Reviews in Medicine

Gastroenterology – I: gastroduodenal disease and *Helicobacter pylori*

M.C. Bateson

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

Provision of gastroenterology services

The increasing number of gastroenterologists in Britain and the spread of the specialty outside university hospitals closely followed the discovery of the usefulness of endoscopic procedures.^{1–3} The British Society of Gastroenterology has recommended that these invasive tests are carried out appropriately in centres where a full range of equipment, technical expertise and adequate resuscitation facilities are available.

Gastroenterology is now almost entirely an outpatient and day-case discipline, and economic pressures are likely to increase this tendency. Comprehensive recommendations are available for services, including the ideas that there should be at least two surgeons with a special interest in gastroenterology in every general hospital, and that there should be a 50% increase in the number of medical gastroenterologists to a ratio of 1:100,000 population served. Though these ideas may seem ambitious now, the whole structure of hospital medicine is under review so we may expect more consultants and specialists (if fewer junior trainees) in future. These levels of staffing will certainly be necessary for the proper handling of the emergency gastrointestinal admission workload which is likely to continue to increase.

Gastroscopy

The explosion in the use of fibre-optic and video endoscopy has led to problems as well as advantages, as recent attempts at audit have indicated.^{4,5} Though gastroscopy in outpatients is generally very safe, many of the in-patients studied are the frail elderly with cardio-respiratory problems which make them vulnerable to sedation and the partial asphyxia of swallowing a tube. Avoidance

of opiates, minimal or no sedation and well-illuminated endoscopy suites are all reasonable suggestions. Routine use of pulse oximetry to improve safety is also in vogue, but this needs to be interpreted with caution.⁶

Audit of the diagnostic benefits of gastroscopy is rather subjective but it has been pointed out that normal examinations are often clinically very useful and important, even if they frustrate the managerial number-crunching efforts. Open-access services to general practitioners seem to yield just as good results as a hospital referral system. Efforts to select patients for the procedure have had only limited success.⁷ For instance, the use of routine *Helicobacter pylori* serology to screen out patients not requiring gastroscopy was found to be useful in Leeds and Southampton, but useless in Belfast and Bishop Auckland.^{8–10} The invention of curative treatment for peptic ulcer disease means that accurate diagnosis is even more essential than before, and the only way to achieve this is by an aggressive investigational approach for all persistent dyspeptic symptoms.

Safety in endoscopy has usually been taken to apply to the patient. The staff have also to be considered. Endoscopists and assistants are advised to be immunized against hepatitis B virus and to wear gloves to reduce the risk of acquisition of *H. pylori* infection. Elaborate ocular protection is used when lasers are operated. The most important area has yet to be resolved: activated glutaraldehyde is required to sterilize equipment. It is toxic and frequently allergenic, so that 30% of staff become sensitized. Use of precautions such as air extraction, cabinets for sterilization and adequate ventilation of the endoscopy room are only part of the solution. Alternatives such as formaldehyde solution and 70% alcohol proved impractical because of their toxicity, and the risk of fire and explosion, respectively. The promising newcomer is peroxygen solution, which is under study at present and may be found suitable as a less harmful alternative.

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

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New investigations

The advent of computerized tomography (CT) scanning has been enormously helpful in staging known carcinomas and lymphomas, but less effective in primary diagnosis of disease of the gastrointestinal tract. Endoscopy and conventional contrast radiology still hold sway. The invention of endosonography may be an advantage in the diagnosis of pancreatic and prostatic carcinoma, and in staging oesophageal and rectal tumours, but is a specialist technique under evaluation at present. Magnetic resonance (MRI) offers a promising non-irradiating method of improved definition and resolution over CT, especially when contrast with gadolinium-DTPA is used.¹¹ It is clearly superior in carcinoma of the oesophagus and can define smaller liver abnormalities. It is also better for other solid organs such as the spleen, pancreas and kidneys, but only equivalent to CT for the adrenals. It offers the fascinating, but as yet incompletely developed potential, for *in vivo* chemical analysis, for example of gallstones considered for non-surgical treatment.

The modern gastroenterologist with free access to MRI could probably dispense with CT altogether.

Oesophageal disease

Reflux

The occurrence of significant gastro-oesophageal reflux disease is usually assessed by gastroscopy to assess oesophagitis and ulceration, supported by 24 hour oesophageal pH monitoring, where there is no hiatus hernia or other abnormality. Criteria for reflux in children are rather different from adults where ranges have been well established.¹² In normal children there may be an oesophageal pH less than 4 for 18% of the 24-hour period, which is a much more liberal limit than for adults. Attempts to replace pH monitoring with non-invasive ambulatory radio-labelled food monitoring have been disappointing.

Carcinoma

The association of chronic gastro-oesophageal reflux disease with the gastric metaplasia of Barrett's oesophagus is well known, and potentially important since some cases proceed to malignancy.

The length of Barrett's oesophagus does not change with time, which is important since it is only the more extensive metaplasia which is premalignant. Frequent surveillance is needed where there is Barrett's oesophagus of 8 cm or more, and is rewarded by detection of earlier operable tumours,

and an improved survival.¹³⁻¹⁵ Adenocarcinoma of the gastro-oesophageal junction and oesophagus is actually increasing in frequency.¹⁶

Where carcinoma of the oesophagus is inoperable and radiotherapy and laser treatment are not effective in controlling dysphagia, use of self-expanding metal stents has been introduced.¹⁷⁻¹⁹ These are probably safer and easier to use than the older plastic Nottingham stents but are very much more expensive. Cost depends on length but it is essential not to use too short a prosthesis if it is to be effective. The lumen is dilated to 16-20 mm and this should allow normal dietary intake. If tumour overgrowth occurs then laser therapy can be used but it is not generally required.

Gastric carcinoma

The good news about this condition is its gradual decline in frequency over the last 60 years. The bad news is the poor prognosis of cases which become clinically apparent. Though pernicious anaemia is known sometimes to be premalignant, it contributes so little to the overall cancer rate that periodic endoscopy surveillance has traditionally not been recommended because of low yield. This may be incorrect for younger patients, since a study using 3-yearly gastroscopy in patients under 60 years did show an appreciable detection rate for early gastric cancer and carcinoid.²⁰ The mass screening of normal populations undertaken in Japan, where the rate of gastric cancer is the highest in the world, is unlikely to be useful in unselected populations elsewhere.

Once carcinomas have occurred, staging by ultrasonography or CT scanning may no longer be the ideal, since endoscopic ultrasonography correlates better with operative appearances.²¹ This may be very important since it is reported that radical surgery is now possible in 53% of diagnosed cases, and confers a 70% 5-year survival.^{22,23} These figures are only achievable by selection of the right cases for operation. For those cases which are inoperable, the options are not attractive. Response to radiotherapy is poor and chemotherapy with drugs like doxorubicin, cisplatin, mitomycin, 5-fluorouracil and BCNU carry only a 25% short-term response rate.²⁴

Peptic ulcer

The management of peptic ulcer has been very much coloured by the discovery of the importance of *Helicobacter pylori* but there have been some other advances as well.

For those patients with bleeding peptic ulcers, operative surgery has become decreasingly com-

mon with the use of vigorous medical treatment including injection therapy. Adrenaline (epinephrine) injected around and into bleeding ulcers will arrest haemorrhage. Injections of 1–2 ml of 1:10,000 to 1:100,000 adrenaline in each of four quadrants around the ulcer and into the bleeding site have been used, and this may be all that is required.^{25,26} Sclerotherapy into the ulcer at the same procedure can be added, and absolute alcohol is convenient and apparently as good as anything else.

For chronic management of peptic ulcer, long-term omeprazole can be safely used instead of the well-established H₂ receptor antagonists such as cimetidine or ranitidine.²⁷ It is, however, known that long-term acid-suppressing therapy will predispose to intestinal infections such as *Salmonella* and this may make radical curative treatment a more attractive option for peptic ulcer disease where possible.²⁸

Helicobacter pylori

There has been an alarming tendency for interest in this organism to swamp gastroenterology in recent years. There are more than one thousand original papers and several books published annually, and journals such as *Gut* now even give the germ its own section. The field is changing very rapidly and the dogma of 1994 may well prove the heresy of 1995. A symposium at the Royal Society of Medicine (published in its Journal in March 1994) reviewed the field comprehensively.

This spiral bacterium inhabits the alkaline layer between the gastric epithelium and its mucus coat in half of mankind. It may be harmless for many but is strongly associated with chronic antral non-immune gastritis, duodenal and gastric ulcers, and probably also gastric neoplasms. Its eradication by antibiotics is definitely useful in curing peptic disease.

Diagnosis

There is a wealth of alternative methods for proving the presence of active *Helicobacter pylori* whose results correlate reasonably well. Where gastroscopy is being performed anyway, the urea gel/indicator test (for example, slide CLO-test) on a gastric antral biopsy is a cheap and quick technique. The *Helicobacter pylori* urease generates ammonia which raises the pH to a level where phenol red turns magenta. A total of 90% of positive tests occur within half an hour but some will only be seen by reading slides the following day.

Though the use of unbuffered urea solutions can be a cheap alternative, these are unstable and require tedious fresh preparation each time they are used.

The organism can be cultured with careful incubation, but this takes a week or more and there is a 5–10% false-negative rate even so. Antral biopsy microscopy with modified Geimsa stain is satisfactory and histology will show the associated gastritis. Both of these require laboratory facilities.

Less invasive tests include IgG ELISA serology, though it is less specific because titres may reflect past not current infection.^{29–32} Complement fixation tests have also been used.³³ The main role of serology is in epidemiology. Assessment of treatment of individual patients requires dual samples before and at least 3–6 months after therapy to compare titres.

A much more attractive non-invasive approach is the use of the urea breath test.³⁴ These can be performed on breath samples collected 20–30 minutes after carbon-13 or carbon-14 radio-labelled urea is taken by mouth. The sample is analysed by mass spectrometry or scintillation counting, respectively. Non-infected patients excrete <0.5% dose/mmol CO₂/kg, infected patients 1.0% or more. The test can be performed a month after anti-*H. pylori* therapy, but should not be done before nor during antibiotic or omeprazole therapy to avoid false negatives.

Polymerase chain reactions have been used to locate small quantities of *H. pylori* DNA such as are present in stool, but this is a research technique.

There is agreement that *H. pylori* prevalence increases with age.^{35–38} Infection correlates with lower social class and overcrowding, and is commoner in developing rather than developed countries.^{39,40} What is more controversial is whether there is a progressive 1% annual additional infection rate in young adults and middle age, or whether different generation cohorts are infected persistently in childhood without acquisition of further cases with ageing.

Two studies showed, respectively, that only two out of 59 and six out of 68 subjects sero-negative for *H. pylori* converted to positive over 11 and 21 years, and this was taken to prove that adult infection or re-infection are rare.^{41,42} This is broadly in agreement with studies after anti-*H. pylori* therapy and implies that eradication should be a once for all process. Active infection rates fall in the elderly, possibly because chronic gastritis even-

tually creates a hostile environment for *H. pylori*^{35,38}

Cigarette smokers, nurses and bare-handed gastroscopists are predisposed to *H. pylori*.^{38,43} Ordinary levels of alcohol intake do not appear to be important though heavy drinking may increase infection rates.

Significance

It is striking that in Africa high rates of *H. pylori* infection are not linked with the diseases associated elsewhere. The mere presence of *H. pylori* gastritis could probably not be blamed for dyspeptic symptoms in adults and this has been shown elegantly for Tibetan monks.⁴⁴⁻⁴⁶ In children the importance of *H. pylori* infection is not so clear. Some believe, and others doubt, its link with symptoms.⁴⁷⁻⁴⁹

The intriguing idea has been put forward by at least two separate groups that, for patients under the age of 45, IgG ELISA would identify a group of sero-negative patients who do not require gastroscopy for dyspeptic symptoms.^{8,9} Unfortunately this could not be confirmed in two other series and invasive investigations are probably unavoidable if important diagnoses are not to be missed.^{10,46}

A side note is that *H. pylori* has no role in producing symptoms in the gastric metaplasia of Meckel's diverticulum.⁵⁰

Peptic ulcer healing

There is now convincing evidence that the use of antibiotics will cure duodenal and gastric ulcer with a lower relapse rate.⁵¹⁻⁵⁷ The World Congress of Gastroenterology recommended a regime of a fortnight's therapy with:⁵⁴ Metronidazole 400 mg three times a day and tetracycline or amoxycillin 500 mg four times a day and bismuth chelate 120 mg four times a day. This will eradicate *H. pylori*, though the treatment is hard to take because of the high tablet load, and because it can cause nausea, diarrhoea and pseudo-melaena.

Analysis of different antibiotic regimes has shown a clear superiority for this triple therapy (82% success) over dual (48%) or single (18%) drug treatments (Table I). Furthermore, tetracycline performs better in the triple regime than amoxycillin. The triple regime including tetracycline should be regarded as standard therapy except where pregnancy is a risk. Published evidence relates to adults rather than children, where amoxycillin would be preferred.

Currently anti-*H. pylori* therapy is recommended for refractory, recurrent or complicated peptic ulcers after healing therapy has been given but a more logical approach would be to offer treatment routinely to all proven benign ulcers.

Table I Eradication of *Helicobacter pylori*

	Studies	Patients	Success rate
Bismuth/metronidazole/tetracycline	3	203	94.1%
Bismuth/metronidazole/amoxycillin	6	150	73%

There is a problem with assessing suitability of drugs for treatment. Laboratory tests suggest efficacy which is not borne out by actual therapy because of intolerance to the doses needed (erythromycin) or primary failure (ciprofloxacin). Metronidazole sensitivity testing requires anaerobic conditions whereas the organism grows best in micro-aerophilic culture. Nevertheless, metronidazole resistance is worryingly common: up to 50% of cultures where the antibiotic is freely used as monotherapy for other conditions such as dental sepsis and pelvic inflammatory disease.⁵⁸⁻⁶⁵ Cigarette use encourages acquisition of metronidazole resistance which might be yet another reason why smokers have more trouble with ulcers.⁶⁶

Bismuth salts and the proton pump inhibitor omeprazole alone will suppress but not eradicate *H. pylori*.⁶⁷⁻⁷¹ Lansoprazole is an analogue of omeprazole which demonstrates rather greater activity against *H. pylori* and could be bactericidal even on its own.^{72,73} Suppression of gastric acidity will, however, facilitate antibiotic activity in the stomach and good results have been obtained with omeprazole plus amoxycillin or clarithromycin, which are useful alternatives to triple therapy.⁷⁴⁻⁷⁶

However, two weeks treatment with omeprazole 20 mg twice daily plus amoxycillin 500 mg four times daily or clarithromycin 500-750 mg three times daily - will be insufficient to guarantee universal rapid ulcer healing, and more prolonged acid suppressant therapy will often be required. A success rate for *H. pylori* eradication of 70-80% may be expected. Though amoxycillin resistance by *H. pylori* has not yet been demonstrated as a problem, the wide use of this drug for other reasons suggests it may become so in the future.

The literature is replete with alternative drug regimes such as the following:⁷⁷⁻⁸²

- Tetracycline plus amoxycillin plus bismuth
- Sucralfate plus tetracycline plus metronidazole
- Omeprazole plus metronidazole plus tetracycline
- Omeprazole plus amoxycillin plus bismuth
- Omeprazole plus tinidazole plus clarithromycin
- Amoxycillin plus furazolidone plus metronidazole
- Omeprazole plus bismuth plus tetracycline plus metronidazole
- Omeprazole plus amoxycillin plus metronidazole
- Omeprazole plus clarithromycin plus tinidazole

It may be concluded from this that we still seek the Holy Grail of a simple totally effective curative treatment for peptic ulcer disease. There is, indeed still an atavistic school of thought which promotes chronic H₂ receptor antagonist therapy in the face of the evidence for anti-*Helicobacter* treatment.⁸³

We should only be satisfied with a system which offers permanent cure with easy temporary treatment. Thirty years ago standard curative treatment for peptic ulcer was gastric surgery, which has all but disappeared in primary therapy. Maybe we shall look back in the future with similar embarrassment at our present stumbling steps towards proper control of peptic ulcer disease.

Gastric cancer and lymphoma

The exception to the depressing scenario described under 'gastric carcinoma' is B-cell gastric lymphoma (MALToma). These cases respond well to radical surgery, and the challenging suggestion has been made that they may even respond to anti-*Helicobacter pylori* drug therapy since they are invariably associated with infection by this organism.⁸⁴

There seems little doubt that *H. pylori* infection is associated as an independent risk factor for carcinoma of the stomach.⁸⁵ Its exact role is still under scrutiny but the concept of progressive mucosal change has great attraction:

The geographical association of positive serology with high prevalence areas for cancer was shown in Britain, and confirmed in a 13-country survey (Eurogast).^{86,87} Independent confirmation has also come from other studies in Italy, Mexico and Costa Rica.⁸⁸⁻⁹¹ A Dutch study could not support this, however, and the authors made the point that proof of association would require demonstration of a reduced gastric cancer risk in those where *H. pylori* had been eliminated.⁹² The ground is clearer with B-cell lymphoma where there is apparently progression from *H. pylori*-induced lymphoid hyperplasia to local lymphoma which is indolent and responds well to gastrectomy.⁹³ This link is persuasive because the normal non-infected stomach does not contain lymphoid tissue.

The burning question, therefore, is whether anti-*H. pylori* therapy should be offered to infected subjects in high-risk areas or groups to try to control gastric malignancy. This might be an appealing public policy in some developed countries, especially Japan.

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