namely, that the present visual restrictions are adequate. There is no occasion to waste our limited resources by subjecting our driving population to regular eye examinations or repetitive visual checks.

[1] Cashell, G. T. W., *Transactions of the Ophthalmological Societies of the United Kingdom*, 1966, **86**, 617.

More about Chenodeoxycholic Acid

After the initial announcement by R. G. Danzinger and his colleagues[1] that cholesterol gallstones could be dissolved by oral chenodeoxycholic acid therapy further studies have confirmed the effectiveness of this bile acid in the medical treatment of gallstones. But at the same time they have shown that the treatment can carry some risk.

In the preliminary report seven women with gallstones received from 0·75 to 4·5 g chenodeoxycholic acid daily. The gallstones disappeared in one patient, became smaller in three others, and were unchanged in the remaining three. Encouraged by these results J. L. Thistle and A. F. Hofmann[2] embarked on a single-blind, controlled therapeutic trial of chenodeoxycholic acid, cholic acid, and placebo in 53 patients with asymptomatic stones. The dose of chenodeoxycholic acid averaged 18 mg/kg of body weight per day. Cholecystograms were obtained at the beginning of therapy and again after six months, at which time 11 of the 18 patients who had received chenodeoxycholic acid showed a reduction in the size or the number of gallstones. No change was observed in those patients taking cholic acid or placebo. Of 13 patients with radio-opaque stones only two showed a partial response to the chenodeoxycholic acid.

Other workers studying this bile acid have had comparable results. Thus G. D. Bell and colleagues,[3] giving a daily dose of 0·75 to 1·0 g, reported that after six months the stones had disappeared in three of 12 patients who had functioning gall bladders, while in three others there was appreciable reduction in stone size. O. James and colleagues[4] gave a similar dose and observed the dissolution of gallstones or considerable diminution in size in four of 11 patients. An improvement in the patients' symptoms may have been associated with dissolution of the gallstones.[4 5] On the other hand there was no return of function in gallbladders which were radiologically non-functioning at the beginning of treatment.[3]

There is much concern over the potential toxicity of chenodeoxycholic acid and its metabolites. Chenodeoxycholic acid is a primary dihydroxy bile acid which undergoes 7-α dehydroxylation in the colon with the formation of lithocholic acid. Lithocholic acid is known to be a potent hepatotoxic agent when fed to a variety of laboratory animals, though some are apparently immune to its effects. Thus feeding large doses of chenodeoxycholic acid to rhesus monkeys induces a severe liver lesion comprising proliferation of bile ducts and periportal infiltration. Damage to the fetal liver has been reported.[6] Perhaps therefore it is not surprising that all three groups using this substance have encountered altered liver function tests in patients under study. The most frequent abnormality was a rise in the concentration of serum aspartate transaminase. It usually occurred during the initial stages of therapy, and the concentration returned to normal during the course of treatment. It is of some interest that no such changes were observed in patients receiving cholic acid.[2] The serum alkaline phosphatase activity also rose. James and colleagues[4] have observed a rise in the concentration of total serum bile acid, but the important question regarding which bile acids were concerned remains to be answered. Thistle and Hofmann[2] performed liver biopsies on 11 patients; eight were reported as normal, but fatty change was present in one and a periportal fibrous reaction was noted in two. In another study of the liver morphology of patients on chenodeoxycholic acid biopsies were obtained from 10 patients.[7] The majority were normal but a few showed steatosis or non-specific changes. Thus far no lesion comparable to that reported in the monkey has been observed. Nonetheless the possibility of damage to the liver cannot be ignored, and the use of this drug in selected patients must be accompanied by rigorous clinical surveillance.

An interesting consequence of chenodeoxycholic acid therapy may be a reduction in serum lipids.[8] Serum triglyceride values fell from average pretreatment levels of 118 to 95 mg/100 ml, whereas serum cholesterol concentrations were unchanged. The mechanism for this action is yet to be explained.

In general patients with cholesterol gallstones secrete a bile saturated or supersaturated with cholesterol. The underlying hepatic abnormality may be a dual defect of a reduced size of the bile acid pool and increased secretion of biliary cholesterol.[9] The administration of bile acids would be expected to cause the bile to become undersaturated, thereby enhancing the solubility of cholesterol and encouraging the dissolution of gallstones. The initial study of Thistle and L. J. Schoenfield[10] suggested that this was so and more recently both Thistle and Hofmann[2] and Bell and colleagues[3] observed an improvement in bile composition in patients on chenodeoxycholic acid. It is therefore surprising that in the study of James and colleagues[4] no improvement in the cholesterol-holding capacity of the bile was apparent. Feeding chenodeoxycholic acid would be expected to expand the total bile salt and chenodeoxycholic acid pools with corresponding reduction of the cholic and deoxycholic acid pool. However, T. C. Northfield and colleagues[11] have reported that the major effect of this bile acid is to decrease the rate of cholesterol secretion into bile in relation to the output of bile acids and phospholipids, and that this may be the major reason for the bile becoming undersaturated in cholesterol.

The chenodeoxycholic acid story is just beginning to unfold and at present more questions are being posed than answered: which patients are likely to respond, what is the optimal dose, what is the correct procedure once stones have been dissolved, is the liver damaged, what is the mode of action, and why does cholic acid not work? But the initial studies have shown convincingly that the dissolution of gallstones is at last becoming a feasible prospect.

[1] Danzinger, R. G., Hofmann, A. F., Schoenfield, L. J., and Thistle, J. L., *New England Journal of Medicine*, 1972, **286**, 1.
[2] Thistle, J. L., and Hofmann, A. F., *New England Journal of Medicine*, 1973, **289**, 655.
[3] Bell, G. D., Whitney, B., and Dowling, R. H., *Lancet*, 1972, **2**, 1213.
[4] James, O., Cullen, J., and Bouchier, I. A. D., *Gut*, 1973, **14**, 827.
[5] Bell, G. D., Whitney, B., Lewis, B., Thwe, M., and Dowling, R. H., *Quarterly Journal of Medicine*, 1973, **42**, 824.
[6] Heywood, R., Palmer, A. K., Foll, C. V., and Lee, M. R., *Lancet*, 1973, **2**, 1021.
[7] James, O. F. W., Scheuer, P. J., and Bouchier, I. A. D., *Digestion*, 1973, **8** 432.
[8] Bell, G. D., Lewis, B., Petrie, A., Dowling, R. H., *British Medical Journal*, 1973, **3**, 520.
[9] Grundy, S. M., Metzger, A. L., and Adler, R. D., *Journal of Clinical Investigation*, 1972, **51**, 3026.
[10] Thistle, J. L., and Schoenfield, L. J., *New England Journal of Medicine*, 1971, **284**, 177.
[11] Northfield, T. C., LaRusso, N. F., Thistle, J. L., and Hofmann, A. F., *Gastroenterology*, 1973, **64**, 780.