The Gallstone Story

R Hermon Dowling MD, FRCP
Director Gastroenterology Unit
Guy’s and St Thomas’s Medical and Dental School

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 and our use of the steady-state secretion perfusion technique to measure the hour-by-hour output of biliary lipids in control subjects and gallstone patients — with particular emphasis on obesity. I might also have recalled our work on gallbladder motor dysfunction in gallstone disease or our early studies in the use of chenodeoxycholic and ursodeoxycholic acids 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 — 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.

We are now close to making the “outrageous assertion” that cholesterol cholelithiasis is an intestinal disease, secondary to changes in large bowel transit. 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) 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).

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 but, given the triple defect theory of GBS formation, the first step was to see if OT also affected bile composition and physical chemistry.

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 ug 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.

© The Ulster Medical Society, 1998
Step 1

Studies of fresh GB bile from acromegalic patients with OT-GBS 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). The hydrophobic DCA is the “bad boy” of bile. (Fig. 2) When present in excess, DCA induces biliary cholesterol hypersecretion and supersaturation. 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.

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. 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. We also showed, again in paired before-and-during treatment studies, that OT significantly prolongs large bowel transit time (LBTT). Furthermore, we found that LBTT was linearly related to: (i) the % DCA in serum (and, by implication, in bile), (ii) the DCA pool size and (iii) the DCA formation (or “synthesis”) rate.

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 is, GBS unrelated to acromegaly or OT treatment? The results of our own and other studies suggest that they do. Indeed, as noted above, we have even suggested that cholecithiasis is a disease of prolonged large bowel transit.

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 dehydroxylation 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. 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-dehydroxylation (p<0.005) enzymes per bacterium (or more correctly, per mg protein in the caecal aspirates), (v) a significantly greater colonic luminal pH\(^1\) (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)

**ACKNOWLEDGEMENTS**

The author is grateful to many colleagues, collaborators and mentors whose work forms the basis of this brief review:

Michael Besser, Gary French, Hyder Hussaini, Paul Jenkins, Tony Mallet, Gerry Murphy, Steve Pereira, Linzi Thomas, Martin Veysey and John Wass.

**REFERENCES**

1. Dowling RH, Bell GD, White J. Lithogenic bile in patients with ileal dysfunction. *Gut*, 1972; 13: 415-420.

2. Shaffer EA and Small DM. Biliary lipid secretion in cholesterol gallstone disease. The effect of cholecystectomy and obesity. *J. Clin Invest*. 1977; 59: 828-840.

3. Northfield TC and Hofmann AF. Biliary lipid secretion in gallstone patients. *Lancet* 1973; i: 747-748.

4. Reuben A, Maton PN, Murphy GM, Dowling RH. Bile lipid secretion in obese and non-obese individuals with and without gallstones. *Clin Sci*, 1985; 69: 71-79.

5. Forgacs IC, Maisey MN, Murphy GM, Dowling RH. Influence of gallstones and ursodeoxycholic acid therapy on gallbladder motor function. *Gastroenterology*, 1984; 87: 299-307.

6. Bell GD, Whitney B, Dowling RH: Gallstone dissolution in man using chenodeoxycholic acid. *Lancet*. 1972; ii: 1213-1216.
7. Iser JH, Dowling RH, Mok HYI, Bell GD. Chenodeoxycholic acid treatment of gallstones: A follow-up report and analysis of factors influencing response to therapy. *New Engl J Med*, 1975; **293**: 378-383.
8. Maton PN, Iser JH, Reuben A, Saxton HM, Murphy GM and Dowling RH. Outcome of chenodeoxycholic acid (CDCA) treatment in 125 patients with radiolucent gallstones. *Medicine (Baltimore)*, 1982; **61**: 85-96.
9. Maton PN, Murphy GM, Dowling RH. Ursodeoxycholic acid treatment of gallstones: dose-response study and possible mechanisms of action. *Lancet*, 1977; **ii**: 1297-1301.
10. Meredith TJ, Williams GV, Maton PN, Murphy GM, Saxton HM and Dowling RH. Retrospective comparison of “Cheno” and “Urso” in the medical treatment of gallstones. *Gut*, 1982; **23**: 382-389.
11. Gleeson D, Ruppin DC, Saunders A, Murphy GM and Dowling RH. Final outcome of ursodeoxycholic acid treatment in 126 patients with radiolucent gallstones. *Quart. J Med*, 1990, **279**: 711-729.
12. Dowling RH, Hussaini SH, Murphy GM, Besser GM, Wass JAH. Gallstones during octreotide therapy. *Metabolism: Clinical and experimental*, 1992; **41**: Suppl.2, 22-33.
13. McKnight JA, McCance DR, Crothers JG, Atkinson AB. Changes in glucose tolerance and development of gall stones during high dose treatment with octreotide for acromegaly. *Br Med J*, 1989; **299**: 604-5, 1989.
14. Thomas LA, Veysey MJ, Murphy GM, Dowling RH, King A, French GR. Is cholelithiasis an intestinal disease? *Gut*, 1997; **40** (Suppl 1) A67.
15. Dowling RH, Veysey MJ, Pereira SP, Hussaini SH, Thomas LA, Wass JAH, Murphy GM. Role of intestinal transit in the pathogenesis of gallbladder stones. *Canadian J. Gastro*, 1997; **11**: 57-64.
16. Dowling RH, Gleeson D, Ruppin DC, Murphy GM and the British/Belgian Gallstone Study Group. Gallstone recurrence and post-dissolution management. In: Enterohepatic Circulation of Bile Acids and Sterol Metabolism. Eds: Paumgartner G, Stiehl A, Gerok W. MTP Press Limited, Lancaster. pp361-369, 1985.
17. Hussaini SH, Pereira SP, Veysey MJ, Kennedy C, Jenkins P, Murphy GM, Wass JAH, Dowling RH. The roles of gallbladder emptying and intestinal transit in the pathogenesis of octreotide-induced gallbladder stones. *Gut*, 1996; **38**: 775-783
18. Hussaini SH, Murphy GM, Kennedy C, Besser GM, Wass JAH, Dowling RH. The role of bile composition and physical chemistry in the pathogenesis of octreotide-associated gallbladder stones. *Gastroenterol*, 1994; **107**: 1503-1513
19. Carulli N, Loria P, Bertolotti C, Ponz de Leon M, Menozzi D, Medici G, Piccagli I. Effects of acute changes in bile acid pool composition on biliary lipid secretion. *J Clin Invest*, 1985; **74**: 616-24.
20. Hussaini SH, Pereira SP, Murphy GM, Dowling RH. Deoxycholic acid influences cholesterol solubilization and microcrystal nucleation time in gallbladder bile. *Hepatology*, 1995; **22**: 1735-1744
21. Fuesl HS, Carolan G, Williams G, and Bloom SR. Effect of a long-acting somatostatin analogue (SNS 201-995) on postprandial gastric emptying of 99mTc-tin colloid and mouth-to-caecum transit time in man. *Digestion*, 1987; **36**: 101-107.
22. Möller N, Petraný G, Cassidy D et al. Effects of the somatostatin analogue SMS 201-955 (Sandostatin) on mouth-to-caecum transit time and absorption of fat and carbohydrates in normal man. *Clin Sci*, 1988; **75**: 345-350.
23. O’Donnell LJD, Watson AJM, Cameron D, Farthing MJG. Effect of octreotide on mouth-to-caecum transit time in healthy subjects and in the irritable bowel syndrome. *Aliment. Pharmacol. Therap*, 1990; **4**: 177-182, 1990.
24. Veysey MJ, Arraton SRD, Mallet A, Jenkins P, Murphy GM, Wass JAH, Dowling RH. Long-term octreotide treatment increases large bowel transit time (LBTT), the proportion of deoxycholic acid (%DCA) in serum and the risk of gallstone formation. *Gut*, 1996; **39** (Suppl 3): A134, (Abstr).
25. Veysey MJ, Arraton SRD, Gilani SS, Mallet A, Jenkins P, Murphy GM, Wass JAH, Dowling RH. The relationship between large bowel transit time (LBTT) and the proportion of deoxycholic acid (%DCA) in serum. *Gut*, 1996; **38** (Suppl 1): A53, (Abstr).
26. Veysey MJ, Mallet A, Murphy GM, Dowling RH. Deoxycholic acid pool size and input rate, measured by stable isotope dilution, are increased in patients with slow transit constipation. *Clin Sci*, 1997; **92**: 3P (Abstr).
27. Thomas LA, Veysey MJ, Murphy GM, Dowling RH, King A, French GL. Bile acid metabolising intestinal bacterial enzyme activity: a novel factor in cholesterol gallstone pathogenesis. *Gut*, 1997; **40** (Suppl 1) A67 (Abstr).

© The Ulster Medical Society, 1998
Gallstones

28. Heaton KW, Emmett PM, Symes CL, Braddon FEM. An explanation for gallstones in normal-weight women: slow intestinal transit. *Lancet*, 1993; 341: 8-10.

29. Shoda J, He B-F, Tanaka N, Matsuzaki Y, Osuga T, Yamamori S, Miyazaki H, Sjövall J. Increase of deoxycholate in supersaturated bile of patients with cholesterol gallstone disease and its correlation with de novo syntheses of cholesterol and bile acids in liver, gallbladder emptying, and small intestinal transit. *Hepatology*, 1995; 21: 1291-1302.

30. Azzaroli F, Mazzella G, De Vegori E, Festi D et al. Sluggish gallbladder and small bowel motility are associated with cholesterol gallstones. *Gastroenterol*, 1997; 112: A499 (Abstr).

31. Thomas LA, Bathgate T, Veysey MJ, King A, French GL, Murphy GM, Dowling RH. Do changes in colonic luminal pH explain the increased proportions of serum and biliary deoxycholic acid seen in patients with cholesterol gallbladder stones (GBS)? *Gut*, 1997; 41 (Suppl 3): A32 (Abstr).

32. Veysey MJ, Arraton SRD, Mallet A, Jenkins P, Murphy GM, Wass JAH, Dowling RH. Cisapride reverses the effects of octreotide (OT) on intestinal transit and the proportion of deoxycholic acid (%DCA) in bile and serum. *Gut*, 1996; 39 (Suppl. 3): A103 (Abstr).

33. Berr F, Schreiber E, Frick U. Interrelationships of bile acid and phospholipid fatty acid species with cholesterol saturation of duodenal bile in health and gallstone disease. *Hepatology*, 1992; 16: 71-81.

34. Hofmann AF, Grundy SM, Lachin JM, Lan SP, Baum RA, Hanson RF, Hersh T et al. Pre-treatment lipid composition in which patients with gallstones in the National Cooperative Gallstone Study. *Gastroenterology*, 1982; 83: 738-52.

35. Pereira SP, Hussaini SH, Cassell TB, Murphy GM, Wass JAH, Dowling RH. Biliary phospholipids and mucin glycoprotein are altered in octreotide-induced gallstones. *Gut* 1995; 36: (Suppl 1), A47 (Abstr)

36. Angelico M, Corradini GS, Masella R, Alvaro D, Cantafora A, Capocaccia L. Molecular composition of biliary phosphatidylcholines, as related to cholesterol saturation, transport and nucleation in human gallbladder bile. *J Hepatol*, 1992; 15: 59-66

37. Hatsuškia S, Tazuma S, Kajiyama G. Nucleation time and fatty acid composition of lecithin in human gallbladder bile. *Scand J Gastroenterol*, 1993; 28: 131-136.

38. Cantafora A, DiBiase A, Alvaro D, Angelico M, Marin M, Attili AF. High performance liquid chromatographic analysis of molecular species of phosphatidylcholine-development of quantitative assay and its application to human bile. *Clin Chim Acta*. 1983; 134: 281-295.

39. van Berge Henegouwen GP, van der Werf SDJ, Ruben AT. Fatty acid composition of phospholipids in bile in man: promoting effect of deoxycholate on arachidonate. *Clin Chim Acta*. 1987; 165: 27-37.

40. Carey MC and Cahalane MJ. Whither biliary sludge? *Gastroenterology*, 1993; 95: 508-523.

41. Lee SP. Lessons from experimental cholelithiasis: gallbladder and mucosa, nonsteroidal antiinflammatory drugs, and gallstones. *Gastroenterology*, 1991; 101: 85760.

42. Marks JW, Bonorris GG, Albers G, Schoenfield LJ. The sequence of biliary events preceding the formation of gallstones in humans. *Gastroenterology*, 1992; 103: 566-70.

43. Shiffman ML, Sugarman HJ, Kellum JM, Moore EW. Changes in gallbladder bile composition following gallstone formation and weight reduction. *Gastroenterology* 1992; 103: 214-21

44. Fisher RS, Stetzer F, Rock E, Melmud LS. Abnormal gallbladder emptying in patients with gallstones. *Dig Dis Sci.* 1982; 27: 1019-1024

45. Pomeranz IS, Shaffer EA. Abnormal gallbladder emptying in a subgroup of patients with gallstones. *Gastroenterology*. 1985; 88: 787-791.

46. Thompson JC, Fried GM, Ogden MD, Fagan CJ, Inoue K, Wiener J, Watson LC. Correlation between release of cholecystokinin and contraction of the gallbladder in patients with gallstones. *Ann. Surg.* 1982; 145: 670-676.