Findings by several groups of investigators have provided a reliable data base that supports a nonoperative approach toward the management of so-called silent gallstones. Considerable progress has been made in the medical dissolution treatment of selected patients with cholesterol gallstones. Ursodeoxycholic acid, and, more recently, a combination of ursodeoxycholic and chenodeoxycholic acids have been shown to be both effective and safe in dissolving gallstones that are predominantly composed of cholesterol. A drawback of the bile acid dissolution therapy lies in a significant recurrence rate after treatment is discontinued. Currently, several new methods of gallstone treatment are under study, which involve either the injection of a cholelitholytic solution, such as methyl tert-butyl ether, into the gallbladder or the use of mechanical means, such as extracorporeally induced shock waves, to disintegrate gallstones. These treatments, however, are effective only if the stones are composed mainly of cholesterol without significant admixtures of calcium salts, pigment, or mucus. Most of the treatment failures are probably related to the presence of calcifications that are not visible on conventional radiographs. Future improvements of gallstone dissolution therapy can be expected from the following possible developments: (a) improvement in ability to predict gallstone composition; (b) dissolution of calcium salt-, pigment-, and mucus-containing stones; (c) early treatment, before calcifications occur; (d) combination of chemical and mechanical methods of treatment; (e) stimulation of gallbladder contraction; (f) prevention of stone recurrence after dissolution; and (g) synthesis of new cholelitholytic agents.

A review of gallstone dissolution therapy appears timely. Cholelithiasis is very common, and questions frequently arise in clinical practice in regard to the management of patients in whom gallstones are incidentally discovered. Studies over the last years have resulted in an impressive body of new epidemiologic, clinical, and experimental data that are relevant to this topic. Two major prospective epidemiologic studies by investigators from the Universities of Bologna and Rome in Italy have not only corroborated the original observations by Gracie and Ransohoff regarding the natural history of gallstones, but have also provided new information concerning several other aspects of cholelithiasis, such as both the factors that predispose to this condition and the relationship that exists between gallstones and serum lipids (1-7). Several developments during the last years are of particular relevance to this update of cholelitholytic therapy. They concern the results of several clinical trials of both ursodeoxycholic acid (UDC) and a combination of this bile acid with chenodeoxycholic acid (CDC), as well as the recent introduction of new modes of nonsurgical treatment, namely, the instillation of methyl tert-butyl ether into the gallbladder, and the extracorporeally induced shock wave crushing of gallstones (8-15). The main purpose of this review is to provide a perspective of gallstone dissolution treatment that will also aid the practicing physician in the management of patients with gallstones. Although this treatise represents the personal view of the author, the areas of...
controversy, as well as alternative approaches, are also emphasized.

Current Status

Epidemiology and Natural History of Gallstones

Recent studies of the epidemiology and natural history of gallstones by investigators in the United States (6,7) and in Italy (1-5) have provided a solid data base for a rational approach to the management of so-called silent gallstones. Although it had been suspected, for many years, by some investigators, that most gallstones do not cause symptoms or complications, many physicians continue to recommend prophylactic cholecystectomy in asymptomatic gallstone carriers (16). As a result of careful studies in relatively large population samples, both in Western Europe (Italy) and in the United States, several groups of investigators have recently reached very similar conclusions regarding the low incidence of symptoms or complications from gallstones (1,2,6). In two systematic ultrasonographic studies of populations in different regions of Italy, 65% and 78%, respectively, of the subjects who were discovered to have gallstones gave no history of biliary symptoms (1,2). In a long-term follow-up study of 123 University of Michigan faculty members, in whom silent gallstones had been identified, the cumulative probability of the development of biliary pain was about 18% after 20 yr (6). The risk of developing biliary pain appeared to diminish with increasing length of follow-up. Biliary complications were always preceded by episodes of biliary pain. The incidence of biliary complications was only about one-tenth of that of biliary pain. Very similar results of long-term studies of asymptomatic gallstone carriers have recently been reported by other investigators (17). Based on these findings, a decision analysis can be conducted which shows that the life expectancy of a 30-yr-old man with silent stones is 4 days higher if he chooses expectant management (7). The costs of expectant management have been calculated to be only about one-fourth those of prophylactic cholecystectomy (7). The data supporting a nonsurgical approach toward the management of silent gallstones are, therefore, very strong.

Gallstone Dissolution With Bile Acids

The low rate of biliary complications in persons with silent gallstones makes long-term therapy with cholelitholytic bile acids feasible in selected cases of cholesterol cholelithiasis (6). The selection of patients for this treatment is based on the demonstration of radiolucent gallstones by an oral cholecystogram (18-22). Two bile acids, CDC and its 7-epimer, UDC, have proven to be effective at doses of about 15 mg/kg · day and 8-13 mg/kg · day, respectively (6-10,16-23). Recently, we and other investigators have shown that a combination of CDC, 7.5 mg/kg · day, and UDC, 6.5 mg/kg · day, is at least as effective as either compound alone (12,24). Dissolution therapy using CDC as a single agent has not gained much popularity, as it causes moderate liver test abnormalities, diarrhea, and minor increases in serum low-density lipoprotein cholesterol in a significant number of patients (22,25). In contrast to CDC, UDC has been found to be very safe (6-12,23,26). No adverse effects or signs of toxicity have ever been reported as a result of UDC treatment in any of the many studies that have been published. Indeed, there are observations that indicate that UDC ingestion may improve liver tests in chronic hepatitis (29).

Although the mechanisms responsible for the marked differences between CDC and UDC in their biologic and toxicologic behavior are not entirely clear, several lines of evidence indicate two factors to be critical. One factor relates to the cholesterol-solubilizing ability of the two epimers, and the other to their effect on cholesterol and bile acid synthesis. As far as the first factor is concerned, it has been shown that CDC and UDC greatly differ in their mode of cholesterol solubilization (27,28). Whereas CDC solubilizes cholesterol in micelles, UDC is characterized by its marked ability to transport cholesterol in a liquid-crystalline form. These fundamental differences in the physical-chemical properties probably explain the dissimilar effects of CDC and UDC on cellular membranes. Ursodeoxycholic acid, in contrast to CDC, has been shown to induce a decrease in the cholesterol to phospholipid ratio in bile (29-31), which probably reflects a similar change in the bile canalicular membrane (32). The limited micellar solubilization by UDC of lipid components of cellular structures, such as the bile canalicular membrane, may, to a large degree, explain both the absence of hepatotoxicity of this bile acid, and the fact that UDC is more powerful than CDC in lowering biliary cholesterol. Similar physical-chemical considerations, in addition to a lower water solubility, probably account for the observation that UDC, unlike CDC, lacks a diarrheal action (33). As regards the second critical factor, the differential effect of the two epimers on sterol synthesis, UDC, in contrast to CDC, does not suppress bile acid synthesis in humans (29,30,34). As a consequence of the lack of a suppression of bile acid synthesis, the enrichment of bile with UDC during administration of this bile acid is significantly less than that with CDC during CDC.
terol absorption has been found to be lower during CDC, if combined with UDC, but slightly positive during CDC treatment. The reason for the apparent protective effect of UDC is opposed by reports by other authors who found that UDC depresses the activity of this enzyme (35,37). However, as cholesterol absorption has been found to be lower during UDC than during CDC treatment (38), the overall sterol balance appears to be either normal or negative, during UDC, but slightly positive during CDC administration. These observations may explain the finding that CDC, but not UDC treatment, leads to a small increase in serum low density lipoprotein cholesterol (22,25).

We and other investigators have observed that CDC, if combined with UDC, is free of adverse effects (12,24). The safety of the CDC-UDC combination may be due to both the relatively low dose at which CDC is used in the combination treatment and the possibility of a protective effect by UDC. The latter is supported by the occurrence of liver test abnormalities in patients who receive CDC alone at the low doses that are used in combination with UDC (22). The reason for the apparent protective effect of UDC may relate to the above discussed physical-chemical properties of UDC and their relation to the interaction of this bile acid with the lipid components of cellular structures, such as the hepatocellular membranes.

The cholelitholytic efficacy of CDC, UDC, and the CDC-UDC combination is similar (8–12,18–23). The appeal of the CDC-UDC combination, in comparison to that of UDC alone, lies mainly in cost-effectiveness, as CDC is less expensive than UDC. However, further studies comparing the CDC-UDC combination with UDC treatment are necessary to determine the comparative value of these two cholelitholytic therapies.

The results of the bile acid treatments are primarily dependent on the chemical composition of the gallstones, and on gallbladder function. Whereas the latter can be reasonably well assessed with the use of oral cholecystography, the former is more difficult to evaluate in vivo. About one-third of the stones, which appear radiolucent on conventional roentgenograms, contain significant admixtures of calcium salts and pigment (39–41). Calcified and pigment stones generally do not respond to bile acid dissolution treatment. Although it is usually difficult to predict gallstone composition by x-ray, there are a few stone characteristics that are associated with a high dissolution rate. The finding on an oral cholecystogram of so-called floating stones is consistent with a high cholesterol content of the latter, and associated with successful dissolution in 80%–90% of the cases (10,22,23). If stones are <1 cm in diameter, and small in number, and if the gallbladder functions well and the patient is compliant with the treatment, then the likelihood of success is about 60%. Patients with larger stones, which occupy much of the volume of the gallbladder, are less likely to respond to bile acid therapy.

A drawback of the dissolution therapy lies in the significant recurrence rate, which has been reported to be about 10% per year after discontinuation of the respective bile acid medication (42–44). In many cases, the recurrences are probably related to very small undissolved stone remnants, which escape detection by currently available image techniques. These small particles could serve as a nidus for recurrent gallstone formation, as biliary cholesterol secretion is likely to revert to the abnormally high pretreatment levels if the bile acid medication is discontinued. Fortunately, in most cases, the recurrent stones will dissolve after reinitiation of bile acid therapy. It is currently our practice to carry out follow-up ultrasonography of the gallbladder at 2-yr intervals in the patients in whom there is evidence of complete gallstone dissolution. Patients who show recurrence are treated with another course of UDC or the UDC-CDC combination.

The question as to whether or not the gallstone dissolution therapy is cost-effective is unresolved. The cost-effectiveness may not be high, if the low risks of cholelithiasis are weighed against the costs of 1–2 yr of bile acid treatment, as well as the rate of both treatment failures and stone recurrences. It is, therefore, necessary to individualize the treatment and discuss with the patient the options that are available, as far as the management of gallstones is concerned. The chances of success of the cholelitholytic treatment should be considered in light of the above-described cholecystographic characteristics of the gallbladder and gallstones.

Gallstone Dissolution With Methyl Tert-Butyl Ether

Recently a new method which allows rapid dissolution of cholesterol gallstones with methyl tert-butyl ether has been described by investigators at the Mayo Clinic (13,45). The compound can be used for dissolving both gallbladder and bile duct stones (13,46). The ether, which has a boiling point of 52.2°C and thus remains liquid at body tempera-
tured, is infused via a catheter into the gallbladder lumen or bile duct, depending upon the location of the stones. In the former case, the catheter is usually placed transhepatically through the liver-gallbladder bed (13). Some investigators have succeeded in placing a nasobiliary catheter endoscopically through the cystic duct into the gallbladder and have dissolved gallstones by the infusion of methyl tert-butyl ether (45,47). However, the anatomy of the cystic duct frequently precluded the cannulation of the gallbladder via this route (48). Gallstone dissolution can be accomplished within hours after repeated cycles of infusion of the ether and complete aspiration (13,45). The procedure is carried out without anesthesia [13].

The patient selection criteria for this method of gallstone dissolution, as far as cholecystographic stone characteristics are concerned, are identical to those for the above-described bile acid treatment. Only cholesterol stones can be dissolved. Unfortunately, dissolution is often not complete, as small residuals may remain and form a nidus for new stone growth (13).

The risks of the procedure are related mainly to those associated with both the transhepatic puncture of the gallbladder and the powerful lipid-dissolving properties of the ether. The latter may lead to hemolysis and necrosis if the compound is accidentally injected intravascularly or into the liver parenchyma. Present data thus suggest that the cholelitholytic treatment with methyl tert-butyl ether should be reserved for very selected patients, and be carried out only by investigators who have experience with this technique. It appears that only those patients with radiolucent gallstones who strongly object to a cholecystectomy should be considered for this mode of therapy. Further studies are needed to determine the therapeutic role of methyl tert-butyl ether in gallstone disease.

**Gallstone Dissolution With Monooctanoin**

The monoglyceride monooctanoin represents another solvent that dissolves cholesterol gallstones without serious side effects (49). As monooctanoin is, in contrast to bile acids, not secreted into bile and as its dissolving power is much lower than that of methyl tert-butyl ether, its suitability as a lytic agent for gallbladder stones is limited. It usually takes several days of constant flow of the monoglyceride solution around the stones to effect dissolution. For these reasons, the compound is used only for the dissolution of bile duct stones. The latter represents a special topic that will not be considered in this review.

**Shock Wave Crushing and Bile Acid Dissolution Therapy of Gallstones**

There are preliminary reports by investigators from Munich that indicate that noncalcified cholesterol gallstones can be crushed by extracorporeally applied shock waves (14,15). The method has been used successfully for several years in a number of centers, both in Europe and in the United States, for the treatment of kidney stones (50,51). The shock waves are generated by high-voltage condenser spark discharge from an electrode. The electrode is placed under water in the geometric focus of an ellipsoidal reflector. The high-voltage discharge of the condenser causes a sudden evaporation of water. The associated expansion of the water results in the generation of shock waves. The shock waves are reflected from the ellipsoidal surrounding wall and bundled into a second focus. The stone is positioned into this focus, which represents the point of highest energy density. The shock waves distribute evenly throughout the body, as the acoustic impedance of most body tissue is similar to that of water. In contrast, the change of acoustic impedance, which takes place in the stone, leads to an absorption of the shock waves. Tear and shear forces then develop, which result in a disintegration of the stone.

Both animal experiments and human studies indicate that the shock wave treatment is, with one exception, well tolerated without serious side effects. The exception is represented by the possibility of damage to the lungs, which has been demonstrated in animal studies. Shielding of the thorax from the shock waves is, therefore, necessary. Although the shock wave technique has the advantage of providing a speedy noninvasive therapeutic solution, it also harbors the risk that stone fragments, which are resistant to pulverization, obstruct either the cystic duct or the common bile duct. Another drawback, which is inherent in any current method of cholelitholytic therapy, relates to the likelihood that small, not fully pulverized stone residues remain in the gallbladder and become the nucleus for renewed stone growth. Finally, the risks of anesthesia, which is used for this treatment, have to be considered in the patient selection. The procedure can be carried out under either general or epidural anesthesia.

Shock wave crushing of cholesterol gallstones may be combined with bile acid dissolution therapy (15). Ursodeoxycholic acid or a UDCA-CDC combination may prove to be effective in dissolving cholesterol stone particles that are incompletely pulverized.

Current experience suggests that the shock wave treatment may benefit only a carefully selected minority of patients with cholelithiasis. Only 6% of the
patients with gallbladder stones and 10% of those with common bile duct stones, who were referred to the hospital, were selected for shock wave fragmentation (15). Among the reasons for excluding patients from the treatment were the following: stones calcified, too large, or too numerous; nonfunctioning gallbladder; inability to visualize the bile ducts by retrograde cholangiography; inadequate visualization of the stones by ultrasound; and increased risks from anesthesia. The most promising clinical application of shock waves to the treatment of cholelithiasis may be its use in stones that are lodged in the common bile duct and cannot be removed by endoscopic means. However, further studies are needed to determine (a) the efficacy, safety, and cost-effectiveness of shock wave crushing of gallstones and (b) the role of the supplementary use of UDC or a UDC-CDC combination in this treatment.

**Lithotripsy of gallstones.** Although this review focuses primarily on noninvasive medical methods for treating gallstones, lithotripsy will be mentioned briefly as a means of avoiding major surgery in some cases of cholelithiasis. Lithotripsy has been used successfully in the removal of gallbladder stones (52,53). In patients with acute cholecystitis, for whom surgery under general anesthesia poses a major risk, a sonographically directed surgical cholecystostomy can be performed under local anesthesia. If the gallstones are too large for removal in a basket, a percutaneous universal nephroscope can be advanced through the cholecystostomy tract into the gallbladder, and the stones can be broken up into small particles, using an ultrasonic lithotriptor (52). The stone fragments are then removed by suction. The ultrasonic lithotriptor is a rigid instrument. As the lithotriptor has to come into direct contact with the stone and, as the introduction of this instrument into the common bile duct is technically very difficult, currently not applicable ultrasonic techniques are usually not applicable to the treatment of choledocholithiasis.

**Future Prospects**

**Improvement of Current Dissolution Therapy**

Improvement in prediction of gallstone composition and in patient selection. The success of dissolution therapy with CDC, UDC, or a CDC-UDC combination is, as has been pointed out, dependent to a large extent upon the presence of relatively pure cholesterol stones. However, calcium salt or pigment admixtures to the stones, which often represent major impediments to the cholelitholytic treatment, are frequently not detectable by conventional roentgenography (39-41). The development of more reliable diagnostic methods for predicting gallstone composition would, therefore, significantly improve patient selection for the treatment. Computed tomography has been shown to be superior to conventional roentgenography in the detection of gallstone calcifications (41). However, in spite of its potential as a sensitive indicator of increased calcium in stones, computed tomography is currently not being used for the selection of patients for cholelitholytic therapy. In addition to further exploring the use of modern imaging techniques for the detection of calcifications, studies of biliary electrolyte, calcium salt, cholesterol, and bilirubinate profiles in relation to gallstone composition may result in the identification of diagnostically useful predictors of the calcium and pigment content of gallstones. There are only few data in the literature that indicate that the analysis of biliary components, other than cholesterol crystals, may provide clinically useful information concerning gallstone composition. Results of a recent preliminary study by one investigator rekindled earlier reports by other authors, which suggested a relation between the presence of certain calcium carbonate crystals, such as vaterite microspheroliths, in bile, and the calcium carbonate content of gallstones (54). However, a major obstacle to the evaluation of the utility of biliary measurements for the prediction of gallstone composition lies in the technical difficulty to reliably determine the concentration of biliary anions, such as bilirubinate, carbonate, phosphate, and palmitate.

**Early dissolution treatments.** The majority of gallstones are predominantly composed of cholesterol. As calcifications usually occur at later stages of gallstone growth, the treatment of small and young stones is much more successful than that of large and old ones. Ultrasonographic screening for gallstones of high risk populations at young ages and early treatment are, therefore, likely to increase the success of dissolution. Significant risk factors, which have been identified thus far, include female gender, multiple pregnancies, hormonal birth control, overweight, and genetic predisposition (the latter appears, for example, to be present in some North American Indian tribes and in relatives of gallstone patients).

**Stimulation of gallbladder contraction.** Changes in the contractile function of the gallbladder probably play a major role in the pathogenesis of gallstones (55). Incomplete emptying is prone to promote the retention and, consequently, the growth of both cholesterol and bilirubinate crystals in the gallbladder. Stimulation of gallbladder contraction would not only increase the contact between the stone and cholelitholytic bile, but also accelerate the evacuation of both cholesterol-saturated bile and
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The development of clinically applicable methods for inducing complete gallbladder contraction should, therefore, be very important for gallstone dissolution therapy as well as the prevention of cholelithiasis. Research toward this goal could focus on both the development of stimulants, which are even more powerful than cholecystokinin, and the discovery of means that enhance the contractile response of the gallbladder to physiologic stimuli.

**Combination of chemical dissolution and physical fragmentation treatment.** The preliminary experience with the above-described shock wave treatment suggests that chemical dissolution therapy can be accelerated and maximized if it is combined with procedures that induce physical fragmentation of the stones (15). The chemical dissolution modality could be effectively used (a) to soften up the stones for the physical fragmentation by, for example, shock waves and (b) to dissolve particles that are not completely pulverized in the physical destruction process.

**Prevention of stone recurrence after complete dissolution.** The stone recurrence rate of about 10% per year represents, as described, a significant drawback of the dissolution therapy. No proven treatment modalities have yet been developed that prevent the recurrence of stones. The feasibility and effectiveness of either continuous low-dose or intermittent therapeutic-dose treatment with UDC and a combination of CDC and UDC, respectively, to prevent stone recurrence have not been conclusively tested. There are also insufficient data concerning the ability of dietary changes, such as increases in fiber intake combined with a lowering of cholesterol and saturated fats in the diet, to reduce biliary cholesterol to normal levels. As the compliance of patients with diets, which, by necessity, may have to be relatively strict, is notoriously unsatisfactory, other methods of lowering biliary cholesterol excretion should be developed and studied. The latter are likely to include the development and use of compounds that not only inhibit cholesterol synthesis, but also reduce the hepatocellular compartment of cholesterol that is destined for export into bile. It appears that biliary cholesterol excretion can be modulated by changes in the fraction of cholesterol in the cell, which is present in the unesterified form (56,57). According to recent observations in our laboratory, the mode of hepatic low-density lipoprotein uptake (apo B, E receptor-dependent or receptor-independent) exerts a major influence on biliary bile acid and lipid excretion (58). Important progress toward the goal of preventing gallstone recurrence may, therefore, occur as the result of a better understanding of the mechanisms in sterol and lipoprotein metabolism that channel cholesterol into the biliary excretion route, bile acid synthesis, or other metabolic reactions. An understanding of these mechanisms, in turn, will facilitate the development of new strategies for reducing biliary cholesterol. The challenge presented by such research goals is considerable, as the consequences of reductions in biliary cholesterol have to be evaluated in the light of the homeostasis of the entire cholesterol and lipoprotein metabolism in the body. Particular attention has to be paid to the prevention of any retention in the body of cholesterol that is not secreted into bile. The reduction in biliary cholesterol export has to be balanced by appropriate adjustments in cholesterol absorption (reduction), cholesterol synthesis (reduction), or bile acid synthesis (increase), or any combination thereof.

**Development of New Therapies**

**Synthesis of new dissolving agents that are secreted into bile.** A significant advance in cholelitholytic therapy could be achieved by the synthesis of bile acid analogues or other compounds that are characterized by the following therapeutically advantageous features: (a) dissolution power higher than that of CDC, UDC, and the CDC-UDC combination; (b) promotion of disintegration of calcium salt, pigment, and mucus components of stones; (c) excretion into bile at high concentrations and efficient reabsorption in the intestine; (d) high resistance to intestinal bacterial biotransformation (this would increase the residence time and concentration of the compounds in the enterohepatic circulation and reduce costs); (e) absence of undesirable side effects, in particular, as far as intestinal mucosal damage, hepatotoxicity, and retention of cholesterol in the body are concerned.

**Synthesis of new dissolving agents that are locally applied.** Continued progress is also likely to occur in the development of new and more powerful cholelitholytic solutions that can be injected into the gallbladder and effect rapid stone dissolution. Ideally such solutions should have the following characteristics: (a) boiling point considerably higher than body temperature; (b) lack of toxic effects on gallbladder, bile ducts, and intestine; (c) ability to dissolve, in addition to cholesterol, calcium salts, pigment, and mucus.

In summary, the last decade has brought considerable progress in gallstone research. Improved methods of cholelitholytic therapy can now be used safely for selected patients with cholesterol cholelithiasis. The ongoing development and investigation of new cholelitholytic agents or treatment principles can be based on a solid body of data concerning the
pathogenesis, epidemiology, and natural history of cholesterol gallstones. Improvements in gallstone therapy are likely to involve not only a combination of mechanical disintegration and chemical dissolution of stones, but also pharmacologic means that decrease biliary cholesterol or improve gallbladder emptying, or do both.

References


32. Salvioli G, Carey MC. A novel in vitro perfusion system to study membrane dissolution by bile salts: different effects of
taurochenodeoxycholate (TCDC) and tauroursodeoxycholate (TUCD) on lipid secretion and membrane resistance (abstr). Gastroenterology 1982:82:1168.


59. Malavolti M, Cervyk S, Fromm H. Modulation of bile flow and of biliary bile acid and cholesterol excretion by hepatic low-density lipoprotein (LDL) uptake and by chenodeoxycholic acid (CDC) and ursodeoxycholic acid (UDC) treatment in the hamster (abstr). Gastroenterology 1986:90:1744.