PostScript

LETTERS

If you have a burning desire to respond to a paper published in *Gut*, why not make use of our "rapid response" option?

Log onto our website (www.gutjnl.com), find the paper that interests you, and send your response via email by clicking on the "eLetters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eLetters" on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Living related liver transplantation: a Japanese experience and development of a checklist for donors' informed consent

In the February 2002 issue of *Gut*, Broelsch *et al* argued for a controversial therapy of living related liver transplantation (*Gut* 2002; **50**:143). The Japanese experience is somewhat different from those of other countries, as indicated in the article. Japan has long been the subject of sociocultural studies because of its delay in using the organs of brain dead persons for transplantation purposes. Since the Organ Transplant Law was enacted in 1997,[1] only 16 liver transplant operations using brain dead donors have taken place. In contrast, more than 700 cases of liver transplants (with both children and adults as recipients) using living donors have been performed at Kyoto University Hospital, and more than 1000 such transplants have taken place in Japan.[2]

The development of this medical procedure at our institute has entailed a strict self regulative process.

(1) Each case is reviewed by an institutional professional committee that examines the medical indication. The transplant team prioritises the safety of donors, and no donor deaths have been reported so far.

(2) Informed consent obtained by transplant teams is reassessed by the institutional ethics committee to check for the absence of coercion and guarantee the right to refuse surgery until the last moment. The ethics committee has developed a checklist (table 1) and basically all donors are interviewed by a member of the ethics committee before surgery. Donor candidates are restricted to a spouse or relatives within the third degree of blood relationship.

(3) Information disclosure to media. In order to facilitate social acceptance of the procedure, relevant information continues to be disclosed to the press.

While these institutional efforts are essential, we suppose there are more substantial reasons for the striking increase in this type of surgery. One obvious explanation is the hesitation in Japan to accept the concept of brain dead organ donors, but another may be the strong family bonds that are fundamental to Japanese culture. Traditionally raised in a family oriented society, Japanese people may not hesitate to give their organs to save a family member even if there is a small but perhaps fatal risk associated with the practice. This hypothesis needs further corroboration; however, on the other hand, many would assert that love for family is a universal value.

Hence we are faced with two academic questions: firstly, whether or not liver transplants using living donors will prevail *to a similar extent* in other countries where organ procurement from the brain dead is socially prohibited there; and secondly, whether or not this procedure can provide a solution to the lack of available organs in countries where organ procurement from the brain dead is permitted.

Japanese transplant surgeons are now going abroad to teach the living related liver transplant technique while patients and their family from countries where transplants from the brain dead are not permitted come to Japan to undergo living donor surgery. The situation described here clearly shows that while the world surgical community freely shares advancements in techniques, regional and sociocultural values greatly influence their implementation.

Table 1 Checklist for interviews with donors for living related liver transplantation

(1) General profile of the recipient and the donor
  (a) A brief medical history of the recipient
  (b) Family tree
(2) Informed consent
  (a) When and how did you come to know about living related donor liver transplant?
  (b) Who explained the details of the transplant surgery, and how many times?
  (c) Under what circumstances (one to one, or with others present)?
  (d) Do you clearly understand the procedure of the surgery?
  (e) Do you fully understand the risks and benefits of the treatment (including short term and long term risks for the donor, and the success rate of graft attachment for the recipient)?
  (f) Have you been given information and explanations about alternative therapies?
  (g) Have you been given enough time to ask questions? Have you been invited to ask questions?
(3) Decision making process
  (a) Have you consulted with anyone?
  (b) Was there any coercion by other family members or relatives? (For example, if you do not agree to be a donor, the patient will surely die.)
  (c) Is your decision completely voluntary?
(4) Psychosocial aspects
  (a) Do you have any anxiety about your surgery?
  (b) Do you have any problems in your life (for example, business or social relationships)?
  (c) Do you have any financial problems?
(5) Protection of the donor's right
  (a) You have the right to refuse or withdraw your consent until the last moment.
  (b) You will not suffer any disadvantage if you decide to refuse or withdrawal.

Interviewer's assessment
  (1) The donor is well informed. □Yes □No
  (2) The donor has a good understandings of the entire process. □Yes □No
  (3) The donor is fully capable of making a decision. □Yes □No
  (4) The donor's decision is completely voluntary and firm. □Yes □No
  (5) The decision has been reached without any evidence of coercion. □Yes □No
  (6) The donor's right has been fully protected. □Yes □No
  (7) The donor is without significant psychosocial problems. □Yes □No

Time of interview min

Interviewer's signature (a member of ethics committee)

Date

A Akabayashi, M Nishimori, M Fujita, B T Slingsby

Department of Biomedical Ethics, School of Public Health, University of Kyoto Graduate School of Medicine, Kyoto, Japan

Correspondence to: Dr A Akabayashi, Department of Biomedical Ethics, School of Public Health, University of Kyoto Graduate School of Medicine, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; akirasan@pbh.med.kyoto-u.ac.jp

References

1 **Akabayashi A**. Japan's parliament passes brain-death law. *Lancet* 1997;**349**:1895.
2 **Todo S**, Furukawa H, Jin MB, *et al*. Living donor living transplantation in adults: outcome in Japan. *Liver Transpl* 2000;**6**(suppl 2):S66–72.

Endoscopic surveillance of premalignant gastric lesions

We read with interest the study by Whiting and colleagues (*Gut* 2002:**50**:378–81). The study has further highlighted the importance of early detection of gastric cancer and also given further emphasis on ways to prevent the multistep progression in gastric carcinogenesis. However, we would like to make the following comments.

Firstly, one in five patients in this group had lesions which, according to Whiting *et al*, should be followed up by yearly endoscopies. Despite the low acceptance rate in screening

programmes as noted by the authors, this would create an enormous workload on already over burdene endoscopic units. Clearly, further modes of selection of high risk patients with atrophy and metaplasia is desirable. Mutations in *p*53, *APC*, and mismatch repair genes have been reported in intestinal metaplasia. Some of these mutations are associated with an enhanced progression to advanced lesions in the multistep sequence of gastric carcinogenesis.[1] High throughput methods for the detection of gene polymorphisms associated with increased cancer risk, such as interleukin 1 polymorphisms, are likely to be available in the near future .[2] In addition, alteration in gastric secretion of pepsinogen may be used as an aid in early detection of premalignant lesions.

Secondly, the authors have not provided us with data regarding the *Helicobacter pylori* status of the patients. Their results may have been different if successful eradication of *H pylori* was achieved in the follow up group, a situation more relevant to current practice. It is now universally accepted that *H pylori* infection is the most important factor in gastric carcinogenesis with both host and bacterial virulence factors playing a role.[3]

The European *Helicobacter pylori* Study Group strongly recommended *H pylori* eradication for patients with atrophic gastritis, after gastric cancer resection, and first degree relatives of patients with gastric cancer (presented at the Maastricht 2–2000 conference[4]). There are emerging data that intestinal metaplasia may be replaced by normal gastric mucosa following *H pylori* eradication.[5]

In summary, we feel that less invasive and more cost effective modes for detection and follow up of premalignant gastric lesions are required and hopefully are on the horizon. In the meantime, it appears that a screen and treat strategy for *H pylori* constitutes one of the most important interventions in the prevention of gastric cancer.

S Sebastian, J Seery, C O'Morain, M Buckley
Department of Gastroenterology, Adelaide and Meath Hospital, Dublin, Ireland.

Correspondence to: Dr M Buckley Department of Gastroenterology, Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland; martin.buckley@amnch.ie

References

1 **Kobayashi K**, Okomoto T, Takayama S, *et al.* Genetic instability in intestinal metaplasia is a frequent event leading to well-differentiated early adenocarcinoma of the stomach. *Eur J Cancer* 2000;**36**:1113–9.
2 **El-Omar EM**, Carrington M,Chow WH, *et al.* IL-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000;**404**:398–402.
3 **Huang JQ**, Sridhar S, Chen Y, *et al.* Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. *Gastroenterology* 1998;**114**:1169–79.
4 **Malfertheiner P**, Megraud F, O'Morain C, *et al.* Current concepts in the management of helicobacter pylori infection- The Maastricht 2–2000 Consensus Report. *Aliment Pharmacol Ther* 2002;**16**:167–80.
5 **Ciok J**, Dzieniszowski J, Lucer C. H pylori eradication and antral intestinal metaplasia: two years follow-up study. *J Physiol Pharmacol* 1997;**48**:115–22.

Smoking and ulcer healing

We read with interest the paper by Wong *et al* (*Gut* 2002;**50**:322–5) on prediction of therapeutic failure in patients with bleeding peptic ulcer but are surprised they did not include smoking in their logistic regression analysis. The background prevalence of smoking is sufficiently high in western communities to be a useful marker if found significant. The association between smoking and ulcer healing[1] and smoking and cardiovascular and respiratory disease raises the issue of whether smoking may be a risk factor both for ulcer rebleeding and mortality. It is recognised that cardiovascular and respiratory comorbidity is a substantial contributor to peptic ulcer disease related mortality.[2] Addition of smoking may improve the predictive performance of their receiver operating curve and the value of their "model" in clinical practice.

A Duggan, N Rutherford
Department of Gastroenterology, John Hunter Hospital, NSW 2310, Australia

Correspondence to: A Duggan, John Hunter Hospital, Locked Bag 1, Hunter Region Mail Centre, NSW 2310, Australia; aduggan@hunter.health.nsw.gov.au

References

1 **Korman MG**, Hansky J, Eaves ER, *et al.* Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. *Gastroenterology* 1983;**85**:871–4.
2 **Rockall TA**, Logan RF, Devlin HB, *et al.* Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ* 1995;**311**:222–6.

Oesophageal pH monitoring in Barrett's oesophagus

We wish to comment on an interesting paper published previously in *Gut* which we inadvertently overlooked at the time. Fass *et al* (*Gut* 2001;**48**:310–13) reported that there was a positive correlation between percentage time that oesophageal pH was less than 4 in 24 hours and the length of the columnar lined segment in 15 patients with long segment Barrett's oesophagus. Some years ago, we published data concerning 24 hour ambulatory oesophageal pH monitoring in untreated patients with Barrett's oesophagus and compared the results with those obtained in patients with reflux oesophagitis but no Barrett's oesophagus.[1] pH monitoring was performed within one week of endoscopy. We found overlap in the 24 hour pH results between Barrett's patients and patients with reflux oesophagitis. However, among Barrett's patients, those with moderate to severe reflux oesophagitis above Barrett's segment had more acid reflux than those with mild reflux oesophagitis or none. At the time we did not correlate pH monitoring results with the length of the Barrett's segment but have now reviewed our pH data and have been able to correlate these results with the length of the columnar lined segment.

We studied 16 patients with long segment Barrett's oesophagus: seven males and nine females, aged 36–78 years (mean 59). Mean length of the Barrett's segment was 7 cm (range 4–16). Mean percentage time that oesophageal pH was <4 in 24 hours was 19.36%, with a very wide range (1.1–70%) but there was a correlation between length of the Barrett's segment and oesophageal acid exposure (r=0.66; confidence interval 0.2–0.8). Thus our older data support those of Fass *et al* as well as those of Sontag and colleagues[2] and Oberg and colleagues[3] in showing a correlation between oesophageal acid exposure and length of Barrett's oesophagus in long segment disease. We found a significant correlation between Barrett's length and supine reflux but unlike Fass *et al*, we were unable to show a significant correlation with upright reflux.

Many studies, including our own,[4] have shown good symptomatic response to proton pump inhibitor (PPI) therapy in patients with Barrett's oesophagus but without significant regression of Barrett's epithelium, although approximately 50% of patients develop squamous islands within the Barrett's segment. Within each study to date, the same dose of PPI has been given to each patient. However, as oesophageal pH monitoring studies show, there is wide variation in acid reflux between patients. Effective control of acid reflux into the oesophagus may be important in preventing dysplasia[5] and our study of patients treated with omeprazole for up to six years showed that none developed dysplasia during follow up.[4] Therefore, PPI dose should be that which inhibits acid reflux effectively and will vary from patient to patient. Patients may resist frequent pH monitoring to determine the effective PPI dose so we would support the views of Fass *et al* that consideration should be given to treating patients with longer segments of Barrett's oesophagus with higher doses of PPI. Moreover, Barrett's patients with associated moderate to severe reflux oesophagitis should also be treated with higher PPI doses.

C S Neumann B T Cooper
City Hospitals NHS Trust, Dudley Road, Birmingham, UK

Correspondence to: Dr BT Cooper, Dudley Road Hospital, Birmingham B18 7QH, UK; cooperbt@hotmail.com

References

1 **Neumann CS**, Cooper BT. 24 hour ambulatory oesophageal pH monitoring in uncomplicated Barrett's oesophagus. *Gut* 1994;**35**:1352–5.
2 **Sontag S**, Schnell T, Chejfec G, *et al.* Length of Barrett's epithelium corresponds directly to esophageal acid contact time in patients with reflux. *Gastroenterology* 1996;**110**:A262.
3 **Oberg S**, DeMeester TR, Peters JH, *et al.* The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. *J Thorac Cardiovasc Surg* 1999;**117**:572–80.
4 **Cooper BT**, Neumann CS, Cox MA, *et al.* Continuous treatment with omeprazole 20mg daily for up to 6 years in Barrett's oesophagus. *Aliment Pharmacol Ther* 1998;**12**:893–7.
5 **Oatu-Lascar R**, Fitzgerald RC, Triadafilopoulos G. Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression. *Gastroenterology* 1999;**117**:327–35.

Author's reply

I would like to thank Drs Neumann and Cooper for their comments on our article on the correlation of oesophageal acid exposure with Barrett's oesophagus length (*Gut* 2001;**48**:310–13). In recent years our laboratory has focused on factors that promote the development of Barrett's oesophagus. Surprisingly, our understanding of the mechanisms that are responsible for the emergence of Barrett's epithelium remains extremely poor. Despite the tendency in the literature to group

Barrett's patients as those with long and short segment Barrett's oesophagus, we believe that the specific length of Barrett's epithelium might be the key for unlocking the mystery of Barrett's evolution. Consequently, we have initiated several research projects that were designed to assess the role of acid reflux in determining the specific length of Barrett's oesophagus.

The results of the above mentioned study have been confirmed by other investigators.[1 2] Oberg *et al* have also demonstrated that the extent of Barrett's mucosa is inversely correlated with lower oesophageal sphincter pressure and length.[2] Furthermore, we recently reported that the size of hiatal hernia correlated with the length of Barrett's oesophagus (r=0.62, p=0.0012).[3] The last two studies suggest that the longer the Barrett's oesophagus the higher the likelihood of finding more severe oesophageal anatomical abnormalities that are strongly associated with increased oesophageal acid exposure.

In another study from our laboratory, Tharalson *et al* have demonstrated a significant relationship between the rate of change in acid exposure along the oesophagus and the length of Barrett's oesophagus, using a pH probe with four sensors located 5 cm apart.[4] The study investigated the rate at which recorded acid exposure values increase from the proximal to the distal oesophagus. This was the first study to demonstrate a statistically significant relationship (for the per cent total and upright time of pH testing) in which the length of Barrett's oesophagus increases as the rate of acid exposure increases.

Presently we are not clear if acid reflux is the sole determining factor for Barrett's appearance. It is likely that other factors, such as bile reflux, might have a synergistic effect. However, the role of bile reflux in determining the length of Barrett's oesophagus remains to be elucidated.

We agree with Drs Neumann and Cooper that due to the close relationship between length of Barrett's mucosa and oesophageal acid exposure, patients with longer Barrett's epithelium may require higher doses of proton pump inhibitors to normalise their oesophageal acid exposure. One should be prepared to increase the dose of proton pump inhibitors in patients with longer segments of Barrett's oesophagus if normalisation of oesophageal acid exposure is desired (not only symptom control).

R Fass

University of Arizona, GI Motility Laboratories, Southern Arizona VA Health Care System, and University of Arizona Health Sciences Center, 3601 S 6th Avenue (1-111G-1), Tucson, AZ 85723, USA; Ronnie.Fass@Med.VA.gov

References

1 **Sontag SJ**, Schnell T, Cheifec G, *et al*. Length of Barrett's epithelium corresponds directly to esophageal acid contact time in patients with reflux. *Gastroenterology* 1996;**110**:A262.
2 **Öberg S**, DeMeester TR, Peters JH, *et al*. The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. *J Thorac Cardiovasc Surg* 1999;**117**:572–80.
3 **Al-Mutawa TS**, Malagon I, Garewal HS, *et al*. Correlation between the length of Barrett's esophagus and the size of hiatal hernia. *Gastrointest Endosc* 2001;**53**:AB154 No 41455.
4 **Tharalson EF**, Martinez SD, Garewal HS, *et al*. Relationship between rate of change in acid exposure along with the esophagus and length of Barrett's epithelium. *Am J Gastroenterol* 2002;**97**:851–6.

Influence of clinical factors, drug use, and food intake on the glutathione system

In a previous issue of *Gut*, Hoensch and colleagues (*Gut* 2002;**50**:235–40) using antral and duodenal biopsies, reported on a variety of factors such as sex, age, drug use, and food intake that influence the concentration of glutathione and the activity of glutathione S-transferase. All of these factors either singly or in combination significantly affect glutathione metabolism within the gastric mucosa.

Curiously, one critical factor that may have influenced their measurements, namely *Helicobacter pylori* infection, was not mentioned in their paper. This omission is particularly important as the majority of the patients that these investigators examined had endoscopic findings strongly suggestive of infection with *H pylori* (gastric erythema, erosions, or ulcers). Previous studies by some of the coauthors in the Hoensch paper[1 2] as well as by our group[3] have clearly demonstrated that *H pylori* infection is associated with marked depletion by approximately 50% of reduced glutathione within the gastric epithelium, and that concentrations of reduced epithelial glutathione are restored to normal by eradication of *H pylori*. Failure to stratify patients for *H pylori* infection makes other conclusions in the study less compelling. Consideration of the presence of *H pylori* may explain why the antrum, the preferred site of *H pylori* colonisation, had the lowest concentration of reduced glutathione in the gastrointestinal tract.

H pylori is well known to induce formation of reactive oxygen species (ROS), particularly in the antrum,[4] and result in oxidative damage to DNA.[5] Inflammatory host cells, such as activated phagocytic leucocytes, are the primary source of this oxidative stress, although *H pylori* per se may generate ROS and result in stimulation of oxidative signalling pathways in gastric epithelial cells.[6] Recent evidence strongly suggests that levels of reduced glutathione correlate inversely with parameters of acute and chronic inflammation in vivo.[3 7] Thus attenuation of reduced glutathione in the gastric mucosa of *H pylori* infected patients may be due to both a direct effect of *H pylori* induced expression of oxidative signalling pathways and the associated inflammatory response.

Intra- and extracellular oxidative stresses induced by *H pylori* in association with depletion of glutathione and/or genetic polymorphisms of enzymes that control its metabolism may compromise normal epithelial cell function and enhance susceptibility to gastric cancers. In considering the gastric glutathione system, the effect of *H pylori* should not be ignored.

H Shirin

Tel Aviv University/Edith Wolfson Medical Center, Holon, Israel

J T Pinto

American Health Foundation, Valhalla, NY, USA

S F Moss

Brown University/Rhode Island Hospital, Providence, RI, USA

Correspondence to: S F Moss, Rhode Island Hospital, 593 Eddy St, APC 445, Providence, RI 02903, USA; Steven_Moss_MD@Brown.edu

References

1 **Verhulst ML**, van Oijen AH, Roelofs HM, *et al*. Antral glutathione concentration and glutathione-S transferase activity in patients with and without *Helicobacter pylori*. *Dig Dis Sci* 2000;**5**:629–32.
2 **Oijen AH**, Verhulst ML, Roelofs HM, *et al*. Eradication of *Helicobacter pylori* restores glutathione S-transferase activity and glutathione levels in antral mucosa. *Jpn J Cancer Res* 2001;**92**:1329–34.
3 **Shirin H**, Pinto JT, Liu LU, *et al*. *Helicobacter pylori* decreases gastric mucosal glutathione. *Cancer Letters* 2001;**64**:127–33.
4 **Davies GR**, Simmonds NJ, Stevens TR, *et al*. *Helicobacter pylori* stimulates antral mucosal reactive oxygen metabolite production in vivo. *Gut* 1994;**35**:179–85.
5 **Baik SC**, You HS, Chung MH, *et al*. Increased oxidative DNA damage in *Helicobacter pylori*-infected human gastric mucosa. *Cancer Res* 1996;**56**:1279–82.
6 **Kim H**, Lim JW, Kim KH. *Helicobacter pylori*-induced expression of interleukin-8 and cyclooxygenase-2 in AGS gastric epithelial cells: mediation by nuclear factor-kappaB. *Scand J Gastroenterol* 2001;**36**:706–16.
7 **Beil W**, Obst B, Sewing KF, *et al*. *Helicobacter pylori* reduces intracellular glutathione in gastric epithelial cells. *Dig Dis Sci* 2000;**5**:1769–73.

Authors' reply

We appreciate very much the comments made by Shirin *et al* concerning our publication (*Gut* 2002;**50**:235–40).

In our study (*Gut* 2002;**50**:235–40), we investigated a wide variety of factors which had not been evaluated entirely at the time this paper was written. In the meantime, the reported new findings of our group on *Helicobacter pylori* were discovered in another patient population from the Netherlands.[1 2]

After we received the comments of Shirin *et al*, we looked again at the data of our patients from Germany to test for *H pylori*. We found that *H pylori* had a significant effect on one of the parameters of the gastrointestinal glutathione (GSH) system. The level of glutathione S- transferase (GST) A (alpha) in the antral mucosa was significantly depressed (p<0.05) in *H pylori* infected patients (4.8 (7.3) µg/mg cytosomal protein (n=63) *v* 5.6 (6.9) (n=60)). The values given are means (SD) using the Wilcoxon test for comparison of means.

The status of *H pylori* infectivity was determined in the gastric mucosal biopsy specimens using the urease test which was read as either positive (*H pylori* present) or negative (*H pylori* absent) from the colour reaction (CLO test).

The other parameters (GSH concentration, GST enzyme activity, levels of GST P (pi) and GST T (theta)) were not affected in the antral and duodenal mucosa by *H pylori* status. The GST A level of the duodenal mucosa was also not significantly influenced by *H pylori*.

These results corroborate the findings published recently by our research group[1 2] and by Shirin and colleagues.[3] In our large group of patients from Germany, *H pylori* infection was associated with lower GST A levels in the antral mucosa. Eradication of *H pylori* was performed only in patients with ulcers and erosions but these patients were not followed up by endoscopy routinely.

H pylori was the only factor that had a significant depressing effect on antral GST A level. *H pylori* had no influence on duodenal GST A, GST P, or antral GST T1, which confirms that vegetable and fruit stimulation of these enzymes was not confounded by *H pylori*.

However, it has to be considered that *H pylori* evaluation and eradication in patients from the Netherlands were done only in non-ulcer dyspepsia while patients from Germany comprised various pathological endoscopic diagnoses apart from non-ulcer dyspepsia.

Our cross sectional study confirms that *H pylori* seems to depress the GST A component of the enzymatic GSH system in the antral mucosa of the stomach. Depression of GST A levels could mean increased susceptibility of the stomach mucosa towards carcinogenic insults.

H Hoensch, I Morgenstern

Leitender Arzt, Innere Abteilung, Gastroenterologie und Onkologie, Kreiskrankenhaus Groβ-Gerau, Wilhelm Seipp-Staβe 3, 64521 Groβ-Gerau, Deutchland

Correspondence to: H Hoensch; H.P.Hoensch@vff.uni-frankfurt.de

References

1 **Verhulst ML**, van Oijen A, Roelofs H, *et al.* Antral glutathione concentration and glutathione S-transferase activity in patients with and without Helicobacter pylori. *Dig Dis Sci* 2000;**5**:629–32.
2 **Oijen AH**, Verhulst ML, Roelofs HM, *et al.* Eradication of Helicobacter pylori restores glutathione S-transferase activity and glutathione levels in antral mucosa. *Jpn J Cancer Res* 2001;**92**:1329–34.
3 **Shirin H**, Pinto JT, Liu LU, Merzianu M, *et al.* Helicobacter pylori decreases gastric mucosal glutathione. *Cancer Letters* 2001;**164**:127–33.

Mycobacterium avium subspecies *paratuberculosis* as a cause of Crohn's disease

The debate by Professor Quirke (*Gut* 2001;**49**:757–60) was an interesting review of the hypothesis of a microbiological aetiology of Crohn's disease. He indicates that "the hypothesis remains controversial and unproved."

The point is that proof is never absolute, and indeed the objective of research is to disprove the hypothesis rather than to prove it, the latter being an impossible objective and scientifically flawed. He goes on to mention that "for the infectious disease hypothesis to be proved for any organism, Koch's postulates need to be fulfilled." This is not correct. Proof is pragmatic not absolute, and in practice it is the fulfilment of a set of predetermined objectives. Koch's postulates are but an example of this, the Euclidian principle of *quod erat demonstrandum*, and an extremely important development of scientific philosophy of the 19th century. Koch himself however recognised the weakness of his postulates in that although he felt that cholera was microbiological in causation, he was unable to apply his postulates to it.

It is important to review Koch's postulates and they are as follows:

(1) "The specific organism should be shown to be present in all cases of animals suffering from a specific disease but should not be found in healthy animals"

This postulate demands a high level of sensitivity of laboratory methods and the clinicopathological identification of a *specific* disease—can Crohn's disease be classified as such? At the time of Koch the important concept of a commensal microbe was not developed.

(2) "The specific microorganism should be isolated from the diseased animal and grown in pure culture on artificial laboratory media"

This demands laboratory methods which have not always been achieved at the present time.

(3) "This freshly isolated microorganism, when inoculated into a healthy laboratory animal, should cause the same disease seen in the original animal"

Animal models are not always available for postulated microbial disease and it is recognised that transgenic transmission might cause a different disease.

(4) "The microorganism should be re-isolated in pure culture from the experimental infection"

Once again, laboratory cultures are not always possible at present.

Koch was a great scientist and he recognised so well that there was more to microbiological explanation for disease than his postulates, which have a very high level of specificity but a very low level of sensitivity. I am afraid that microbiological science must look beyond Koch's postulates for its "proofs" and we must rethink the concepts of proof for the newly recognised microbiological diseases in the present century.

In that there is no such thing as absolute proof, science works in paradigms. These are models which come to be accepted as the best explanation of the phenomena that we see around us. However, there is no real paradigm for Crohn's disease. I remember farfetched "psychosomatic" concepts in the 1960s, to be replaced by food allergy during the latter part of the 20th century. But these paradigms have fallen into disfavour, being replaced by a lack of any clear idea of the type of disease that we are dealing with in respect of Crohn's disease. Genetic factors are probably an influence only on susceptibility but not causation.

But in the treatment of patients clinical doctors require a paradigm on which to base explanations and understanding, treatment, and research. The nearest we have to a paradigm of causation of Crohn's disease is that it is "inflammatory", and so conforming to the allopathic principle of *contraria contrariis curantur* we give anti-inflammatory medications. The clinical manifestations of the disease are a direct result of the inflammatory process but is this a protective mechanism in itself? The assumption that it is only damaging led to the paradigm of "autoimmunity", a concept which itself lacks "proof", and indeed the criteria of proof in putative autoimmune disease have never been defined.

A paradigm of a microbiological causation of Crohn's disease must be based on two factors. The first of these is the statistical association between the disease and a putative microbe but the difficulty of this is the lack of robust detection methods for identification. The second is plausibility. It is interesting to reflect that for many years acute hepatitis was accepted as being a viral disease and indeed became known as "viral hepatitis", well before the viruses had been identified. The plausibility was clear even though microbiological science had not progressed so far to identify the viruses themselves. In respect of Crohn's disease, we need to continue to think as to whether it is plausible that the disease might be microbiological, even in the absence of a definite microbe. The development of the paradigm and identification of a specific microbe are different scientific processes.

Plausibility is founded on existing knowledge and models, based mainly on epidemiology and pathology, the main foundations of Western clinical medicine. What therefore do we think of the pathology of Crohn's disease? Firstly, it is clear that Crohn's disease is not a homogenous pattern of disease but a variety of different patterns of inflammatory disease of the intestinal tract. The hallmark of Crohn's disease is firstly a patchy inflammation of the gastrointestinal tract, including perioral and perianal areas of skin. Granulomas are another hallmark and fissuring a third. We can go on in this way but the more criteria that we add, the more it would appear that the disease is a heterogynous group. In other words we cannot define Crohn's disease, we do not really know what it is, and so a concept of causation is going to be based on a very fragile foundation.

However, we can make progress, especially if we look at the "classical" type of Crohn's disease involving the right side of the colon, the caecum, and the terminal ileum, with fissuring and granulomatous disease. This type of disease looks very much like tuberculosis, so much so that if it presents in an Asian patient the disease is usually called tuberculosis whereas if it presents in a non-Asian patient it is usually called Crohn's disease. If the similarities to tuberculosis are so powerful, then clearly causation is likely to be very similar. A further important feature is the epidemiological observation of family clustering across genetic boundaries, the husband/wife associations which point very much towards a transmissible agent. Finally, there are the parallels with Johne's disease in animals which continue to be suggestive of Crohn's disease being an equivalent in the human. In terms of response to antimicrobial compounds, do we feel that some studies suggesting benefit are more, less, or equally important to those that suggest no benefit? It depends on the attractiveness of the microbiological paradigm to the individual—some people are anxious to find a cause for Crohn's disease whereas others see no practical advantage of this and are happy to remain without a paradigm other than "inflammatory bowel disease". Response to one or more given antibiotics cannot be laid down as a criterion of proof of microbiological causation but could help strengthen a paradigm.

What we need to do in respect of Crohn's disease is consider which is the most plausible hypothesis and then continue to test it, in this case with microbiological scientific efforts, the importance of which Professor Quirke emphasises. As with every other paradigm in science, it must be under continual review and we must always be prepared to reconsider our perceptions of causation. Although we can always be wrong, and indeed we often are, to be totally sceptical denies the opportunities for scientific progress. Research must be based on hypothesis and paradigm.

D S Grimes

Blackburn Royal Infirmary, Blackburn, Lancs BB1 3LR, UK; susan.rogers@mail.bhrv.nwest.nhs.uk

BOOK REVIEWS

Modern Management of Cancer of the Rectum

Edited by R A Audisio, J G Geraghty, W E Longo. Berlin: Springer-Verlag, 2001, B/W, pp 234. ISBN 1-85233-287-5.

This is a remarkable little book. A brief review of contributors will whet the appetite: a quick read of the first chapter by Drs Shelton and Goldberg will soon confirm your decision to buy. This initial chapter is an engaging review of the key writings of the leaders of surgical thought over the centuries and provides a rare insight into how we have arrived where we are today. The book continues with the rich but often all too brief reviews of the many components of the colorectal cancer scene. This is the most important of all of the human cancers as we already know enough to cure more people of bowel cancer than all of the other internal cancers put together. Nevertheless, even those involved in the disease have areas where knowledge may be incomplete: this book will provide a brief summary of what the surgeon must know about P53 or the medical oncologist about TME. The obvious and the necessary are mercifully omitted while the uncommon is usually well covered. Rare tumours, for example, are splendidly complete and the book provides valuable detail and formidable lists of references.

For any book the scene is moving too rapidly to be completely up to date. Details of the potential of magnetic resonance imaging (MRI) for example and the currently confused state of knowledge about who should have which type of radiotherapy. Nevertheless, even in these difficult areas, the writers have a constant sense of direction which will seldom be felt, even by an expert, to be off target. Seen through the eyes of a somewhat reactionary reviewer, the importance of laparoscopic surgery in the management of colorectal cancer seems a little overplayed. The "may be" of this still emerging modality seems to be pointing a way that not all doctors will agree with. We have after all still to hear even the most ardent supporters of laparoscopic surgery claim that they can cure more people, perform less colostomies, or save more nerves. In most hospitals around the world open surgery remains both the norm and the probable future for rectal cancer at least. It could have been given more space in the book.

The histopathology chapter is exceptionally good and has much practical content. An area that will not commend itself to most European readers in the multimodality postoperative chemo radio therapeutic onslaught that characterises modern American thought and is unequivocally recommended in this book. I would have liked to have read some questioning of the enormous amounts of money expended on chemotherapy and radiotherapy given postoperatively. Many serious oncologists, well aware of the strength of the argument for chemotherapy after colon cancer resections, nevertheless seriously doubt its value for rectal cancer. Minsky *et al* in an otherwise superb review of chemotherapy dismiss on grounds which I consider spurious the argument that better surgery may make some patients better managed without chemotherapy. I would personally prefer to read about honest controversy and to see current American dogma questioned rather than reinforced.

These few criticisms are offered as a surgeon's affectionate commentary on an essentially splendid little book with something worthwhile for all serious doctors in the field of rectal cancer.

R J Heald

Management of Chronic Viral Hepatitis

Edited by S C Gordon. New York: Marcel Dekker, 2002, B/W, pp 380. ISBN 08247-0582-3

Management of Chronic Viral Hepatitis is an A5 sized multiauthor textbook of over 300 pages which forms one of eight books in a gastroenterology and hepatology series. Curiously, the only other hepatological title in this series is a book entitled *Viral Hepatitis: Diagnosis, Treatment, Prevention* by a different editor. The stated intention of the book is to bring the recent advances in clinical and basic research into the doctor's office. Through the use of clinical vignettes, it tries to cover some of the recent advances in the treatment of viral hepatitis and to demonstrate how these treatments are incorporated into everyday practice. This is a good idea, which works well, particularly in those chapters concerning treatment. In addition to looking at the general treatment of viral hepatitis, the book also has informative chapters on specific disease subsets such as those with chronic hepatitis C and normal alanine aminotransferase levels or those with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection. The authors include an interesting sounding chapter on alternative therapies for hepatitis C but this focuses primarily on conventional allopathic treatments that have been shown to be of little or no benefit for hepatitis C and disappointingly only touches on the frequently used alternatives such as herbal products and glycyrrhizin.

There are several chapters on hepatitis B virus (HBV) covering treatment, future treatments, management of post-transplant hepatitis B, and HIV-HBV coinfection. The chapter on the treatment of HBV covers the debate on interferon versus lamivudine or interferon and lamivudine combination therapy fairly well, but in all of these chapters there is surprisingly little reference to the management of the widespread pre-core mutant strain.

Additional chapters cover diagnostic techniques and some molecular virology. The chapter on HBV virology and the review of various molecular mechanisms that can be used as targets for antiviral treatment included in the chapter on future HCV therapy were particularly well written. The pace of change in viral hepatitis is fast, and as ever with multiauthor texts, delays are inevitable between writing and publishing. There are several indicators that the publishers have tried to keep this delay to a minimum, such as the figures that have clearly been lifted straight out of someone's powerpoint slide presentation, the references that are left in a reference manager format, and a few minor inaccuracies in the text. Despite these measures to speed publication, there have been predictable advances in treatment that are not well covered, such as the rapidly accumulating data on the efficacy of pegylated interferon alpha in combination with ribavirin in the treatment of hepatitis C.

Despite these criticisms, there are a number of very good chapters and the book provides a good overview and a fairly up to date understanding of hepatitis and its management. The target audience is hard to define but anyone involved in looking after patients with viral hepatitis will find something of use. For those new to viral hepatitis this is a helpful textbook that shows how an understanding of both the natural history and treatment options should be used to guide management decisions.

M Cramp

Abdominal Ultrasound

M Stocksley. Greenwich Medical Media, 2001, £35.00, B/W, pp 286. ISBN 1-90015-166-9

Mike Stocksley moved from a career in clinical ultrasound to teaching and is now senior lecturer in the Faculty of Health at South Bank University. His background as an educator is readily apparent in this excellent book which for him was clearly a labour of love.

Despite the increasing complexity of investigations available, ultrasound remains an important tool in the investigation of abdominal pathology. Its ready availability and resulting popularity do not however imply that it is a straightforward or simple skill. It is probably the most operator dependent imaging modality, and mastery of the underlying concepts, proper performance of a scan, awareness of normal appearances, detection of relevant findings, and their correlation into a unifying diagnosis requires not only appropriate training but also extensive hands-on experience. These factors are often under appreciated by physicians, and if there is one thing guaranteed to aggravate the busy radiologist, it is a request for a "quick ultrasound" or for one to "just have a look".

Mr Stocksley clearly appreciates the complexities of the topic and has produced a book which, while quite short and inexpensive, manages to be both practical and informative. The opening chapter covers the basics including choice of probe, use of coupling gel, patient preparation, and scanning positions. There follows a straightforward explanation of the principles and applications of Doppler ultrasound; reading this chapter caused the reviewer to heartily wish that Mr Stocksley had been in close proximity while he was studying for his part 1 FRCR physics! Having dealt with the basics, the book proceeds with the nitty gritty of practical abdominal ultrasound and there are excellent chapters on the "usual suspects": the liver, biliary tree, pancreas, spleen, and urinary tract, as well as

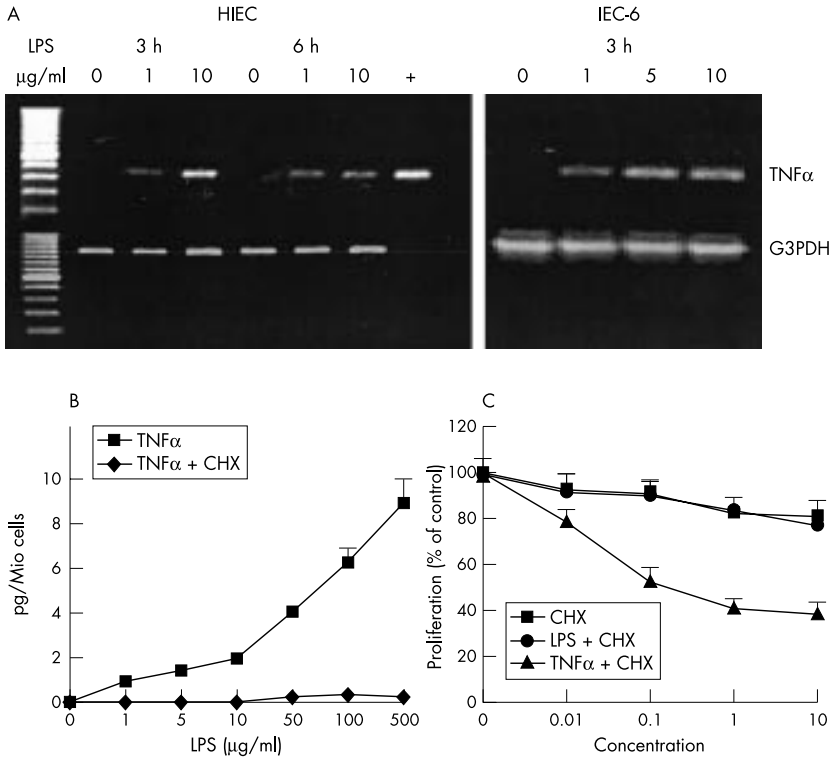
more esoteric subjects such as the adrenal glands, muscle, and bowel. Each chapter is laid out similarly, with an initial description of functions and anatomy of the organ followed by the optimal scanning technique and normal ultrasound appearances before a discussion of pathology. The book is lavishly illustrated with over 250 illustrations, including line drawings, photographs to demonstrate scanning positions, and ultrasound images, with a nice balance between normal and pathological appearances. Advice boxes scattered throughout the text give useful tips on pitfalls to avoid, measures to improve scanning technique, and the relevance of findings.

Quibbles with this book are relatively minor. I would have welcomed a chapter on endoscopic ultrasound including endoanal; this area is underrepresented in the text. Also, one feels the clinical advice is in places oversimplistic: for example, in a table on abdominal pain, stating that "pain in both left sides and right=cancer" is of limited value. The impression that this book is predominantly aimed at ultrasonographers in training is reinforced by emphasis on such topics as planning an ultrasound room and report wording. However, these caveats aside, this is an excellent book which would be a useful purchase for any gastroenterologist wishing to expand their knowledge in this complex and ever changing field.

N Power

CORRECTION

Due to an error in the production process, parts B and C of figure 2 in the paper by Ruemmele *et al* in the December issue of the journal (*Gut* 2002;**51**:842–8) were printed incorrectly. The figure is reprinted here.



NOTICES

Sir Francis Avery Jones BSG Research Award 2003

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2003 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2002 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in March 2003. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2002.

Broad Medical Research Program—Inflammatory Bowel Disease Grants

Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US$100,000 per year are available for basic or clinical projects. Larger erquests may be considered. Initial letter of interest (no submission deadline), simple application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www-.broadmedical.org

The national register of hepatitis C infections with a known date of acquisition.

The register steering group invite clinical and epidemiological researchers to submit proposals to accessdata held in the register. It is envisaged that a variety of studies might benefit from linkage with or access to the register, and proposals from all specialties and institutions are welcomed. Any researchers interested in applying for access to information held within the national register should contact the register co-ordinator (see below) for a list of available data and an application form. Study proposals should then be submitted to the register co-ordinator by **16 December 2002**.

Further information: Dr Helen Harris (Register Co-ordinator) or Ms Lisa Beck (Research Assistant), Immunisation Division, Communicable Diseases Surveillance Centre, Public Health Laboratory Service, 61 Colindale Avenue, London NW9 6EQ. Tel: +44 (0)20 8200 6868 ext 4496; fax: +44 (0)20 8200 7868; email: hharris@phls.nhs.uk or lbeck@phls.nhs.uk

17th International Workshop on Therapeutic Endoscopy

This will be held on 3–5 December 2002 in Hong Kong. Further information: Professor SC Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong. Tel: +852 2632 2233; fax: +852 2635 0075; email: info@hksde.org

Advances in the Inflammatory Bowel Diseases

This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imedex.com; website: www.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy

This course will take place on 16–17 December 2002 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis Rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58.

The Future of Gastro-entero-hepato-pancreatology is bright

This Academic Farewell Symposium of Guido NJ Tytgat will be held on 12 December 2002 in Amsterdam, the Netherlands. Deadline for registration is 1 November 2002 (no registration fee) and registration should be done via email to: j.goedkop@amc.uva.nl.

Cancer of Oesophagus and Gastric Cardia: from Gene to Cure

This conference will be held on 13–15 December 2002 in Amsterdam, The Netherlands. Further information: European Cancer Centre, PO Box 9236, NL 1006 AE Amsterdam, The Netherlands. Tel: +31 (0)20 346 2547; fax: +31 (0)20 346 2525; email: ecc@ikca.nl

Imaging of the Abdomen: an Update

This will be held on 23–24 January 2003 in Amsterdam, the Netherlands. Further information: visit the website www.epgs.nl or email epgs@amc.uva.nl. Tel: +31 20566 3926/4386.

The Sheila Sherlock Memorial Symposium

Dame Sheila Sherlock, who died earlier this year, was responsible for creating hepatology at the Royal Free Hospital, London. This memorial symposium will take place on 26–28 January 2003 at the Royal Free Hospital, London, UK. Further information: Terri Dolan, Royal Free and University College Medical School, Royal Free Campus, Centre for Hepatology, Upper 3rd Floor, Rowland Hill Street, London NW3 3PF, UK. Tel: +44 (0)207 433 2851; email: t.dolan@rfc.ucl.ac.uk

3rd Chester International Inflammatory Bowel Disease Meeting

This meeting will be held on 10–11 February 2003 in Chester, UK. An international programme includes speakers from the USA, France, Italy, and the UK, and will cover clinical problems, pathogenesis, medical and surgical treatment. Registration details and programme from: Professor Jonathan Rhodes, Department of Medicine, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK. Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesjm@liverpool.ac.uk

Surgery of the Foregut

This meeting will be held on 17–18 February 2003 in Florida, USA. Further information: Cleveland Clinic Florida, Office of CME, 2950 Cleveland Clinic Boulevard, Weston, FL 3331, USA. Tel: +1 954 659 5490; (toll free: +1 866 293 7866); fax: +1 954 659 5491; email: cme@ccf.org

38th EASL Annual Meeting

The European Association for the Study of the Liver will be holding its 38th annual meeting on 29 March–1 April 2003 in Istanbul, Turkey. Further information can be found on the website www.easl.ch/easl2003.

International Symposium on Viral Hepatitis and Liver Disease

This conference will take place on 6–10 April 2003 in Sydney, Australia. Further information: ISVHLD 2003 Congress Managers, GPO Box 128, Sydney NSW 2001, Australia. Tel: +612 9262 2277; fax: +612 9262 3135; email: isvhld@tourhosts.com.au; website: www.tourhosts.com.au/isvhld