colleagues themselves seem to rule out the hypothesis that gastric metaplasia in duodenal ulcer patients is secondary to the *H pylori* induced augment of gastric acid production with subsequent greater duodenal acidity.[3] As it is well known that *H pylori* infection is usually present in all patients bearing duodenal ulcer,[4] all these patients should be acid hypersecretors, but this is true only in about one third of cases.[5] Moreover, several studies on the effect of both medical and surgical antisecretory measures have failed to show any reversal of gastric metaplasia in the duodenum.[6 7] Unfortunately, neither Khulusi *et al* nor Noach *et al* reported data on the acid secretory patterns before and after *H pylori* eradication in the patients in whom they, respectively, showed regressed or unchanged gastric metaplasia in duodenum. The knowledge of this variable would have been of great help in interpreting the role of acid in the reversal or not of duodenal gastric metaplasia in the patients where *H pylori* has been eradicated. We recently studied the circadian pattern of gastric acidity in *H pylori* positive duodenal ulcer patients with (n=24) and without (n=14) gastric metaplasia in duodenum.[8] Although the acidity of both groups was significantly higher than normal, there was no significant difference between them as regards the 24 hour mean (SD) pH values (1·56 (0·35) *v* 1·44 (0·37)). These findings raise further doubts on the responsibility of hyperacidity in the induction of gastric type epithelium in duodenal mucosa and seem to support the conclusion by Khulusi *et al* that factors other than acid, and possibly also the reduction of duodenal inflammation, are implicated in the partial reversal of gastric metaplasia after eradication of *H pylori*.

V SAVARINO
G S MELA
G CELLE
Dipartimento di Medicina Interna, Università di Genova, Italy

S VIGNERI
Istituto di Medicina Interna e Geriatria, Università di Palermo, Italy

Correspondence to: Dr V Savarino, Gastroenterology Unit, Department of Internal Medicine (DIMI), Viale Benedetto XV, 6, 16132 Genova, Italy.

1 Noach LA, Rolf TM, Bosma NB, Schartz MP, Oosting J, Rauws EAJ, *et al*. Gastric metaplasia and Helicobacter pylori infection. *Gut* 1993; **34:** 1510–4.
2 Savarino V, Mela GS, Vigneri S, Celle G. Acid and gastric metaplasia in the duodenum. *Gut* 1994; **35:** 1151–2.
3 Levi S, Beardshall K, Haddad G, Playford R, Ghosh P, Calam J. Campylobacter pylori and duodenal ulcers: the gastrin link. *Lancet* 1989; i: 1167–8.
4 Blaser MJ. Helicobacter pylori and the pathogenesis of gastroduodenal inflammation. *J Infect Dis* 1990; **161:** 626–33.
5 Lam SK. Pathogenesis and pathophysiology of duodenal ulcer. *Clin Gastroenterol* 1984; **13:** 447–72.
6 Tovey FI, Husband EM, Yiu Chu Yiu, Baker L, McPhail G, Lewin MR, *et al*. Comparison of relapse rates and of mucosal abnormalities after healing of duodenal ulceration and after one year's maintenance with cimetidine or sucralfate. *Gut* 1989; **30:** 586–93.
7 Jönsson KA, Strom M, Bodemar G, Norrby K. Histologic changes in the gastroduodenal mucosa after long-term medical treatment with cimetidine or parietal cell vagotomy in patients with juxtapyloric ulcer disease. *Scand J Gastroenterol* 1988; **23:** 433–41.
8 Savarino V, Mela GS, Zentilin P, Mele MR, Lapertosa G, Patetta R, *et al*. Does circadian gastric acidity differ in Helicobacter pylori positive duodenal ulcer patients with and without duodenal gastric metaplasia? *Gastroenterology* 1995; **108:** A211.

Reply

EDITOR,—We are grateful for the comments of Savarino *et al*. The pathogenesis of gastric metaplasia is indeed a complex issue. Our paper (*Gut* 1995; **36:** 193–7) and other work recently completed in our department[1] suggests that *H pylori* is responsible for extending pre-existing gastric metaplasia, probably as a result of increased duodenal inflammation. The study by Noach *et al*[2] did show a trend towards reduction in gastric metaplasia with *H pylori* eradication but their small study size had insufficient power to detect a significant reduction. Hence their results cannot be considered to 'contrast' with our own although their interpretation does. We have recently studied the role of acid in the pathogenesis of gastric metaplasia.[1] In a double blind placebo controlled trial we found that profound and prolonged acid suppression with omeprazole does reduce the extent of gastric metaplasia without affecting the severity of duodenitis. Taken together, it seems that *H pylori* extends gastric metaplasia by provoking duodenitis and that acid also extends gastric metaplasia but by a mechanism independent of inflammation.

S KHULUSI
M A MENDALL
P PATEL
T C NORTHFIELD
St George's Hospital, London SW17 0RE

1 Khulusi S, Patel P, Badve S, Lloyd R, Marrero J, Finlayson C, *et al*. Pathogenesis of gastric metaplasia in duodenal ulcer disease. *Gut* 1995; **36** (suppl 1): A51.
2 Noach LA, Rolf TM, Bosma NB, Schwartz MP, Oosting J, Rauws EAJ, *et al*. Gastric metaplasia and Helicobacter pylori infection. *Gut* 1993; **34:** 1510–4.

Helicobacter pylori and gastric metaplasia of the duodenum

EDITOR,—Professor Northfield's group (*Gut* 1995; **36:** 193–7) found a significant decrease in gastric metaplasia in the duodenal bulb after *Helicobacter pylori* eradication. We have three questions.

(1) Duodenal biopsy specimens were examined by two histopathologists. Were they independent, did their results agree, and if not, whose were used?

(2) The extent of gastric metaplasia in the duodenal bulb biopsy specimens was assessed as a percentage of the total duodenal epithelial surface. How was this technique validated? What were the intra- and inter-observer variation of these measurements?

(3) Why were six of 32 (19%) patients with duodenal ulcer without gastric metaplasia or duodenitis in the duodenal bulb?

A W HARRIS
J H BARON
Parkside Helicobacter Study Group, Gastroenterology Unit, St Mary's Hospital, London W2 1NY

Reply

EDITOR,—We thank Dr Baron's group for their questions, in reply:

(1) The assessment of histological sections was carried out by two histopathologists unaware of the treatment status of the subject and working together on the same sections. The grading of gastric metaplasia and duodenitis was based on their mutually agreed values.

(2) The extent of gastric metaplasia in the duodenal bulb biopsy specimens was assessed as 'total epithelial surface present' in the biopsy sections themselves. We validated the results on 30 randomly selected sections by a morphometric technique using an interactive image analysis system (OsteoMeasure, Osteometrics, Atlanta, USA). There was a close correlation between the semiquantitative values given in the paper and quantitative measurements (r_s=0·89, p<0·001).

(3) Duodenitis and gastric metaplasia occur in close proximity to duodenal ulcers. Both have a patchy distribution, however, and can be absent from biopsy specimens,[1] especially if the samples are obtained from specific sites regardless of the endoscopic appearance.

S KHULUSI
M A MENDALL
P PATEL
C FINLAYSON
T C NORTHFIELD
St George's Hospital, London SW17 0RE

1 Hasan M, Sircus W, Ferguson A. Duodenal mucosal architecture in non-specific and ulcer associated duodenitis. *Gut* 1981; **22:** 637–41.

Cell proliferation and polyposis

EDITOR,—Mills *et al* (*Gut* 1995; **36:** 391–4) describe a small but significant increase in the proportion of Ki-67 labelled cells within the upper crypt and surface epithelium of the colon in polyposis versus control subjects. Conversely there was a small, but non-statistically significant reduction in the number of labelled cells in the crypt base. These small differences were detected by assessing seven perfectly oriented hemicrypts in 20 study and 20 control subjects (showing considerable interindividual variation in the labelling index). In both groups, most labelled cells were limited to the lower three fifths of the crypt. The findings are interpreted as confirming the existence of stage II lesions as detected by in vitro studies on mucosal samples obtained from polyposis patients.[1] In fact, the authors are describing stage I lesions, which are characterised by the redistribution of a few cycling cells into the upper third of the crypt with no major shift of the proliferative zone. Stage II lesions are focal and characterised by redistribution of the entire proliferative compartment into the upper two thirds of the crypt.[1] As the authorship includes expertise in the field of histopathology, microadenomas were correctly diagnosed as such. The fact that they do not demonstrate stage II lesions as defined by Deschner[1] suggests that stage II lesions are indeed microadenomas.

Stage I lesions occur in subjects at low risk for colorectal cancer.[1] Minor proliferative deviation may be related to sex, age, anatomical site, dietary supplementation, a variety of colorectal disorders, and surgery.[2] It is difficult to integrate a putative pre-neoplastic role for minor proliferative changes with current molecular insights into familial adenomatous polyposis.[2] Is it not more likely that the subtle cell kinetic changes encompassed by stage I lesions are reactive and in the case of polyposis are secondary to adenoma generation? The study negates the existence of the stage II lesion and lends support to the elegant work of Nakamura *et al*.[3] I would suggest that

the real conclusions of the study are rather different from those stated.

J R JASS
Department of Pathology, School of Medicine, University of Auckland, Private Bag 92 019, Auckland, New Zealand

1 Deschner EE. Early proliferative changes in gastrointestinal neoplasia. *Am J Gastroenterol* 1982; **77:** 207–11.
2 Jass JR. Evolution of hereditary bowel cancer. *Mutation Res* 1993; **290:** 13–25.
3 Nakamura S, Kino I, Baba S. Nuclear DNA content of isolated crypts of background colonic mucosa from patients with familial adenomatous polyposis and sporadic colorectal cancer. *Gut* 1993; **34:** 1240–4.

Coeliac disease and autoimmune thyroid disease

EDITOR,—In their article Counsell *et al* state that the association between coeliac disease and autoimmune thyroid disease is not astonishing given that the HLA haplotypes B8 and DR3 are found more commonly in both than in the general population (*Gut* 1994; **35:** 844–6). Based on the results of their data obtained in patients with coeliac disease they even suggest a routine check for thyroid function at presentation and a recheck if a gluten free diet fails to repair macrocytosis or symptoms, or both.

Screening patients with autoimmune thyroid disease for coeliac disease, as it has been performed by Collin *et al*[1] and by our group[2] also unveils a clinically possibly important association between the two diseases. We, therefore, agree also with their second suggestion that coeliac disease should be considered in patients with autoimmune thyroid disease.

It seems noteworthy to me, however, to point out that patients with Hashimoto's thyroiditis seem to have a higher risk of developing coeliac disease than patients with Graves' disease. Patients with coeliac disease on the other hand also seem to develop hypothyroidism (Hashimoto's ?) rather than Graves' disease. Indeed, the young woman in our series of 27 patients with Hashimoto's disease, who was found to have oligosymptomatic coeliac disease was HLA-B8, DR 3 negative. This was not surprising, as we have shown earlier[3] that the goitrous variant of this disease is associated with the HLA-DR5 haplotype.

I therefore want to suggest that there must be another (additional ?) link between the two diseases. This in my view is even more plausible if you consider the reports that both, Hashimoto's thyroiditis and coeliac disease, may eventually result in lymphoma,[4 5] whereas this has never been described in Graves' disease patients.

M WEISSEL
Medical University Clinic III, Waehringer Guertel 18–20, University of Vienna, A-1097 Vienna, Austria

1 Collin P, Salmi J, Hällström O, Reunala T, Pasternack A. Autoimmune thyroid disorders and celiac disease. *Eur J Endocrinol* 1994; **130:** 137–40.
2 Weissel M, Vogelsang H, Penner E, Flores J. Celiac disease in autoimmune thyroid disease. *Thyroid* 1993; **3** (suppl 1): T30.
3 Weissel M, Höfer R, Zasmeta H, Mayr WR, HLA-DR and Hashimoto's thyroiditis. *Tissue Antigens* 1980; **16:** 256–8.
4 Loughran TP jr, Kadin ME, Deeg J. T-cell intestinal lymphoma associated with celiac sprue. *Ann Intern Med* 1986; **104:** 44–8.
5 Hamburger JI, Miller JM, Kiri SR. Lymphoma of the thyroid. *Ann Intern Med* 1983; **99:** 685–9.

BOOK REVIEWS

Infections of the gastrointestinal tract. Edited by M J Blaser, P D Smith, J I Ravdin, H B Greenberg, R L Guerrant. (Pp xxix+ 1578; illustrated; $282.00.) New York: Raven Press, 1995. ISBN: 0–7817–0226–7.

Yet another massive tome on infection, this time directed solely to the gastrointestinal tract! Ten parts, 97 chapters, 162 contributors – all but 11 from North America, and the weight is 3·8 kg.

The editors begin their preface (to a volume that they have endeavoured to make 'comprehensive and practical'): 'Gastrointestinal infections are a major cause of disease and death, particularly in the developing world'; absolutely true, but surprisingly only one of the contributors (from Peru) resides there! The goal (of their labours) is, they state 'to provide a comprehensive source that combines the scientific basis and the art of medicine relevant to enteric infections'; while also emphasising that '. . . the clinician who understands the new technologies . . . becomes their master, not their slave' they also write that . . . there are many opportunities for simple, low-technology, low-cost approaches' for dealing with this group of infections. To keep the text to reasonable length (?), and to 'avoid dilution of interest and focus', hepatic infections are not included and should, the reader is informed, '. . . be treated as a separate subject'. The intended readership consists of: 'the healthcare practitioner, the clinical investigator, and all who seek not only the latest clinical details but also an understanding of the breadth and limitations of our knowledge of enteric infections'.

Part I focuses on the history and epidemiological aspects (in both developed and developing countries) of diarrhoeal disease; not surprisingly there is a good deal on cholera, and also the impact of gastrointestinal infection on the course of military campaigns – both well trodden paths! Anatomy, physiology, and immunology are covered in Parts II and III; normal flora, mucins, adherence factors, fluid and electrolyte transport, mucosal IgA, secretory antibody responses to enteric pathogens, cellular immune mechanisms, and immunophysiology of mast cells are some of the subjects tackled. In Parts IV to VI major clinical syndromes are considered – both in the immunointact and immunosuppressed subject; the coverage starts with food poisoning and travellers' diarrhoea, and meanders along through enteric fever, tropical sprue, appendicitis, diverticulitis, peritonitis, and infective complications of inflammatory bowel disease; there is also a great deal on *Helicobacter pylori* (53 pages) and HIV infection. Microbiology, epidemiology, and pathophysiological considerations form the basis for Part VII; bacterial and fungal, viral, and parasitic (protozoan and helminthic) infections are dealt with in this order. It is noteworthy that mycobacterial disease of the gastrointestinal tract (including *Mycobacterium tuberculosis* – which is arguably the world's most common bacterial disease) is allocated 19 pages, whereas that on Whipple's disease gets 18! Perhaps the editors should have taken more time with balance and priorities! The protozoan sections are on the whole well done; *Cyclospora cayatenensis* has just about made it! In a world context, helminthic infections (not least *Schistosoma* spp) are a dominant and important group; may be 168 pages represents rather short shrift! The remaining three parts focus on diagnosis (laboratory, endoscopic, and radiological), therapy, and preventive strategies – including vaccination (against viruses, bacteria, and parasites). A particularly useful chapter is one devoted to the treatment of paediatric diarrhoea. Although the various parts are clearly stated in the list of contents, there is no indication of this in the text itself.

One strength of this book lies in the substantial reference lists at the end of each chapter; most are appropriate and up to date, and most (but not all) accurate. The line diagrams and half-tone photographs are of good quality; 44 colour plates are included; these range from histological, endoscopic, and parasitological figures. The index is comprehensive.

But what about other books that cover this scenario? Of the American texts, Gorbach, Bartlett and Blacklow's *Infectious Diseases* (1992) covers these infections well, as does the fourth edition of 'Mandell' (1995). Of British tomes, the nearest is probably Bouchier, Allan, Hodgson, and Keighley's *Gastroenterology: Clinical Science and Practice* 2nd ed (1993). The advantage of Blaser *et al* is that it is devoted in entirety to gut infections and will inevitably become the reference book for some time to come in this specific area dominated by the gastroenterologist and infectious diseases physician.

G C COOK

Drug-Induced Liver Disease. By G C Farrell. (Pp 704; illustrated; £95). Edinburgh: Longmans Group, 1994. ISBN 0–443–04368–X.

Books exist describing untoward reactions of the liver to various drugs. The largest and most comprehensive is by H J Zimmerman (*Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*; New York: Appleton-Century Crofts, 1978) but it is sadly out of date. The book edited by B C Ch Stricker (*Drug-Induced Liver Injury*; 2nd edition; Amsterdam: Elsevier, 1992) is justifiably in wide use. However, the drugs scene, particularly in relation to hepatotoxicity, is changing rapidly and this book from Australia, edited by Geoffrey C Farrell is both comprehensive and timely.

The first part describes underlying concepts of drug metabolism and hepatic reactions to drugs. The role of the liver in drug metabolism is contributed by Michael Murray and biochemical mechanisms by G C Farrell. Immunological mediation of drug reactions is discussed by Ian R Mackay, perhaps Australia's most outstanding clinical immunologist. Pdela M Hall contributes an excellent chapter on histopathology, which includes 54 figures, many of them in colour.

Various drugs are discussed under the headings frequency, risk factors, clinical features, hepatic-histology and course, outcome, and prevention. An up to date table covering 29 pages summarises the effects of each drug alphabetically. I could not find any omissions. Even ecstasy, a currently much discussed hepatotoxin is annotated. This table, on floppy disc, is available free of charge on request by those who purchase the book.