Leading article

Debits and credits: a current account of cholesterol gall stone disease

The past 25 years has seen both progress and disappointment in our understanding of cholesterol cholelithiasis. Although there was much activity in the latter part of the 19th century\(^1\)\(^2\) the developments during the late 1950s and early 60s laid the foundation for our present concepts of gall stone formation which culminated in the dissolution of stones by drug therapy.

Pathogenesis

An improved understanding of bile acid chemistry,\(^3\) the development of techniques permitting clarification of bile acid physiology and of the enterohepatic circulation\(^4\)\(^6\) and an appreciation of the solubility relationship of cholesterol in bile,\(^7\)\(^8\) provided the background against which cholesterol gall stone disease appeared as the consequence of a metabolic disorder whereby the liver secretes bile saturated, or supersaturated with cholesterol. The concept of a primary hepatic defect was encouraged by reports of an abnormality in the rate binding enzymes for biliary lipid synthesis: an increased activity of 3-hydroxy-3 methylglutaryl-CoA (HMG-CoA) reductase (rate limiting for the synthesis of cholesterol) and a decreased \(7\alpha\)-hydroxylase activity (rate limiting for the synthesis of bile acids).\(^9\) Subjects with this hepatic defect secrete bile saturated with cholesterol and can form crystals, microspheroliths and stones.

This relatively simple and attractive hypothesis has been found wanting. It is now apparent that in many non-obese individuals with gall stones the hepatic HMG CoA reductase activity does not differ from stone-free persons.\(^10\)\(^11\) Patients with cholesterol gall stones may have a smaller total body pool of bile acids, but nonetheless the bile salt secretion will be normal\(^12\) and the correlation between total bile acid pool size and biliary cholesterol saturation is poor.\(^13\) It is possible that the small pool of bile acids is related to increased recycling of bile acids within the enterohepatic circulation, which reflects the capacity of the gall bladder to fill and empty.\(^14\) It is recognised that nocturnal storage in the gall bladder is an important factor determining cholesterol saturation of bile.\(^13\)\(^15\)

Any statement regarding the metabolic background to the formation of cholesterol gall stones must take account of the numerous conditions known to be associated with an increased prevalence of gall stones: race, age, sex, obesity, high calorie diet, disease of the distal ileum, clofibrate therapy, cystic fibrosis, diabetes mellitus, use of oral contraceptives and, more recently, total parenteral nutrition.\(^16\)\(^19\) An awareness of the many factors known to influence biliary cholesterol secretion and saturation has
made it necessary to broaden our concepts of the pathogenesis. Carey has classified cholesterol gall stones into six types according to the different metabolic disorders producing abnormal bile.20

Type 1: defective bile acid synthesis: congenital 12α-hydroxylase deficiency, oestrogens, cerebrotendinous xanthomatosis. Type 2: excessive bile acid loss: ileectomy, ileal disease, cystic fibrosis with pancreatic insufficiency, primary bile acid malabsorption. Type 3: oversensitive bile acid feedback: reduced bile acid secretion in some white people with gall stones. Type 4: excessive cholesterol secretion: obesity, type IV hyperlipoproteinaemia, clofibrate therapy, oestrogens. Type 5: mixed defect (3+4): reduced bile acid and increased cholesterol secretion in American Indians and white people. Type 6: primary extrahepatic gall stone disease: cholecystitis, salmonellosis, total parenteral nutrition, somatostatinoma, vagotomy.

There is an analogy between the variety of biochemical and physiological disturbances which produce supersaturated bile and the range of metabolic disturbances predisposing to hyperglycaemia and hyperlipidaemia.

But cholesterol gall stone formation is not merely a matter of producing supersaturated bile; the situation is more complex than initially proposed by Admirand and Small.7 Holzbach et al published data of their own and from previously published studies showing that normal human bile is commonly supersaturated with cholesterol; bile from subjects with cholesterol gall stones differs in having a greater excess of cholesterol above saturation.21 Supersaturation of bile with cholesterol is essential for stone formation, but not everyone with supersaturated bile forms stones and a proper understanding of this phenomenon remains one of the major tasks for researchers in gall stone disease. The concept of metastable bile8 and the process of nucleation22 is crucial to the problems. Many subjects have bile which is only mildly supersaturated with cholesterol and from which cholesterol precipitates only very slowly.21 Precipitation from such bile requires the addition of particulate material, the process being called heterogeneous nucleation in contrast with homogeneous nucleation where crystal growth occurs spontaneously at concentrations of saturation above the metastable limit.

The difference between stone formers and non-stone formers appears to be in their ability to form cholesterol crystals22-24 and this may be caused by the presence of nucleating factors, or their absence, or the presence of inhibitors in bile. Whiting and Watts have studied growth crystals of cholesterol in bile from obese patients without stones and from patients with either pigment, or cholesterol stones and conclude that the difference between stone and non-stone forming bile lies in the nucleation stage of crystal formation, rather than the presence of inhibitors.24 Bacteria, desquamated cells and mucus (mucin, glycoproteins) are all candidates for the nucleation process. There is much evidence to suggest that mucin has a prime role. Most gall stones contain a core of mucin and mucus glycoproteins form part of the lattice structure of gall stones,25 mucin can act as an area for epitactic contact in crystal growth,26 it binds bilirubin in vitro27 and enhances in vitro nucleation of cholesterol crystals;28 most animal models for gall stones show that excessive mucus formation accompanies, or precedes gall stone formation.29 30 Whiting and Watts, however, did not observe any relation between crystal formation and
biliary hexosamine concentration which was used as an indicator of bile mucin content. Calcium is probably also important. The extent to which ionised calcium is bound to bile salt, or bile salt/phospholipid micelles will affect the formation of microcrystalline inorganic calcium salts. Calcium/bile salt interactions will assume greater importance in the future.

The role of the gall bladder is probably central to the process of gall stone formation. Nucleation occurs more rapidly in the gall bladder than hepatic bile and, after all, it is in the gall bladder that most stones are formed. There are many ways whereby the gall bladder may contribute to gall stone formation. These may be summarised as being either because of an effect of gall bladder motility or following particular metabolic activities of the gall bladder mucosa which could alter unfavourably bile lipid relations, or influence nucleation.

The use of real time ultrasonography and scintiscanning has provided important information on gall bladder motility in the presence of gall stone disease. It has been suggested that gall bladder emptying is increased in patients with cholesterol gall stone disease and that this may be related to an increased sensitivity to cholecystokinin in such individuals. Fisher et al., however, reported reduced gall bladder emptying in gall stone patients in response to a meal, but no difference between normal and stone-containing gall bladders in response to synthetic octapeptide of cholecystokinin. Pregnancy and prolonged use of contraceptive steroid, both associated with an increased frequency of gall stones, cause the gall bladder to retain bile. Animal studies support the importance of defective contractility and impaired emptying in gall stone formation and it is of particular interest (cf the observations on mucin production) that emptying of the gall bladder is diminished before the gall stones form. The other approach, an evaluation of the influence of gall bladder mucosal function on lithogenesis, has yet to be developed. There is the inherent problem of being able to study normal human gall bladder mucosa. In a series of publications, Hopwood and Ross and their colleagues have studied a variety of enzyme activities in gall bladder mucosa including β glucuronidase, alkaline phosphatase and non-specific esterases in an attempt to define those aspects of gall bladder mucosal formation which are altered in the event of gall stone disease. Such work is in its infancy but may well produce important clues to the ways in which the gall bladder mucosa might change biliary lipids and provide nucleating factors for crystal formation. At present the emphasis in gall stone research is very much on studies of the different facets of gall bladder function, in the belief that this organ plays a critical role in the initial stages of nucleation and stone growth.

Epidemiology

Epidemiological data on the prevalence of gall stones are derived mainly from necropsy studies and consequently are subject to a number of potential fallacies: bias in the selection of patients dying in hospital, bias in the selection for necropsy, variation in attention paid to the biliary tract and completeness of recording information. It is therefore encouraging that ultrasonic scanning of the gall bladder is being used to examine free living population samples and the results of large studies, particularly from
Italy, will be awaited with interest. Not only should they provide data on general prevalence and conditions associated with an increased risk, but invaluable information on the development of gall stones from biliary sludge and on the natural history of stones should be obtained.

Necropsy data suggest that most (possibly 90%), of patients with gall stones are asymptomatic – that is, they possess 'silent' gall stones.\textsuperscript{46, 47} Furthermore, the unique long term study of Gracie and Ransohoff\textsuperscript{48} on 123 persons with silent stones suggested that most remain asymptomatic, an observation supported by the National Cooperative Gallstone Study. 'Silent', however, remains to be defined to everyone's satisfaction. Symptomatic implies the occurrence of biliary pain or complications, but a clear comprehensive definition of biliary pain which applies to all clinical situations is not available.

One important question which remains unanswered is whether the prevalence of gall stones is increasing. Although the crude prevalence rates for Dundee, Scotland, suggested an increase when prevalence was expressed as the age-sex-specific morbidity ratio (ASSMR), a fluctuating prevalence was observed with no constant increase in frequency.\textsuperscript{46} Bateson (personal communication) has calculated the ASSMR from more recent Dundee data and finds an increase in the ratio. Further observations are needed to determine whether this represents a trend of increased prevalence or merely fluctuation in ratios. Barker and coworkers observed a considerable variation in the necropsy prevalence of gall stones in nine towns in England and Wales.\textsuperscript{49} They also concluded that socioeconomic factors are not a major determinant of gall stone distribution which is of interest, because of the suggestion that the prevalence of gall stones is increased in countries with a high standard of living.\textsuperscript{50} It is unfortunate that there are so few reliable data on gall stone prevalence in third world countries. Lack of facilities and cultural inhibitions have precluded necropsy studies and we do not know whether gall stones in underdeveloped countries are less frequent, or more likely to be asymptomatic. The frequently cited example of the Masai of East Africa being free of gall stones is based on very limited information\textsuperscript{51} derived from surgical experience.

Indeed, cholecystectomy rates have been used to study changes in prevalence and most studies do suggest that the operation is increasing in frequency.\textsuperscript{47, 52-54} Unfortunately, this finding is difficult to interpret: does it reflect a true increase in prevalence, has there been a change in the symptoms of the disease; is it a reflection of a change in surgical practice, or an increased availability of surgical services?

Gall stone disease increases in frequency with age and there is evidence that bile is more often supersaturated in older women at least. Is this because of a change in cholesterol secretion\textsuperscript{55} and, if so, do obesity and increased parity have an influence; is there a similar phenomenon in men?

Godfrey et al report in this issue that the number of cholecystectomies per head of population at risk increased with age in both men and women, but there was a greater chance of a woman undergoing a cholecystectomy.\textsuperscript{47} Are gall stones looked for more vigorously or are they more likely to cause symptoms in women? These authors also report that the cholecystectomy rate declined sharply in women in their 70s and men in their 80s. Does this imply a reduced tendency for gall stones to cause symptoms in the very
elderly, or is it a reflection of the reluctance of surgeons to operate on the aged. Many surgeons hold that elective cholecystectomy can be undertaken with relative safety in the elderly.\textsuperscript{56–58} Surgical experience is that choledocholithiasis is encountered with increased frequency in the older patients.\textsuperscript{56 58 59} This needs explaining. Most necropsy studies do not make special mention of stones in the common bile duct, information which would be useful. Common bile duct stones too can be silent.

One of the most important topics in gall stone disease is the further study of biliary sludge: its diagnosis, composition and natural history. Sludge can be recognised by real time ultrasonography as non-shadowing layering of homogeneous echogenic particles in the gall bladder forming a fluid/fluid concentration.\textsuperscript{60–62} It probably represents viscous bile containing cholesterol, or calcium bilirubinate crystals,\textsuperscript{61–63} but more work is needed to define the precise composition of sludge. Given good technical circumstances, gall stones as small as 1 mm can be detected so we should be able to define accurately the progression of sludge to stone. The large prospective ultrasonography studies at present in progress could provide important information on the frequency with which sludge occurs and whether it is inevitably associated with gall stone formation.

**Treatment**

The impact of medical treatment on the management of gall stones has been disappointing. There are a number of reasons for this: less than 30\% of all patients with gall stones are suitable for dissolution therapy, compliance for a course of treatment lasting two, or more years is often poor and the knowledge that gall stones often recur has inhibited many practitioners from using bile acid therapy. Surgeons who tend to see a large proportion of patients with gall stones in particular have been reluctant to offer tablets in exchange for an operation and while this is wholly understandable, it is regrettable that an opportunity to obtain potentially valuable information about gall stone disease is being lost. It appears that in many parts of the country there is a delay before patients can undergo an elective cholecystectomy. It would be highly informative to place such patients on bile acid therapy during their wait for the operation. Then data could be obtained about the nature of the gall stone response to dissolution therapy, the changes in stones and bile at various stages of therapy and the physicochemical state of gall bladder bile during treatment with ursodeoxycholic and/or chenodeoxycholic acids. We do not know whether the gall bladder mucosa returns morphologically and functionally to normal once gall stones have dissolved. Properly designed studies could answer many of these questions and would, I believe, be ethical, because gall stones are known to recur and so if a decision were taken to remove the gall bladder, even if the stones were to dissolve before the planned date of operation, it would be justifiable to proceed to cholecystectomy. Drug therapy during the waiting time for cholecystectomy would be quite safe.

The availability of drugs to dissolve gall stones might tempt clinicians into using them inappropriately in all subjects who happen to have gall stones. Bile acid therapy may have a beneficial effect of biliary pain\textsuperscript{64 65} but non-specific dyspepsia associated with\textsuperscript{65} or without gall stone disease\textsuperscript{66 67} is also alleviated. Present surgical teaching is that pain of
biliary origin, or the complications of gall stones are indications for surgery, but dyspeptic symptoms are not. Should the same principle apply to gall stone dissolving drugs? Probably not, for effective drug therapy for non-specific dyspepsia cannot be ignored. Nevertheless, clinicians should not succumb too readily to the temptation to use bile acid therapy in every patient with dyspeptic symptoms who also happens to have gall stones. The dilemma will be if, in the course of treating ‘non-specific dyspepsia’, fortuitous stones are also dissolved. All the evidence is that most gall stones not only are asymptomatic, but remain so; the mortality from gall stone disease, in the absence of operation, is very low.

Gall stones are likely to recur once therapy is stopped, and the widespread, indiscriminate use of gall stone dissolving drugs might result in a situation when either many persons are on drug therapy (continuous or intermittent) for life, or many more patients will eventually be subjected to cholecystectomy – a circumstance which Godfrey and his colleagues rightly view with alarm in their paper, for surely the mortality rate of gall stone disease will rise. The proper roles for medical and surgical treatment of gall stones need defining, now that technology has enabled apparently asymptomatic gall stones to be readily identified.

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A current account of cholesterol gall stone disease


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