Reviews in Medicine

Gastroenterology – II: small and large bowel, pancreas and biliary system

M.C. Bateson

General Hospital, Bishop Auckland, Co. Durham, DL14 6AD, UK

Iron deficiency

This is often a frustratingly non-specific reason for referral to gastrointestinal clinics for investigation. For a few patients, serology with gliadin antibodies supported by endomysial antibody tests positive will lead to small bowel biopsy and the diagnosis of coeliac disease. However, for the majority where menorrhagia and epistaxis have been excluded, invasive tests are needed as a primary manoeuvre.^{1–3}

In the USA the routine use of gastroscopy and colonoscopy in 100 such patients showed that concurrent upper and lower gastrointestinal causes for anaemia were rare (one case only). A total of 36 had a diagnosis established on gastroscopy and 25 on colonoscopy. In the 38 where both tests were negative, small bowel radiology was performed in 26 and was negative in all, suggesting this was not a useful procedure. Where there were lower bowel symptoms and positive occult blood tests, the positive predictive value for colonoscopy was 86%.¹

In Britain, for iron deficiency without specific symptomatic clues, one approach has been to perform gastroscopy including forceps biopsy of the small bowel plus barium enema.² This approach may still yield negative results, but follow-up of the patients on iron therapy did not uncover any significant diagnosis which might have been missed.²

An attractive suggestion is the use of gastroscopy in all with small bowel biopsy where no macroscopic diagnosis for problems is found, reserving barium enema for older patients where upper gastrointestinal investigations are negative.³ Proctosigmoidoscopy should always be performed before barium enema to avoid missing low rectal tumours, piles and superficial colitis.

There may be an advantage in performing colonoscopy instead of lower bowel radiology where facilities permit.

There is clearly no point in performing routine small bowel studies unless there are other clues than mere chronic iron deficiency anaemia to suggest that Crohn's disease or vascular malformation may be present.

Inflammatory bowel disease

Ulcerative colitis

The prevalence of ulcerative colitis is about 1:1,000 of the population and appears to be somewhat higher in those of South Asian extraction. By contrast Crohn's disease is now thought to affect about 1:1,200 of the population, but to be less than half as common in South Asians.⁴ For both conditions there is a much increased risk of inflammatory bowel disease of both sorts among relatives.

Treatment with aminosaliclates has been shown to be safe in pregnancy, as gastroenterologists have always suspected.^{5,6} For distal ulcerative colitis, bismuth citrate enemas are just as effective as aminosaliclate enemas, though the relevance to therapy is not immediately clear.⁷ A big disappointment has been the use of the poorly absorbed steroid fluticasone, which is not as effective as oral prednisolone in active ulcerative colitis, and has also been shown to be of no benefit in Crohn's disease despite its theoretical attractions.^{8,9} There may be a dose effect which needs to be overcome but the agent does not look very promising at the moment.

Cancer surveillance in ulcerative colitis

This has become a very controversial area indeed. Despite the known increased frequency of large bowel carcinoma in extensive and total ulcerative colitis, this does not translate into an obvious effect

Correspondence: M.C. Bateson, M.D., F.R.C.P., F.R.C.P. Edin.

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on mortality. A Danish study of 1,161 patients with ulcerative colitis followed for a mean of 11.7 years identified 141 deaths.¹⁰ Only 26 of these related to ulcerative colitis itself, of which six were from carcinoma of the colon. The ultimate colectomy rate 25 years after diagnosis was only 32%. Survival was identical with the general population except in the first year and even more interestingly the overall prevalence of carcinoma of the colon was not raised in this survey.

A Swedish study confirmed the lack of increased mortality after the first year from diagnosis but reported a relative risk of 15.2 for carcinomas of the colon.¹¹ Ten year survival was 96% of the expected rate for both ulcerative colitis and Crohn's disease, and the extent of colitis or site of Crohn's disease was interestingly irrelevant. The relative risk of death from chronic obstructive airways disease was 1.5, underlying the importance of non-bowel problems in these patients.

Though regular surveillance colonoscopy has been widely used, it does carry a complication rate of about 5%, and patients are often distressed by preparation and procedure so they are less than enthusiastic about repeats.^{12,13}

The technique may not be completely accurate in identifying risk patients who really do need prophylactic colectomy.^{14,15} One response has been to offer colectomy to all patients with any sort of dysplasia.¹⁶ This is quite a hard thing to do when actual symptoms are absent or not bothersome, but there is certainly a school of thought that feels it is appropriate.

The discrepancy in approach may reflect different referral patterns of patients, but the important fact is that inflammatory bowel disease patients have a normal life expectancy after the first year (so are insurable!). A conservative approach to management is again justified, with elective colectomy being reserved in general for those with active disease not well controlled by medical therapy.

Crohn's disease

In addition to studies of both ulcerative colitis and Crohn's disease,¹¹ there is a good long-term follow-up of 20 years in 373 Danish Crohn's disease patients.¹⁷ Again survival was found to be equivalent to the general population, but there appeared to be a small excess of deaths in patients aged 20–29 in the first 5 years from diagnosis. Though there did seem to be an increased risk of small bowel cancer, this was only found in two cases. The requirement for surgery was high, as might have been predicted from previous experience: 50% had had a bowel resection by 7 years and 70% by 15 years.

A series from Cleveland, Ohio, suggested that stricture-plasty by widening but not excising diseased bowel carries a good success rate, and may prove to be a useful general alternative to conventional surgery.¹⁸

Assessment of the extent of disease without laparotomy is often problematical. Small bowel enema is the gold-standard test, but may be difficult to perform and interpret and cannot often be repeated. White blood cell scanning with technetium-99m radiolabelled granulocytes has been a reliable simple additional test to assess activity and extent of disease, and is easily repeatable if necessary.¹⁹

The primary induction of remission in active Crohn's disease has traditionally been by oral or intravenous steroids. It has been clearly demonstrated that the effect of prednisolone 60 mg daily is enhanced by the addition of azathioprine 2.5 mg/kg/day in the acute phase, rather than reserving azathioprine for maintenance of remission as in the past.²² Similarly early use of aminosalicylate such as mesalazine 4 g daily can be effective in the acute phase of Crohn's disease as well as in maintenance.^{20,21} Whether the exact formulation of aminosalicylate in small bowel Crohn's disease matters remains uncertain, but there may well be a good place for continuously released formulations rather than the timed release drugs which are designed only to be active in the terminal ileum or colon.

Patients are always keen to know about the link between diet and bowel disease. Those with inflammatory bowel disease are encouraged to eat a nourishing diet and avoid food fads to keep well, unless secondary alactasia has been shown to make dairy products unadvisable. The use of elemental diets to exclude potentially allergenic food and induce remission has now been proved to be as good as steroid therapy.^{23,24} Unfortunately there is disagreement as to whether the duration of remission is better or worse on diet management as against steroids, but relapses are common. Perhaps unsurprisingly the rather unpalatable elemental diet therapy regime was not acceptable at all to 31% of patients after the first fortnight.

Gastroenterologists are likely to remain rather sharply divided into Crohn's diet true believers and sceptics, though nutritional agnosticism might be more appropriate on the present evidence.

Acute appendicitis

This has been a somewhat neglected field but there have been some epidemiological advances. The condition does not regularly cluster, suggesting there is no overwhelmingly important environmental or infective cause. It is not associated with the

luminal obstruction of the appendix which has been a long-term surgical favourite.²⁵ A particularly important recent study has suggested that acute appendicitis may actually be two different conditions.²⁶ It was observed that perforating acute appendicitis accounts for only about 15% of cases coming to appendectomy, and there is no age trend between 10–80 years. By contrast non-perforating appendicitis, and even more markedly, removal of a normal appendix, show a sharp peak in teenage followed by a rapid decline in frequency to the age of 40.

If we could identify which of the appendices are not going to perforate, then non-operative management might well be appropriate for the majority of cases.

Colonic carcinoma

This is the commonest gastrointestinal malignancy. Although good results can be obtained by surgical management of early cases, most patients are seen too late to hope for a cure.

Surveillance of risk populations has been proposed but remains a contentious area.²⁷ We are not much helped by the knowledge that, in men, beer drinking and obesity, and in both sexes diverticular disease, are all linked with increased prevalence, since these are also common.^{28–30} What may be more use is the observation that prevalence has increased two or three times in first-degree relatives of large bowel cancer cases, and this may justify selective sigmoidoscopy or occult blood testing.³¹ It has also been shown in Gardner's syndrome and polyposis coli families that endoscopic surveillance may be useful even after the age of 30, which was previously taken as the cut-off for lower bowel endoscopy in asymptomatic relatives.³²

There may be scope for a more vigorous approach in management of advanced cases with adjuvant radiotherapy and chemotherapy with agents such as 5-fluorouracil and nitrosoureas. Certainly aggressive radical surgery appears to have produced gratifying results in Aberdeen and adds fuel to the idea that large bowel surgery should be in the hands of dedicated specialist surgeons rather than generalists.^{33,34}

Pancreatic disease

Probably the most significant development in this area was the publication of a further edition of Go's standard textbook.³⁵ Diagnosis and management of pancreatic disease remains difficult and unsatisfactory. Particularly depressing was a recent

description of colonic strictures in cystic fibrosis patients treated with high-dose pancreatic enzyme replacement therapy.

Acute pancreatitis is known to be increasing in Finnish males where alcohol intake has also gone up.³⁶ Conversely the prevalence has fallen in Finnish women whose disease is most importantly linked with gallstones. Since moderate quantities of alcohol will probably protect from gallstones by reducing cholesterol saturation of bile, there is presumably a critical average intake which might reduce prevalence in women. There is no real progress in management of the condition once it has arisen, and similarly carcinoma of the pancreas continues to carry its dreadful prognosis of a 99% mortality at 2 years. Surgery is purely palliative. Chemotherapy with 5-fluorouracil, mitomycin, CCNU and streptozotocin provide a 15–25% temporary response rate and deep X-ray therapy has also been used, but it is debatable whether these measures represent a kindness to any but the occasional robust young patient.

Gallstone disease

Surgery

The major recent change in practice has been the shift to laparoscopic cholecystectomy for uncomplicated gallstones. There is an enormous amount of information from US hospitals on this technique which was only widely adopted 6 years ago, and has increased the already high prevalence of biliary surgery.^{37,38}

The overall complication rate is 2% with a 0.5% rate of injury to the common bile duct.³⁹ The procedure is very popular with patients and clearly here to stay, though it is not necessarily cheaper than open cholecystectomy through a small wound ('mini-cholecystectomy').³⁸ There is no agreement on whether the common bile duct should be investigated routinely with preliminary endoscopic retrograde cholangiopancreatography (ERCP), or peroperative cholangiography and oral choledochoscopy, with proponents and opponents for each technique. If common bile duct stones become apparent after cholecystectomy, then ERCP with papillotomy and stone extraction is the preferred approach.⁴⁰

Cholecystectomy apparently reduces the risk of extrahepatic bile duct cancer (RR 0.27 at 10 years) despite the fact that it definitely increases the risk of colorectal cancer (RR 1.34 at 15 years).^{41,42} These may be felt to counterbalance each other, though large bowel cancer is much commoner than cholangiocarcinoma in Caucasians. Analysis of the effect of cholecystectomy on bowel cancer has been the subject of many studies in the past and analysis has

always been difficult especially as gallstones themselves may be associated with colonic carcinoma.

Two specialized areas where cholecystectomy is definitely useful is in Amerindians and typhoid carriers.^{43,44} Red Indians not only hold the world record for gallstone prevalence but, unlike other population groups, have a very high rate of death from biliary tract cancer. Removal of the gallbladder can be justified in view of the fact that cancer mortality in these patients is increased to a relative risk of 6.6, with an overall mortality RR of 1.9. At least the frequency of gallbladder cancer can be avoided by prior cholecystectomy, and possibly bile duct cancer and other tumours too.⁴³ Chronic typhoid and paratyphoid carriers have a very much increased risk of gallbladder cancer (RR 167) as well as cancers of the pancreas (RR 8.1), large bowel (RR 3) and all cancers (RR 2.6). Eradication of carriage by elective cholecystectomy (or suitable antibiotic therapy) can be recommended as in the interests of the subject rather than merely on public health grounds.⁴⁴

Where malignant disease of the biliary tract requires attention because of obstructive symptoms, self-expanding metal stents can now offer good palliation if resection surgery is not possible or desirable.⁴⁵

Other treatment

Gallstones are more frequent in the obese and especially so in the morbidly obese whose weight has fallen rapidly, possibly because of increased gallbladder mucin.⁴⁶ These and other cholesterol-rich stones can sometimes be dissolved by oral bile

acid therapy. Ursodeoxycholic acid (UDCA) therapy is superior to chenodeoxycholic acid (CDCA) alone for this because of better tolerance, and there is no advantage in combining suboptimal doses of UDCA plus CDCA over UDCA alone. However, night-time dosage does give better results than divided doses.⁴⁷

Despite many studies there is no general consensus on the role of extra-corporal shock-wave lithotripsy for gallbladder stones. Some advocate its wide use even in larger stones with calcified rims,^{48,49} while others would restrict it to solitary radiolucent stones less than 20 mm in diameter.⁵⁰

Whatever the technique for clearing gallbladder stones, if the gallbladder is left in position, recurrence of stones may be expected in half the patients over 5 years and cannot reliably be prevented by a high-fibre regime or low-dose UDCA.⁵¹ It has always seemed logical that full-dose treatment with bile acids such as UDCA would be effective in preventing stone recurrence, particularly where this was the treatment that was responsible for stone clearance in the first place. However, this remains a speculation as it has never been rigorously tried.

Direct instillation of solvents has been used in specialist centres for dissolution of gallbladder and common bile duct stones. There are technical problems and toxicity has been a real difficulty. It may be that the use of ethyl propionate will supersede methyl tertiary butyl ether and the older mono-octanoin because of lesser side-effect problems.⁵² The use of these agents is likely to remain restricted to highly specialized centres in view of the technical expertise required in their use.

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