

Progress in gall stone disease

The effective non-operative management of gall stones with bile acids was described in 1972. The predicted therapeutic revolution has not occurred, but the treatment has stimulated research into the clinical course and management of gall stone disease—with some unexpected results—and the latest findings were discussed at the eighth international bile acid meeting in Berne this summer.

Many ideas about the epidemiology of gall stones have had to be revised. For instance, two Italian studies of the prevalence of gall stones using ultrasound techniques have convincingly refuted the link said to exist with oral contraceptives. They confirmed earlier circumstantial evidence derived from the unaltered frequencies of gall stone disease in women of childbearing years in this century,^{1,2} and of cholecystectomy rates in women exposed to oral contraceptives,³ and from the lack of any association with treatment with oestrogens in men.⁴ These new findings contradict earlier suggestive work based on less satisfactory epidemiological studies and on biliary lipid analysis. Clearly we should be slow to accept any statements about changes in gall stone disease. Nevertheless, one would have to be a calvinist not to welcome the news that a moderate intake of alcohol appears actually to protect against gall stones, as well as protecting against heart disease and prolonging life.⁵

The Italian ultrasound studies clearly incriminate obesity and higher parity in younger women as risk factors for gall stones. They also showed that only about one fifth of patients with gall stones have associated symptoms, which were more frequent in women with gall stones than in men. The Rome study also suggested that clofibrate does not cause gall stones and does protect men against heart disease—contrary to received wisdom.^{6,7}

On the aetiology of gall stones attention has shifted from the important concepts of oversaturation of bile with cholesterol to what may be even more crucial—the nucleating factors which initiate the formation of gall stones. These are present in the gall bladder bile of patients with gall stones,^{8,9} but not in the gall bladder bile of obese patients without gall stones.¹⁰ Another factor is the potential protective part played by antinucleating factors in bile, such as lipid vesicles and apolipoproteins I and II.

Ultrasound has now become the investigation of choice for gall bladder cholelithiasis—in hospitals where it is available. Though this technique may detect small calculi missed by oral cholecystography, the British Gallstone Study Group reported that the reverse is also true, so that both procedures may be needed before a patient can

reasonably be dismissed as free of stones.¹¹ Population studies using ultrasound screens and follow up after oral cholecystography have shown that most gall stones are asymptomatic, so the clinician should be cautious in ordering investigations in patients with atypical symptoms.¹² Prophylactic cholecystectomy for silent gall stones may, indeed, decrease overall survival.¹³ Perhaps even more disturbing is a prospective British survey which has shown that even where typical biliary pain was present before surgery, a year after cholecystectomy as many as 43% of patients rated their operation as less than completely successful.¹⁴

The controversy whether cholecystectomy causes cancer of the colon remains unresolved. Quite possibly gall stone disease may be associated with various types of tumour of the intestines and the reproductive organs, but hospital necropsies also suggest spurious associations between diseases.¹⁵ Cholecystectomy for gall stone disease is one of the most common abdominal operations in Western countries, and the rates show remarkable international and national variations. The overall need for gall bladder surgery is impossible to define on objective criteria, but we should probably welcome its recent decline in popularity in Britain after a long period of growth in frequency.¹

Though some advances have been made in the medical treatment of stones in the common bile duct their poor prognosis (in contrast with the relatively benign outlook of gall bladder stones) means that they should be removed without delay. This usually will require endoscopic papillotomy, instrumentation of T tube tracts after cholecystectomy, or open choledochotomy. If an attempt is made to dissolve radiolucent stones by local infusion then mono-octanoin is the treatment of choice and is very effective for stones of 7 mm or less in diameter.^{16,17} Other, more powerful solvents such as methyl-butyl-tertiary ether may be used in the future. In the few cases where oral treatment has to be chosen for stones in the common duct ursodeoxycholic acid 750 mg daily for up to two years will dissolve stones in half the patients treated and also control symptoms effectively.¹⁸ Adjuvant treatment with the terpene mixture Rowachol may possibly improve the success rate achieved with bile acid treatment alone.¹⁹

For those patients selected for oral dissolution of stones in the gall bladder a dose of ursodeoxycholic acid of at least 500 mg daily is probably needed.²⁰⁻²³ Stones less than 5 mm diameter respond much better in the short term than larger stones, and are especially suitable for an attempt at

dissolution. Whether doses of ursodeoxycholic acid larger than 500 mg daily are more effective is not clear, but in one study a more rapid response was observed with 900-1000 mg than with 250-600 mg daily.²⁴ One manufacturer offering ursodeoxycholic acid for clinical use in Britain recommends a dose of 450-600 mg daily, and the other recommends 8-12 mg/kg a day, even though the response to treatment does not relate to body size. A simple compromise is to treat all patients with ursodeoxycholic acid 750 mg daily, giving most of the dose after the last meal of the day. There is no evidence of any real difference in the dissolution rates given by the two bile acids commonly used in treatment, but some difference may eventually emerge.²⁵ Ursodeoxycholic acid is prone to cause calcification of radiolucent stones during treatment, though this may not affect dissolution rates.^{22 25} In an effort to prevent induced calcification, however, combinations of the two bile acids have been used with apparently good results.²⁶ Similarly, use of newer agents such as ursocholic acid or a combination of chenodeoxycholic acid 7-10 mg/kg a day with Rowachol have been proposed but have not yet been fully evaluated.^{27 28}

Gall stone dissolution treatment is unreliable and often protracted, for continued treatment even after two years may eventually completely dissolve stones which had previously shown only a partial response.²⁹ Dietary treatment has been combined with chenodeoxycholic acid to speed up the dissolution rate,³⁰ though the overall success rate was not improved and dietary treatment conferred no advantage when used with ursodeoxycholic acid.³¹ The rare condition cerebrotendinous xanthomatosis is an absolute indication for treatment with chenodeoxycholic acid, which not only corrects the abnormality of bile acid metabolism but also improves neurological performance.

Fourteen years on, therefore, we know that some gall stones can be dissolved but whether this is practical therapeutics is still under debate. The high rate of recurrence after treatment compromises the overall usefulness of the treatment, even though the recurrent stones are readily dissolved.³² The British Gallstone Study Group reported that dietary manipulation had not shown potential in preventing recurrence. Continued low dose chenodeoxycholic acid is ineffective.³³ Continuation of alternate month full dose chenodeoxycholic acid treatment has shown promise in preventing recurrence,³⁴ and the use of continuous low dose ursodeoxycholic acid is under investigation. At present the consensus seems to be that after confirmed complete dissolution of gall stones the clinician should await developments and then deal with recurrent symptoms as they arise. That advice may well have to be changed when the results of trials in progress are reported.

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Are all mesotheliomas due to asbestos?

Mesotheliomas became well known only in the 1960s. Their occurrence is closely related to exposure to asbestos; in most cases the exposure has been heavy, but in others it has been light, transient, and discoverable only by painstaking inquiry. In 100 patients with pleural mesothelioma in Liverpool exposure was established in 88, and in all but one of these light microscopy showed over 20 000 coated and uncoated asbestos fibres per gram of dried lung.¹ In seven no exposure was discovered and in six of these the counts were below 20 000. In only two were no fibres seen, whereas the lungs of the other four contained several thousand per gram. Were these mesotheliomas caused by asbestos picked up from the environment?

Most lungs nowadays contain asbestos: 29% of specimens from controls in the Liverpool study had over 20 000 fibres per gram, and in only seven were none seen.¹ In East Anglia 4% of specimens taken at surgery and 30% of those taken at necropsy did not show fibres.² Such figures are influenced by the technique used.³ Furthermore, light microscopy greatly underestimates the number of fibres; electron microscopy would probably show considerable numbers in many of the negative cases. These, however, would be mainly chrysotile and not amphibole fibres, which are the main determinants of the development of mesothelioma.⁴