

## PAPERS AND SHORT REPORTS

**Gall-stone dissolution and recurrence: are we being misled?**

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**Abstract**

**Oral cholecystography repeated at six-month intervals is the standard method for determining reduction in size of gall stones (partial success) and complete dissolution of stones (complete success). In a comparative study of oral cholecystography and cholecystosonography six out of 14 patients with gall stones achieving complete success by oral cholecystographic criteria had stones still detectable by ultrasonography. Repeat oral cholecystography in a further 11 patients receiving post-dissolution maintenance treatment detected stones in two, whereas ultrasonography detected stones in seven.**

**In future complete dissolution of gall stones should be reported only if both oral cholecystography and ultrasonographic studies give negative results and the progress of patients receiving post-dissolution maintenance treatment is monitored by ultrasonography rather than serial oral cholecystography.**

**Introduction**

Both chenodeoxycholic acid<sup>1</sup> and ursodeoxycholic acid<sup>2</sup> lower the cholesterol saturation of bile. Cholesterol-rich radio-translucent gall stones exposed to such bile may gradually get smaller and even dissolve completely.<sup>1,2</sup> Since the first reports in 1972<sup>3,4</sup> dissolution treatment has relied on oral cholecystography to show the disappearance of previously confirmed gall stones, indicating complete success.<sup>5,6</sup> The extent to which treatment must reduce the diameter, volume, and number of gall stones to qualify as a partial success varies from one series to another.<sup>5</sup> Such partial success is of doubtful clinical importance,<sup>7</sup> and the value of various cholelitholytic regimens

should be assessed by complete dissolution of gall stones rather than by the so-called response rate (complete and partial dissolution).

When cholelitholytic treatment is stopped the bile rapidly becomes resaturated with cholesterol. Stones are particularly likely to reform if any particulate matter is left in the gall bladder, since this may act as a seeding or nucleating agent.<sup>8</sup> Hence patients should continue with full-dose cholelitholytic treatment for three months after the oral cholecystogram has failed to detect any remaining stones,<sup>9</sup> since once these are reduced to less than 2 mm diameter they are below the resolution of the radiographic technique.<sup>9</sup> An oral cholecystogram repeated three months after the first occasionally detects stones missed on the first occasion.<sup>5</sup> The recent National Co-operative Gallstone Study would accept gall-stone dissolution as truly complete only when both post-treatment oral cholecystograms were negative.<sup>5</sup> The Guy's Hospital group,<sup>10</sup> using similarly rigid criteria to define complete dissolution of gall stones, found that when treatment was withdrawn gall stones recurred in over half of the patients within two years. The British Gall-stone Study Group Post-dissolution Trial is aiming to determine (a) the timing and frequency of recurrence in patients whose stones have been dissolved medically and (b) which form of treatment will most effectively prevent recurrence. Similar studies are in progress in the USA.<sup>5</sup>

Since ultrasound was first used to detect gall stones in 1972, refinements in instrumentation, diagnostic criteria, and scanning technique have increased the detection rate for cholelithiasis to over 95%.<sup>11,12</sup> If gall stones are often not detected by oral cholecystography but are by ultrasonography in patients treated medically,<sup>13</sup> then (a) complete success is being diagnosed when tiny stones are still present; (b) treatment is being stopped too early as a result; and (c) many so-called recurrences in the post-dissolution period may simply be persistent stones which have regrown to a size at which they are once more detectable by oral cholecystography. We have therefore used ultrasonography to determine whether incomplete dissolution occurs often enough with a negative oral cholecystogram to be an important clinical problem.

**Patients and methods**

At this hospital patients with gall stones have been treated medically for almost five years with either chenodeoxycholic acid or the

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proprietary choleretic Rowachol (Rowa Ltd, Bantry, Eire) alone<sup>14</sup> or in combination.<sup>15</sup> Until 1980 dissolution was taken as complete if two adequate oral cholecystograms (3 g sodium ipodate at 2100 the evening before, plus 3 g calcium ipodate at 0900 on the morning of the examination) performed three months apart failed to detect stones in the gall bladder. During 1981 we used ultrasonography (Diasonograph 4200B scanner with real-time sector scanner attachment) at the same time or within a few days of the second oral cholecystogram. The gall bladder was examined longitudinally and transversely by ultrasound with the patient supine, supine with the right side raised, and in the same positions after the patient had lain prone for a short time. Occasionally we had to scan between the ribs to obtain an adequate view. The criteria for diagnosing gall stones by ultrasonography were: an echogenic focus within the gall bladder; posterior acoustic shadowing; and dependent movement of the echogenic focus with gravity.<sup>12</sup>

During the year 14 patients with gall stones satisfied the oral cholecystographic criteria for complete dissolution, and all were also examined by ultrasonography (see table; group 1). We also recalled 11 patients whose gall stones had been completely dissolved before routine ultrasonography became available (see table; group 2). One of these had subsequently had a cholecystectomy because her gall stones had reformed and the gall bladder had become radiologically non-functioning. The remaining 10 patients, whose stones had all completely dissolved according to radiological evidence between six and 30 months before the study, agreed to undergo further oral cholecystography and abdominal ultrasonography. All 10 patients were taking a single Rowachol capsule at night to prevent reformation of gall stones. Two had had at least one recent attack of abdominal pain suggesting biliary colic; the other eight had no symptoms.

## Results

Gall-bladder ultrasound showed definite evidence of at least one small stone in the gall bladder of six of the 14 patients who had had negative oral cholecystograms during the year (table). Oral chole-

*Accuracy of oral cholecystography compared with gall-bladder ultrasound in detecting gall stones in patients completing course of cholelitholytic treatment (group 1) and those receiving post-dissolution maintenance treatment (group 2)*

	Total No of patients	No (%) of positive results by:	
		Oral cholecystography	Ultrasonography
Group 1	14	0	6 (43)
Group 2	11*	2 (18)	7/10* (70)
All patients	25*	2 (8)	13/24* (54)

\*Ultrasonography not performed in one patient.

cystography in the 10 patients receiving post-dissolution maintenance treatment showed small stones in only one, who had complained of recent pain. Cholecystosonography detected gall stones in this patient and in a further six of the remaining nine patients with normal oral cholecystograms (table). The first patient's gall stones had reformed after apparently complete dissolution and were confirmed by cholecystectomy. The other patient receiving maintenance treatment who had developed biliary symptoms had a negative oral cholecystogram but a positive ultrasound result. He opted to restart chenodeoxycholic acid as well as Rowachol and his symptoms disappeared. The other five patients receiving maintenance treatment who had positive ultrasound results but negative oral cholecystograms had no symptoms but restarted full-dose cholelitholytic treatment.

## Discussion

These results clearly confirm the value of cholecystosonography in detecting small gall stones which are missed on oral cholecystography.<sup>12-13</sup> At present a negative oral cholecystogram is taken as evidence of complete dissolution in all reports on treatment with chenodeoxycholic acid and ursodeoxycholic acid,<sup>5,6</sup> and cholecystography is used to monitor recurrence of

gall stones<sup>10</sup> both without treatment and during various different forms of post-dissolution maintenance treatment; hence the implications of our study are far reaching.

At the time of our study the Canadian Co-operative Gallstone Study<sup>16</sup> reported on 13 patients treated with chenodeoxycholic acid who had achieved complete dissolution as defined by two consecutive negative oral cholecystograms at least one month apart; 6 (46%) had small stones still detectable by ultrasonography, which was almost identical with the proportion (43%) in our series. Probably in neither series had these patients had true complete dissolution, since the false-positive rate for cholecystosonography is 1% or less.<sup>17</sup> Complete dissolution of gall stones on cholecystography may thus be apparent rather than real.<sup>16</sup>

Had we not used ultrasonography as well as oral cholecystography all 14 of our patients in group 1 would have been reported as having had complete dissolution and have either stopped treatment or started some form of maintenance treatment to prevent recurrence. In fact, six of them still had stones detectable by ultrasonography. For the 11 patients who had previously apparently had complete dissolution by cholecystographic criteria our recurrence rate would have been 18% (two cases), which is low compared with others.<sup>10</sup> When ultrasonography was used seven out of 10 had gall stones. Our pilot post-dissolution maintenance study using one Rowachol capsule at night was totally invalidated because it was impossible to know how many of our patients with recurrences had ever really achieved true complete dissolution before entry to the trial. Unless ultrasonography as well as oral cholecystographic criteria are used to define true complete dissolution, post-dissolution maintenance studies<sup>5</sup> are of limited value.

The first repeat oral cholecystogram six to nine months after starting treatment with chenodeoxycholic acid and ursodeoxycholic acid indicates clearly which patient's gall stones will eventually progress to complete dissolution<sup>5,18</sup>; hence we now monitor patients' initial progress by oral cholecystography alone. Once the stones are seen to get smaller progress is monitored at six-month intervals by ultrasonography alone. With real-time ultrasound apparatus, particularly a sector scanner with its small transducer head, the gall bladder is seen much more clearly and small calculi can be detected easily. Once ultrasonography gives negative results on two occasions three months apart we stop cholelitholytic treatment. Patients given post-dissolution maintenance treatment can be monitored yearly by cholecystosonography; those who develop biliary symptoms may be examined at an earlier stage.<sup>11</sup> Compared with oral cholecystography the ultrasound examination is cheaper, saves time, does not entail radiation and so can be done at any time during the menstrual cycle, and does not run the risk of toxicity, which may occur with iodinated cholecystographic media. If partially dissolved gall stones fail to dissolve completely after six-monthly ultrasonograms plain abdominal x-ray films may be taken to ensure that the stones have not developed a calcified rim, a complication which is more common with ursodeoxycholic acid than chenodeoxycholic acid.<sup>19</sup>

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(Accepted 22 March 1982)

## Sarcoidosis and membranous glomerulonephritis: a significant association

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### Abstract

Three patients were seen who had sarcoidosis associated with glomerulonephritis. Subsequent review of published reports of cases in which the two conditions occurred simultaneously showed a pattern of histological type of glomerulonephritis different from that seen in patients without associated disease. In sarcoidosis with glomerulonephritis there appeared to be a dearth of minimal-change disease and an excess of membranous glomerulonephritis compared with the prevalence that would be expected if the renal disease was merely a chance occurrence.

These findings may provide evidence for an important relation between sarcoidosis and glomerulonephritis.

### Introduction

Several mainly isolated cases have been reported of sarcoidosis and glomerulonephritis occurring in the same patient. Some workers consider this relation to be significant, particularly with respect to membranous glomerulonephritis,<sup>1</sup> but others regard it as a chance occurrence.<sup>2</sup> We recently saw three patients with histologically proved sarcoidosis and glomerulonephritis. The possibility of an association between the two diseases prompted us to review reports of similar cases.

### Case reports

**Case 1**—A 24-year-old man presented in November 1973 with the nephrotic syndrome and normal creatinine clearance. Percutaneous

renal biopsy disclosed membranoproliferative glomerulonephritis with reduplication of the glomerular capillary basement membrane. Hypocomplementaemia was noted on several occasions. A chest x-ray film was normal in March 1979, but three months later he developed wheezing and was found to have bilateral hilar lymphadenopathy. A Kveim test yielded positive results. Serum calcium concentration and activity of angiotensin-converting enzyme were normal. Tests for circulating immune complexes by C1q binding were negative. His renal function and serum albumin concentration remained normal, though he continued to have heavy proteinuria and developed hypertension requiring treatment. The bilateral hilar lymphadenopathy persisted.

**Case 2**—In 1977 a 32-year-old man with longstanding epilepsy was found to have persistent haematuria and proteinuria, with granular casts in the urine and normal renal function. Histological appearances of a renal biopsy specimen obtained in January 1978 were those of segmental proliferative nephritis. In February 1980 he developed acute arthritis of both knees and ankles, erythema nodosum, and increased haematuria and proteinuria. Percutaneous renal biopsy confirmed the previous findings and indicated mesangial IgA disease. A Kveim test gave a positive result. A chest x-ray film was normal, as were the serum calcium concentration and angiotensin-converting enzyme activity. Circulating immune complexes as estimated by the polyethylene glycol precipitation method amounted to 152 mg/l IgG (upper limit of normal 100 mg/l IgG).

**Case 3**—In June 1980 a 36-year-old man received penicillin as treatment for a tooth abscess. Proteinuria and haematuria were found a week later, and after a further two weeks he developed erythema nodosum. Creatinine clearance and serum calcium concentration and angiotensin-converting enzyme activity were normal. Percutaneous renal biopsy disclosed membranous glomerulonephritis. The overall appearances and the predominantly intramembranous distribution of the immune complexes were not entirely characteristic of an idiopathic membranous nephropathy but were not those of poststreptococcal glomerulonephritis. Serum complement concentration and the concentration of circulating immune complexes (polyethylene glycol precipitation method) were both normal. A chest x-ray film showed bilateral hilar lymph-node enlargement. Histology of a paratracheal lymph-node biopsy specimen showed typical sarcoid granulomas, and a Kveim test gave a positive result. His renal function remained normal, though proteinuria persisted.

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### Review of literature

We found 30 reports of cases of sarcoidosis and glomerulonephritis occurring in the same patient and examined critically the renal histo-