Reviews in Medicine

Gastroenterology

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Introduction

Gastroenterology and gastrointestinal science continue to develop at an impressive pace. During the past year we have seen the appearance of new drugs for the treatment of inflammatory bowel disease and peptic ulcer, *Campylobacter pylori* has changed its name to *Helicobacter pylori* and new enteropathogens have entered the clinical arena. Endoscopists continue to develop new tricks for overcoming obstructive jaundice and the choices for the management of patients with gallstones increase without necessarily providing the clinician with clearcut answers. Liver disease increases in complexity particularly with respect to the categorization of autoimmune chronic active hepatitis, although the enigma of non-A, non-B hepatitis is beginning to unfold with the description of a new transmissible agent, hepatitis C virus. From this wealth of new information we have selected some important contributions to the literature which we admit reflect, to some degree, our own interests but nevertheless highlight important developing areas in the subject.

Gastrointestinal emergencies

Endoscopic treatment of bleeding peptic ulcers

During the past decade a number of therapeutic endoscopic techniques have emerged for the treatment of actively bleeding peptic ulcers. In a recent Consensus Development Conference the benefits of the therapeutic modalities were considered.¹ The panel agreed that a combination of clinical features (haemodynamic instability, frank red haematemesis or blood rectally, high transfusion requirement, the presence of a coagulopathy, rebleeding in hospital) and endoscopic features (arterial spurting or oozing, visible vessel, adherent clot) indicate a high risk of rebleeding and emergency surgery. It is in this group of patients that endoscopic thera-

peutic intervention is most likely to be of benefit by either arresting bleeding completely or by allowing full resuscitation prior to surgery.

Although techniques using the Neodymium: YAG laser appear to be effective for achieving haemostasis and preventing rebleeding, the technique is difficult to master and is costly relative to other approaches. The panel felt that multipolar electro-coagulation or heater probe coagulation are the most promising techniques because of their effectiveness and relative ease of use. The size and cost of these devices make them a practical proposition for all endoscopic units involved in the management of gastrointestinal bleeding. The main safety risk associated with these interventions is that of perforation in about 1% of cases and thus the surgical team should be involved in the patients care from the outset and facilities for emergency surgery should be available if necessary.

As bleeding will stop spontaneously in about 75% of patients with peptic ulcers, endoscopic therapy is only indicated in a selected high-risk group of patients as outlined above. Controlled clinical trials of heater probe treatment indicate that haemostasis can be achieved in 80% of high risk patients.²

The panel made two further important points. Firstly, that injection therapy with adrenaline or ethanol appears promising but there are insufficient data available to make specific recommendations regarding their use. Secondly, that a surgeon should be involved from the outset in the decisions involved in the patient's care.

Fulminant hepatic failure

Fulminant hepatic failure (FHF) may be defined as acute liver failure and the development of hepatic encephalopathy less than 8 weeks after the onset of symptoms of hepatocellular dysfunction in a patient with no pre-existing liver disease. There are a wide variety of causes and light microscopic examination of the liver in patients with FHF shows one of two characteristics patterns, either massive hepatocellular necrosis or extensive micro-

vesicular steatosis.

One of the main clinical features of FHF is hepatic encephalopathy, which has been reviewed recently by Gammal & Jones.³ There are several hypotheses to explain the pathogenesis of hepatic encephalopathy, none of which is proven nor mutually exclusive. It is clear that neither hyperammonaemia alone, nor the accumulation of ammonia with other toxins, including mercaptans, short-chain fatty acids and phenols, are the only cause of encephalopathy, although all of these substances may be involved. The false neurotransmitter hypothesis is not fully tenable as it now seems unlikely that alterations in dopaminergic neurotransmission are as important as had previously been thought in the pathogenesis of hepatic encephalopathy.

The gamma-aminobenzoic acid/benzodiazepine (GABA/BZ) receptor complex hypothesis is currently attracting much attention. There are theoretical reasons why GABA-ergic transmission may be increased in liver failure³ particularly as hepatic encephalopathy has been reported to be associated with increased plasma GABA levels. The GABA/BZ receptor complex is important in the regulation of GABA-mediated inhibitory neurotransmission which may contribute to the manifestations of hepatic encephalopathy and it is possible the BZ receptors may be responsible for allosterically potentiating the action of GABA in this condition.⁴ GABA is the most important inhibitory neurotransmitter in the brain, causing neuronal membrane hyperpolarization by an increase in chloride flux across the membrane through a GABA-gated chloride channel in the GABA-BZ receptor complex. The opening of the chloride channel is induced by binding of GABA to its receptors and is potentiated by benzodiazepines and barbiturates. There is some experimental evidence in animal models that improvements in encephalopathy can be produced by the administration of benzodiazepine antagonists and there is preliminary evidence that flumazenil produces clinical improvement in patients with encephalopathy.^{5,6} The results of further controlled trials are awaited.

The management of fulminant hepatic failure is principally supportive, in an intensive care unit (ideally a specialized liver failure unit). The complex problems associated with multiple organ failure require close monitoring and prompt treatment. The supportive care of these patients has improved in the last decade, but specific therapy has not advanced far. Many methods of artificial hepatic support or specific treatments for FHF have been described, but there are few good clinical trials and little evidence of benefit.

Reported survival rates in fulminant hepatic failure (FHF) vary from <20–67% depending on

aetiology and other factors. At present there is no simple method to predict those patients who will do badly. With orthotopic liver transplantation in FHF, survival rates of greater than 50% are being reported.⁷ It is therefore important to identify those patients with a poor prognosis who may benefit from transplantation. In a large retrospective study of 588 patients with FHF, O'Grady *et al.*⁸ evaluated prognostic factors from variables easily obtained during routine medical care, to assess the need for liver transplantation. They tested their model prospectively on another group of 175 patients and found that it was valid in predicting prognosis and it has been adopted by the King's group for referring patients for transplantation.

In paracetamol-induced hepatic failure, the criteria for transplantation are arterial blood pH <7.3 (irrespective of grade of encephalopathy) or a prothrombin time of >100 seconds and serum creatinine >0.3 mmol/l in those with grade III or IV encephalopathy. In viral hepatitis and drug reactions, the criteria are a prothrombin time >100 seconds (irrespective of grade of encephalopathy) or any three of the following (irrespective of grade of encephalopathy); an aetiology of non-A, non-B hepatitis, halothane hepatitis or idiosyncratic drug reactions, age less than 10 or more than 40 years, or an interval of more than 7 days between onset of encephalopathy and jaundice with a prothrombin time >50 seconds or serum bilirubin >300 µmol/l.

Oesophagus

Motility disorders

A new research tool which is gaining in popularity is 24-hour oesophageal ambulatory motility monitoring in addition to the now well established continuous pH monitoring. Continuous motility monitoring may have particular relevance to the investigation of non-cardiac chest pain. This approach clearly allows evaluation of chest pain episodes over a prolonged period, during normal activities and permits correlation between symptoms and motor and reflux events in the oesophagus. However, there is no universally accepted approach to the analysis of such data nor is it clear as to the significance that should be attributed to pain-associated motor events. Janssens *et al.*⁹ were able to attribute severe recurrent angina-like chest pain as being of oesophageal origin in 35% of 60 patients on the basis of 24-hour recordings. However, Peters *et al.*¹⁰ had less clear cut findings in 22 patients with similar non-cardiac chest pain when they found that the majority of pain episodes (64%) had no association with either disturbances of oesophageal motility or pH.

Twenty-four-hour motility recordings produce an enormous amount of data and there is as yet no generally accepted approach to analysis. Does one have to analyse, for example, the entire 24-hour recording or would it be sufficient to analyse motility data immediately prior to an episode of chest pain? Richter & Castell¹¹ investigated 30 patients with suspected oesophageal chest pain and analysed the 24-hour motility data in two ways. The first was a 24-hour analysis technique in which the patient's baseline data during asymptomatic periods was established by studying 5 minute samples on the hour in addition to 5 minute random samples of any apparently abnormal motility activity occurring during the asymptomatic period. These data therefore provided the normal asymptomatic motility pattern for each patient. In the 10 minute baseline analysis technique only the 10 minute period prior to each individual chest pain episode was examined. Using the 10 minute baseline technique there was a 2.5-fold increase in the number of chest pain episodes associated with abnormal motility compared to the 24-hour technique. In line with their previous study, these investigators found that the majority of chest pain episodes occurred in the absence of abnormal motility or acid reflux. The authors stress that caution should be exercised when only limited analysis is performed as that may lead to over diagnosis of motility-related chest pain events and possibly lead to inappropriate treatment.

There is increasing awareness that functional disorders of the gastrointestinal tract are common and may be related to anxiety and depression. Ayers *et al.*¹² have performed oesophageal manometry in healthy volunteers and patients with the irritable bowel syndrome both at rest and while stressed by hyperventilation, a dichotic hearing challenge and a cold pressor test. Stress increased the mean amplitude of oesophageal peristalsis and the percentage of simultaneous waves in healthy volunteers and although similar in patients with the irritable bowel syndrome these findings failed to achieve statistical significance. Interestingly, the resting mean oesophageal peristaltic amplitude was significantly higher in irritable bowel syndrome patients than normal volunteers. This study suggests therefore that although stress may modify oesophageal motility, patients with the irritable bowel syndrome do not appear to have an increased sensitivity to stress.

Achalasia of the cardia was first described more than two centuries ago and continues to be a controversial subject with respect to both its aetiology and treatment. Recent family studies showed that achalasia or diffuse oesophageal spasm were found in more than one family member suggesting that genetic factors may be involved.¹³ Pneumatic dilatation is usually the treatment of choice and was satisfactory in 116 of 132 patients

treated in this way.¹⁴ However, many patients required more than one dilatation and the authors indicated that up to four or five dilatations was safe and may be required in some patients. Approximately a quarter of patients developed significant gastro-oesophageal reflux.

The usual way of assessing the response to treatment in patients with achalasia is on the basis of their symptoms. Robertson *et al.*¹⁵ used the radionuclide ^{99m}Tc-tin colloid and a gamma camera to assess oesophageal clearance. Untreated patients had marked retention of tracer in the oesophagus but cardiomyotomy and pneumatic dilatation, while reducing lower oesophageal sphincter pressure, failed to improve the 50% clearance time or percentage dose retained at 100 seconds. However, clearance of tracer after an additional drink of water was improved by pneumatic dilatation. Thus, the technique contributes to the objective assessment of treatment for achalasia and indicates that myotomy and pneumatic dilatation have similar effects. Holloway *et al.*¹⁶ described a similar radionuclide method for assessing oesophageal transit for use as a screening test for oesophageal motor dysfunction. Although the test was considered abnormal in all patients with achalasia or diffuse oesophageal spasm the sensitivity was low for other oesophageal motor disorders and failed to detect a proportion of patients with high amplitude peristalsis ('nut-cracker oesophagus') and patients with high resting tone in the lower oesophageal sphincter. In addition abnormalities were found in a few apparently normal subjects who had normal oesophageal manometry. The authors conclude that it is unlikely that this test will be of value as a screening test for oesophageal motor disorders.

Carcinoma of the oesophagus

There is wide variation in the incidence of oesophageal carcinoma which is thought to be largely due to variations in diet, smoking and alcohol habits and possibly other local customs. A large study from California confirms the association between tobacco smoking and alcohol and carcinoma of the oesophagus and showed a dose response relationship for each.¹⁷ In addition, this study showed that prolonged occupational exposure to beryllium, chromium and nickel was also significantly associated with carcinoma in the lower third of the oesophagus.

Barrett's oesophagus, a condition in which the squamous epithelium of the oesophagus is replaced by a columnar epithelium, is a premalignant condition with an incidence of adenocarcinoma of around 0.6% per year. Diagnosis of Barrett's oesophagus is generally made at endoscopy and confirmed by biopsy. However, ^{99m}Tc-pertechn-

tate scintigraphy has been evaluated as a non-invasive screening test for Barrett's oesophagus. The principle is that the radionuclide is taken up by acid-producing epithelium (hence its use for diagnosis of Meckel's diverticulum) and thus a positive scan would be obtained in Barrett's oesophagus but a negative in simple reflux oesophagitis. However, evaluation in 17 patients with Barrett's oesophagus showed the technique to be of too low sensitivity to be of clinical value.¹⁸

Once Barrett's oesophagus is present, two major dilemmas remain. One is how often to screen the individual for malignant change and the other to determine the criteria for and timing of surgical intervention. Yearly surveillance is generally recommended¹⁹ although more frequent examination may be indicated in those with high-grade dysplasia.²⁰ The presence of dysplasia does appear to indicate the increased risk of developing overt oesophageal carcinoma (as it does in the colon for colonic carcinoma)²¹ and detection of an unstable epithelium may be assisted by DNA image cytometry since aneuploid cells may be detected by this technique which can be missed on routine histological examination.²²

Gastro-oesophageal reflux

One of the most important pathophysiological mechanisms involved in the pathogenesis of reflux oesophagitis is that of intermittent relaxation of the lower oesophageal sphincter, which accounts for the majority of reflux episodes. A similar situation was thought to operate in infancy, although a recent study suggests that in infants with pathological gastro-oesophageal reflux there was a significant reduction in swallowing rate during reflux episodes from a mean of 0.5 per minute compared to 3.5 per minute in controls.²³ The authors suggest that there may be an abnormality of sensory input from the oesophageal chemoreceptors or possibly an abnormal central response to that input.

Primary treatment of oesophageal reflux continues to be medical. Omeprazole 40 mg daily has an impressive ability to relieve symptoms of reflux and to improve endoscopic appearances.²⁴ Despite concerns about its longterm use, omeprazole seems to be relatively safe in the short-term.

Stomach

Pathogenesis of acid-peptic disorders: the role of Helicobacter pylori

Helicobacter pylori (previously known as *Campylobacter pylori*) was first cultured in 1983. The human stomach appears to be the main natural

reservoir for *H. pylori* and the organism is only found in the duodenum in association with gastric metaplasia. *H. pylori* produces large amounts of urease which, by production of ammonia from urea in gastric juice, protects it from the otherwise hostile low intragastric pH. Despite the enthusiasm of microbiologists and gastroenterologists to attribute an important pathogenetic role for this organism in gastritis and duodenal ulcer, a number of questions remain unanswered.

Firstly, *H. pylori* is commonly found in otherwise healthy, asymptomatic individuals. Prevalence increases with advancing age. Dooley *et al.*²⁵ gastroscopied 113 asymptomatic individuals and documented the prevalence of *H. pylori* infection and histological gastritis. Gastritis was found in 42 individuals (37%) of whom 36 were infected with *H. pylori*. *H. pylori* was not detected in any of the 71 individuals with normal antral histology. As in previous studies *H. pylori* infection increased with age, with 47% infected between the ages of 60–69 years. This study suggests that there is a strong association between *H. pylori* infection and gastritis supporting the view that it does have an aetiological role in this condition. However, the importance of this organism in producing the symptoms of dyspepsia must be questioned since all patients in this study were asymptomatic.

The role of *H. pylori* in the pathogenesis of non-ulcer dyspepsia remains in doubt. Loffeld *et al.*²⁶ studied 50 consecutive patients with non-ulcer dyspepsia and associated *H. pylori* gastritis and randomly assigned them to receive either colloidal bismuth subcitrate or placebo. Bismuth significantly reduced colonization by *H. pylori* and improved gastritis but the effect on symptoms was not significantly different from that of placebo. Thus, the clinical significance of *H. pylori* gastritis, with respect to symptoms, is unconvincing. However, there is increasing evidence to suggest that eradication of *H. pylori* from the gastric antrum of duodenal ulcer patients significantly reduces ulcer relapse rate. This was first apparent with single agent therapy using colloidal bismuth subcitrate and even more impressive results have been obtained using triple therapy with bismuth, tetracycline (or amoxycillin) and metronidazole.²⁷

The mechanism by which *H. pylori* produces duodenal ulcer disease is intriguing. Levi *et al.*²⁸ have suggested that *H. pylori* increases antral surface pH by releasing ammonia which in turn increases gastrin release thereby stimulating acid secretion. They were able to show that in patients with duodenal ulcer who were positive for *H. pylori*, basal gastrin concentrations were significantly higher than in duodenal ulcer patients who were *H. pylori* negative. Integrated plasma gastrin responses following a standard meal were also significantly higher in *H. pylori*-positive than -negative

patients. Following treatment and eradication of *H. pylori* in some of these patients, the integrated post-prandial gastrin responses decreased although basal gastrin concentrations remained unaltered.²⁹ However, parietal cell mass, as judged by peak acid output following pentagastrin, was also unchanged. The authors suggest that the beneficial effect of eradicating *H. pylori* relates to this gastrin lowering effect and propose that a longer period of *H. pylori* eradication may be required before the parietal cell mass decreases.

An alternative hypothesis has recently been advanced which proposes that the ammonia released by *H. pylori* urease inhibits the biosynthesis of mucus or possibly causes mucus disassembly at the mucosal surface.³⁰ It is proposed that this facilitates colonization of the epithelium by *H. pylori* which, by as yet undetermined mechanisms, then produces gastric ulceration. Further direct evidence will be required to confirm or refute these hypotheses.

Carrick *et al.*³¹ suggest that *H. pylori* and acid have a synergistic role in the production of duodenal ulcer. They studied patients with active duodenal ulceration, patients with healed ulcers and a group of normal subjects. In addition to taking biopsies for histology and *H. pylori* detection they demonstrated the presence of functioning parietal cells in the duodenum (i.e. gastric metaplasia) by pentagastrin-induced congo red staining of the duodenal bulb. This method involves giving an intramuscular injection of pentagastrin 30 minutes before the endoscopy and during the procedure 10 ml of 0.3% congo red in 0.5% of sodium bicarbonate is sprayed into the duodenal bulb. Acid production by the duodenal mucosa is indicated by a change in dye colour from bright red to blue/black. Using multivariate logistic regression analysis they showed that *H. pylori* infection of the duodenum was the strongest risk factor for duodenal ulceration followed by the presence of duodenal gastric metaplasia and the presence of *H. pylori* in the gastric antrum. Interestingly, endogenous acid production was detected at the edges of duodenal ulcers, perhaps suggesting that ulceration occurs at the site of gastric metaplasia, possibly facilitated by colonization with *H. pylori*.

New drugs for peptic ulcer – the rise of omeprazole

Omeprazole received a product licence in the UK in 1989 for the treatment of peptic ulceration refractory to conventional management and for the suppression of gastric acid secretion in the Zollinger-Ellison syndrome. As time goes by, and if no severe unexpected side effects are noted with the usage of this drug, it is likely to challenge the position of pre-eminence enjoyed by the H_2 -receptor antagonists in the management of peptic ulcer disease. Omeprazole inhibits the action of the

proton (H^+) pump in the gastric mucosa and in this way exerts its powerful anti-secretory effect. It is readily taken up and concentrated within the gastric parietal cells close to its site of action; hence suppression of gastric acid secretion is not reliant on drug plasma levels and once daily dosage provides almost complete suppression of acid secretion for at least 24 hours.

In routine clinical practice omeprazole is having its greatest impact in the management of oesophagitis. Oesophagitis often produces intractable symptoms of heartburn and dysphagia which may be difficult to treat successfully with H_2 -antagonists. Omeprazole 20 mg daily has been shown in patients with moderate and severe oesophagitis to produce complete re-epithelialization of the oesophagus in 85% of cases after 8 weeks' treatment compared to 50% healing rate with a conventional dose of ranitidine (150 mg twice daily). Symptomatic improvement was also greater with omeprazole.³² In patients with severe oesophagitis unresponsive to conventional dose H_2 -antagonists, omeprazole 40 mg daily resulted in endoscopic healing in 80% of cases after 8 weeks compared to 32% in a group taking high dose ranitidine (600 mg/day).³³ In a small series of patients with Barrett's oesophagus, high dose omeprazole (60 mg/day) produced regression of the metaplasia and symptom relief.³⁴ If this report is confirmed it will have important clinical implications as it may reduce the risk of developing oesophageal carcinoma in these patients.

In patients with duodenal or gastric ulcers refractory to conventional or high dose H_2 -antagonists, omeprazole produces substantial healing rates, up to 100% in some series. In a study of 11 duodenal ulcer patients and 43 gastric ulcer patients who had failed to respond to at least 3 months high-dose ranitidine, omeprazole produced healing of all the duodenal ulcers after 4 weeks' treatment and in 34 of 43 gastric ulcers in 8 weeks.³⁵

In the Zollinger-Ellison syndrome controlled trials are not appropriate and it is difficult to assess ulcer healing rates. Nevertheless, omeprazole after titration of dosage (60 mg–120 mg) produced satisfactory control of acid secretion in an international group of 80 patients. No significant drug related side effects were experienced despite use of the drug for up to 5 years.³⁶ Omeprazole has a central role to play in the management of these patients.

Few side effects attributable to omeprazole have been reported despite use in over 1,500 clinical trial subjects. Omeprazole is metabolized by the cytochrome P450 enzyme system and hence drugs such as phenytoin, which also are metabolized by this system, may have their pharmacokinetics modified.³⁷ Enterochromaffin-like cell hyperplasia has been noted in rats administered 5–400 times

the usual therapeutic dose of omeprazole in rat life-time studies.³⁸ However, rats given high dose ranitidine also develop enterochromaffin-like cell hyperplasia.³⁹ This phenomenon has not been encountered in other animal species nor in humans. It is likely that it is due to a special propensity of the rat stomach to produce enterochromaffin-like cells in the presence of hypergastrinaemia.

Small bowel

Absorption and secretion

Control of absorptive and secretory mechanisms in the intestine continues to be an important area for investigation particularly of the neurohumoral regulation of intestinal transport and the unraveling of the complex intracellular mediator systems through which many neuroendocrine substances and exogenous secretagogues modify intestinal transport processes. Ultimately these studies are aimed at enhancing intestinal absorption and controlling intestinal secretion in disease states. The final common pathway for many of these studies is the development of new drugs to control these processes. The importance of understanding these mechanisms in diarrhoeal disease has recently been reviewed by Field *et al.*^{40,41}

Sodium is absorbed by the intestine by a number of different mechanisms. The most widely studied mechanism is that of nutrient-coupled sodium transport such as that which occurs during the active transport of glucose and amino acids. In recent years, however, there has been increasing interest in the Na/H exchange mechanism which has been extensively studied in animal intestine. Recent work has confirmed the presence of the Na/H exchanger in human small intestine and has produced evidence for the presence of conductive transport pathways for both Na and H.⁴² These studies in human ileal brush border membrane vesicles have measured Na uptake by monitoring ²²Na flux and hydrogen transport has been followed by fluorescent pH sensitive indicators. Outward directed proton gradients stimulated Na uptake and this process was inhibited by amiloride, a specific inhibitor of Na/H exchange.

A third mechanism by which Na is absorbed by the intestine is nutrient-independent electrogenic Na absorption. This mechanism is thought to operate throughout the small intestine and has been partially characterized in rabbit and rat intestine. However, characterization of this pathway has been limited because of the lack of a selective inhibitor. However, the amiloride analogue, phenamil has been shown to block an amiloride-resistant electrogenic Na absorptive pathway in rabbit caecum.⁴³ This agent has a high affinity for

Na channels but little or no effect on Na/H exchange short-circuit current or conductance in isolated rabbit ileal mucosa. Phenamil also had no effect on nutrient-coupled electrogenic Na absorption nor electrogenic Cl secretion. These studies suggest that more than half of ileal sodium absorption may occur via this nutrient-independent electrogenic Na absorptive mechanism. The availability of this Na channel blocker should permit more detailed study of this Na absorptive mechanism.

It is well known that diarrhoea can be a consequence of distal ileal and right colonic resection. Current dogma suggests that the mechanism involved depends largely on the secretory effects of unabsorbed bile salts and fat in the colon. However, whole gut steady-state perfusion of patients with severe post-resection diarrhoea indicated that increased faecal water and electrolyte losses continue during a 48 hour fast in all patients and that water, Na and Cl absorption was reduced by 20–30% compared to normal controls.⁴⁴ The importance of the right colon for sodium and water absorption is well recognized but this study confirms its biological relevance in resected patients. Interestingly, although malabsorption of the bile salt sodium taurocholate was demonstrated in these patients, administration of the bile salt-binding resin cholestyramine failed to reduce stool output.

The fact that nutrient-coupled Na absorption remains intact in many acute diarrhoeal diseases, principally those of infective origin, has enabled oral rehydration therapy with glucose-electrolyte solutions to emerge during the past 20 years as the mainstay of treatment for the dehydration and acidosis associated with these conditions. Glucose-Na transport remains intact not only in enterotoxin-mediated diarrhoeas such as cholera but also in rotavirus infection when the epithelium is damaged. A major new development in the design of oral rehydration solution has been the replacement of glucose with complex substrates such as rice water or rice powder.⁴⁵ These commodities are widely available in the developing world and when added to an appropriate electrolyte solution significantly reduce the volume of diarrhoea, the volume of oral rehydration solution required for rehydration and maintenance and the duration of the illness.⁴⁵ More recent work suggests that, in addition to rice, other foods such as maize, sorghum, millet, wheat and potato are all superior to an equivalent glucose based solution.⁴⁶ Food-based oral rehydration solutions are attractive since many of the constituents are already in the home but during the early stages of acute diarrhoea they are sometimes less well tolerated than a glucose-electrolyte solution and have the disadvantage that they require additional time to prepare.

Gluten-free diet and cancer risk in coeliac disease

Since the first descriptions of the association between coeliac disease and lymphoma by Read's group from Bristol in 1962⁴⁷ it has been unclear as to whether adherence to a strict gluten-free diet (GFD) would prevent this complication. As many patients find a strict GFD difficult to tolerate and appear to suffer little from ingesting a low gluten diet, the demonstration of a link between dietary indigestion of gluten and lymphoma would have major implications. Data from the General Hospital, Birmingham now indicate that adherence to a GFD reduces the possibility of developing a malignancy in coeliac disease.⁴⁸ Two hundred and ten patients with coeliac disease were followed for a minimum of 13 years (average 18 years). The overall follow-up rate was 98%. Thirty one cancers occurred in this group of patients during the follow-up period compared to an expected rate of 15, as calculated from the West Midlands Cancer Registry ($P < 0.01$). Fifteen cancers of the mouth, pharynx, oesophagus or small bowel occurred in the cohort compared to an expected occurrence of 0.76 in the general population. Non-Hodgkin's lymphoma was a particularly prominent cause of death in the coeliac patients (9 observed vs 0.21 expected; $P < 0.001$).

The occurrence of malignancies was then compared between those patients who had adhered to a strict GFD for 5 years or more and those patients eating a normal or low gluten diet. Although no differences between the groups could be detected for cancer occurrence at individual sites, on combining them (mouth, pharynx, oesophagus and lymphoma) the difference between the relative risks in comparison to the general population (6.7 for strict adherence and 38.7 for low/normal gluten diet) was statistically significant ($P < 0.05$).

Despite some deficiencies in the presentation of the data it would be a foolhardy clinician who now would not advise coeliacs to 'stick' to their GFD diets. In this way it would appear that it is possible to prevent the occurrence of malignant disease.

New treatments for inflammatory bowel disease

Identifying the causes of inflammatory bowel disease and producing a cure are still distant prospects. Nevertheless, there has been confirmation of the efficacy of a number of novel treatments in inflammatory bowel disease in the last year which should provide benefit for individual patients.

Olsalazine has recently received a product licence and is now available on prescription. Olsalazine consists of two molecules of 5-aminosalicylic acid (the active moiety of sulphasalazine) linked by an azo bond. In the large bowel colonic

bacteria split this azo bond thus releasing two salicylate molecules. Most patients suffering an attack of distal colitis are prescribed local enema treatments but if the patient is not already taking oral sulphasalazine this alone may be sufficient to treat the attack successfully. It has now been shown that one month's treatment with olsalazine 2 g/day is as good as sulphasalazine 3 g/day in the treatment of a first attack of mild or moderately severe ulcerative colitis with an overall response rate of 83% and 69% respectively.⁴⁹ Olsalazine is also of similar efficacy to sulphasalazine in the maintenance of remission in ulcerative colitis. Jewel and colleagues from Oxford have observed, in a double blind, controlled trial, that over a 6-month follow-up period the symptomatic relapse rate in patients taking olsalazine 2 g/day (12.2%) or sulphasalazine 3 g/day (19.5%) was similar.⁵⁰ Adverse effects were minor and were similar in both groups. However, diarrhoea can be a problem for some patients taking olsalazine.⁵¹ As olsalazine has only recently been introduced the long-term safety cannot be guaranteed as yet. However, for patients intolerant of sulphasalazine, olsalazine, like mesalazine, represents an alternative therapeutic option for treatment of acute episodes and the maintenance of remission.

Azathioprine is well known to be of value in the maintenance of remission of Crohn's disease. Until recently, although prescribed by many gastroenterologists, the value of azathioprine in ulcerative colitis was unclear. Hawkey and colleagues from Nottingham⁵² have now observed that in patients with resistant ulcerative colitis requiring prolonged and repeated corticosteroid treatment it was possible to achieve complete remission in 85% of 41 patients able to tolerate azathioprine (50–150 mg/day). This is a remarkable response rate and although the study was not controlled or double-blind it provides some evidence for the usefulness of azathioprine in ulcerative colitis.

Anecdotal evidence of the usefulness of cyclosporin in Crohn's disease has been forthcoming for a number of years. Recently, however, the results of a placebo controlled, double-blind trial in Denmark and Italy have been reported.⁵³ Among 71 patients with chronic Crohn's disease resistant to, or intolerant of, corticosteroids, 59% and 32% of patients receiving either cyclosporin or placebo respectively, improved over a 3-month period. In the cyclosporin group, 30% of patients had mild to moderate improvement and 30% had substantial improvement; this compared to 21% and 12%, respectively, in the placebo group. Treatment with azathioprine (or its metabolite 6-mercaptopurine) had been used previously in only 15% of the trial groups. Thus cyclosporin may produce substantial benefit for a number of patients with chronically

active Crohn's disease but the relative value of this drug compared to azathioprine is unknown.

Small bowel transplantation

Transplantation of the small bowel has been attempted in animals since the beginning of this century. Overall the results have been disappointing, principally because of the complex immunological changes that occur including both graft rejection and graft versus host disease. In addition there are the physiological disturbances resulting from temporary devascularization of the graft and interruption of the nervous and lymphatic supply. Nevertheless, progress has been made during the past decade, largely in animal models, notably rat, dog and pig.⁵⁴ Conventional immunosuppression in these models with prednisolone and azathioprine is ineffective but cyclosporin A prolongs graft survival but is less effective in preventing graft versus host disease than it is in controlling rejection.⁵⁴ Other approaches to improve graft survival include close matching of major histocompatibility complex antigens, pretransplant blood transfusion⁵⁵ and possibly graft irradiation or lymph node resection to reduce the amount of lymphoid tissue transplanted.

Preservation of graft function is clearly essential if small bowel transplantation is to become a reality in man. Although in animal models nutrient absorption appears surprisingly good, diarrhoea occurs in some animals and may well be related to reduction in water and sodium absorption that has recently been described in a rat model treated with cyclosporin A.⁵⁶ It has been suggested that reduction in net absorption rates is probably due to enhanced intestinal secretion due largely to loss of sympathetic innervation which under basal conditions is known to be an inhibitor of intestinal secretion.

The world experience of human small bowel transplantation is disappointing. Before the advent of cyclosporin, small bowel transplants were universally unsuccessful. However, six small bowel transplants have now been reported with cyclosporin A, 3 patients surviving more than 6 months.^{54,57-59} Complex transplants have also been reported in which the small bowel is transplanted with stomach, colon, pancreas and liver⁵⁸ or alone with the liver.⁵⁹ Although there is still some way to go before small bowel transplantation can be widely recommended for the treatment of small intestinal failure there is hope that intensive immunosuppressive regimens which include cyclosporin A combined with other agents together with other methods for reducing the amount of lymphoid tissue included in the transplant offers some hope for the future.

Colon

Screening for colorectal cancer

Colorectal cancer is the second commonest cause of cancer in the United States with an overall mortality rate approaching 60%. The detection of early lesions reduces the mortality to 20% or less. Primary prevention is not possible as the aetio-pathogenesis of the disease is not fully understood. Therefore secondary prevention involving population screening using faecal occult blood testing to identify early malignant lesions has been studied both in the UK and United States.⁶⁰ Many screening studies are still in progress and thus the final word on the efficacy of screening is still awaited.^{61,62}

A recent report of screening more than 46,000 subjects in Minnesota⁶¹ showed the sensitivity of the haemocult test to be 89.3% with a specificity of 92.7% and a positive predictive value of 2.5%. Although the specificity of the test appears high, there are a substantial number of false positives. Using this method, we will be subjecting patients without cancer to costly investigations which are not without risk.

The data from the Minnesota and Nottingham groups are awaited to see whether faecal occult blood testing and appropriate investigation of a positive result actually reduces the mortality from colorectal cancer in the general population, rather than just by increasing the lead-time bias.

Individuals with a previous history of a colorectal adenoma or carcinoma are at increased risk of having further neoplasms. Grossman *et al.*⁶³ reported the results of colonoscopic screening of 544 asymptomatic subjects with past histories of colorectal index lesions ranging from small tubular adenomas to invasive carcinomas. A subgroup of 133 subjects whose index lesion was a single small tubular adenoma (< 10 mm) and with no affected first degree relatives, had a 3% prevalence of large adenomas or cancers. Of the remaining 411 subjects with more severe index lesions, 8-18% had advanced neoplasms.

Interest has focused on the role of calcium and vitamins such as folic acid, beta-carotene and vitamin B12 in colonic proliferation and predisposition to colorectal cancer. Dietary calcium supplementation has been suggested to lower the high colonic mucosal proliferation rates in patients at increased risk of colorectal cancer.

Gregoire *et al.*⁶⁴ reported the results of a double-blind placebo controlled trial of calcium supplements (120 mg/day) for 30 days in patients with a past history of colorectal cancer. Calcium did not decrease mucosal proliferation (assessed by ³H-thymidine labelling) in the short period studied.

Screening for cancer is very expensive. Colonoscopic surveillance of patients with ulcerative col-

itis has been estimated to prevent a very small number of cancers compared to the large amount of effort by patients and staff and a strain on medical resources. The cost-effectiveness of surveillance colonoscopy could be improved by targeting the highest risk patients at appropriate intervals.⁶⁵ Colonoscopy in patients over 50 years with positive faecal occult blood tests will yield at least 10 times more cancers than screening patients with chronic ulcerative colitis. Recent developments in molecular biology which facilitate the detection of subtle genetic abnormalities in preneoplastic cells may offer hope for the future.⁶⁵

There have been rapid advances in our understanding of the genetics of colorectal cancer. Two main types of genetic alteration have been described in colorectal tumours. These are (i) point mutations which activate the 'ras' oncogene, present in up to 50% of carcinomas and large adenomas, and (ii) gene deletion. Familial linkage studies have mapped the gene for familial adenomatous polyposis on the long arm of chromosome 5. More than one gene deletion or mutation appears to be necessary before a tumour develops.^{66,67}

Further application of these findings may allow early prediction of premalignant changes in the colon.

Ultrasound in acute appendicitis

During the last year further reports have appeared examining the usefulness of ultrasonography in the diagnosis of acute appendicitis. Ultrasonography is performed with gentle, graded compression to displace intervening fat and gas in the right iliac fossa with a 5 MHz or 7.5 MHz high resolution transducer. An inflamed appendix appears as a non-compressible, aperistaltic tubular structure with a dilated lumen. In one study 62 patients with clinical features suspicious of appendicitis were divided into two groups.⁶⁸ In the first group of 34 patients with a clinical diagnosis of appendicitis there were 8 normal ultrasound scans and 26 positive scans. All patients in this group with a positive scan had proven acute appendicitis at operation. However, the operative and histological findings in the 8 patients with a normal scan indicated that 4 had acute appendicitis, a false negative rate of 13%. In the second group of 28 patients with possible appendicitis, 21 went to surgery and 7 were followed up clinically and clearly did not have appendicitis. All patients in this group with possible appendicitis clinically and with a positive ultrasound scan had proven appendicitis at operation. However, two patients in this group with a normal scan turned out to have acute appendicitis (false negative rate of 6%). Hence clinical appraisal and measurement of the white cell

count are as good as ultrasound in the diagnosis of appendicitis when the clinical features are classic. In doubtful cases a positive ultrasound scan accurately diagnoses appendicitis (100%) but a negative scan may be misleading and clinical observation is necessary. Thus a normal ultrasound scan in a patient with suspected acute appendicitis cannot reliably identify a non-inflamed appendix and hence it is unlikely that it will help to reduce the number of operations for appendicitis in which the appendix is found to be normal.

Routine ultrasound in this situation, therefore, cannot be recommended. However, in situations in which the clinical presentation is atypical and gynaecological pathology is suspected ultrasound is useful in making alternative diagnoses⁶⁹ although it cannot detect salpingitis.⁷⁰

Constipation

There are many causes for constipation some of which are understood and some continue to elude physiological explanation and treatment. Severe idiopathic constipation in patients with a rectum and colon of normal diameter is found almost exclusively in young women. Constipation is almost invariably associated with chronic lower abdominal pain and increased prevalence of painful and irregular menstrual periods and often a past history of gynaecological surgery. These clinical observations have suggested that there might be a relationship between idiopathic constipation in young women and a gynaecological disorder. However, a recent ultrasound study in 26 patients with severe idiopathic constipation and 21 age-matched control women failed to detect any gynaecological abnormality.⁷¹ In particular there was no association with polycystic ovaries or abnormality of pelvic veins which have previously been shown to be a contributory factor to the 'pelvic pain syndrome'. Thus, although this condition is almost exclusively found in young women there would appear to be no obvious gynaecological component suggesting that the associated pain is of bowel origin.

The pathogenesis of severe idiopathic slow transit constipation remains unknown. Investigation of this and related conditions has been hindered by difficulties with investigative techniques and the limited available information on normal colonic activity. Bassotti *et al.*⁷² have studied mass movements in the proximal and distal colon during a 24-hour period using a colonoscopically positioned multilumen manometric probe. Their findings indicate that there is a circadian rhythm in both patients and controls, mass movements being significantly more frequent between 06.00 h and 14.00 h than between 16.00 h and 04.00 h. Consti-

pated patients had significantly fewer mass movements which were of shorter duration. This study suggests that one pathophysiological mechanism of constipation may be decreased propulsive activity.

There is no universally accepted or reliable medical treatment for severe idiopathic constipation. Almost invariably these women fail to respond to bulking agents and generally resort to powerful anthraquinone laxatives. The use of osmotic purgatives such as magnesium sulphate, however, is generally preferred by clinicians treating such patients. Some women, however, continue to have severe constipation and pain and it is in such individuals that colectomy is considered. Kamm *et al.*⁷² studied the results of colectomy in 44 women with severe idiopathic constipation and found that while 22 patients had normal bowel frequency following surgery, 5 had persistent or recurrent constipation and many patients continued to have abdominal pain. Almost a quarter of patients required psychiatric treatment for severe psychological disorders raising the important issue that in some individuals, at least, underlying psychological problems may have an important part to play in symptom production. This has been studied in depth by Fisher *et al.*⁷⁴ who, before treating patients with chronic constipation surgically, assessed their mental state by questionnaire. Compared to age and sex-matched controls, constipated patients had significantly higher anxiety and depression scores. Of particular importance was their observation that patients who did well following surgery had lower preoperative scores than those who were not improved. This study suggests that the results of surgery for severe idiopathic constipation can be predicted on the basis of preoperative mental state.

Liver

New developments in viral hepatitis

During 1989 the first published data on hepatitis C (HCV) emerged. The cloning and sequencing of the RNA hepatitis C virus⁷⁵ and the development of a serological assay to detect antibody to this (anti-HCV)⁷⁶ have been major breakthroughs in the long search for a causative agent for non-A, non-B hepatitis. The virus is an enveloped virus, 50–60 nm with a single translational reading frame and some characteristics resembling a flavivirus. There may be other viruses causing 'non-A, non-B' hepatitis, but HCV accounts for many of these cases.

There is good evidence for hepatitis C in transfusion recipients who developed non-A, non-B hepatitis and their donors.⁷⁷ Anti-HCV serocon-

version was shown in most patients who developed non-A, non-B hepatitis and some donors were anti-HCV positive. There may be a prolonged (4–6 month) interval between exposure to HCV or the onset of illness and the development of anti-HCV, so the test is not always useful in diagnosis of acute hepatitis C but it may be more useful in the screening of blood donors⁷⁸ and in patients with chronic liver disease due to HCV. The first generation immunoassay currently available gives a high false-positive rate and it is not yet a useful tool in routine clinical practice.

Although non-A, non-B hepatitis was initially characterized in relation to blood transfusion, this accounts for only a small proportion (5–10%) of the cases occurring in the community. About 40% of patients have a history of parenteral drug use, and in 10% the source of infection seems to be heterosexual contact. This leaves about 40% of patients with no obvious source of infection (sporadic). Therefore further prevention of hepatitis C will depend on measuring the risk associated with sexual activity and occupational exposure, identifying other routes of transmission and developing effective prophylactic measures.

There is a strong suggestion that about 50% of people who have acute HCV infection go on to develop chronic liver disease.⁷⁸ Anti-HCV antibody is present in the blood of about 90% of patients with post-transfusion hepatitis, 68% of cryptogenic cirrhosis and 43–77% of patients with hepatocellular carcinoma, but the significance of these findings will need to be determined.

Enteric (epidemic) or waterborne non-A, non-B hepatitis may now be known as hepatitis E. There are no distinct clinical features to differentiate this illness from hepatitis A, but it has been shown to occur in India and other developing countries in epidemics. A 27–30 nm virus-like particle has been found in stool of affected individuals and seroconversion to these particles occurs. Prevention of spread of this disease will come from public health measures and improved sanitation and there is preliminary evidence that immunoglobulins made from pooled plasma from individuals in endemic areas may be protective. Further controlled studies are needed and further studies on the characteristics of the virus are awaited.

Current research is focused on identifying other non-A, non-B hepatitis viruses. At least one other agent which is oral/enterally transmitted has been implicated and further developments in this exciting field are awaited.

Chronic hepatitis

Currently, the best studied and most promising agent for the treatment of chronic hepatitis B virus (HBV) infection is interferon. All types of inter-

feron have broad antiviral and immuno-modulatory properties. Interferon is theoretically an attractive treatment for chronic HBV infection because there is evidence of a defective immune response to the virus due to diminished interferon production; decreased cellular activation in response to interferon has also been described. Existing clinical studies of interferon in chronic HBV infection have shown that 30–40% of patients will respond to interferon alone with a sustained loss of viral replication markers.⁷⁹ Treatment is required for 3–6 months and is associated with symptoms of fatigue, muscle aching and hair loss. The therapeutic end-points of trials of interferon have been elimination of circulating HBeAg, HBV DNA polymerase and HBV DNA. HBeAg seroconversion is generally accompanied by disappearance of HBV DNA in serum, reduced plasma aminotransferase concentrations and improved liver histology. Disappearance of HBsAg is relatively rare and tends only to occur when treatment is in the early stage of the carrier state.⁸⁰

The accumulation of evidence indicating the effectiveness of interferon in chronic HBV has been slow, partly due to inadequacies in the design of trials with small numbers and poor control data. It is likely there will be dramatic developments in this field over the next few years and the results of a US multicentre trial comparing alpha-interferon and prednisolone with alpha-interferon alone or to no treatment will provide important new information.⁷⁹ A recent study of a combination of beta and gamma-interferon has suggested that this combination may be useful for chronic HBV infection when started early after infection.⁸⁰

About 50% of patients with chronic HCV infection will develop biochemical evidence of chronic liver disease. Preliminary results of alpha-interferon therapy in patients with transfusion-related non-A, non-B hepatitis (presumably HCV) have shown a transient improvement in plasma aminotransferases and liver histology, but longterm results have not yet been evaluated.^{81,82}

Octreotide and bleeding oesophageal varices

Sclerotherapy or if this fails, oesophageal transection are now regarded as the treatments of choice for the management of bleeding oesophageal varices. Temporary pharmacological control of haemorrhage, however, may be important if sclerotherapy is not available locally or if there is a delay with surgery. There have been a number of recent reports which suggest that somatostatin or octreotide infusion may be of benefit.

Kravetz *et al.* have shown that an infusion of somatostatin (50 µg bolus followed by 250 µg/h infusion) is as good as vasopressin infusion for up to 48 hours after starting treatment, stopping 87%

of bleeds in the first 3 hours.⁸³ Jenkins *et al.*⁸⁴ in a similar study have shown that somatostatin infusion is better than vasopressin infusion in controlling variceal haemorrhage during the first 18–24 hours; bleeding stopped in all 10 patients treated with somatostatin compared with 4 of 12 treated with vasopressin ($P = 0.003$). Somatostatin, in both studies, produced far less complications than vasopressin.

Moreover, somatostatin and octreotide are at least as effective as balloon-tube tamponade in the management of bleeding varices. It has been shown that 24 hours after starting treatment bleeding was controlled in 18 of 20 patients receiving somatostatin infusion compared to 10 of 18 treated with tamponade ($P < 0.03$).⁸⁵ Octreotide infusion (25 µg/h) is also as good, if not better than, variceal tamponade. Control of bleeding was similar 4 hours and 48 hours after starting treatment in two groups of 20 patients treated with octreotide or balloon tamponade.⁸⁶

Enthusiasm for octreotide in the treatment of actively bleeding varices, however, must be tempered as a very recent report suggests that it has no advantage over placebo.⁸⁷ Among 102 patients entered into the trial 83% and 65% stopped bleeding for 12 consecutive hours after infusion of placebo and somatostatin respectively. The exclusion criteria for this trial included patients needing immediate surgery, balloon tamponade, local application of coagulants, vasopressin infusion or sclerotherapy. The study population must have, therefore, been a highly selected group and hence the general applicability is in doubt. In conclusion, octreotide appears to be a promising early treatment for bleeding oesophageal varices but further clinical trial confirmation is required of its efficacy before it can be recommended for routine clinical practice.

Management of ascites in cirrhosis

Repeated large-volume paracentesis (4–6 litres/day) is an effective and safe therapy of ascites in patients with cirrhosis, provided albumin (20–60 g/day) is infused intravenously. Albumin infusion is essential to prevent impairment of systemic haemodynamics and renal function. Total paracentesis (of 6–22 litres) on one occasion, over 1–2 hours with intravenous albumin replacement has been shown to be safe in 38 cirrhotic patients with tense ascites in a recent Spanish study.⁸⁸

The results of this study should not be taken as an indication that therapeutic paracentesis is the treatment for every patient with cirrhosis and ascites. In patients who have high urinary sodium excretion, reducing dietary sodium may be all that is required. In other cirrhotic patients with ascites, sodium excretion is not high enough to allow the

development of a negative sodium balance on a sodium-restricted diet. However, they easily respond when treated with diuretics, either spironolactone alone or in combination with a low dose of a loop diuretic.⁸⁸ Patients who require admission to hospital generally have tense ascites which is difficult to control with sodium restriction and need high dose diuretics and these patients are predisposed to diuretic-induced complications. These are the patients who are candidates for paracentesis. Further studies are required to confirm the safety of total paracentesis and to compare its efficacy for longterm treatment with other methods of managing cirrhotic patients with refractory ascites.

Liver transplantation

Liver transplantation is now an established therapy for severe, irreversible liver disease and its success and availability has changed the clinician's approach to the management of patients with end-stage chronic liver disease. The most important considerations are patient selection and the timing of surgery. Specific selection criteria have evolved for transplantation in different liver diseases and currently about 50% of all patients considered for transplantation undergo liver replacement. The current indications for transplantation are reviewed by Munoz *et al.*⁸⁹ The clinical indications for consideration for liver transplantation in patients with chronic liver disease include ascites refractory to medical therapy, recurrent or severe encephalopathy, recurrent variceal bleeding, recurrent spontaneous bacterial peritonitis or cholangitis, severe malnutrition, progressive bone disease, intractable coagulopathy and severe chronic fatigue and weakness. There are few absolute contraindications to liver transplantation. These are currently extrahepatic hepatobiliary malignancy, active sepsis outside the hepatobiliary tree, severe cardiopulmonary disease, AIDS and portal vein or superior mesenteric vein thrombosis. The overall survival from liver transplantation is 60–70%. For patients who survive more than 6 months after transplantation, the longterm prognosis is excellent and their quality of life approaches that of the normal population. At present, the major limiting factor is the availability of donor livers, and there are numerous unresolved medical, ethical and economic issues surrounding liver transplantation. Of the medical issues, most important is the reevaluation of the natural history and of prognostic indicators in liver diseases now that transplantation is widely available. Further attention is being directed towards improved, less toxic approaches to immunosuppression and the management of the medical complications of liver transplantation.

The role of transplantation for FHF^{7,8} is still to be defined. In end-stage chronic liver disease,

particularly primary biliary cirrhosis (PBC), liver transplantation is an established treatment and will now never be subjected to a controlled trial. Markus *et al.*⁹⁰ tested a survival model for PBC⁹¹ to compare the hypothetical predicted survival without a transplant with the real survival of 161 patients with PBC at Pittsburgh who had had liver transplants. The one year survival after transplantation was significantly improved at 76% compared to a predicted 45% ($P < 0.001$). There is also evidence from this group that good pre-transplantation status significantly influenced post-transplantation survival. These data confirm the benefit of liver transplantation in PBC, although, due to the use of a hypothetical mathematical model which may be more unreliable in patients with more severe liver disease, care should be taken when extrapolating to the individual patient considered for transplantation.

The prediction of survival in liver disease has become more important with the increased efficacy of liver transplantation. The answer to improving prediction of survival may be to evaluate serial changes of the prognostic variables in chronic liver disease as outlined by Christensen.⁹²

Biliary disease

Management of biliary obstruction

There are now several possible options for the treatment of patients with benign and malignant biliary strictures. Interpretation of many of the studies reported is made more difficult by the fact that most investigators do not separate benign and malignant disease or high and low duct obstruction making the groups heterogeneous. Further prospective randomized trials are badly needed.

The use of endoscopic biliary prostheses as treatment for benign postoperative bile duct strictures was evaluated in a study from Toronto.⁹³ Endobiliary prostheses were successfully placed in 25 of 29 (85%) patients. These were removed when the patient had clinically and biochemically improved. Patients who presented within 3 months of their initial surgery had a better chance of a good result (90%) compared with 62% in those who presented later. In four patients with biliary fistulae and distal obstruction who were stented, the fistula healed. The long-term follow-up of these patients will need to be assessed before the incidence of later recurrence of strictures is known.

One study from Boston compared endoscopic sphincterotomy with transhepatic drainage and surgery in a group of 157 patients.⁹⁴ The types of patients in the 3 groups were different, with more patients with stone disease in the endoscopic sphincterotomy group and more with malignant biliary obstruction in the transhepatic drainage

and operative group. This makes interpretation of the results difficult. Transhepatic drainage seemed to be the least satisfactory option since it resulted in cholangitis in 40% and further transhepatic or surgical intervention in 77%. The mortality in this group was 28% but they were a highly selected group, mostly unsuitable for the other modalities and nearly all with malignant biliary obstruction.

A large series of 537 patients with obstructive jaundice has been reported from Hamburg.⁹⁵ Among these patients, 208 had malignant biliary obstruction, with an average age of 71 years. They report an 85% success rate for the placement of endoscopic prostheses with a 1% mortality rate and 2% complication rate.

A series from the Middlesex and London Hospitals of 463 patients with inoperable low common bile duct obstruction reports that endoscopic stenting (which has fewer complications than percutaneous stenting) is a good approach with successful drainage in 75–97% of patients and a 5% or less major complication rate.⁹⁶ Few patients required surgery but up to a third of patients required a stent change, which is a relatively simple procedure. The Middlesex group reported the results of a prospective randomized trial comparing endoscopic stenting with bypass surgery in 133 patients.⁹⁷ They concluded that the two treatments are equally effective in the relief of malignant low biliary obstruction (94% success with both), but endoscopic stenting had no procedure-related complications and a lower 30-day mortality (6% vs 15%). There was no difference in long-term survival between the two groups. Readmission was rarely required in the surgical patients who survived, but some stented patients required readmission because of duodenal obstruction (14%) and stent blockage (17%).

A Danish study also reports that palliation of malignant obstructive jaundice is as effective by endoscopic stenting as by operative bypass and in centres where the expertise is available, stenting would appear to be the treatment of choice,⁹⁸ except in patients with duodenal obstruction.

Non-operative approaches to the treatment of gallstones

Non-surgical modalities for the treatment of gallstones have continued to receive increasing attention in the literature over the last year. Oral bile acid therapy, extracorporeal lithotripsy and contact dissolution with solvents instilled via percutaneous transhepatic catheters are the mainstays of the non-surgical approach. Extracorporeal-lithotripsy is known to fragment 98% of single and multiple non-calcified gallstones and in combination with oral bile acid treatment gallbladder clearance is achieved in 75% and 40% of cases

respectively after 1 year.⁹⁹ Little new regarding this has appeared during the last year.

Regarding oral bile acid treatment of gallstones a Milanese group have reported that use of a combination of chenodeoxycholic acid (5 mg/kg) and ursodeoxycholic acid (5 mg/kg) produces faster dissolution of radiolucent gallstones, smaller than 1.5 cm in a functioning gallbladder (the usual selection criteria) compared to the use of ursodeoxycholic acid (10 mg/kg) alone.¹⁰⁰ Dissolution rates of 60–70% can be expected with the combination, and rim calcification of the gallstones is less frequent with the combination treatment compared to ursodeoxycholic acid alone.

The Mayo Clinic group which pioneered the use of contact dissolution of cholesterol gallstones with methyl tert-butyl ether, administered via a percutaneous transhepatic catheter, have now reported on the outcome of the first 75 patients treated.¹⁰¹ This technique involves placement of the catheter in the gallbladder under intravenous sedation and continuous manual infusion and aspiration of the solvent four to six times a minute for an average of 5.3 hours. In 72 of the 75 patients there was complete or greater than 95% dissolution of the gallstones. Sixteen per cent of the patients required parenteral administration of analgesics after removal of the catheter, one patient had a significant biliary leak which cleared up after 3 days of conservative management and 1 patient had a septicaemia responding to antibiotics. The high success rate of the procedure was tainted by the fact that 40% of the patients had small amounts of 'debris' persisting in their gallbladder which could possibly act as a nidus for the formation of new gallstones. Nevertheless this technique may become increasingly used as it is automated¹⁰² and as solvents which can dissolve calcium containing stones become available.¹⁰³ In the future it may be possible to clear debris with oral bile acid therapy or gallbladder prokinetic agents. Doubts remain however, regarding the longterm safety of bathing the gallbladder mucosa in a noxious chemical solution.

The major drawbacks of non-surgical treatment of gallstones are that only 10–20% of gallstones are amenable to these therapies, and stones may recur. Italian researchers have now reported that administration of 300 mg of ursodeoxycholic acid daily after successful dissolution can reduce the recurrence rate from 50–60% to 30% at 6 years in patients under 50 years of age.¹⁰⁴ They also noted that recurrence was less in those who originally had multiple stones rather than single stones. These data require confirmation as previously no benefit has been noted with low dose chenodeoxycholic acid. Finally, reports continue to appear that asymptomatic gallstones, accounting for 80% of all gallstones, do not require treatment.¹⁰⁵

Conclusions

Gastroenterology, as a clinical specialty, benefited enormously by the arrival of fiberoptic endoscopy in the late 1960s. During the past 20 years this has evolved as a vital diagnostic tool for gastrointestinal disease but also as a therapeutic modality, in many instances taking trade from general and abdominal surgeons. In some instances the application of the new biotechnology to the investigation

of the pathogenesis of gastrointestinal disease has lagged behind the other areas, but clearly offers great promise for the future. Nevertheless new, useful drugs continue to be made available and the potential for non-operative treatment of gastrointestinal disease is certainly as yet not exhausted. The next decade will probably witness the widespread introduction of minimally invasive surgery into gastroenterology as it has been so successfully used in urology and gynaecology.

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