Progress report

The present position concerning gallstone dissolution

In preListerian times, when conservative measures were the only means available to the doctor for the relief of his patients, it was hardly surprising that numerous brews, potions, and diets should be recommended as a cure for gallstones. In the earlier days of surgery, when operative mortality was high, it was natural that special efforts should have been made to discover a means of safely dissolving gallstones thereby avoiding a hazardous operation. As surgical techniques improved the incentive to find a medical cure for cholelithiasis became less and the medical profession became increasingly disenchanted as repeated attempts to dissolve gallstones proved either ineffective or potentially dangerous. However, within the past five to 10 years, considerable advances have been made in our understanding not only of the physiochemical changes in bile which lead to the formation of cholesterol gallstones but also what induced changes in the bile composition are necessary in such patients to promote gallstone dissolution. It is the purpose of this report to review some of these physicochemical principles and the attempts that have been made to dissolve cholesterol gallstones.* Most emphasis will be placed on the use of chenodeoxycholic acid—the agent which is currently the most promising one undergoing clinical trials.[1]

Dissolving Gallstones after Operation

The principle involved here is to infuse the dissolving liquid down the horizontal limb of the T tube into the common bile duct and thence directly over the retained common duct stone or stones. The type of agent used for T tube infusion may be either (1) a cholesterol solvent, eg, ether, chloroform, bile salt solution, or (2) 'fragmenting' agents, eg, heparin or quaternary amines.

Medical Dissolution of Gallstones

An attempt is made, either by dietary manipulation or by oral ingestion of some compound, to alter the composition of the bile secreted by the patient's liver from one which is saturated or even supersaturated with cholesterol (vide infra) to one which is less than saturated. The rationale for this is made clearer from a consideration of the following facts: (1) Cholesterol is the major component of most gallstones found by patients in westernized communities.[2] (2) Cholesterol is virtually insoluble in water.[3] (3) The cholesterol in bile is normally solubilized by the combined detergent action of bile salts and phospholipid in the form of mixed micelles.[4] (4) The cholesterol in gallstones comes from biliary cholesterol. (5) Cholesterol-rich gall-

* For the purpose of this article a cholesterol gallstone is defined as one containing more than 70% cholesterol.

stones form and grow in the gallbladder when the bile is saturated with cholesterol.[5] (6) In cholesterol gallstone patients the bile secreted by the liver is supersaturated with cholesterol.[6,7] It has been suggested that this might occur as a consequence of—(a) the increased secretion of biliary cholesterol without parallel increase in bile salt and biliary phospholipid secretion[8,9] and/or (b) reduced secretion of bile salts and phospholipid into bile without a parallel fall in biliary cholesterol output.[10,11] (7) It is known to be possible to dissolve human gallstones (or more accurately the cholesterol in those stones) by suspending them in animal bile which is less than saturated with cholesterol.[12] (8) To convert the composition of a patient's bile from one which is saturated with cholesterol to one with 'cholesterol holding capacity' it would be necessary to (a) reduce the biliary secretion of cholesterol without parallel fall in bile salt and phospholipid secretion and/or (b) increase the biliary secretion of bile salts and phospholipid with relatively less increase in biliary cholesterol output. (9) Human cholesterol gallstones which have formed and grown in the gallbladder from bile which is saturated with cholesterol should theoretically get smaller again and finally disappear if the bile to which they are exposed becomes less than saturated with cholesterol.

Dissolving Gallstones after Operation

CHOLESTEROL SOLVENTS

Attempts to disperse stones or sludge that remain in the common bile duct after choledochotomy probably date from about 1891.[13] Workers at that time were well aware of the solubility characteristics of cholesterol and for this reason agents such as ether, chloroform, and turpentine were among the first used. Walker [14] was the first to report the dissolution of a cholesterol gallstone using ether. There were many reports of successful dissolution of retained common duct stones using ether[15–18] and chloroform.[19,20] In 1953 Best *et al*[21] evaluated 113 agents but found only ether and chloroform to be satisfactory calculus solvents. The potential dangers of using either of these agents are discussed elsewhere[13] and their use is no longer recommended.[13]

Way *et al* 1971[22] reported their experience of treating retained common duct stones with a 'T'-tube infusion of sodium cholate. They infused this bile acid (100 millimolar) at a rate of 30 ml per hour for periods of three to 14 days. In their series, six of eight patients with single retained stones and five of nine patients with multiple stones were successfully treated.[22] Other workers have recently confirmed these findings.[23,24] The diarrhoea which would normally occur as a result of infusing this massive dose of bile acid (approximately 31·3 g/24 h) is reduced by the simultaneous oral administration of cholestyramine.[22–24] The reported complications of sodium cholate infusions include diarrhoea,[22–24] impaction of a stone at the ampulla of Vater,[23,25] pancreatitis,[23] and cholangitis.[23,25] Small (1970)[26] found that human cholesterol gallstones incubated in a 6% bile salt solution for 100 days lost less than 15% of their original weight. It is therefore unlikely that the sodium cholate infusion has time to dissolve retained stones completely in as few as three to 14 days,[22] more likely the stones get slightly smaller, permitting their passage into the duodenum. Ernest and Admirand (1971)[27]

studied the effects of individual bile acids on cholesterol solubilization and gallstone dissolution *in vitro*. They found that deoxycholic acid (3α 12α dihydroxycholanoic acid) was better than chenodeoxycholic acid 3α,7α dihydroxycholanoic acid) which in turn was better than cholic acid (3α 7α 12α trihydroxycholanoic acid) at solubilizing cholesterol. Although it would be safer to use conjugated bile salts rather than free bile acids for the T tube infusions[28] they are not only prohibitively expensive but also less effective at solubilizing cholesterol.[27,29] The reason cholic acid and not one of the theoretically superior[27] dihydroxy bile acids such as deoxycholic acid is used in practice is that it is less toxic[28] and less prone to cause diarrhoea.[30]

It would be more logical to infuse a mixture of bile acid and phospholipid rather than simply bile acid solutions alone since it has been repeatedly shown that the addition of phospholipid to bile salt solutions greatly enhance their capacity to solubilize cholesterol.[29,31-35] The maximum solubilization of cholesterol occurred when the bile salt to phospholipid ratio approached 3.[36] At present, however, the addition of phospholipid to sodium cholate 'T'-tube infusions is not a practical proposition as purified phospholipid preparations are expensive and tend to be unstable. Thus at the present time sodium cholate[22-24] is probably the best available of the cholesterol solvents for 'T'-tube infusion therapy.

FRAGMENTING AGENTS

A series of patients with retained common duct stones have been treated with heparinized saline T tube infusions.[37,38] Gardner (1974) has recently reported[39] that he has been successful with 22 out of 30 such patients. Unlike sodium cholate, the infusion of heparinized saline does not cause diarrhoea and the simultaneous use of cholestyramine (which is so unpalatable to many patients) is not required. Some successes[40] and failures[24,41] using this form of therapy have also been reported from other centres. Gardner[39] stresses that he does not claim to have fully elucidated the mechanism of action of heparin on gallstones; however, tests *in vitro* indicate a tendency for the stones to fragment (not dissolve). Fragmentation in heparin possibly occurs as a result of its action on the suspension stability of particles suspended in bile.[42,43] It is certainly convincing that in two cases a progressive decrease in dimension of stones was demonstrated during heparinized saline infusion.[38] If Gardner's finding[39] can be confirmed in a larger series of patients then heparinized saline infusion therapy may well prove particularly useful, since it is not only more readily available and causes fewer side effects than sodium cholate, it should also theoretically be equally effective in treating non-cholesterol stones.

Lahana *et al* 1973[44] reported that some quaternary amines, such as heparin, were active in fragmenting gallstones. They also found *in vitro* that a combination of heparin and sodium cholate was better than either agent used separately in reducing gallstone size.[44]

Retained common duct stones may be removed by instrumentation either down the T tube itself or down the tract left after its removal. References to many of these methods are given in a recent paper by Burhenne[45] (1973). In the hands of the inexperienced, T tube infusion is likely to be safer than instrumentation. In assessing the results obtained using either technique it is important to realize that a small percentage of retained stones pass spontaneously.[46] The morbidity of a second operation on the common duct

for choledocholithiasis, although higher than the first, is not excessive.[47] However, the preliminary results obtained using both sodium cholate[22,23] and heparinized infusions[38-40] have been sufficiently encouraging to make a case for treating all patients with retained stones with one or other of these two agents (or even possibly a combination of both[44]) and operating only if these methods fail. Other more effective compounds for dissolving retained stones are likely to be developed over the next few years and as a result fewer patients should require a second operation.

Medical Dissolution of Gallstones

As discussed above, the principle involved in this form of treatment is to try to cause the liver to secrete a bile which is less than saturated with cholesterol. As a result of its 'cholesterol-holding capacity' the bile should be able to solubilize additional cholesterol and as a consequence bring about the dissolution of cholesterol gallstones exposed to it. The importance of phospholipid as well as bile salts in the solubilization of cholesterol has already been mentioned.[31-35] The physical characteristics and interrelations of cholesterol, phospholipid, and bile sals in aqueous systems is necessary to the understanding of cholesterol gallstone formation and dissolution is well described elsewhere.[26] A good account of the biosynthesis, kinetics, and secretion of these three biliary lipids is given in a recent review article.[48] But before going on to discuss the attempts which have been made to alter the relative proportion of the three major lipids secreted by the liver it is important to be familiar with the ways in which these changes have been mathematically and graphically represented.

EXPRESSION OF RESULTS
The relative proportion of bile salt, phospholipid, and cholesterol present in a given sample of bile may be expressed as the 'cholesterol solubilizing capacity'[31] which is the ratio of bile salt + phospholipid/cholesterol. Isaksson[31] found that if this ratio fell below 12:1 cholesterol tended to come out of solution.

An elegant and convenient way of expressing the relative proportion of the three lipids in bile, and also of predicting the physical state of the mixture, is to use a triangular coordinate diagram.[5] This is comprised of equilateral triangles each side of which reflects the molar concentration of one component expressed as a percentage of the total number of moles in the mixture. The composition of any three component mixtures may be plotted as a single point. Such a figure can also be used as a phase diagram by indicating which areas within the triangle, ie, what ranges of relative concentration, correspond to which physical state or phase equilibria. Admirand and Small in 1968[5] defined a boundary zone which indicated the limit of cholesterol solubility both *in vitro* and in human bile. They thought that points falling below this line represented the composition of bile samples which contained mixed micelles which were less than saturated with cholesterol. However, recently the exact position of the boundary line has been challenged.[33,34,49-52] It would now seem that the true physicochemically defined line of maximum cholesterol solubility[34,49-51] is nearer the base of the triangle than had originally been suggested.[5] Points which fall between the newer physicochemically defined boundary[34,49-51] and the original line of Admirand and Small[5] probably represent the composition of biles which are in a 'metastable

labile' state[53], ie, ones in which the micelles are actually supersaturated before precipitation. Although there has been a considerable debate as to which of the various 'lines' defining cholesterol solubility should be used[54,55] in studying populations of patients with and without gallstones, it seems clear that for dissolution studies, in which the object is to produce biliary micelles which are less than saturated with cholesterol, the only meaningful reference point is the true physicochemically defined boundary line.

The degree of cholesterol saturation of bile may be estimated not only by plotting the lipid composition on pictorial diagrams such as those devised by Admirand and Small[5] and Hegard and Dam[34] but also by numerical indices. The simple 'cholesterol solubilizing capacity' has already been discussed: others include the 'lithogenic index'[56] or 'index of saturation', which may be calculated by the tie line concept proposed by Metzger et al[56] or from algebraic equations of the saturation curve proposed by Thomas and Hofmann[57], and more recently the 'cholesterol saturation index.[52]

Therapeutic Attempts to Promote Gallstone Dissolution by Inducing Change in Biliary Lipid Composition

DIETARY MANIPULATION
Diets high in glucose or sucrose which are fat and fibre free regularly promote cholesterol-rich gallstones in hamsters, together with a fall in biliary bile salt concentration and rise in cholesterol concentration.[58,59] Their effects are reduced or abolished by substituting uncooked starch for the sugar, by adding bulk agents such as carboxymethyl cellulose, or by feeding fat, especially in the form of polyunsaturated fatty acids.[58,59] However in man, Dam et al[60] and Watanabe[61] et al found no change in the 'cholesterol-solubilizing capacity' of bile when unsaturated fats were substituted for saturated ones. The possible role of low-fibre diets, rich in refined low molecular weight carbohydrates, in the aetiology of human gallstones is discussed in more detail elsewhere.[62] Feeding bran to human subjects increases the percentage of chenodeoxycholic acid (CDCA) in the bile[63] and expands the CDCA pool size.[64] The effect on bile lipid composition of feeding a high fibre diet to subjects with gallstones is currently being investigated. However, preliminary results have shown that a high fibre diet improves the cholesterol solubility in bile.[64]

DRUGS
Cholestyramine
The bile-acid-binding resin cholestyramine has been shown to prevent the formation of gallstones in hamsters fed a high sugar, fat-free diet.[65] Disappointingly cholestyramine was not effective in altering the bile acid to cholesterol ratio in man.[66-68]

Phenobarbitone
This well known microsomal enzyme inducer can effect bile acid synthesis from cholesterol by altering the activity of cholesterol 7α hydroxylase[69]— the rate-limiting enzyme in bile acid synthesis.[70] Hepatic phospholipid content and synthesis are also increased in proliferating endoplasmic reticulum by giving phenobarbitone.[71,72] Although phenobarbitone increased bile salt pool size in both the rhesus monkey[73] and the rat[74] improvement in the

cholesterol-holding capacity of the bile was only found in the former species.[73,74] Studies of the effect of phenobarbitone on human biliary lipid composition are at present in progress but preliminary results have not been encouraging.[74]

Clofibrate (Atromid)

Although this compound inhibits cholesterol synthesis between acetate and mevalonate it was found in man to increase the ratio of cholesterol to bile salts in bile.[68] It would, therefore, clearly be unsuitable for gallstone dissolution therapy.

Phospholipid feeding

Several studies have suggested that the concentration of phospholipids in the bile of patients with cholesterol gallstones is low.[75,76] Although there have been some reports that phospholipid feeding improves the cholesterol-holding capacity of bile[75,77], others have denied this.[78] Since phospholipid does not undergo a significant enterohepatic circulation[79] it seems unlikely that lecithin feeding will be useful in the treatment of gallstones.

BILE ACID FEEDING

Of all the agents considered so far bile acids were always potentially the most likely to produce change in biliary lipid composition. They undergo an efficient enterohepatic circulation and are thought to be one of the prime motive forces in the formation of bile by the hepatocyte.[80] The more bile salt returning to the liver the greater the output of phospholipid and cholesterol.[81–87] Bile acids not only stimulate the secretion of phospholipids into bile they also stimulate the hepatic synthesis of phospholipid.[88] Biliary cholesterol output does not parallel that of bile salts to the same extent as phospholipid, and, as a result, when bile acid output in man falls below 10μ moles/kg body weight/hour the bile becomes saturated with cholesterol.[89] The composition of bile being secreted by the liver is rapidly altered by quantitative (and probably also qualitative) changes in the amount of bile acid returning to the liver in the enterohepatic circulation.[90,91]

So much for these theoretical considerations let us now see what happens in practice when bile salts are given orally to patients with gallstones.

CRUDE BILE EXTRACTS

These preparations were manufactured from animal bile and contained varying amounts of different bile salts. Rewbridge[92] in 1939 gave 180 mg of such a preparation three times a day to five patients with gallstones. In two out of the five cases the patients' gallstones were found to have disappeared after nine months therapy with bile extract.[92] Rewbridge was unfortunately unable to repeat this finding.[93] Cole et al[94] (1957) described the disappearance of 'stone shadows' from postoperative cholangiograms of seven to nine patients fed 3-4 grams per day of bile extracts for period of eight to 13 weeks, but their observations were uncontrolled and bile composition was not analysed. Swell and Bell[95] (1968) reported improvement in the cholesterol-solubilizing capacity of two out of three patients fed 1·8 to 2·9 g per day of a proprietory bile salt preparation. However, encouraging as these early reports were, the real break through did not come until a more systematic study was made of the effects of feeding individual bile acids in comparatively pure form.[68]

EFFECTS OF INDIVIDUAL BILE ACIDS
Hyodeoxycholic acid (3α 6α dihydroxycholanoic acid)
This bile acid was found to inhibit experimental cholesterol gallstone forma-tion in the hamster[96] but when given in a dose of 1 g/day to man it did not produce any change in the cholesterol solubility of the bile.[68]

Cholic acid (3α 7α 12α trihydroxycholanoic acid)
Cholic acid given in a dose of 0·75 g to 1 g/day failed to produce any improve-ment in the bile lipid composition of gallstone patients[68]: not surprisingly therefore no decrease in gallstone size was observed in any of the 17 patients treated for six months with this bile acid.[97]

Chenodeoxycholic Acid (CDCA)

In hamsters,[96] dogs,[98] and the rhesus monkey[99] chenodeoxycholic acid (3α 7α dihydroxycholanoic acid) causes a deterioration in the cholesterol solubility of bile while in man the reverse is the case.[100] In 1969 Thistle and Schoenfield[100] were the first to show that the 'cholesterol-solubilizing capacity' of the bile of gallstone patients was dramatically increased by giving 1 g of CDCA/day. This important observation was confirmed both in Cauca-sians[68,101,102] and in North American Indian women[103]—a group with a remarkably high incidence of cholelithiasis.[104-106] Thus at last an agent had been found which would consistently enhance the cholesterol solubility of human bile. What was the evidence that cholesterol gallstones would in fact be likely to dissolve if exposed to desaturated bile?

HUMAN GALLSTONE DISSOLUTION IN ANIMAL BILE
Naunyn in 1892[12] had described how human cholesterol gallstones would dissolve over a period of weeks if placed in the gallbladder of the dog. Other workers have confirmed this finding both in the dog and in other species of animal which secrete bile which is less than saturated with cholesterol.[107-117] Nakayama and Johnston in 1960[115] showed that human gallstones dissolved more slowly in the gallbladder of the rhesus monkey than they did in that of the dog. This was because dog bile is much more desaturated with choles-terol and is a a result more efficient at solubilizing any additonal cholesterol to which it might be exposed.

GALLSTONE DISSOLUTION IN MAN USING CDCA
What Thistle and Schoenfield[68,100,103] had managed to do was to alter the composition of the bile of their patients to one which, like those of the experimental animals described above, was desaturated with cholesterol and as a result potentially capable of dissolving cholesterol gallstones. In 1972 Danzinger and his colleagues[101] from the Mayo Clinic reported that, when CDCA was given in a dose of 0·74 to 4·5 g/day for a period of from 6 to 22 months, gallstone dissolution, partial or complete, was seen in four out of seven patients. Successful dissolution of gallstones using CDCA has now been reported from several different centres[95,102,118]. The results are summarized in table I. Undoubtedly the most convincing of these series is the single blind controlled therapeutic trial of Thistle and Hofmann[97] in which the response to CDCA, cholic acid, or placebo was compared in 53 patients. The dose of CDCA averaged 18 mg/kg body weight per day. After

Series	No. of Patients*	Dose of CDCA (g/day)	Length of Treatment (mth)	Gallstone	
				Smaller or Disappeared	No Change
Danzinger et al[101]†	7	0·75-4·5	6-22	4	3
Bell et al [102]	12	0·75-1·25	6	6	6
James et al [118]	11	0·75-1·0	3-18	4	7
Thistle and Hofmann [97]	18	18mg/kg body wt/day range 10-26mg/kg/day	6	11	7
Bell [96]	17	0·75-1·25	6-18	8	9

Table   *Gallstone dissolution in man using chenodeoxycholic acid.*

*Only patients with radiolucent presumed cholesterol gallstones in a radiologically 'functioning' gallbladder are included.

†Six of the seven patients in this original uncontrolled trial showed diminution in gallstone size at 18 months.[97]

six months 11 of the 18 patients who received CDCA showed a reduction in the size or number of gallstones. No change was observed in any of the groups receiving either cholic acid or placebo.[97]

DO GALLSTONES DISAPPEAR SPONTANEOUSLY?

This phenomenon is well recognized[119] in 230 untreated cases of cholelithiasis followed for an average of seven years the spontaneous disappearance rate of single cholesterol stones was 0·8% and that for multiple radiolucent stones was 6·7%.[120] Thus since the maximum spontaneous disappearance rate is less than 1% per year, the results shown in table I could not be explained on this basis.

Having established that gallstones can be dissolved using CDCA we will now discuss the use of this compound in greater detail.

WHAT IS THE OPTIMAL DOSE OF CDCA?

Further work is needed to establish the smallest dose which will consistently produce an adequate improvement in the cholesterol solubility of the patient's bile. In the rhesus monkey[99] a dose equivalent to 350 mgs per day for a 70 kg man was as effective as one of 2·1 g per day for a 70 kg man in increasing bile salt secretion.

Successful gallstone dissolution has been reported[25] in one case treated with only 500 mg CDCA per day for six months, and Mok et al[121] reported a satisfactory rise in the cholesterol-solubilizing capacity of the bile of five of seven patients receiving only 250 mg of CDCA per day. It seems likely that the optimal dose will be in the range of 5 to 10mg per kg body weight per day.

MECHANISM OF ACTION OF CDCA

Chenodeoxycholic acid, which is a free dihydroxy bile acid, has a pKa of 6·3.[122] In the jejunum, when the pH is approximately 6, over half the adminis-tered CDCA will not be ionized and available for absorption by non-ionic diffusion. In the ileum virtually all the free and conjugated bile salts are in the ionized form and most absorption at this site occurs by an active transport system.[123] However, free dihydroxy bile acids are absorbed less efficiently than conjugated trihydroxy bile salts[124] by this system. In man the percentage absorption of CDCA (given in 250 mg gelatin capsules (Weddel Pharma-ceutical, London) averages 60%.[125] Once absorbed, CDCA is carried with the patient's own bile salts in the portal blood, probably bound to serum

albumin,[126] to the liver where it is conjugated with either glycine or taurine. Feeding 0·75-4·5 g of CDCA per day to patients must stress their hepatic conjugating and 'clearing' mechanisms, since the glycine to taurine ratio found in the bile increases significantly,[125,127]and a small amount of free CDCA 'spills' into the systemic circulation causing an elevation of serum bile acid levels.[128–130] Once conjugated the CDCA is secreted with the patient's own endogenous bile salts into the bile in association with biliary phospholipid and cholesterol.

The synthesis of bile salts by the liver is regulated by the concentration of these substances reaching the liver from the gut[131] at the level of the rate-limiting enzyme cholesterol 7α hydroxylase.[70] It was therefore to be expected that feeding CDCA would depress the bile acid synthesis rate.[125] Giving CDCA to patients was found in most cases to increase the bile acid pool size,[101,125] which is normally depleted in patients with gallstones.[10,11] Although the CDCA pool size increased an average of sixfold during CDCA therapy,[125] the total bile acid pool expanded less (about twofold[125]) because of a decrease in the pools of deoxycholic acid and cholic acid.[125] The cholic acid pool size is reduced as a consequence of both decreased synthesis and decreased efficiency of intestinal absorption[125] during CDCA administration.

Why should the passage of CDCA through the liver and into the bile produce an increase in its cholesterol solubility while the other primary bile acid in man, cholic acid, does not do so? Although there is a relationship between bile acid pool size and formation of 'lithogenic bile,'[10,11] it seems unlikely that CDCA exerts its therapeutic effect simply by increasing total bile acid pool size. First, cholic acid administration also increased pool size in both man[125] and the rhesus monkey[99] and yet did not improve biliary lipid composition.[68] Second, not all patients treated with CDCA showed an increase in total bile acid pool size but when CDCA became the predominant bile acid the bile became desaturated and the stones dissolved.[125] Together these observations suggest that CDCA has a specific effect on biliary lipid secretion in man.

Northfield *et al*[89] have studied biliary lipid secretion in man using a perfusion technique, and found that in Caucasians with gallstones (unlike North American Indian women[8]) the total daily biliary cholesterol output was the same as in controls. Although total bile salt pool size was reduced in gallstone subjects,[10,11,89] total 24-hour bile salt secretion was not markedly reduced as a result of more frequent circulation of the bile salt pool.[89,132] After oral administration of CDCA to gallstone patients the 24-hour bile salt and phospholipid secretion rates were not significantly increased.[133] This latter finding is surprising since feeding CDCA to rhesus monkeys, in which secretion rate could be measured directly, both bile salt and phospholipid secretion into bile were markedly increased.[99] However Northfield and colleagues[133] have made the important observation that when gallstone patients were fed CDCA the total biliary cholesterol output fell from an average of 56 to 35μ moles/kg/day.[133] There was a linear relationship between the hourly rates of bile acid and cholesterol output both before and after CDCA but the slope of the regression line was twice as steep before as during treatment.[133] Particularly strong evidence for CDCA reducing biliary cholesterol output in man is provided by the change in the dose-response curve for bile acid-cholesterol coupling.[134]

Hepatic cholesterol synthesis is regulated by the microsomal enzyme

HMG-CoA reductase which controls the formation of mevalonate from 3-hydroxy-3 methyl-glutaryl CoA (HMG-CoA). In two patients treated with 0·75g of CDCA/day for four months a marked reduction in both hepatic HMG-CoA reductase and liver cholesterol was found.[135] This finding[135] may provide a possible explanation for the finding that CDCA inhibits biliary cholesterol concentration in man.[133] In the rat[136] and hamster[137] CDCA inhibits hepatic cholesterogenesis to a greater extent than it inhibits the bile acid synthesis from cholesterol; in contrast cholic acid inhibits cholesterol and bile acid synthesis to a similar extent. If these results can be extrapolated to man they may explain why cholic acid, unlike CDCA, is unable to enhance cholesterol solubility in human bile.[66]

Conjugates of the bile acid CDCA are better than those of cholic acid at solubilizing cholesterol *in vitro*.[27] Since approximately 95% of the bile salts secreted by patients treated with CDCA are conjugates of this bile acid[101,125], it might be thought that this would enhance the rate of cholesterol gallstone dissolution. This is, however, unlikely to be an important factor since the differences in the capacities of the various bile acids and salts to dissolve cholesterol are greatly diminished in the presence of phospholipid.[34]

EFFECT OF WITHDRAWAL OF CDCA THERAPY
An important consideration is, Will the gallstones reform once CDCA treatment is stopped? It has certainly been convincingly shown that the bile composition tends to revert to its former 'lithogenic state' when CDCA therapy is stopped.[25,121] However, this does not necessarily mean that stones will inevitably reform in the gallbladder since many control subjects secrete bile which is frequently supersaturated,[138] furthermore the use of the three-lumen tube to study biliary lipid secretion rates has shown that there is a diurnal variation in biliary lipid composition[91] and intermittent secretion by the liver of bile which is supersaturated with cholesterol (particularly after an overnight fast) can be considered to be a physiological variant.[89,91] The reason why more people do not have cholelithiasis is presumably related to the fact that at the time their bile is supersaturated with cholesterol the essential nucleating agents to initiate stone growth are lacking or alternatively as soon as microstones do form they are washed away by contraction of the gallbladder. Once CDCA is withdrawn following successful treatment the patient is always going to be prone to form gallstones again. In fact gallstones have reformed in at least two patients after nine[25] and 12[97] months of stopping treatment. It is probably worth continuing CDCA treatment for three to six months after oral cholecystograms have shown complete disappearance of gallstones, since stones less than about 2 mm are below the resolution of the radiographic technique and could be easily missed. If such minute stones are left they might provide the seeding or nucleating agent necessary for stone reformation in the presence of supersaturated bile. Further work is, however, required before we are able to answer the question as to what is the best procedure once CDCA treatment is withdrawn.[1]

SELECTION OF PATIENTS FOR CDCA THERAPY
In order to select only those patients who are likely to respond to CDCA therapy it is necessary to appreciate the factors which influence the rate of human gallstone dissolution in bile. These factors have been studied using a rhesus monkey model[25,140] and in summary the animal studies have shown

that the rate of human gallstone dissolution in bile depends on (1) cholesterol content of the gallstone, (2) cholesterol solubility of the bile, (3) surface area: weight ratio of the stone, and (4) presence or absence of a calcified rim around the stone. On the basis of these findings one could predict that the patients with multiple small gallstones rich in cholesterol and devoid of a radioopaque rim would be those most likely to respond to CDCA.[25,140] In practice patients with radioopaque gallstones have not responded to CDCA treatment,[25,97,102,141,142] nor have those with radiologically 'non-functioning' gallbladders.[25,102] This leads us to ask, how good are we clinically at predicting gallstone type? This topic has recently been discussed[143] but suffice it to say that in Great Britain the majority of gallstones contain over 70% cholesterol[2] and unless the patient has a haemolytic disorder or hepatic cirrhosis (both conditions predisposing to pigment stone formation[144]) the chances are on epidemiological grounds that the patient's stones will consist predominantly of cholesterol. The majority of radiolucent gallstones in Great Britain consist predominantly of cholesterol.[25] There is still approximately a one in five chance that a radiolucent gallstone will be composed of predominantly amorphous non-cholesterol material[25] or contain significant amounts of calcium which would be likely to retard gallstone dissolution.[25]

Since the time taken for CDCA to dissolve patients' gallstones may vary from less than six months to more than two years[25,97,101,102] only patients who are relatively asymptomatic, or have some surgical or medical contraindication to surgery, should be considered. At the present time it is generally recommended that CDCA is not used in females of childbearing age.

In summary, CDCA should only be used in relatively asymptomatic patients who have radiolucent gallstones and a radiologically 'functioning' gallbladder. When we recently looked at an unselected series of 47 patients undergoing cholecystectomy at Hammersmith Hospital only nine cases had both radiolucent gallstones and a radiologically opacifying gallbladder.[145] Thus at maximum less than 20% of these patients might have been considered potentially suitable for CDCA therapy.

COMPLICATIONS OF TREATMENT WITH CDCA

The complications of bile acid therapy may be logically considered under two headings: first the complications that occur as a result of the continued presence of the gallstones themselves and second the possible side effects caused by ingestion of the bile acid itself.[143]

The possible complications of the continued presence of the gallstones include recurrent abdominal pain, cholecystitis, biliary colic, and obstructive jaundice, and indeed in a small percentage of patients treated with CDCA these complications have been reported.[25,102,143]

Side effects of CDCA

On the whole CDCA is well tolerated by patients,[97,101,102] and there is a subjective impression that many patients' symptoms improve during treatment,[1,118,146] CDCA has been given to most patients in the form of 250 mg gelatine capsules (Weddel Pharmaceuticals Ltd, London) and has not been reported to cause gastric irritations,[97,101,102,118,141] this is possibly because at the pH of the stomach CDCA is insoluble.[122] The majority of patients noted an increased frequency of bowel action of even frank diarrhoea when CDCA treatment was started[97,101,102] though in the vast majority of cases

this settles down spontaneously[102] or after a slight reduction in dosage.[97,101] The diarrhoea is almost certainly due to the unabsorbed free CDCA inducing the colon to secrete water and electrolytes.[30] In the colon CDCA (3α 7α dihydroxy cholanoic acid) may be 7α dehydroxylated by bacteria to litho-cholic acid[147] (3α monohydroxy cholanoic acid). The faecal bile acid of patients ingesting CDCA may vary in composition from nearly all CDCA to mostly lithocholic acid.[125] Diarrhoea tended to occur in those patients whose stool contained mainly CDCA;[125] in contrast if lithocholate was the predominant faecal bile salt diarrhoea was not found.[125]

Small (1971)[148] predicted two possible major complications of CDCA therapy, namely, hypercholesterolaemia and hepatotoxicity.

Hypercholesterolaemia
The major catabolic and excretory pathway of cholesterol is its conversion to bile acids.[149,150] Feeding an exogenous bile acid such as CDCA might theoretically block endogenous bile acid synthesis from cholesterol.[70,131] It has been conjectured that administration of CDCA might expand the cholesterol pool, which in turn could have the undesirable effect of promoting atherosclerosis.[148] There is evidence of depressed bile acid synthesis in patients treated with CDCA.[125] However, careful studies have not revealed any evidence of an increase in either the serum cholesterol level[151,152] or to either the exchangeable cholesterol pool or the cholesterol input to that pool.[152] Although the levels of serum cholesterol in patients treated with CDCA did not change, a small but significant reduction of serum triglyceride concentration has been reported.[151,152] The mechanism for the triglyceride lowering effect of CDCA is not yet understood but further documentation of this interesting observation appears warranted.

Hepatotoxicity
Bile duct hyperplasia and frank hepatic cirrhosis have been found in rabbits given either CDCA or its bacterial metabolite, lithocholic acid[153,154] and similar changes have been seen in rats after lithocholate,[155-157] in hamsters and mice following CDCA,[158] in guinea pigs fed lithocholate,[157] and in monkeys given CDCA.[159-162] As a result of the report that CDCA in doses of 40 to 120 mg/kg body weight/day adversely affected the liver of the rhesus monkey[160] the Committee for Safety of Medicines recommended in April of 1973 that all clinical trials with CDCA in the UK be terminated until further toxicological investigations had been completed.[160] However, in contrast to the studies in experimental animals the available evidence in man suggests that in doses up to 1·5 g/day CDCA is not significantly hepatotoxic in man.[97,101,102,128,130] Although a slight but statistically significant rise in serum isocitric dehydrogenase levels was initially reported after treatment with CDCA,[102] subsequently in a larger number of patients this difference was shown to be no longer significant.[130] In Thistle and Hofmann's recent paper,[97] nine out of 31 patients showed transient slight rises in SGOT levels which returned spontaneously to normal with continued bile acid treatment. The incidence of abnormal liver function tests appears to be dose related[121] and little or no elevation of SGOT level was found when lower doses of CDCA were used.[128,130,141] In patients no change in serum protein, bilirubin, alkaline phosphatase,[97,128,130,141] and gamma glutamyl transpeptidase levels[130] were noticed during CDCA therapy. The kinetics of clearance of a

single bolus injection of bromsulphthalein[130] and the apparent maximum excretory capacity (Tm) of infused BSP[130] were unchanged during CDCA treatment. Liver biopsies in patients with gallstones often show minor histological changes[163,164] but the frequency with which positive features were found was not increased in cholelithiasis cases treated with CDCA.[97,128,130] As a result of these encouraging findings in man an application has been made to the Committee of Safety of Medicines for a clinical trial certificate to resume clinical trials in several specified centresin the UK.[165] In contrast to the situation in this country the Food and Drugs Agency did not stop clinical trials using CDCA in the United States where several clinical trials are at present in progress. The significance of finding raised serum bile acid levels during CDCA treatment[128-130] is discussed more fully elsewhere.[130]

Cost of CDCA

The cost of treating a patient for 18 months with CDCA in a dose of $0.75 g/day$ would at present (May 1974) be approximately £400.[165] This amount would compare not too unfavourably with the financial outlay incurred by the country as a result of a patient having a cholecystectomy in an NHS bed, and his losing time from work as a consequence of that operation. However, if CDCA were required to prevent a recurrence of stones once successfully dissolved (see section on effect of withdrawing CDCA) this medical form of treatment would work out in the long term to be considerably more expensive than surgery.

FUTURE STUDIES ON CDCA

If further studies continue to document the efficacy and safety (particularly with regard to possible liver damage) of CDCA, it would be necessary to conduct a comparison under controlled conditions with surgery in order to establish whether or not CDCA has a place in the management of patients with cholesterol gallstones.[97] Further work is needed both on the dosage of CDCA required and on the prevention of recurrence of gallstones once treatment is withdrawn.

Development of Other Agents for Dissolving Gallstones

A tremendous amount of interest is now being shown in the effect of different compounds on bile lipid composition; from this work drugs may be discovered which favourably alter the cholesterol solubility of bile, and, hence like CDCA, dissolve gallstones. Bromsulphthalein, for example, is excreted into bile following intravenous injection and causes a reduction in cholesterol-solubilizing capacity while iodipamide (Biligraphin) in contrast markedly enhanced this ratio[166] despite not altering the bile salt secretion rate.[167] There is a place for the development of a drug which will exert an effect similar to iodipamide[166] as a result of its excretion into bile following oral administration. Research workers are also trying to develop a synthetic non-bile salt detergent which will undergo an efficient enterohepatic circulation and thus dissolve gallstones by its own direct detergent action without actually altering the biliary lipid composition itself. The role of high fibre diets in the prevention and perhaps even the treatment of gallstones provides further scope for exciting research in the future.

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