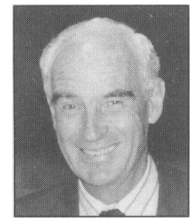
The Gallstone Story



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When the organisers of the RVH Bicentenary kindly approached some expatriate "old boys", inviting us to talk at the celebratory meeting, our brief as we approached retirement was to review some aspect of our professional work. I opted to focus on gallstones and initially, was tempted to begin by reminiscing about our studies of bile lipid composition in patients with ileal disease or resection[1] and our use of the steady-state secretion perfusion technique[2,3] to measure the hour-by-hour output of biliary lipids in control subjects and gallstone patients — with particular emphasis on obesity.[4] I might also have recalled our work on gallbladder motor dysfunction in gallstone disease[5] or our early studies in the use of chenodeoxycholic[6-8] and ursodeoxycholic acids[9-11] as oral treatment for the dissolution of gallstones in symptomatic patients.

In their day, each of these chapters held its own fascination and the research fellows who worked on these projects made valuable contributions to the literature. But rather than wallow in nostalgia, I have chosen to review, briefly, the results of exciting recent studies, performed by my colleagues at Guy's, over the past five years. They began with a collaborative study of acromegalic patients treated with octreotide who develop iatrogenic gallstones[12] - a phenomenon well known at the RVH since one of the first observations on this topic was made by McKnight and colleagues from the Metabolic Unit of the RVH.[13]

We are now close to making the "outrageous assertion" that cholesterol cholelithiasis is an intestinal disease,[14] secondary to changes in large bowel transit.[15] This chapter reviews the evidence behind this assertion and, in keeping with the theme of the meeting, the chapter ends with a discussion of strategies for preventing gallstone formation, in the next millennium.

Clinical Science of Gallstone Formation

The types and composition of gallbladder stones (GBS) are discussed briefly before the classical theory of cholesterol (CH) GBS formation is reviewed. This suggests that, before stones can form, at least three abnormalities (the so-called triple defect)[16] must co-exist: (i) supersaturated GB bile, (ii) abnormal nucleation of CH microcrystals and (iii) stasis due to impaired GB emptying and/or crystal trapping by mucus on the surface of the GB mucosa. However, most of this presentation is based on a modern-day detective story (still evolving) which describes why GBS develop in many acromegalic patients treated with the somatostatin analogue, octreotide (OT).

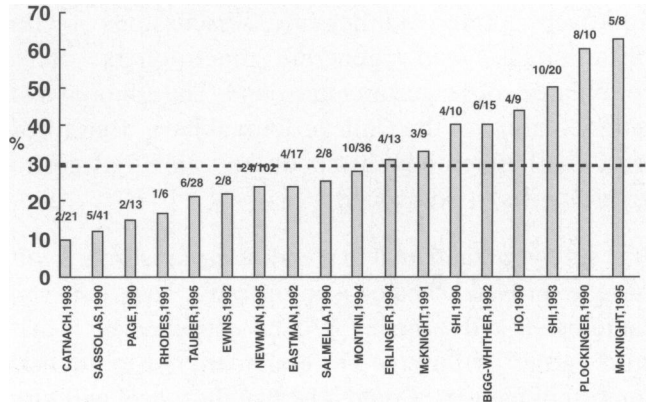

Fig 1 Reported incidence of gallbladder stones (GBS) in acromegalic patients treated with octreotide (OT) in doses ranging from 100-1500 ug /day for periods ranging from 3-70 mo. (Most patients received 100-200 µg tds by sub-cutaneous injection, for approximately 1-2 yr). Since at the start of OT treatment these patients were free of GBS by ultrasound, the results of these 18 studies represent the frequency of OT-induced (rather than OT-associated) GBS. The vertical bars represent the percentage of patients developing cholelithiasis: the numbers at the top of the columns refer to the numbers of patients developing stones, over the numbers of patients treated. The broken horizontal line represents the mean incidence of OT-induced stones (29%) in these 18 studies.

OT is an effective treatment for acromegaly. It acts by suppressing growth hormone and insulin like growth factor-I levels but it also inhibits meal-stimulated cholecystokinin release and GB contraction. We confirmed that OT virtually paralyses the gallbladder[17] but, given the triple defect theory of GBS formation,[16] the first step was to see if OT also affected bile composition and physical chemistry.

Step 1

Studies of fresh GB bile from acromegalic patients with OT-GBS[18] showed that they all have: (i) supersaturated bile, (ii) a high proportion of their biliary CH present in unstable vesicles, and (iii) abnormally rapid nucleation (precipitation) of CH microcrystals. These changes were associated with, and may well be due to, excess biliary deoxycholic acid (DCA % of total bile acids).[18] The hydrophobic DCA is the "bad boy" of bile. (Fig. 2) When present in

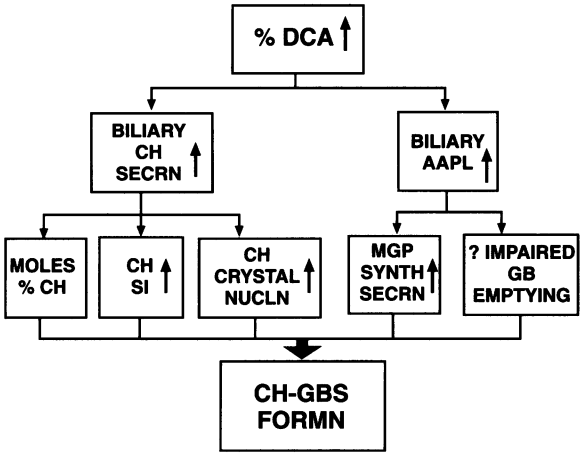

Fig 2 Schematic flow diagram to explain how an increase in the percentage of deoxycholic acid (%DCA) in bile might lead to an increased incidence of cholesterol gallbladder stones (CHGBS). Thus, enrichment of bile with DCA leads to a relative increase in biliary cholesterol secretion (secrn).[19] This may explain why we,[20] and others [33, 34] find that there is a significant linear relationship between the %DCA in bile and: (I) the molar percentage (moles %) cholesterol and (II) the cholesterol saturation index (SI), in gallbladder bile. It may also explain, at least in part, why we find that the mean %DCA in bile is approximately twice as high in patients with abnormally rapid (< 5d) nucleation or precipitation of cholesterol microcrystals, as in individuals with normal (> 10 d) nucleation times[20].

We[35] and others[36-39] also showed that the %DCA in bile was linearly related to the % arachidonic acid-rich phospholipids (AAPL) in bile. In turn, this may explain[40] why mucus glycoprotein (MGP) synthesis by, and secretion into, the gallbladder are increased in gallstone patients[41-43]. An increase in the proportion of AAPLs in GB bile could also contribute to the reduced meal-stimulated gallbladder emptying[5, 44-46] which characterises cholesterol gallstone disease.

excess, DCA induces biliary cholesterol hypersecretion and supersaturation.[19,20] Our results suggest that the increased biliary DCA seen in OT-treated acromegalics is due to the somatostatin analogue treatment, and not to the stones. Thus paired, before-and-during treatment, studies showed that within weeks, OT doubled the percent DCA in bile and induced biliary CH supersaturation - even in the absence of stones.[18]

Step 2

The next step was to determine why OT treatment doubles the % DCA in bile. Previous studies in control subjects had suggested that OT prolongs small bowel transit.[21-23] But would it do the same thing in acromegalics? And, more important, would it also affect large bowel transit (of importance since DCA is formed in the caecum and proximal colon - rather than in the small intestine)?

We confirmed that OT markedly prolongs small bowel transit both in control subjects and in acromegalic patients.[17] We also showed, again in paired before-and-during treatment studies,[24] that OT significantly prolongs large bowel transit time (LBTT). Furthermore, we found that LBTT was linearly related to: (i) the % DCA in serum[25](and, by implication, in bile), (ii) the DCA pool size[26] and (iii) the DCA formation (or "synthesis") rate.[26]

Step 3

If prolonged intestinal transit and altered DCA metabolism play a major role in the pathogenesis of the exotic OT-induced GBS, could these factors also play a similar role in "conventional" GBS disease — that this, GBS unrelated to acromegaly or OT treatment? The results of our own,[14,27] and other,[28-30] studies suggest that they do. Indeed, as noted above, we have even suggested that cholelithiasis is a disease of prolonged large bowel transit.[14]

Step 4

The mechanism whereby prolongation of intestinal transit increases the percentage of DCA in serum and bile, raises several questions. Does prolonged LBTT increase DCA formation by increasing the number of anaerobic bacteria in the right colon? Does it affect the activity of their deconjugating and dehydroxylating enzymes (cholylglycine hydrolase and 7-alpha dehydroxylase) which produce unconjugated (newly-formed) DCA from the glycine and taurine conjugates of cholic acid? Does prolongation of LBTT affect colonic luminal pH - thereby increasing the solubilisation and bioavailability of the newly-formed DCA? Or does a longer than normal LBTT allow more time for DCA absorption from the colon (presumably by passive non-ionic diffusion)?

The answer to these rhetorical questions seems to be - yes, yes and yes.[14] By comparison with "controls", patients with conventional GBS have: (i) significantly prolonged LBTT, (ii) significantly more total anaerobes in the caecum and right colon, (iii)

significantly more gram positive anaerobes, (iv) more deconjugating ($p>0.05$) and 7 alpha-dehydroxylating ($p<0.005$) enzymes per bacterium (or more correctly, per mg protein in the caecal aspirates), (v) a significantly greater colonic luminal pH[31] (probably because the prolonged transit allows more time for absorption of the acidic short chain fatty acids) and, again, (vi) a significant increase in the %DCA in fasting serum.

Thus, there is an intriguing web of complex interactions whereby prolongation of LBTT favours increased DCA: (i) formation, (ii) solubilisation/ bioavailability and (iii) absorption.(Fig. 3)

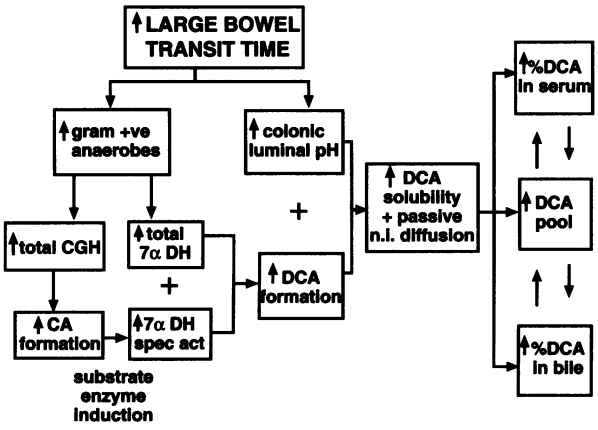

Fig 3 Flow diagram summarising the results of several studies from the authors department[16, 17, 24-27, 31, 32] showing how prolongation of large bowel transit might increase the proportion of deoxycholic acid (DCA) in the bile acid pool, and in serum and bile. Thus, an increase in large bowel transit time favours an increase in the numbers of Gram positive (+ve) anaerobes in the proximal colon. This increase in the numbers of anaerobes leads to increases in the total amounts (masses) of the intestinal bacterial bile acid metabolising enzymes responsible for deconjugation (cholylglycine hydrolase: CGH) and 7a-dehydroxylation (7α-dehydroxylase: 7α- DH) of the conjugated bile acids, in the caecum and colon. The resultant increase in deconjugation means that more cholic acid (CA) is formed in the proximal colon and this, in turn, may increase the specific activity (spec act) of 7α-DH.

The combination of increased total amounts of 7a-DH and increased 7α-DH specific activity, favours enhanced DCA formation. At the same time, the prolongation in large bowel transit time increases colonic lummal pH which ensures that the newly-formed unconjugated DCA is solubilised in, and is therefore made bioavailable for passive non-ionic (n.i.) diffusion from, the colon. This expands the proportion of DCA in the bile acid pool which is in dynamic equilibrium with the %DCA in serum and bile. The consequences of increased proportions of DCA in bile are summarised in Fig 2.

Step 5

If prolonged colonic transit really is important in the development of GBS, can all the resultant abnormalities be prevented or reversed, by the use of commonly-prescribed prokinetic drugs which accelerate intestinal transit? Again, the answer seems to be yes. In a prospective, random-allocation, double-blind, crossover design, controlled trial, we showed that the 5HT4 agonist, cisapride, completely prevented the prolongation of both small and large bowel transit seen in acromegalic patients treated with OT. More important, cisapride "normalised" the % DCA in fasting serum.[32] It remains to be proven, in prospective controlled trials, that the use of colonic prokinetic drugs, such as cisapride, can prevent cholesterol GBS formation in high-risk groups.

This, then, is the challenge for clinical investigators studying gallstone pathogenesis who, as we look BACKWARDS in this century, moved from "the bedside to the bench". As we move FORWARDS to the year 2000, they must now put this process into reverse and translate scientific theory into the clinical practice of gallstone prevention.

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