Medical aspects of gallstones – 1985: sixty years on

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Introduction

Memories are short in clinical and scientific medicine. Too often, the fashionable theories and apparently new scientific discoveries of today are, in fact, re-discoveries of old beliefs. In the self-congratulatory myopia of medical writing in the mid-1980s, clinical scientists often ignore (or perhaps are ignorant about) the contributions of their predecessors. Nowhere is this more clearly illustrated than in the field of gallstone research. It was a chastening experience, therefore, to be stimulated to read an account of 'Medical Aspects of Gallstones', written some 60 years ago in the first volume of this journal (Rolleston, 1925) by no less a person than a Knight of the Realm, a physician to HM the King and the President of the Royal College of Physicians at that time – Sir Humphrey Rolleston*.

In his article, Rolleston discusses the symptoms of gallstone disease, with reference both to diagnosis and to the indications for medical and surgical treatment. He describes, at length, possible mechanisms for gallstone formation: many of these theories are still current today. He also deals with some aspects of gallstone epidemiology – an active domain in gallstone research at present. And, as the title of his article implies, he describes not only the medical treatment of established gallstone disease, but also the prophylactic and preventative therapy of the day.

Given the benefits of cumulated wisdom, of technical advances and of the huge investment in time and money which has been made into gallstone research, it is not surprising that Rolleston's paper should provoke the occasional wry smile, or even a misplaced sense of patronising superiority about the apparently bizarre ideas of the mid-1920s. Nonetheless, there is much of interest and relevance in that first volume of the *Postgraduate Medical Journal*. The present article, therefore, is as much a tribute to Rolleston's perspicacity, and that of his contemporaries, as it is an attempt to provide the reader with a 'state-of-the-art' on medical aspects of gallstones today.

Symptoms and diagnosis

Rolleston quite rightly draws the distinction between the presence of gallstones and 'the symptoms common to them' – particularly those arising from inflammation of the gallbladder and biliary colic. He goes on to suggest that unless a calculus is detected by X-rays, or is passed in the stools, the diagnosis of gallstones, even after an acute attack of biliary colic, is open to doubt. Graham and Cole did not describe the technique of oral cholecystography until 1924. It seems likely that Rolleston was unaware of this report and that he must have been referring to the X-ray diagnosis of radio-opaque stones which, in different series, account for only 10–40% of the total.

Six, rather than 60 years ago, an article discussing gallstone diagnosis would have emphasized oral cholecystography as the diagnostic method of choice. Today, that emphasis has changed in favour of ultrasonography. Increasingly, real-time ultrasound is being used as the principal method of confirming the presence of gallstones suspected clinically. Ultrasonography has also been used extensively in epidemiological studies of gallstone disease in representative segments of the population (GREPCO, 1984; Lalloni *et al.*, 1984) or in whole communities (Barbara *et al.*, 1984b). However, ultrasonography has not replaced oral cholecystography: the two techniques provide different and complementary information. In the selection of patients for oral gallstone dissolution therapy, oral cholecystography is still required since ultrasonography cannot distinguish between radiolucent and radio-opaque stones and it is relatively insensitive in the detection of cystic duct obstruction. Only patients with radiolucent stones in 'functioning' gallbladders (those which opacify during oral cholecystography), are suitable for medical treatment. Oral cholecystography has also been used in epidemiological studies (Gilat *et al.*, 1983).

In some parts of the world, abdominal ultrason-

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ography is now being used almost routinely – to complement the physical examination in much the same way that the sphygmomanometer is used to record the blood pressure. Whether this approach is right or wrong is a matter for debate. But one thing is certain, more widespread use of ultrasonography will lead to the detection of silent or asymptomatic gallstones in hundreds, or perhaps even thousands, of patients. Before deciding whether or not such patients require any form of active treatment, logically the physician (or surgeon) should know something about the natural history of silent stones, and should weigh up the risks and benefits of an expectant approach against those of medical or surgical treatment.

Knowledge about the long-term outcome of a conservative approach in patients with 'silent' gallstones was not available in Rolleston's time. Indeed there is precious little scientifically-based information about the fate of asymptomatic patients with untreated cholelithiasis, today. We still largely depend on the results of a few major studies which were based mainly on symptomatic patients (Comfort *et al.*, 1948; Lund, 1960; Wenckert & Robertson, 1966) even though there is more limited recent information based on a highly selected population (Gracie & Ransohoff, 1982) or a short-term (2 year) follow-up (Thistle *et al.*, 1984). However, in two large series from Italy, one from Rome (GREPCO, 1984) and the other from the small town of Sirmione on the shores of Lake Garda (Barbara, 1984) – when gallstones were detected by ultrasound, some 66–80% of the carriers were unaware that they had stones. Since the average diameter of these stones was 19 mm (Capocaccia, personal communication) and since gallstones take many years to reach this size, we can conclude that most of these individuals must have had no major symptoms as a result of their gallstones. On this evidence, therefore, we are now in a position to contradict Rolleston by suggesting that 'symptoms common to them (gallstones)' are *not* present in the majority of gallstone carriers: most have neither cholecystitis nor biliary colic.

Longitudinal studies based on long-term follow-up of individuals found to have gallstones by ultrasound screening, who undergo neither medical nor surgical treatment, should provide badly needed information about the natural history of the silent gallstone. Despite the paucity of data, however, the limited results available at present suggest that while a number of asymptomatic gallstone carriers will go on to develop symptoms (and an even smaller number will progress to complications requiring surgery – such as cholecystitis, cholangitis, obstructive jaundice, pancreatitis and severe or recurrent biliary colic), the majority will not. It is against this background, that the medical treatment of gallstones is reviewed in this article. But before addressing this question, it seems

appropriate to comment further on Rolleston's article and on his hypotheses about gallstone formation.

The pathogenesis of cholesterol-rich gallstones

Cholecystitis – chicken or egg?

In 1925, Naunyn's theory of the late 19th century (Naunyn, 1882) that gallstones develop secondary to inflammation of the gallbladder, still held sway. According to this hypothesis, inflammation of the gallbladder mucosa stimulated increased cholesterol formation. The crystals of cholesterol so produced were then liberated into the gallbladder lumen where they became cemented together by 'bilirubin calcium'. Cholecystitis was, therefore, considered to be a necessary antecedent to calculus formation although Rolleston 'urged that cholelithiasis does not invariably follow cholecystitis'.

We know that most, if not all, the cholesterol in cholesterol-rich gallstones comes from the bile and not from the gallbladder mucosa – even if there is still some debate about the origins of biliary cholesterol (hepatic cholesterol synthesis versus lipoprotein cholesterol uptake by the liver). The results of studies in which 'steady-state' bile lipid secretion has been measured (by duodenal intubation and perfusion of recovery markers together with stimulants to bile flow), clearly show that patients with cholesterol-rich gallstones secrete more cholesterol – either in absolute terms or relative to biliary bile acids – than do non-gallstone control subjects (Grundy *et al.*, 1972; Northfield & Hofmann, 1975; Mabee *et al.*, 1976; Shaffer & Small, 1977; Valdivieso *et al.*, 1979; Key *et al.*, 1980; Reuben *et al.*, 1985).

Acalculous cholecystitis probably does occur (Andersson *et al.*, 1971), but it is comparatively rare and in the large majority of patients, when cholecystitis develops, it does so as a consequence, rather than as a cause, of the gallstones.

Biliary cholesterol supersaturation

Rolleston did recognize the importance of excess (biliary) cholesterol in the pathogenesis of gallstones – a concept that was given scientific credibility by the results of physico-chemical studies carried out in Paris by Small and Dervichian during the mid 1960s (Small & Bourges 1966; Small *et al.*, 1966 a,b). This work culminated in the publication of a classic paper by Admirand & Small (1968). In this paper, the authors showed that by plotting bile lipid composition on a triangular co-ordinate phase diagram, they could completely separate the results in gallstone patients from those in control subjects. Bile from patients with cholesterol gallstones was either saturated or super-

saturated with cholesterol, relative to the given amount (molar ratio) of bile acids and phospholipids present in that bile sample. In contrast, bile from control subjects was always in the one-phase micellar zone. Even though the results of subsequent studies could not confirm the complete separation between control subjects and gallstone patients (there is approximately a 30% overlap between the two groups), nevertheless, it was Admirand and Small's studies which stimulated the subsequent work on bile lipid secretion mentioned above.

Stasis: altered gallbladder motility

Rolleston also suggested that stagnation of bile within the gallbladder was necessary for gallstone formation – a concept which remains in vogue today. In fact, the results of several recent studies (Fisher *et al.*, 1982; Forgacs *et al.*, 1984; Pomerantz & Shaffer, 1985) clearly show that gallbladder emptying is abnormal in gallstone patients. For example, Forgacs *et al.*, (1984) found that gallbladder contraction was slower and less complete in gallstone patients than in controls. This was true when gallbladder emptying was induced by exogenous (IV cholecystokinin-octapeptide) or endogenous (a liquid Lundh meal) stimuli and whether studied by ultrasound or by radionuclide scanning of the gallbladder after IV⁹⁹Tcm-HIDA. Similar findings were reported by Fisher *et al.* (1982) and by Pomerantz & Shaffer (1985) in some, but not all, of their gallstone patients. However, we still do not know whether this altered gallbladder motor function is a consequence of the gallstones, and of a diseased gallbladder, or whether the abnormalities antedate, and even predispose to, the gallstone formation.

Effect of bile concentration by the gallbladder

So far, therefore, there is little disagreement between the beliefs of the 1920s and those of today. However, Rolleston's concept that excessive concentration of bile within the gallbladder is a necessary prerequisite for gallstone formation, would not find favour in 1985. Carey & Ko (1979) extended Small's physico-chemical studies and showed that as bile became more concentrated (that is, as the total lipids in bile increased) it could hold progressively more cholesterol in a one-phase mixed micellar solution. In other words, the excessive bile concentration that Rolleston suggested 'must be premised' as a result of stasis, would by itself *favour* cholesterol solubilization in bile rather than diminish it and would, thereby, reduce the chances of gallstone formation.

The role of infection

In much the same way that theories about gallbladder

stasis and the origins of excess biliary cholesterol have changed with time, so the pendulum of opinion about the importance of infection in the pathogenesis of gallstones has also swung to and fro.

Rolleston states that '... the association of infection – post or proper – with gall-stones is universally acknowledged...'. Indeed before him, Lord Moynihan – a surgical doyen from Leeds – had claimed that 'every gallstone is a tombstone erected in the memory of a bacteria'. But despite 60 to 80 years or more of hypothesis, the role of infection as a factor leading to the formation of most gallstones, has not been proven. It is true that in parts of Asia, stones in the bile ducts are often associated with parasitic (such as *Clonorchis senesis*) or bacterial infections in the biliary tree. It is also true that in some South American countries, such as Chile, the prevalence of both gallstones and *Salmonella typhi* infection is high, and a cause-and-effect relationship between these two phenomena has been implied (Nervi *et al.*, 1984). Indeed, Rolleston himself states that 'typhoid bacilli are constant in the bile'. However, he goes on to dismiss the idea that *B. typhosus* infections might lead to cholecystitis and gallstone formation because 'enteric fever has become comparatively rare in this country' whilst gallbladder 'affections' are, if anything, more frequent. Agreed – but does this argument necessarily apply to countries such as Chile where the incidence of *S. typhi* carriers is high, the organism is frequently found in the stools as well as in the bile, where unprocessed human faeces are mixed with water and sprayed as a fertilizer directly on to salad and vegetable crops?

Non-cholesterol nucleating agents

In 1985, there is growing interest in the formation of non-cholesterol stones and in the precipitation of calcium in the form of carbonate, bilirubinate, phosphate or fatty acid salts. For too long, investigation has focused on cholesterol-rich gallstones – not only because they are the most common variety in Western society but also because until now, they are the only sort which could be dissolved by oral dissolution therapy. However, even radiolucent cholesterol-rich gallstones (arbitrarily >70% cholesterol by weight) are usually mixed in composition and often contain calcium salts. Furthermore, calcium salts are major constituents of the so-called brown or black pigment stones. And, as was well known when this journal was born, calcium bilirubinate is often found in the nucleus of otherwise pure cholesterol gallstones (Rovsing, 1923; Been *et al.*, 1979).

For a while, Maki's attractively simple hypothesis (Maki, 1966) about the role of infection in the pathogenesis of calcium bilirubinate stones, held sway. This theory seemed to marry the ideas of infection and calcium bilirubinate nucleation of

cholesterol gallstones, together. Maki proposed that the bacterial enzyme β -glucuronidase cleaved the mono- and di-glucuronide conjugates of bilirubin to liberate unconjugated bilirubin which then co-precipitated with calcium to form calcium bilirubinate stones (or at least calcium bilirubinate nuclei in cholesterol-rich stones). But as Rolleston points out, repeated attempts to obtain positive bacterial cultures from the bile of gallstone patients, or indeed from the centre of the gallstones themselves, have been unsuccessful. For this reason, the focus of attention has now shifted from infection to the hepatic transport of unconjugated bilirubin (Ostrow, 1984) and to the physical chemistry of biliary calcium and its associated anions (carbonate, phosphate, palmitate and bilirubinate) – the so-called ‘calcium-sensitive’ anions (Moore, 1984).

The origins of biliary cholesterol

Perhaps the greatest difference between the theories of 1925 and those of today relate to the origins of the cholesterol found in gallstones. The speculative discussions in Rolleston’s article about a possible hereditary ‘diathesis’ of cholesterol retention in the body as a source of the cholesterol-laden villi in the gallbladder mucosa, which then becomes detached to provide the nuclei of future calculi, emphasize the limitations imposed on our colleagues of 60 years ago by the lack of isotope technology. Given the benefit of ^{14}C -labels for cholesterol and its precursors, we now know that cholesterol is synthesized by almost every tissue in the body, but that the intestinal mucosa and the liver are the principle sites for cholesterologenesis (Dietschy & Wilson 1968). We no longer need to reason that because the central nervous system, adrenal cortex and the corporea lutea are rich in cholesterol, that these organs must, therefore, be the source of the serum and biliary cholesterol.

Hepatic cholesterol synthesis

Hepatic cholesterol synthesis is controlled by the rate-limiting enzyme, hydroxy methyl glutaryl co-enzyme A reductase (HMGCoAR). Measurement of the activity of this enzyme in liver tissue, therefore, provides a measure of hepatic cholesterologenesis. In man, this can be studied in small surgical biopsies of the liver and several investigators have now shown that in untreated gallstone patients, the activity of hepatic HMGCoAR is considerably increased, when compared to normal (Salen *et al.*, 1975; Coyne *et al.*, 1975; Maton *et al.*, 1980). Given this information, it was tempting to speculate that increased cholesterol production by the liver might be the major metabolic defect in cholesterol cholelithiasis. For at least two reasons (which may be inter-related), however, this

speculation is incomplete. First, in patients undergoing elective abdominal surgery, when biliary cholesterol secretion was measured on the eve of laparotomy and related to hepatic HMGCoAR activity measured the following day, there was no significant correlation between the two variables (Key *et al.*, 1980; Maton *et al.*, 1982b). Indeed from the results of animal studies, we know that hepatic cholesterol synthesis accounts for only 20% (approximately) of biliary cholesterol secretion (Turley & Dietschy, 1980). The remainder probably comes from chylomicron remnant and lipoprotein cholesterol uptake by the liver. Second, although some of the cholesterol produced by the liver is exported directly into bile, there are many other potential destinies for the newly synthesized cholesterol: it may act as a substrate for bile acid synthesis, be incorporated into cell and intra-cellular organelles or may be transported into the circulation bound to apoproteins.

The relationship between serum and biliary cholesterol

It also seems that Rolleston’s* ‘biochemical view of the aetiology’ of gallstones ‘that there is an increase in the cholesterol content of the blood and so in the bile, and thus pure cholesterol calculi are produced’ would not generally be accepted today. There is no simple relationship between serum and biliary cholesterol and no direct epidemiological link between hypercholesterolaemia and cholelithiasis. Some contemporary investigators believe that there is, in fact, an inverse relationship between serum HDL cholesterol and the moles % cholesterol or the cholesterol saturation index, in bile (Thornton *et al.*, 1981; Petitti, 1983; Scragg *et al.*, 1984). There is more universal agreement that the propensity to develop gallstones is related to hypertriglyceridaemia (Angelico *et al.*, 1984). The situation is complex, however, since hypertriglyceridaemia is related to obesity and in turn gallstones are more common in the obese than in the non-obese (Gross, 1929; Friedman *et al.*, 1966; Zahor *et al.*, 1974). Furthermore, total body cholesterol synthesis is greater in the obese than in the non-obese (Miettinen, 1971; Nestel *et al.*, 1973) and obese individuals secrete more cholesterol in their bile (Reuben *et al.*, 1985).

Cholesterol gallstone formation: summary of the 1985 concepts

The contemporary view of cholesterol gallstone formation may be summarized as follows. The first and essential step is the secretion of supersaturated bile by

*More correctly, Rolleston’s citation of theories proposed by Aschoff and Bachmeister.

the liver. This may result from one of several metabolic abnormalities:

(i) hypersecretion of cholesterol (as happens, for example, in the obese), (ii) hyposecretion of bile acids and/or phospholipids (the solubilisers of cholesterol) – often seen in non-obese gallstone patients who have a reduced bile acid pool size, (iii) a combined defect and (iv) hypo-secretion of biliary phospholipids etc. However, supersaturation alone is inadequate to explain gallstone formation; in addition, there must be a defect in nucleation which induces precipitation of cholesterol crystals from the supersaturated solution within the gallbladder (Holan *et al.*, 1979; Sedaghat & Grundy, 1980; Gollish *et al.*, 1983). Many normal individuals secrete supersaturated bile, especially in the morning after an overnight fast, but yet do not form gallstones.

Bile samples with comparable degrees of cholesterol supersaturation deposit crystals at very different rates. Those from non-gallstone subjects may remain clear for up to three weeks before crystals form while those from patients with gallstones yield crystals in only 1–2 days (Holan *et al.*, 1979; Sedaghat & Grundy, 1980). Recently, Gallinger and colleagues (1984) have shown that the addition of only 10% of bile from gallstone patients to the equally supersaturated bile from a control subject, will induce crystal formation in 1–2 days. Therefore, in addition to the primary defect in the secretion of supersaturated bile, there is a secondary defect of nucleation and the selected evidence quoted above strongly favours an excess of cholesterol promoters, rather than a deficiency of inhibitors, as the major abnormality favouring nucleation.

The third component in the proposed triple defect is stasis within the gallbladder. The evidence for altered gallbladder motor function in patients with cholelithiasis is strong (Fisher *et al.*, 1982; Forgacs *et al.*, 1984; Pomerantz & Shaffer, 1985) but as discussed above, we still do not know if the slower and less complete gallbladder emptying in gallstone patients, is cause or effect.

The importance of geographic, racial and other factors in gallstone formation

Although this summary emphasizes the biochemical and pathophysiological events leading to cholesterol gallstone formation, this does not imply that dietary, hormonal, familial, geographic, racial and other factors are unimportant. Indeed, we know that there are considerable differences in gallstone incidence and prevalence rates in different parts of the world. However, we now benefit from a more substantial data base than was available 60 years ago. Rolleston suggests that gallstones are common in German women but rare in Russians, Indians and Japanese. It is doubtful if today's experts in gallstone

epidemiology would single out German women for emphasis. Indeed, they would more likely stress the high gallstone prevalence rates in peoples from North (Comess *et al.*, 1967; Sampliner *et al.*, 1970) and South America (Covarrubias *et al.*, 1983) with Indian genes and in those from developed societies as a whole. The Japanese are no longer relatively immune from developing gallstone disease: indeed, with increasing affluence, the Japanese now have prevalence figures for gallstones comparable to those seen in the West (Hikasa *et al.*, 1980).

Although one might quibble over some details in Rolleston's article about factors influencing gallstone formation, many of his other statements are now supported by scientific evidence. For example, he states that 'gall-stones are not infrequently hereditary'. From studies of bile lipid composition, we now know that first-degree relatives (siblings) of patients with gallstones have supersaturated bile more often than matched controls (Danzinger *et al.*, 1972b). We also know from epidemiology studies that gallstones are more common in the relatives of gallstone carriers, than normal (Barbara *et al.*, 1984a).

To sum up, our knowledge about the formation of gallstones has advanced considerably since 1925 but we remain ignorant about the quantitative importance of many of the individual factors which influence pathogenesis. Sixty years on we are still forced to discuss, as Rolleston did, the evidence for and against multiple aetiological factors of gallstones – including the metabolic and infective theories which dominated the beliefs of 1925.

Prophylactic or preventative treatment

In contrast to the large body of knowledge about gallstone formation, there are very few data on prophylactic treatment and at present there is no known way of preventing gallstone formation. Having said that, it may still be useful to consider in outline, potential forms of prophylactic treatment. But before doing so, we must review briefly the different arbitrary stages in the evolution of gallstone disease. Logically, the type of treatment, both prophylactic and active, depends on how far the patient has progressed along this evolutionary pathway.

Stage I – The formation of supersaturated bile

At present this stage can be detected only by measuring the lipid composition of fasting gallbladder bile. This is usually obtained by duodenal intubation but occasionally by needle aspiration of the gallbladder during laparotomy. Ideally, prophylactic treatment should be aimed at patients who are still at this stage in the evolution of their disease *before* the gallstones have

formed. In theory, effective prophylaxis might be achieved either by using desaturating agents (see below) or by suppressing nucleation. Lee and colleagues (1981 a,b) studied the prairie-dog model of gallstone formation and suggested that mucin production by the gallbladder mucosa promoted nucleation of cholesterol crystals from the supersaturated bile. Indeed they showed that the increased mucus production was induced by the presence of supersaturated bile within the gallbladder and antedated the development of the gallstones. Since mucin production may be controlled by mucosal prostaglandins, the authors treated the prairie-dogs with either indomethacin or aspirin (inhibitors of prostaglandin synthesis), and prevented both cholesterol crystal precipitation and gallstone formation, within the gallbladder (Lee *et al.*, 1981b). This therapeutic approach has not yet been extended to man but logically might be tested in high-risk groups, such as the Pima Indians, who have a particularly high incidence of cholelithiasis. By the age of 30, some 70% of Pima Indian women have developed gallstones (Comess *et al.*, 1967; Sampliner *et al.*, 1970). In theory, inhibition or prevention of nucleation might also be tried as prophylaxis against recurrence in patients whose gallstones have been dissolved completely by medical treatment.

Stage II – The development of silent or asymptomatic gallstones

The progression from Stage I to Stage II may involve the triple defect discussed above. It includes an intermediate step during which a suspension of cholesterol microcrystals develops within the gallbladder. The presence of microcrystals can only be detected by sampling the bile directly, but the presence of silent gallstones may be diagnosed by oral cholecystography and/or ultrasonography. Once macroscopic gallstones have developed, treatment can only be considered as prophylactic in terms of preventing progression of the disease and the development of surgical complications.

Stage III – Symptomatic gallstone disease

Here attacks of biliary pain, and possibly also the presence of non-specific upper abdominal symptoms, signal the presence of gallstones. However, the frequency and severity of symptoms may remain tolerable enough so that surgery is not mandatory. Most of our knowledge about the natural history of untreated gallstone disease today (Comfort *et al.*, 1948; Wenckert & Robertson, 1973; Lund, 1960) (and all of it in Rolleston's day) is based on patients with Stage III and Stage IV disease. We badly need information about the natural history of 'silent' (Stage II) gallstones based on longitudinal studies in cohorts

of patients found to have gallstones by ultrasound screening.

Stage IV – The onset of complications requiring surgery

'Surgical' complications occur mainly when there is cystic or common duct obstruction. They include cholecystitis and empyema formation, obstructive jaundice, severe and/or recurrent biliary colic, cholangitis and pancreatitis. These complications were well described by Rolleston who classified them logically into mechanical problems (although today one might question the validity of including 'reflex dyspepsia' in this category), and problems due to supervening infection. However, his emphasis on gallbladder cancer and on the rare, but interesting, complication of gallstone ileus, seems inappropriate in 1985. Although these problems still occur, they do so so rarely that the theoretical risk should not influence decisions about patient management.

From what has been said above, it is obvious that while medical treatment of patients with Stage II disease *might* prevent progression to Stages III and IV, true prophylactic treatment should be confined to individuals with Stage I disease. At present, the relatively high cost of long-term, prophylactic bile acid treatment and the benign nature of untreated gallstone disease in the majority of patients means that, with the possible exception of clinical trials in high-risk groups, there is no place for prophylactic medical treatment today.

Oral dissolution therapy

Some thirteen years after the first reports of complete gallstone dissolution with oral chenodeoxycholic acid (Danzinger *et al.*, 1972a; Bell *et al.*, 1972), we can now cheerfully refute Rolleston's speculation that 'attempts to dissolve gall-stones cannot be regarded as likely to succeed'. Since 1972, tens of thousands of gallstone patients have been treated with oral bile acids and hundreds of cases of confirmed complete gallstone dissolution have been recorded. Despite this, bile acid therapy does not enjoy widespread popularity. When active therapy for gallstones is indicated, dissolution therapy has certainly not replaced surgery as the treatment of choice. But when is active treatment, either medical or surgical, indicated? – certainly for Stage IV disease when surgery is required although, only a minority of gallstone carriers in the general population will ever progress to this stage. On present evidence (Gracie & Ransohoff, 1982; Thistle *et al.*, 1984), however, neither medical nor surgical treatment is necessary for Stage II disease (asymptomatic stones) and there is considerable doubt if it is justified for every patient with Stage III disease

(symptomatic stones). The irony is that although Rolleston's pessimism about gallstone dissolution is ill-founded, not many patients in the general population pass through a critical selection filter when considering patients for oral therapy. Either their gallstone disease is too early in its evolution to justify medical treatment, or it is too late and requires surgery.

Who then should be considered for bile acid treatment? All investigators agree that it should be confined to patients with radiolucent, presumed cholesterol-rich gallstones in 'functioning' gallbladders (that is, a patent cystic duct). These requirements are best established by oral cholecystography. Patients with large stones (arbitrarily >15–20 mm in maximum diameter measured on cholecystogram films) respond poorly: not only is the overall efficacy rate of bile acid treatment low in such patients, but in the rare instances when the therapy is successful, it takes many months (up to five years) to achieve.

If these are the minimum 'admission requirements', which patients within this category should be advised to consider dissolution therapy? Probably only those whose gallstone disease has evolved to Stage II although a percentage of those with Stage II disease, when offered the *informed* choice of: (i) an expectant approach, treating symptoms if and when they arise; (ii) oral dissolution therapy or (iii) elective cholecystectomy – will also opt for a trial of medical treatment. The 'ideal' candidate is a patient who fulfils the minimum requirements, is judged to need active treatment but is considered to be at a higher than normal risk for surgery and/or anaesthesia. Such patients constitute a tiny minority. But there are others who, for business or family reasons, are unable and/or unwilling to come into hospital and to 'lose' time off work or away from dependent relatives, for surgery and during subsequent convalescence. A further group of patients are adamant that they do not wish to consider surgery for psychological, religious or other reasons. But apart from these patients, a frequent reason for considering medical treatment is the rationalisation that if it works, cholecystectomy may be avoided and that if it does not, nothing other than time has been lost and the option of elective surgery remains.

Details of the medical treatment of gallstones, including the choice of bile acid, the dose, timing of administration, duration of therapy, frequency of follow-up, complications and side effects, monitoring of compliance and of the efficacy of treatment in producing partial and/or complete gallstone dissolution and recurrence rates and post-dissolution management, have been described many times before (Dowling, 1983, 1985; Dowling *et al.*, 1984). For this reason, the subject is not reviewed here: instead, a brief statement of the authors' views is given with a

summary of recent developments and recommendations in the medical management of gallstones.

Chenodeoxycholic acid (CDCA)

CDCA treatment is moderately effective in selected patients. It dissolves gallstones in approximately 40% of patients who initially have radiolucent gallstones in a functioning gallbladder, in approximately 60% of those who fulfil the 'ideal' selection criteria described above and in a maximum of 80% of compliant, selected patients *if* the incidence of radiolucent non-cholesterol stones is low and *if* supervening problems (such as the onset of surgical complications or the development of a non-functioning gallbladder) do not interrupt continuous full-dose treatment for 12 months or more (Maton *et al.*, 1982). However, CDCA causes dose-related (although often transient) diarrhoea, hypertransaminasaemia (Mok *et al.*, 1974) and, in one major study at least, hypercholesterolaemia (Schoenfield *et al.*, 1981). In a minority of patients, the diarrhoea is persistent or recurrent, and affects compliance (Bateson *et al.*, 1978) in taking the full recommended bile acid dose (15 mg/kg/d) (Iser *et al.*, 1975).

Ursodeoxycholic acid (UDCA)

UDCA is the 7 β epimer of CDCA. This apparently tiny difference in molecular structure between CDCA and UDCA markedly affects the properties of the two bile acids. UDCA treatment does not cause diarrhoea or raise serum transaminase levels. It probably does not affect serum cholesterol levels – unless in a beneficial way by increasing HDL cholesterol. On a mole for mole basis, UDCA is more potent than CDCA. In comparable doses (15 mg/kg/d), it lowers biliary cholesterol secretion (von Bergman *et al.*, 1979) and the moles % cholesterol in bile (Stiehl *et al.*, 1978; Stiehl *et al.*, 1980), more effectively than does CDCA. Alternatively, smaller doses of UDCA (10 mg/kg/d) produce a comparable effect on bile lipids to than seen with the standard dose of CDCA (15 mg/kg/d). But there is a fundamental difference in the way the two bile acids dissolve the crystalline cholesterol in the gallstones. UDCA treatment induces the formation of a liquid crystalline mesophase at the surface of the stone (Corrigan *et al.*, 1980; Salvioli *et al.*, 1981). This non-micellar solubilization of cholesterol cannot yet be quantified. Until it can, we must reserve judgement about the apparently greater potency of UDCA in reducing biliary cholesterol saturation.

At first sight, the absence of *symptomatic* side effects might suggest that UDCA is now the medical treatment of choice for patients with cholesterol-rich gallstones. Indeed, until recently this was also the conclusion of the authors (Meredith *et al.*, 1982).

However, there is a *silent* disadvantage of UDCA treatment – it leads to acquired surface or rim calcification of the stones in up to 25% of patients (Gleeson *et al.*, 1984). In the majority of these, the deposition of a layer of calcium halts, or seriously inhibits, subsequent gallstone dissolution.

We now know that this acquired calcification is due to the precipitation of crystalline calcium carbonate (in the form of calcite, vaterite or aragonite) on the surface of the stones (Gleeson, Bills and Dowling, unpublished). The mechanism for this phenomenon is currently under intensive investigation by ourselves (Gleeson *et al.*, 1985 a,b,c, and others (Williamson & Percy-Robb, 1980; Cummings & Hofmann, 1984; Moore *et al.*, 1982), but it seems likely that it is due to an effect of UDCA on biliary bicarbonate secretion (Dumont *et al.*, 1980), with secondary changes in biliary pH and in the concentration of the carbonate anion, rather than the calcium cation, in bile.

Chenodeoxycholic acid plus ursodeoxycholic acid

Before the importance of non-micellar solubilization of cholesterol in UDCA-rich bile was appreciated, Carey & Ko (1979) suggested that because UDCA itself is a relatively poor detergent, one should apply a correction factor when estimating the percent saturation of bile with cholesterol, in patients taking UDCA. Based on the results of careful *in vitro* studies, he suggested that the greater the percentage of UDCA conjugates in bile, the lower was its capacity to solubilize cholesterol. Since the enrichment of bile, with UDCA conjugates is roughly proportional to the UDCA dose (up to a plateau) (Maton *et al.*, 1977; Stiehl *et al.*, 1977), it was argued that to achieve maximum efficiency, one should restrict the dose of UDCA and, as a result, the enrichment of bile with the administered bile acids. Indeed, it was based on this logic that Stiehl *et al.*, (1980) 'diluted' the administered dose of UDCA with CDCA. Subsequently, when it was realised that UDCA induced liquid crystalline mesophase formation at the surface of the stone, it became clear that the advantage of this non-micellar solubilization of cholesterol might outweigh the disadvantage of UDCA's poor detergent properties. Thus Stiehl's original logic for advocating a mixture of CDCA and UDCA collapsed. Despite this, a 50:50 mixture of these two bile acids – or perhaps a mixture of the two, each being given at half the normal recommended dose (that is CDCA 7.5 mg/kg/d and UDCA 5.0 mg/kg/d), is probably 'best buy' in bile acid treatment of gallstones today (Podda *et al.*, 1982). Why? – because the side effects of CDCA and possibly also of UDCA (although this has not been proven), are dose-dependent. Therefore, by giving each bile acid in a 'sub-toxic' dose, one should avoid problems, such as diarrhoea and acquired gallstone calcification, whilst

retaining (hopefully) dissolution efficacy. Certainly the results of biliary bile acid and bile lipid studies suggest that the mixture of the two bile acids should be effective (Podda *et al.*, 1982) and preliminary results of gallstone dissolution efficacy with the combination of CDCA and UDCA are encouraging. However, more clinical experience is needed before this recommendation can be consolidated. *Proof* that treatment with the combination of CDCA and UDCA is more effective than with either bile acid alone, is never likely to be forthcoming. The expense of large-scale studies, such as the US National Co-operative Gallstone Study (Schoenfield *et al.*, 1981), which would be needed to establish this point, could not be justified on either clinical or scientific grounds.

Other bile acids

Although oral CDCA, UDCA and the combination of the two bile acids has a small, but definite place in the management of patients with cholesterol-rich gallstones, the treatment is too slow, too expensive and too uncertain to enjoy widespread acclaim (Dowling, 1985). Moreover, although gallstones can be dissolved by bile acid therapy, when treatment stops, the stones recur with unacceptable frequency (Dowling *et al.*, 1984). Until recurrence can be reliably and inexpensively prevented, dissolution therapy is likely to enjoy only a limited place in the treatment of cholelithiasis. For this reason, the hunt is on for more effective and cheaper bile acids (or other oral agents) which will dissolve gallstones and yet have no side effects. Unfortunately, there is no animal model in which the biliary cholesterol desaturating effect of different bile acid treatments reproduces the pattern of response seen in man. For obvious ethical reasons, widespread testing of the effect of different bile acids on bile acid and bile lipid composition (which normally requires 4–6 weeks of continuous therapy) in control subjects or patients with gallstones, is difficult or even impossible. For this reason, recent research has been directed towards unravelling the mysteries of structure/activity 'rules'. We need a bile acid that is well absorbed, remains within the enterohepatic circulation, desaturates bile efficiently, is non-toxic to liver, biliary tree and intestine and does not cause diarrhoea, hyperlipidaemia or acquired gallstone calcification. This is a tall, but not impossible, order. We now know which bile acids reduce biliary cholesterol secretion and saturation in man, and which do not (Dowling, 1985; Carulli *et al.*, 1984). We also know that diarrhoea occurs when dihydroxy bile acids, such as CDCA and deoxycholic acid, spill into the colon (Chadwick *et al.*, 1979). We also know that choleric bile acids, such as UDCA (and probably also ursodeoxycholic acid, the 7 β epimer of cholic acid) Howard *et al.*, 1984; Loria *et al.*, 1984), induce biliary bicarbonate secretion and the

chance of acquired gallstone calcification. However, we must also consider not only the effect of the administered bile acid, but also of its metabolites, on all the variables listed above. As a result of systematically varying bile acid ring structure, side-chain structure and conjugation (at different sites), it is hoped that the 'ideal' bile acid treatment will ultimately emerge. In the meantime, one or two other approaches in the medical management of patients with gallstones, deserve brief mention.

Non-surgical removal of stones in the biliary tree

In patients with choledocholithiasis ($\pm$ stones in the gallbladder), there is now a wide range of non-surgical management options – including endoscopic sphincterotomy and stone removal, endoscopic placement of naso-biliary catheters with solvent perfusion, endoscopic ultrasonic stone disintegration, T-tube solvent infusion, T-tube stone extraction (with, for example, Dormia baskets) and even oral dissolution therapy. These mechanical approaches are the result of important recent technical advances. However exciting, they are beyond the scope of this article but for further information on this topic, the reader is referred to a recent review (Dowling, 1983a).

The future

Until recently, it was assumed that the gallbladder (and the stones within it) was inaccessible to direct solvent infusions. Within the past year, however, Allen *et al.*, 1985a,b) have described the technique of

percutaneous, transhepatic cannulation of the gallbladder as a route for the instillation of powerful, and it is hoped, non-toxic, cholesterol solvents such as methyl tertiary butyl ether. So far, this exciting new approach has been applied only to a handful of patients in whom cholesterol-rich stones have been dissolved in a matter of hours. However, it is an invasive technique and is a relatively major 'minor procedure', whose safety remains to be established. Nonetheless, it breaks new ground and establishes principles which may have wider applications. It has been assumed, for example, that the narrow cystic duct with its spiral valve of Heister could not be cannulated retrogradely, during endoscopy. But this barrier too may soon be overcome. If so, given the development of new solvents such as methyl tertiary butyl ether (Allen *et al.*, 1985a,b) and dipolar aprotic solvents (Corrigan *et al.*, 1984) for cholesterol stones or bile acid/EDTA mixtures for calcium-containing stones, a new management option for patients with gallbladder stones, may emerge.

Conclusion

Our understanding of the 'medical aspects of gallstones' has come a long way since the first issue of the *Postgraduate Medical Journal* in 1925. It is to be hoped that when the Journal publishes its 120th birthday issue in the year 2045, Rolleston's emphasis on prophylactic and preventive treatment will have been vindicated and that this 'state-of-the-art' in 1985 will have become redundant by the primary prevention of gallstone development.

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