were carried out: clinical assessment by a cardiologist¹ blind to the treatment, a 12-lead ECG, serum creatinine and electrolyte concentrations, and routine liver function tests. There was no significant change in any of these during the study (paired Student's *t* tests in the case of parametric and χ^2 tests with Yates's correction or Fisher's exact test for non-parametric data). Venous blood samples for digoxin assay (β -Lanoxitest) were collected just before the dose, one during the third week and a second during the fourth on each formulation. Since there was no significant difference in concentration between weeks on either formulation (paired *t* tests, $P > 0.2$) steady state conditions may be assumed.

Relationship between dose of tablets and dose of capsules calculated to achieve a concentration of 1.3 nmol/l (1.0 ng/ml) in each patient and creatinine clearance.

The mean dose given was $0.27 \pm \text{SD} - 0.12$ mg in the case of tablets and 0.22 ± 0.09 mg for capsules. The mean concentrations achieved, 1.3 ± 0.4 nmol/l and 1.1 ± 0.3 nmol/l (1.0 ± 0.3 ng/ml and 0.8 ± 0.2 ng/ml) respectively, were in about the same ratio as the doses given. There was a significantly greater difference (+ve) between the two serum digoxin concentrations on tablets, mean 0.24 ± 0.17 nmol/l (0.18 ± 0.12 ng/ml), than between those on capsules, 0.12 ± 0.12 nmol/l (0.09 ± 0.09 ng/ml) (paired *t* test, $P < 0.025$). The dose of tablets and of capsules required by each patient to achieve the same concentration (1.3 nmol/l (1.0 ng/ml)) was calculated by proportionality.⁵ The correlation between the calculated dose of each formulation and creatinine clearance is shown in the figure.

Comment

By 24 h after the dose there seemed to be no difference in the proportion of digoxin absorbed from the two formulations. Nevertheless, higher concentrations from capsules may have occurred before 24 h and have been detected by earlier sampling. Contrary to hypothesis, the ability to predict the dose required to achieve a chosen concentration from renal function was not improved by the use of capsules. This suggests that the between-patient variation in absorption, unlike the within-patient, was not reduced on capsules. The facilitation of intestinal transport of digoxin by polyethylene glycol, postulated by Johnson and Bye,² may have been variable in our patients whereas it was consistent in their normal subjects. The introduction of capsules would probably not represent an advance in the management of patients. Theoretically the higher fat solubility of digitoxin and medigoxin should result in more consistent absorption, but such an advantage could be negated by their greater biliary excretion and metabolism making prediction of dose requirements more difficult.³

We thank the Wellcome Clinical Department (UK and Ireland region) for their support and for supplying the capsules.

¹ Dobbs, S M, *et al*, *British Journal of Clinical Pharmacology*, 1976, **3**, 231.

² Johnson, B F, and Bye, C, *British Heart Journal*, 1975, **37**, 203.

³ Johnson, B F, *et al*, *European Journal of Clinical Pharmacology*, 1976, **10**, 231.

⁴ Dobbs, S M, *et al*, *British Medical Journal*, 1977, **1**, 749.

⁵ Dobbs, S M, *et al*, *British Journal of Clinical Pharmacology*, 1976, **3**, 940.

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X-ray negative dyspepsia

The barium meal remains the procedure of choice for the initial investigation of patients presenting with dyspeptic symptoms. Formerly the only check on the radiologist's performance was obtained at laparotomy or necropsy. The advent of fiberoptic endoscopy quickly showed the shortcomings of the conventional barium meal technique and in particular it was realised that a negative barium meal could not be equated with the absence of upper gastrointestinal pathology. Consequently x-ray negative dyspepsia has been accepted as a major indication for endoscopy with an appreciable yield.

After pioneer work in Japan the double contrast barium meal is gradually gaining acceptance in the United Kingdom and has been employed exclusively in the radiology department at the Cumberland Infirmary for the past nine years. The availability of upper gastrointestinal endoscopy at the same hospital since 1972 has permitted the assessment of the accuracy of the double contrast method in excluding disease of the upper gastrointestinal tract in patients presenting with dyspepsia.

Patients, methods, and results

One hundred and forty consecutive patients referred for endoscopy with "x-ray negative dyspepsia" were studied. Each patient had initially undergone a double contrast barium meal using the technique of Scott-Harden.¹ All the examinations were performed by experienced consultant radiologists and the results had been reported as showing no abnormality in the oesophagus, stomach, or duodenum. The endoscopic examinations were all performed by a consultant physician using an Olympus GIF-D instrument within one month of the double contrast barium meal examination.

Of the 140 patients studied, endoscopy showed no significant abnormality in 133. The lesions noted in the remaining seven patients were as follows: oesophagitis (2); antral erosions (2); duodenal ulcer (2); and chronic benign gastric ulcer (1). Thus the endoscopist confirmed the absence of definite upper gastrointestinal disease in 95% of the patients studied, the yield of lesions not shown at radiology being 5%. Of these, just over half were superficial mucosal lesions and the remainder chronic peptic ulcers. The gastric and one of the duodenal ulcers were noted when the x-ray films of the latter patients were reviewed.

Discussion

The investigation of x-ray negative dyspepsia when the barium meal has been of the conventional type accounts for an appreciable percentage of an endoscopist's work load.² This study has shown that the endoscopic yield from the investigation of x-ray negative dyspepsia after a double contrast barium meal is minimal. The

particular double contrast technique employed¹ is quick, no more time-consuming than the conventional method, well tolerated by the patient, and admirably suited for use in a hard-pressed district hospital radiology department. In fact, the conventional barium meal technique should by now have died a natural death.

Implicit in radiological endoscopic comparisons of this type is the assumption that endoscopy is the final arbiter. Nevertheless, the endoscopist is not infallible, but endoscopic error is unlikely to be greater than 2 to 3%. An obvious implication of the increased accuracy of the double contrast technique is to release the endoscopist from an obligation to examine every patient with x-ray negative dyspepsia, allowing him to concentrate on the investigation of radiological abnormalities which need visual or histological confirmation—in other words, to adopt the role of sophisticated trouble-shooter.³

In conclusion, if a double contrast barium meal performed by an experienced radiologist has not shown any abnormality, an alternative explanation for the patient's dyspeptic symptoms should be sought unless other clinical pointers suggest upper gastrointestinal tract disease. Hence endoscopy, albeit with its minimal morbidity and mortality, would usually assume third rather than second place in the sequence of investigations.

I am grateful to Dr W G Scott-Harden and Dr T G Girdwood, consultant radiologists, for their enthusiastic co-operation during this study.

¹ Scott-Harden, W G, *British Journal of Radiology*, 1973, **46**, 153.

² Cotton, P B, *British Medical Journal*, 1973, **2**, 161.

³ Scott-Harden, W G, *British Journal of Radiology*, 1976, **49**, 658.

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Liver biopsy in "difficult" jaundice

In a small proportion of patients with jaundice the cause cannot be resolved from the history and the results of clinical examination and simple investigations alone. Liver biopsy is one way of making a diagnosis, but has been criticised on the grounds of difficulty in differentiating extrahepatic from intrahepatic cholestasis and because of possible danger in jaundiced patients. We set out to assess the accuracy and complications of biopsy in patients with "difficult" jaundice.

Patients and results

There were 156 patients with "difficult" jaundice in whom liver biopsy had been performed during 1959-75. We confined results to the four common groups of infective hepatitis, drug jaundice, malignant obstruction, and gallstones. Percutaneous biopsy had been attempted in 136 patients with three failures, the remainder being surgical specimens. Generally accepted histological criteria for intrahepatic and extrahepatic obstruction were used,^{1 2} and each biopsy was placed in one of three categories according to the final diagnosis: (1) "correct"; (2) "incorrect" where the biopsy suggested intrahepatic cholestasis and the eventual diagnosis was extrahepatic or vice versa; and (3) "unhelpful" where the histology was equivocal or non-specific.

Infective hepatitis (23 patients). Twenty biopsies (87%) were "correct." Of these, four were surgical specimens and two patients died postoperatively

from hepatic failure. Percutaneous biopsy was "incorrect" in one patient and "unhelpful" in two others. All eventually recovered without operation. There were no complications following biopsy.

Drug jaundice (20 patients). The 14 "correct" biopsies (70%) included three surgical specimens taken from patients who subsequently recovered. Three of the percutaneous biopsies were "incorrect": two patients recovered before laparotomy but the third died of postoperative hepatic failure. Biopsy was "unhelpful" in one patient. If two patients in whom biopsy failed are excluded the diagnostic success rate becomes 77%. There were no complications.

Malignant obstruction (49 patients). The tumours affected pancreas (21), common bile duct (11), common hepatic duct (9), ampulla of Vater (5), gall bladder (2), and duodenum (1). Apart from one lymphoma all were carcinomas. Eight biopsies were taken at operation. Interpretation was "incorrect" in three percutaneous and one surgical biopsy and was "unhelpful" in a further five. Large duct obstruction was therefore correctly identified in 40 patients (81%). Two patients with carcinoma of pancreas developed biliary peritonitis after percutaneous biopsy and eventually died.

Gallstones (64 patients). There were 52 "correct" biopsies (82%), five being operative specimens. An "incorrect" diagnosis was made in six instances (two surgical) and there were five "unhelpful" biopsies, of which three were operative. No tissue was obtained from one patient and another developed mild cholangitis following percutaneous biopsy.

Discussion

Biopsy was "correct" in 81% of 156 patients with "difficult" jaundice. This is probably comparable in accuracy with most other types of investigation. Morris *et al*³ have recently challenged the belief that percutaneous biopsy is dangerous in patients with large duct obstruction. They had no deaths in 125 patients, though one developed biliary peritonitis and there were seven minor complications. We had two fatalities after percutaneous biopsy in 100 patients with large duct obstruction. Both had malignant disease, and there were no serious complications in patients with gallstones or intrahepatic cholestasis. The risks have to be set against the hazards of operating inadvertently on patients with intrahepatic cholestasis; in the present series two such patients died postoperatively of liver failure.

Facilities for liver biopsy are easily provided and must include full haematological investigation, which is particularly important in jaundiced patients. Other techniques, such as endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography, are more complicated and expensive and may themselves be hazardous. Grey scale ultrasonography is not yet generally available but could well become the initial investigation of choice. Nevertheless, none of these more recent techniques is infallible. Although histological interpretation requires skill, we still regard percutaneous biopsy as a valuable diagnostic aid in patients with "difficult" jaundice.

This study could not have been undertaken without the co-operation of many colleagues and for this we are grateful.

¹ Shorter, R G, Paton, A, and Pinniger, J L, *Quarterly Journal of Medicine*, 1959, **28**, 43.

² Scheuer, P J, *Liver Biopsy Interpretation*, 2nd edn. London, Baillière Tindall, 1973.

³ Morris, J S, *et al*, *Gastroenterology*, 1975, **68**, 750.

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