bacteria (usually E. coli) may elaborate a β-glucuronidase that deconjugates the bilirubin in the bile. Unconjugated bilirubin is virtually insoluble in water and thus may precipitate to form a pigment stone. Finally, the incidence of pigment stones increases with age.

In the Far East, pigment stones account for the vast majority of gallstones, probably as a result of the high incidence of ascaris infestation. In contrast, in the United States pigment stones account for only 20% of all gallstones. Notably, pigment stones are rare in American Indians.

TABLE 2. RISK FACTORS FOR CHOLESTEROL GALLSTONE FORMATION

1. Obesity.
2. Female sex hormones.
3. Bile acid malabsorption.
4. High calorie diet. ? high polyunsaturated fat diet.
5. Clofibrate, Gemfibrozil, ? Cholestyramine.
6. Rapid weight loss.
7. Demographic characteristics: Northern European, North and South Americans, American Indians, and a family history of cholesterol gallstones.

Table 2 lists the known and suspected risk factors for cholesterol gallstone formation. At the top of the list is obesity which has unequivocally been shown to be a major risk factor. Virtually all people (living in the West) whose weight exceeds 130% of their ideal body weight secrete a bile that is supersaturated with cholesterol, and thus are predisposed to cholesterol gallstones. Women during child bearing years are at risk, as are people taking estrogenic medications. Any disorder that interferes with bile acid absorption (such as ileitis due to Crohn's disease, ileal resection or bypass, cystic fibrosis, etc.) places the patient at risk. Diets rich in polyunsaturated fats or rich in cholesterol are said to be a risk, but the data on this are inconclusive. The renewed interest in the use of drugs in the treatment of people who have elevated (or even high normal) plasma cholesterol concentrations may unfortunately lead to excessive biliary cholesterol concentrations. An example of such a drug is clofibrate, which doubles the risk of cholesterol gallstones. Gemfibrozil, which acts through a similar mechanism, will probably also double the risk. Even the bile acid binding resin cholestyramine has been linked to increased biliary cholesterol secretion. The newly released lovastatin can, in laboratory animals, lead to dramatic elevation in biliary cholesterol secretion. Only time will tell if our efforts to treat hypercholesterolemia will have untoward effects on the already high incidence of cholesterol gallstone disease. Finally, a surprising observation was recently made when patients on a 500 kcal liquid diet for the purpose of weight reduction were followed prospectively with gallbladder sonograms. Twenty-five percent of these patients developed asymptomatic cholesterol gallstones during the 19-week study period. It is not yet known if these stones persist after the weight stabilizes.

Two epidemiological points warrant emphasis. First, the formation of gallstones, especially cholesterol stones, is an extraordinarily common occurrence in Western societies. Secondly, several seemingly healthy activities, such as eating a diet high in polyunsaturated fats, taking a cholesterol-lowering drug or losing weight may ironically increase the risk of cholesterol gallstone disease.

II. PATHOPHYSIOLOGY

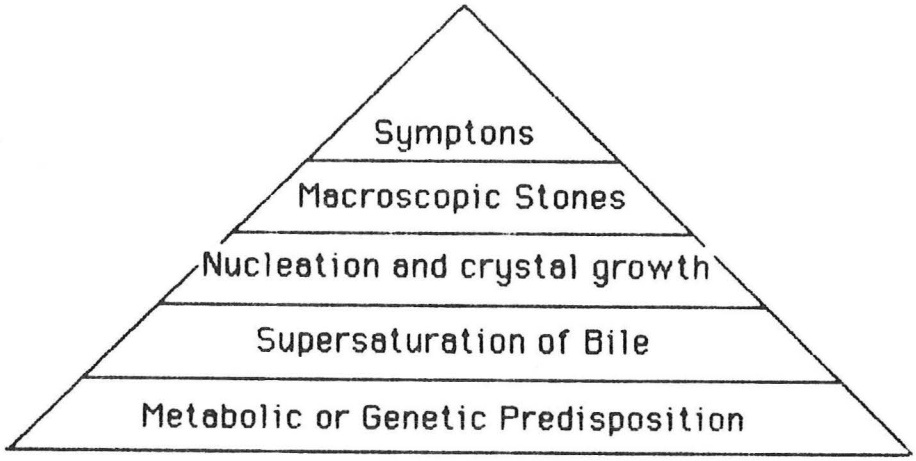


Figure 1

Cholesterol gallstone formation proceeds in an orderly manner through five well-defined stages. Each stage is a prerequisite of the next. Initially, a concealed genetic or metabolic abnormality is present in the liver that predisposes the production of a bile supersaturated with cholesterol. In the next chemical stage, the bile is saturated with more cholesterol than can be held in solution by the accompanying bile acids. In time, if the appropriate pro-nucleating agents are present in bile or if the necessary anti-nucleating agents are absent, the excess cholesterol will precipitate out and a microscopic cholesterol crystal will form.

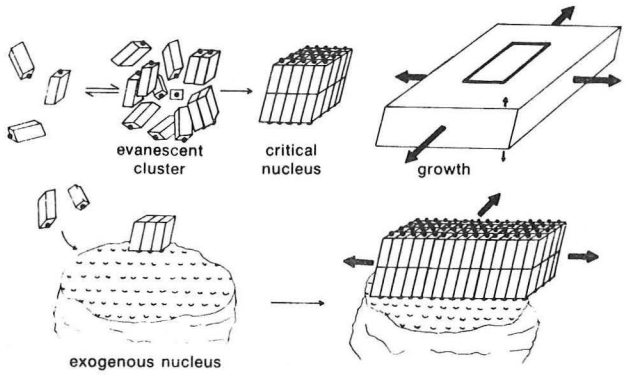


Figure 2 (Ref. 4)

Under normal conditions, the microscopic crystals are emptied out by the millions into the intestine with each meal. However, in some patients (perhaps those with inadequate gallbladder emptying) the crystals grow into

macroscopic stones which can be detected by various imaging procedures. In some patients with macroscopic stones, the stone will either impact in the cystic duct causing biliary colic or acute cholecystitis or will migrate out of the gall bladder into the common bile duct and impact at the ampulla causing ascending cholangitis or acute pancreatitis. I should emphasize that there is <u>not</u> an inevitable progression from one stage to the next (e.g. many people have supersaturated bile but never develop microscopic crystals); therefore, there would seemingly be many points at which intervention could be attempted to prevent the development of disease.

III. NATURAL HISTORY

In the early years of this century Sir William Osler observed that "most gall stones caused no symptoms". In 1911, however, none other than William Mayo reported in the JAMA that the "innocent" gallstone was a myth. Mayo based this assertion on a misunderstanding of the true prevalence of gallstones. Despite published autopsy series placing the prevalence of gallstones (at the time of death) at 10%, Mayo felt the true prevalence was 0.5% and thus he grossly underestimated the frequency of "innocent" gallstones. These two giants of twentieth century American medicine thus framed a controversy that continued for many years.

Now, however, carefully done long-term longitudinal studies have clearly shown that the majority of gallstones cause no symptoms whatsoever and can be managed conservatively with no treatment at all. The results of the best of these studies are shown in Figure 3.

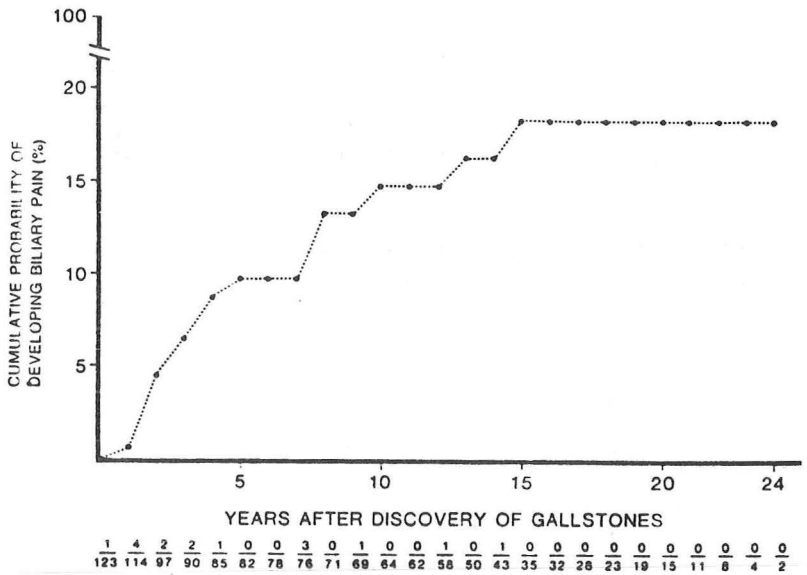


Figure 3 (Ref. 10)

From 1956 until 1969, all faculty members at the University of Michigan underwent a comprehensive medical evaluation that included oral

cholecystograms. One hundred and twenty-three people were discovered to have incidental gallstones. Of these, none died of gallstone disease. Sixteen of the 123 subsequently developed biliary pain; three of whom required emergency cholecystectomy and 11 of whom underwent elective cholecystectomy. The point to be made from Figure 3 is that, at least in this predominantly male group of professionals with incidental gallstones, the vast majority (over 80%) do not develop symptoms referable to these stones with long term follow-up.

The risk of carcinoma of the gallbladder is sometimes cited as an indication for prophylactic cholecystectomy in patients with asymptomatic gallstones. While it is true that the presence of a gallstone predisposes to the development of gallbladder adenocarcinoma (80% of cancerous gallbladders contain a gallstone), this is fortunately a relatively rare occurrence. Furthermore, since cancer of the gallbladder occurs late in life (mean age of 69), the actual increase in lifespan that would be brought about by prophylactic cholecystectomy for asymptomatic gallstones would be modest and not worth the cost and morbidity of many operations in young people.

Figure 3 suggests that most gallstones cause no symptoms. A second question concerning the natural history of this disease is HOW LONG HAVE STONES THAT ARE CAUSING SYMPTOMS BEEN PRESENT? This important question was answered in a novel way using as a tracer for the timing of stone formation the ^{14}C carbon released into the atmosphere during nuclear weapons testing in the 1960s. This study, done in 11 patients, showed that no patient developed symptoms until the gallstone had been present for at least two years. On average there was a lag time of 12 years between intial stone formation and the need for cholecystectomy. This long latentcy period would allow for the natural progression of gallstone disease to be interrupted with medical therapy.

IV. DIAGNOSIS

There are five diagnostic tests available for the diagnosis of gallstone disease.

a. SONOGRAPHY. Sonography is a quick, non invasive way of detecting gallstones. For stones within the gallbladder, the sensitivity and specificity of this test exceed 95%. If the stone is in the common bile duct, it is seldom seen sonographically and its presence is known only indirectly through bile duct dilation. Thus the sensitivity of sonography for detecting common duct stones is much less than it is for stones in the gallbladder (75%). Unfortunately, sonography cannot distinguish between calcified stones and noncalcified stones.

b. CT SCAN. CT scan of the abdomen is not a very sensitive test for detecting the presence of gallstones. When seen on CT, the finding is highly specific and gives some information as to the calcium content of the stone.

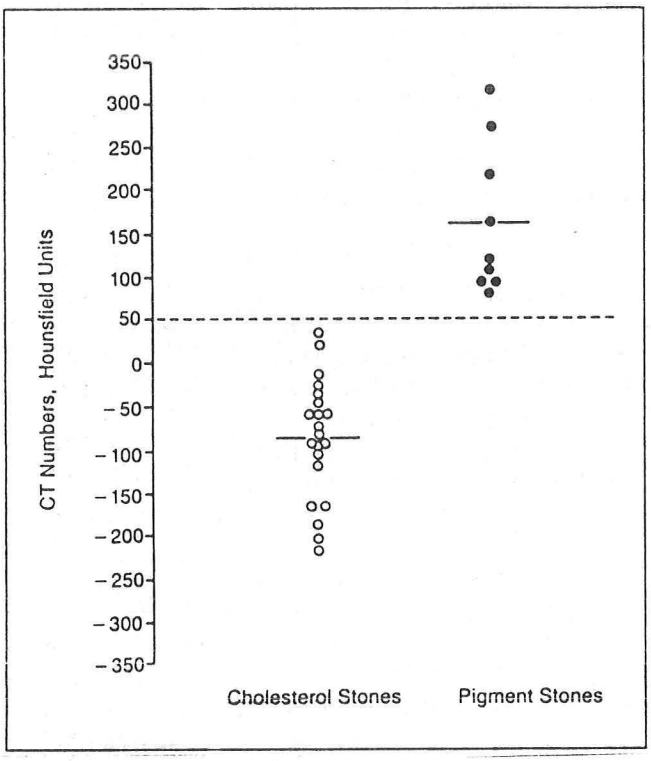


Figure 4 (Ref. 15)

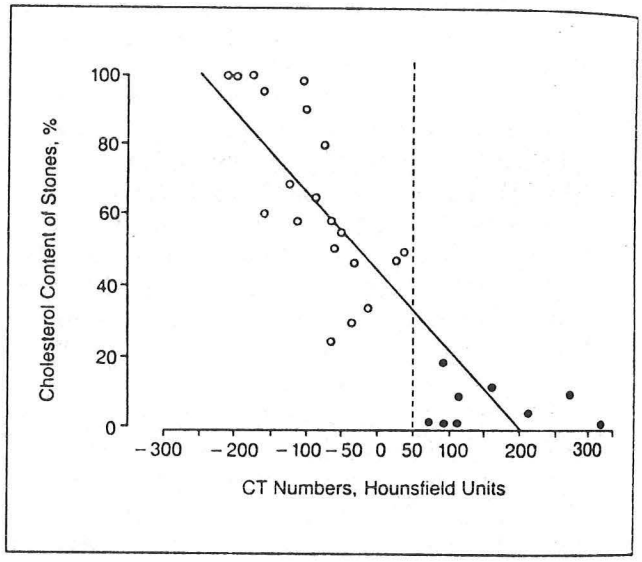


Figure 5 (Ref. 15)

Figure 4 shows an in vitro CT analysis of gallstones. First, the stones were removed from the gallbladder, assayed for their cholesterol and bilirubin content and catagorized as cholesterol or pigment stones. They were next placed in a plexiglass phantom chamber, suspended in water, and scanned in a conventional (Siemens Somaton DR3) CT scanner. As is apparent, all cholesterol stones had a CT number of 50 Hounsfield units or less, whereas all pigment stones had a CT number greater than 50.

In Figure 5 the cholesterol content of the stone is plotted as a function of the CT number. Based on this in vitro study, the CT scanner would appear to be useful in differentiating pigment from cholesterol stones. In practice the stones must be large enough to be clearly identifiable on the CT scan. The CT radiologist needs to be alerted in advance to take extra scans of the right upper quadrant.

The ability to distinguish cholesterol from pigment stones and noncalcified stones from rim-calcified stones is of more than mere academic interest. As will be discussed in the next section, only noncalcified cholesterol stones are amendable to dissolution therapy with bile acids, and thus a carefully done CT scan may help direct the choice of treatment. A CT scan is also useful at detecting the presence of extrabiliary masses that may be causing biliary obstruction (e.g. pancreatic tumor, pancreatitis, etc.). A normal CT scan cannot be used to exclude the presence of gallstones.

c. OCG. In the past, oral cholecystography was the gold standard for the diagnosis of cholelithiasis. Now, however, with its ease and speed, sonography has generally replaced this diagnostic method. OCG does however still have certain advantages over sonography, particularly in identifying that subset of patients with gallstones that would likely respond to medical therapy. First, the scout film done at the beginning of the OCG may demonstrate calcium within the gallstone. As will be discussed in the next section, the presence of calcium in a stone makes it unlikely that the stone will dissolve with medical therapy. Second, when the iodinated contrast material from the OCG is concentrated within the gallbladder, the density of the bile increases and cholesterol stones (but usually not pigment stones) float to the top of the gallbladder. Thus, a carefully performed OCG looking for the absence of calcifications and the presence of floating stones can select out those patients most likely to respond to medical therapy.

d. DUODENAL DRAINAGE - In this test the duodenum is intubated per orally and bile is collected before and after stimulation of gallbladder contraction by an exogenous agent (CCK or Mg sulfate). The bile is then examined under a polarizing microscope for the presence of cholesterol crystals. The presence of cholesterol crystals in the bile correlates with the presence of cholesterol gallstones in the gallbladder. The main use of this test has been in evaluating patients in whom the clinical suspicion for cholelithiasis is very high but who have no stones detectable by sonography. A drawback to the use of this test is that we don't really know what the specificity of the test is, i.e., we don't know how many normal people without stones have crystals in their bile. Until the test is better standardized, I would not recommend cholecystectomy merely for the presence of crystals in the bile.

e. ERCP - ERCP is currently the gold standard for the diagnosis of common bile duct stones. If the bile duct is successfully visualized, as it is in 90% of attempts, then the sensitivity and specificity of ERCP for common duct stones is in excess of 95%. In addition to diagnosis, ERCP can be used therapeutically to retrieve or pulverize common duct stones. The main drawback to the use of this test is the expense and the small but real risk of inducing pancreatitis.

V. TREATMENT

As of now there are only two fully approved and recognized means of treating cholelithiasis: cholecystectomy and long term treatment with chenodiol (Chenix). There are, however, three other new ways of treating gallstones which are on the horizon and will be available for general use within the next few years. What follows then is a brief review of current and future ways of treating gallstones.

1. CHOLECYSTECTOMY - Surgical removal of the gallbladder remains the gold standard of therapy for both pigment and cholesterol gallstones. It is curative in virtually 100% of the patients (primary common duct stone formation is extremely rare). Figure 6 shows the estimated operative mortality rates for men undergoing cholecystectomy.

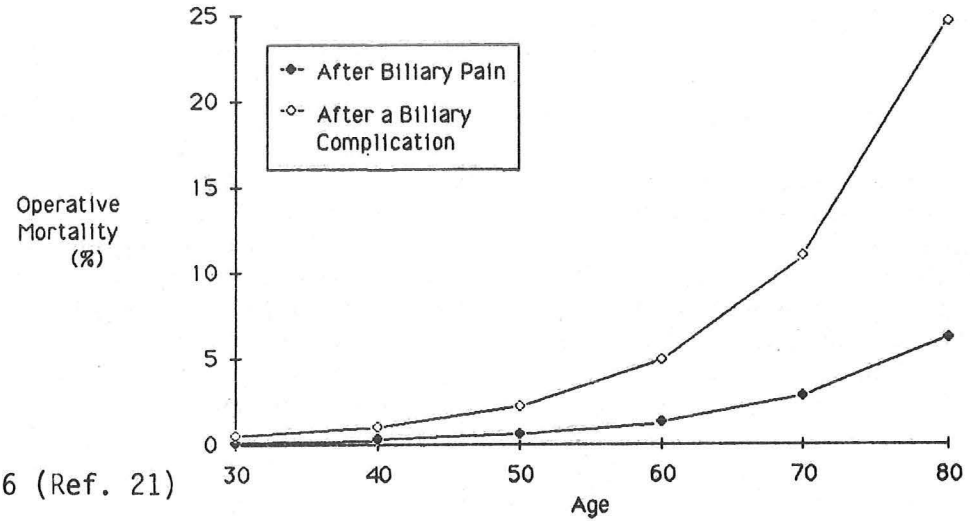


Figure 6 (Ref. 21)

As is shown, the operative mortality rate is lowest for young, healthy men who are being operated on for simple biliary colic and is highest for elderly men who are being operated on after a complication from a gallstone. For every age, the operative mortality for women is one-half of that for men.

If a few assumptioins are made regarding the natural history of gallstones, then a formal decision analysis can be done to assess the impact on medical cost and survival of prophylactic cholecystectomy in patients with asymptomatic gallstones. Based on actuarial data from the University of Michigan experience (Figure 3) the mean yearly probability of developing biliary pain is 2% during the first 5 years, 1% during the second 5 years, 0.5% during the third 5 years, and 0% thereafter. Although no patients in the Michigan study presented with a complication as the initial manifestation of their gallstone, other studies have suggested that about 10% of gallstones will present with a complication as the initial event. Given these assumptions and the above operative mortalities, the following decision analysis is obtained.

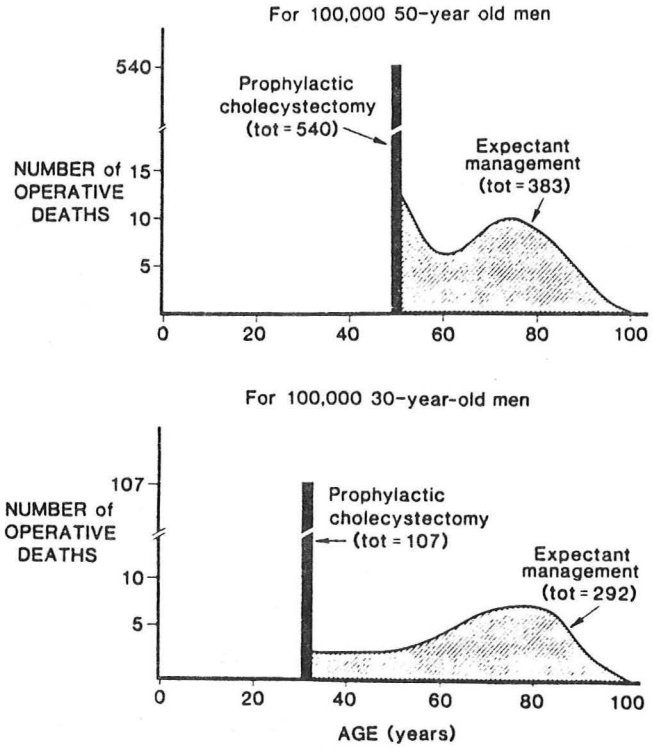


Figure 7

The upper panel shows the total number of operative deaths for either prophylactic cholecystectomy or expectant management (i.e., operating only after biliary pain or a complication has developed) in 100,000 fifty-year-old men. As shown, 540 operative deaths occur immediately in the prophylactic surgery group, whereas only 383 deaths could occur with expectant management. Clearly then, for 50-year-old men, it is better to wait until the gallstone is causing symptoms. A similar analysis for a 30-year-old man is in the lower panel. Although the total number of deaths in the group treated with expectant management exceeds that for prophylactic cholecystectomy, the deaths in the latter group are all in asymptomatic 30-year-old men. Thus, the overall effect on life expectancy favors expectant management of asymptomatic gallstones regardless of age. An exception to this general rule for leaving asymptomatic gallstones alone would be a gallstone in a calcified gallbladder. In this case, the risk of subsequently developing gallbladder carcinoma is an indication for prophylactic cholecystectomy.

It is my opinion that as of now, patients who are having symptoms from gallstones and who do not have a compelling reason not to operate should undergo a cholecystectomy as the primary treatment of their stones.

2. GALLSTONE DISSOLUTION WITH BILE ACIDS (slow dissolution) - Bile acids are biological detergents that are made by the liver from cholesterol for the purpose of solubilizing dietary triglycerides and thereby permitting absorption of dietary fat. These detergent molecules undergo an enterohepatic circulation in that they are taken up by specific receptors in the distal ileum, transported via the portal circulation to the liver, taken up by

hepatocytes and resecreted into the bile. During their transport across the hepatocyte, they extract phospholipid and cholesterol out of the cell and carry it into the bile. In some people (i.e. those with risk factors for cholesterol gallstone formation) more cholesterol is extracted from the hepatocyte than can be maintained in solution in the bile. Thus the stage is set for crystal formation and ultimately gallstone disease. There are two naturally occurring bile acids that when fed to people for a long time bring about a subtle alteration in the internal structure of the hepatacyte such that less cholesterol is extracted by the bile acid passing through the liver cell. This diminished coupling of cholesterol to bile acids results in a bile that is no longer saturated with cholesterol. Thus a cholesterol gallstone that is in contact with this desaturated bile will eventually dissolve. These two bile acids go by a variety of names and are listed below.

chemical name	chenodeoxycholic acid	ursodeoxycholic acid
abbreviation	CDC	UDC
common name	chenodiol	urso
trade name	Chenix	Urso falk

At the present time only chenodiol is approved for use in the United States. Urso is already available in Europe and the Far East and is currently undergoing phase 4 clinical trials in the United States but will probably not be approved for general use until sometime next year.

a. Chenodiol

In the early 1970s, chenodiol was shown to have successfully dissolved cholesterol gallstones in a few patients. Of course, there was a great deal of enthusiasm about its potential use, and a National Cooperative Gallstone Study was begun in the late 1970s to determine if this bile acid would be useful clinically. This was an extremely complex, multi-centered, nine million dollar study, the gist of which is summarized in Figure 8.

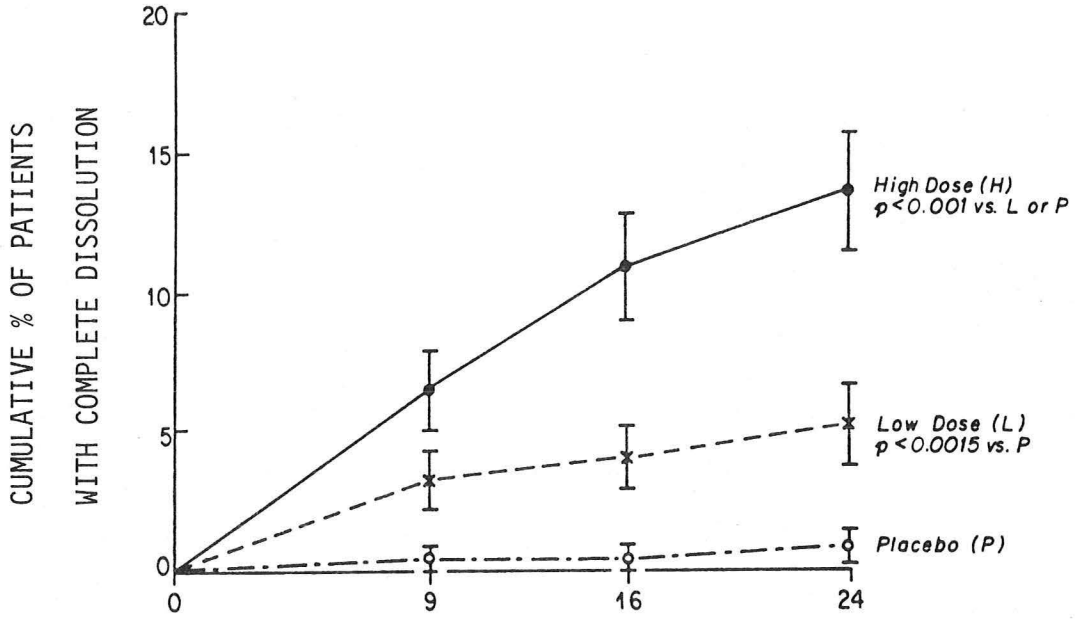


Figure 8 (Ref. 52)

After 24 months of continuous therapy, a dismal 13.5% of the patients taking the high dose chenodiol achieved complete dissolution of the gallstones. Clearly, no matter how you try to rationalize these findings, the study was a disappointment. It is possible to dissect out of the study subgroups of patients who are more likely to achieve complete dissolution than the group as a whole. The factors that best predicted complete dissolution with chenodiol were a) less than 100% of ideal body weight, b) stones that floated on the OCG exam, c) a small total number of gallstones (less than three), d) small size of the stones (less than one inch diameter) and finally e) a high plasma cholesterol (greater than 227 mg/dl). Additionally there was a trend towards women having a higher rate of complete dissolution than men. Thus the ideal patient for chenodiol therapy would be a skinny woman with hypercholesterolemia and a small number of small floating gallstones. Given all those parameters, the patient perhaps has a 50% chance of achieving a complete dissolution.

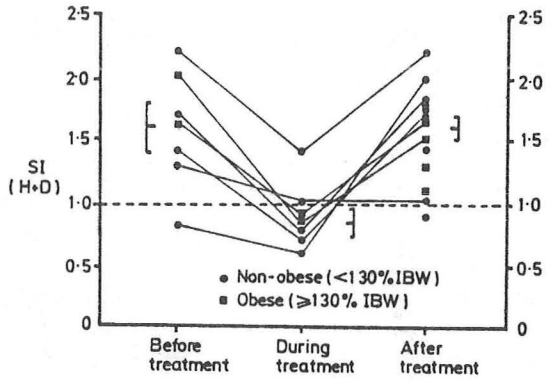


Figure 9 (Ref. 34)

Another drawback to the use of chenodiol is illustrated in Figure 9. The saturation index, SI, of fasting duodenal bile (an SI of >1.0 means the bile is thermodynamically unstable and precipitation of cholesterol is likely to occur) is plotted before, during, and after treatment with chenodiol. Before treatment, these gallstone patients had bile that was markedly supersaturated with cholesterol. During treatment with chenodiol the SI fell in all the patients and, in all but two, became desaturated. Unfortunately, after treatment was discontinued, the SI returned to pretreatment values. Thus, the underlying pathogenetic defect remains despite the intervention and eventual gallstone recurrence would be predicted. Indeed, a number of studies have examined the frequency of gallstone recurrence after dissolution therapy and in general have shown a recurrence rate of approximately 10% per year. Of course, it may take a number of years before the recurrent stones cause any symptoms, if ever. Efforts to prevent stone recurrence by administration of low doses of chenodiol have been unsuccessful. If dissolution therapy with chenodiol is successful, however, it can "buy time" during which risk factors such as obesity can be corrected. Ultimately, of course, a better understanding at the cellular level of the underlying pathogenetic defect may make stone recurrence, and perhaps even primary stone formation, preventable.

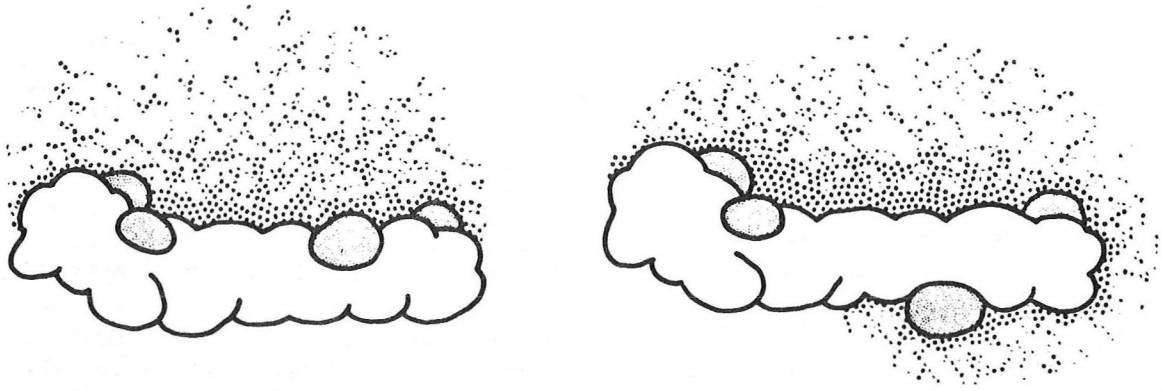
In addition to low efficacy and the problem of stone recurrence, chenodiol has several untoward side effects. One-third of patients taking chenodiol will develop a mild, watery diarrhea due to the direct secretagogue effect of the chenodiol on the colon. The diarrhea can be managed by temporarily decreasing the dose. Of more concern is the fact that patients taking chenodiol increased their total plasma cholesterol concentration by an average of 20 mg/dl (8.7%) This increase was mostly due to an increase in the concentration of LDL. Thus, long term therapy with chenodiol could conceivably promote atherogenesis. Finally, one-third of patients taking chenodiol experienced a mild increase in AST levels. The transaminase levels returned to normal when the dose of the drug was reduced. In 3% of the patients, significant biochemical or morphologic abnormalities of the liver occurred that required cessation of therapy. The clinical significance of this liver disease is not known.

Overall, chenodiol is far from being the ideal treatment of gallstones. The side effects might be tolerable if only the drug had a good chance of

working; however, even with selected patients less than half will achieve a complete dissolution with two years of therapy.

In my opinion, chenodiol should be used in patients who are symptomatic with gallstone disease, have small non calcified, floating stones present on OCG and in whom there is a compelling reason not to operate. For the patient who poses a prohibitive surgical risk (or as is more common a patient who simply is terrified of surgery) I think that chenodiol is worth a try.

b. Urso. Urso, like chenodiol, is a naturally occurring bile acid. Though present in very small amounts in normal humans, it is abundant in the bile of certain species such as the polar bear and the South American nutria. Urso is structurally very similar to chenodio, differing only in the orientation of the hydroxyl group at the three position. (A space-filling model of the two compounds is depicted in Figure 10).



Chenodeoxycholic Acid

Ursodeoxycholic Acid

Figure 10

This small change in chemical structure has profound physiologic effects. Urso, compared to chenodiol, is much more hydrophilic and much less effective as a detergent. Accordingly, it is less efficient at solubilizing dietary cholesterol and thus limits cholesterol absorption. Additonally, on a mole for mole basis, urso extracts less cholesterol from the hepatocyte on its passage through the liver.

Once in bile, urso has an additional mechanism for dissolving the stone that is not available to chenodiol.

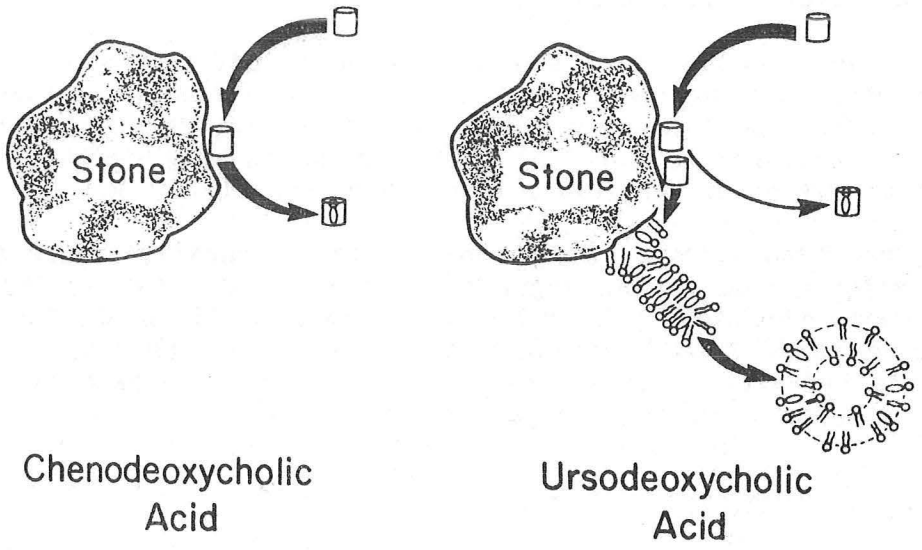


Figure 11.

As depicted in Figure 11, in bile, chenodiol exists in mixed micelles containing bile acid, phospholipid and cholesterol. The micelle diffuses to the surface of the stone. If the micelle is not already saturated with cholesterol, then cholesterol molecules from the stone may be incorporated into the micelle. The rate at which cholesterol is removed from the stone is a function of the rate of diffusion of the micelle through the aqueous phase, the surface area of the cholesterol stone that is exposed to bile and the degree of saturation of the bile. In contrast, as depicted on the right, if the bile is enriched with urso, then a second mechanism of stone dissolution, namely liquid crystal or mesophase formation, becomes quantitatively important. The urso-rich mixed micelle again diffuses up to the surface of the stone. Urso, being more hydrophilic and a weaker detergent, is unable to hold the phosphalipids in the micelle. Instead, the phospholipids "prefer" to flow onto the hydrophobic surface of the stone, coating it with a monolayer of hydrophobic phospholipid. Molecules of cholesterol from the stone enter into the "liquid crystalline" phospholipid monolayer. The surface area of the stone that interacts with the phospholipid monolayer is much greater than the area that comes into contact with a micelle and the "dwell time" is much longer. As the liquid crystalline monolayer becomes saturated with cholesterol, it begins streaming away from the stone surface and into the aqueous phase, finally budding off to form unilaminar vesicles. Hence, an urso-rich bile, through the mechanism of liquid crystal formation, is able to solubilize cholesterol stones more rapidly than a chenodiol-rich bile.

Unlike chenodiol, urso does not suppress bile acid synthesis. This is an important difference in that conversion of cholesterol into bile acids is the primary means of eliminating cholesterol from the body. This fact explains why the plasma cholesterol level is unchanged with chronic urso therapy. Urso does not result in an elevated transaminase level, nor is it associated in any

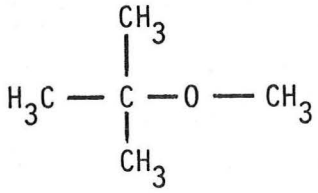
way with chronic liver damage. Finally, urso is not a colonic secretagogue so there is no diarrhea with urso.

In summary urso has several major advantages over chenodiol. These are: a) no liver damage, b) no diarrhea, c) no elevation of plasma LDL, d) no inhibition of bile acid synthesis, e) inhibition of dietary cholesterol absorption. Its efficacy at dissolving established gallstones is at least equal to and probably better than chenodiol.

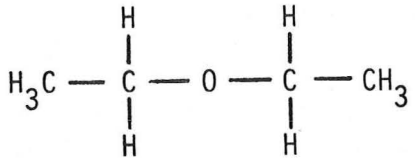
In my opinion, when urso is available (i.e. FDA approved) in the United States, it will largely replace chenodiol for gallstone dissolution. The main drawback to either urso or chenodiol therapy will be the significant percentage of patients that simply fail to dissolve their stones on either agent. Moreover, once the gallstones are dissolved, the underlying pathophysiology is still present and the gallstones will recur in at least 50% of the cases.

3. GALLSTONE DISSOLUTION WITH METHYL TERTIARY BUTYL ETHER (MTBE) (fast dissolution).

MTBE is a powerful organic solvent that is more than a thousand times more effective at solublelizing cholesterol than an aqueous solution of bile acids. Its primary use now is as an octane booster in gasoline.



Methyl Tert-butyl ether
(MTBE)



Diethyl ether

Figure 12

As shown in the above figure, it is chemically similar to diethyl ether (the old ether general anesthetic) but with an important distinction. Diethy ether boils at 35°, expanding to 20 times it original volume. Thus, at 37° it would not be safe to instill into a closed body cavity. MTBE, on the other hand, is much less volatile than diethyl ether and has a boiling point of 55°.

This technique of rapid gallstone dissolution was first developed in 1983 at the Mayo Clinic. It remains a promising but as of now experimental treatment modality. The technique involves placement of a pigtail catheter through

the skin, through the liver and into the gallbladder. The placement of the catheter is done under sonographic guidance (usually by a radiologist).

The sonographer must first ascertain that the gallbladder is attached to the inferior surface of the liver. If that is the case, as it is in >90% of people, then a 5 French pigtail catheter is placed in the gallbladder. If possible, the gallstones are maneuvered away from the vicinity of the cystic duct. As much bile as possible is aspirated from the gallbladder.

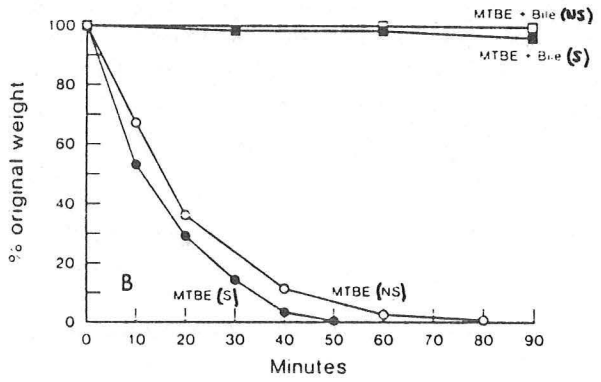


Figure 13 (Ref. 43)

The importance of excluding bile from the gallbladder is illustrated in Figure 13. The weight of a cholesterol stone is plotted as a function of time of exposure to MTBE in vitro. The upper lines (squares) show that if bile is present with the MTBE (vol/vol, 50:50) then the stones do not dissolve. This is because MTBE has a density of only 0.74 and therefore floats above the bile. The gallstones either sink to the bottom or at best float to the interface. In either case, dissolution is very slow. The bottom lines (circles) show that when MTBE alone is present, the stones dissolve in about an hour. Stirring (S) or no stirring (NS) had little effect.

It should be emphasized that the time scale for complete stone dissolution with MTBE is measured in minutes whereas dissolution time was measured in months with chenodiol therapy. (c.f. Figure 8). Once correct catheter placement has been demonstrated, the bile is aspirated out of the gallbladder and replaced with 5 to 10 ml of MTBE. The MTBE is allowed to remain in the gallbladder for several minutes in contact with the stones. The MTBE is aspirated out and fresh MTBE is instilled into the ballbladder repeatedly every few minutes for however many hours it takes to dissolve the stones. Complete dissolution of the gallstones is documented by injection of contrast material into the gallbladder.

Using this technique, Thistle from the Mayo Clinic has recently reported succesful dissolution of stones in 47/48 patients. Obviously this technique though seemingly very effective is fraught with certain dangers. There is the danger of bleeding from the liver and perforation of the gallbladder with resultant bile peritonitis. Furthermore there is the question of toxity of the MTBE to the gallbladder mucosa and to the whole person if absorbed in appreciable quantities.

Prolonged exposure of canine gallbladder mucosa to MTBE failed to induce anything more than mild, nonspecific inflammation of the mucosa. If some of the MTBE spills out of the gallbladder through the cystic duct, then the duodenal mucosa may show a mild duodenitis. Additionally, some of the MTBE is absorbed through the duodenal mucosa and excreted in the breath. Mild anesthesia may occur and requires careful monitoring.

Through meticulous attention to detail the group at the Mayo Clinic has avoided these potential complications in the first few dozen patients that they have treated in this manner.

In my opinion, rapid dissolution of gallstones using MTBE is a very promising new treatment. It is subject to the same limitations that treatment with urso and chenodiol have in that it will be ineffective against either pigment stones or calcified cholesterol stones. As of right now in September 1987, the only people who are reporting experience with this technique are at the Mayo Clinic but my guess is that perhaps a dozen investigators across the country have begun applying this technique to selected patients. If this technique proves to be as safe and efficacious as the intial reports suggest, I think it will have widespread application in the very near future.

4. EXTRACOPOREAL SHOCK WAVE THERAPY OF GALLSTONES (ECSW) - This technique was originally developed to treat kidney stones and as you know has revolutionized the treatment of that entity. The group in West Germany that developed the lithotripser has recently begun applying this technique to the treatment of gallstones. The technique is schematically outlined in Figure 14.

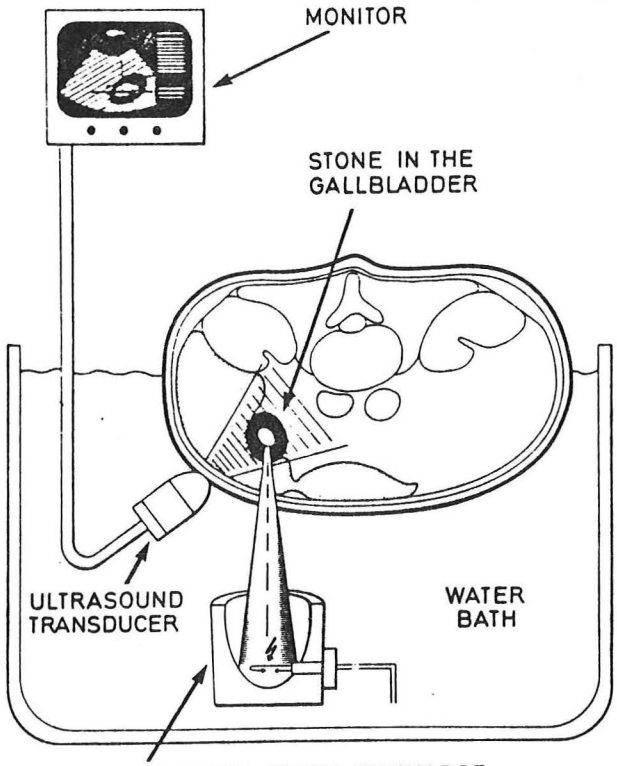


Figure 14.

The patient is placed in a prone position with his body in a tank of water. The gallstone is localized by sonography and the patient is positioned such that the stone is at the focal point of an ellipsoid shock wave generator. High energy shock waves are generated by a spark discharge and focused by the reflector on the gallstone. Between 600 and 1500 shock waves are applied to the patient. In the initial cases, general anesthesia was used and the procedure took between one and two hours to complete. This month, the group from Munich reported successful ECSW lithotripsy in 10 patients who chose to have only mild sedation instead of general anesthesia.

As with MTBE, the initial results obtained by ECSW therapy of gallstones are very encouraging. Almost all of the gallstones treated were disintegrated into sludge or else small stone fragments. The patients were placed on a combination of chonodiol and urso following the lithotripsy. In vitro studies have shown that if stones can be fractured into fragments of 2 mm or less, then an urso-rich bile will completely dissolve the fragments within a few weeks.

The only serious complication reported was a mild case of pancreatitis in one patient (presumably due to passage of a small fragment into the common bile duct).

In my opinion, ECSW therapy of gallstones also shows a great deal of promise. The main drawback will be the initial cost of the lithotripser which currently runs to between one and two million dollars. My prediction would be that within the next five years it will become a standard means of therapy for cholelithiasis in large hospitals and referral centers.

In summary:

1. Gallstone disease (especially cholesterol gallstones) is a very common disease that is probably in some way related to a Western diet.

2. The underlying pathogenesis is a subtle alteration in the liver such that excessive cholesterol is extracted from the liver cell by bile acids undergoing an enterohepatic recirculation.

3. Gallstone disease progresses through well-defined stages beginning with a bile supersaturated with cholesterol and proceeding on to crystal formation, stone growth and finally symptoms due to impaction of a stone in either the cystic duct or the common bile duct.

4. The natural history of gallstones is that most stones never cause symptoms. Stones that do cause symptoms have been present for an average of 12 years. The treatment of truly asymptomatic stones should be simple observation.

5. Ultrasonography of the right upper quadrant is the gold standard for the diagnosis of stones in the gallbladder. ERCP is the gold standard for the diagnosis of stones in the common bile duct. OCG has a role in selecting out patients with noncalcified, floating stones that may be amenable to dissolution with either bile acids or MTBE.
6. Therapy of gallstones with chenodiol has been a disappointment because of a low complete response rate. The ideal candidate for attempted dissolution with chenodiol would be a thin woman with hypercholesterolemia and a small number of symptomatic, small, floating, radiolucent gallstones.

7. Urso, when it is available (? next year), will have all the attributes of chenodiol and virtually none of the side effects.

8. Rapid dissolution of gallstones with MTBE shows a great deal of promise as being a generally available means of dissolving gallstones.

9. ECSW also shows promise, but its general availability may be limited by the cost of the sophisticated equipment needed.

10. As of September, 1987, the treatment of choice for symptomatic gallstones remains cholecystectomy unless there is a compelling reason not to operate.

REFERENCES

EPIDEMIOLOGY

1. Risk factors for the development of cholelithiasis in man. L. J. Bennion, et al. NEJM 299:1161, 1978

2. Effects of pregnancy and contraceptive steroids on gallbladder function. D. Z. Braverman, et al. NEJM 302:, 1980.

3. Development of lithogenic bile during puberty in Pima indians. L. J. Bennion, et al. NEJM 300:873, 1979.

PATHOPHYSIOLOGY

4. Cholesterol nucleation and growth in gallstone formation. D. M. Small. NEJM 302:1305, 1980.

5. Pathogenesis of gallstones. H. F. Weisberg. Ann Clin Lab Sci 14:243, 1984.

6. Biliary lipids, bile acids, and gallbladder function in the human female. Fred Kern, Jr., et al. J Clin Invest 68:1229, 1981.

7. Kinetics of the Enterohepatic circulation during fasting: Biliary lipid secretion and gallbladder storage. H. Y. I. Mok. Gastroenterology 78:1023, 1980.

8. Effects of obesity and caloric intake on biliary lipid metabolism in man. L. J. Bennion, et al. J Clin Invest 56:996, 1975.

NATURAL HISTORY

9. "Innocent" gallstones. A myth. W. J. Mayo. JAMA 56:1021, 1911.

10. The natural history of silent gallstones. The innocent gallstone is not a myth. W. A. Gracie, et al. NEJM 307:798, 1982.

11. The natural history of diagnosed gallstone disease in symptomatic and asymptomtic patients. C. K. McSherry, et al. Ann Surg 202:59, 1985.

12. Chronology of cholelithiasis. Dating gallstones from atmospheric radiocarbon produced by nuclear bomb explosions. H.Y.I. Mok, et al. NEJM 314:1075, 1986.

13. Neoplasms of the gallbladder and bile ducts. L. Way, et al. Schlesinger & Fordtran, 3rd Edition.

14. Complications of cholelithiasis. H. F. Newman, et al. Am J Gastroenterology 50:476, 1968.

DIAGNOSIS

15. Computed tomographic analysis of gallstones. M. S. Hickman, et al. Arch Surg 121:289, 1986.

16. Evaluation of radiographic lucency or opaqueness of gallstones as a means of identifying cholesterol or pigment stones. Correlation of lucency or opaqueness with calcium and mineral. B. W. Trotman, et al. Gastroenterology 68:1563, 1975.

17. Cholesterol crystals and the formation of cholesterol gallstones. NEJM 302:1274, 1980.

18. Intermittency of cholesterol crystals in duodenal bile from gallstone patients. J. W. Marks, et al. Gastroenterology 87:622, 1984.

19. Utility of biliary microscopy for the prediction of the chemical composition of gallstones and the outcome of dissolution therapy with ursodeoxycholic acid. E. Ros, et al. Gastroenterology 91:703, 1986.

20. Endoscopic therapy of biliary calculi. U. Leuschner. Clinics in Gastroenterology 15:333, 1986.

TREATMENT - CHOLECYSTECTOMY

21. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. D. F. Ransohoff, et al. Ann Intern Med 99:199, 1983.

TREATMENT - ORAL BILE ACID THERAPY

22. The medical treatment of cholesterol gallstones. A major advance in preventive gastroenterology. A. F. Hofmann. Am J Med 69:4, 1980.

23. Effect of obesity and weight reduction on biliary cholesterol saturation and the response to chenodeoxycholic acid. A. Reuben, et al. Euro J Clin Invest 16:133, 1985.

24. The cholesterol saturation of bile and its reduction by chenodeoxycholic acid in massively obese patients. M. J. Whiting, et al. Intern J Obes 8:681, 1984.

25. Differences in the effects of chenodeoxycholic and ursodeoxycholic acid on biliary lipid secretion and bile acid synthesis in patients with gallstones. K. von Bergmann, et all. Gastroenterology 87:136, 1984.

26. The effect of diet on bile acid kinetics and biliary lipid secretion in gallstone patients treated with ursodeoxycholic acid[1-3]. P. G. Frenkiel, et al. Am J Clin Nutri 43:239, 1986.

27. The effect of ursodeoxycholic acid on biliary bile acid composition in patients with cholesterol gallstone. Y. Kanazawa, et al. Tohoku J exp. med. 136:235, 1982.

28. Gallstone dissolution with ursodeoxycholic acid in patients with chronic active hepatitis and two years follow up. U. Leuschner. Dig Dis Sci 30:642, 1985.

29. A combination of chenodeoxycholic acid and ursodeoxycholic acid is more effective than either alone in reducing biliary cholesterol saturation. M. Podda, et al. Hepatology 2:334, 1982.

30. Efficacy and indications of ursodeoxycholic acid treatment for dissolving gallstones. Tokyo Cooperative Gallstone Study Group, Gastroenterology 78:542, 1980.

31. Mesophase formation during cholesterol gallstone dissolution in human bile: effect of bile acid composition. C. C. Su, et al. J Pharma Sci 73:1160, 1984.

32. Liquid crystal solubilization of cholesterol: Potential method for gallstone dissolution. J. B. Bogardus. J Pharma Sci 72:338, 1983.

33. Is recurrence inevitable after gallstone dissolution by bile acid treatment? D. C. Ruppin, et al. The Lancet i:181, 1982.

34. Gallstone disease without gallstones - bile acid and bile lipid metabolism after complete gallstone dissolution. D. C. Ruppin, et al. Gut 27:559, 1986.

35. The present status of agents for dissolving gallstones. T. Tangedahl, et al. Am J Gastroent 80:64, 1985.

36. Gallstone dissolution and the cholesterol-bile acid-lipoprotein axis. Propitious effects of ursodeoxycholic acid. H. Fromm. Gastroenterology 87:229, 1984.

37. Gallstone dissolution therapy. Current status and future prospects. H. Fromm. Gastroenterology 91:1560, 1986.

38. Chenodeoxycholic acid desaturates bile- But how? J. M. Anderson. Gastroenterology 77:1146, 1979.

39. How does urso dissolve gallstones? B. Angelin, et al. Gastroenterology 85:1222, 1983.

TREATMENT - METHYL TERT-BUTYL ETHER (MTBE)

40. Cholelitholysis using methyl tertiary butyl ether. M. J. Allen, et al. Gastroenterology 88:122, 1985.

41. Rapid dissolution of gallstones by methyl tert-butyl ether. M. J. Allen, et al. NEJM 312:217, 1985.

42. Dissolution of gallstones by methyl tert-butyl ether. R. A. F. Gonzaga, et al. NEJM 313:385, 1985.

43. In vitro dissolution of cholesterol gallstones. A study of factors influencing rate and a comparison of solvents. M. J. Allen, et al. Gastroenterology 89:1097, 1985.

44. Methyl tert-butyl ether fails to dissolve retained radiolucent common bile duct stones. C. D'Padova, et al. Gastroenterology 91:1296, 1986.

45. Agents for gallstone dissolution. H. A. Pitt, et al. Am J Surg 153:233, 1987.

TREATMENT - EXTRACORPOREAL SHOCK WAVE THERAPY (ECSW)

46. Shock waves for gallstones: animal studies. W. Brendel, et al. Lancet 1054, 1983.

47. Fragmentation of gallstones by extracorporeal shock waves. T. Saurerbruch, et al. NEJM 314:818, 1986.

48. Shock waves: A new physical principle in medicine. W. Brendel. Eur Surg Res 18:177, 1986.

49. In vitro cholesterol gallstone dissolution after fragmentation with shock waves. M. Neubrand. Digestion 34:51, 1986.

50. Treatment of retained cystic duct stones using extracorporeal shockwave lithotripsy. C. D. Becker, et al. AJR 148:1121, 1987.

51. Extracorporeal shock-wave lithotripsy of gallstones without general anesthesia: First clinical experience. M. Sackmann, et al. Ann Intern Med 107:347, 1987.

NATIONAL COOPERATIVE GALLSTONE STUDY

52. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: The National Cooperative Gallstone Study. L. J. Schoenfield, et al. Ann Intern Med 95:257, 1981.

53. Pretreatment biliary lipid composition in white patients with radiolucent gallstones in the National Cooperative Gallstone Study. A. F. Hofmann, et al. Gastroenterology 83:738, 1982.

54. Low-dose chenodiol to prevent gallstone recurrence after dissolution. J. W. Marks, et al. Ann Intern Med 100:376, 1984.

55. Additional chenodiol therapy after partial dissolution of gallstones with two years of treatment. J. W. Marks, et al. Ann Intern Med 100:382, 1984.

56. More on chenodiol: Continued treatment and prevention of recurrences. R. H. Palmer. Ann Intern Med 100:450, 1984.

57. The natural history of cholelithiasis: The National Cooperative Gallstone Study. J. L. Thistle, et al. Ann Intern Med 101:171, 1984.

58. The effects of chenodiol on biliary lipids and their association with gallstone dissolution in the National Cooperative Gallstone Study (NCGS). S. M. Grundy, et al. J Clin Invest 73:1156, 1984.

59. Lack of correlation between serum lipoproteins and biliary cholesterol saturation in patients with gallstones. J. W. Marks, et al. Dig Dis Sci 29:1118, 1984.

60. Chemical and morphologic characteristics of cholesterol gallstones that failed to dissolve on chenodiol. H. S. Freilich, et al. Gastroenterology 91:713, 1986.