# LETTERS TO THE EDITOR

## Gastric cancer cell lines lack Fas ligand (FasL) expression but kill T cells via a FasL independent pathway

EDITOR,—Bennett *et al* (*Gut* 1999;**44**:156–162) reported that in each of 30 paraffin wax specimens of human gastric adenocarcinomas, FasL mRNA and protein co-localised to neoplastic epithelial cells. TUNEL staining revealed that a high number of tumour infiltrating lymphocytes (TIL) displayed apoptotic features. From these results and from their findings of FasL expression in human colon[1] and oesophageal cancer,[2] the authors propose that FasL might be a mediator of immune privilege in gastrointestinal cancers.

We studied intrinsic FasL expression in gastric cancer cell lines derived from primary (RF-1, SNU-1) or from metastatic sites (SNU-16, Kato-III , N-87, RF-48). We did not detect FasL mRNA or protein in any of the six cell lines analysed by RT-PCR and by flow cytometry (table 1).[3 4] We then performed the JAM assay to rule out the presence of a functional FasL expression below the detection limit of our assays.[5] Although we found that gastric cancer cells were able to induce DNA fragmentation in the Fas sensitive T-acute lymphocytic leukaemia cell line CEM-C7H2 (fig 1A), blocking FasL on the effector cell site did not reduce the extent of cytotoxicity. This result was confirmed by replacing the target cell line by a subclone stably expressing the viral cowpox protein crmA, which inhibits activation of caspases 1 and 8 and thereby mediates resistance to Fas triggering (fig 1B).[6]

Owing to the discrepancy between our results (all cell lines were FasL negative) and those of Bennett *et al* (all 30 primary neoplasias were FasL positive), we wondered whether tissue derived factors such as tumour necrosis factor (TNF) α and interferon (IFN) γ might upregulate FasL in vivo, thus explaining the differences observed. In our setting, neither of the cytokines was able to modify FasL expression on gastric cancer cell lines (table 1). In addition, killing of T cell lines was not mediated via secretion of TNF-α as blocking the cytokine using a monoclonal antibody did not influence the result of the JAM assay (fig 1A). How can the

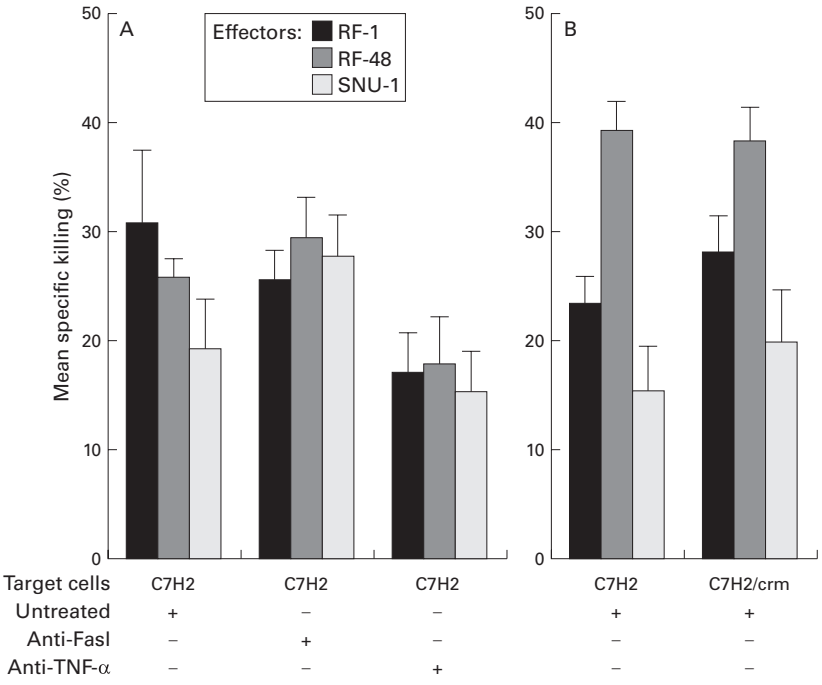


*Figure 1 CEM-C7H2 T-acute lymphocytic leukaemia cells are killed by gastric carcinoma cell lines via a FasL independent pathway. (A) CEM-C7H2 target cells were incubated with 10 μCi/ml [³H]-thymidine for 16 hours and cocultivated with the gastric cancer cell lines at a target:effector ratio of 1:10. Cocultivation of cells was performed for 72 hours at 37°C. The reduction in radioactivity was used to calculate the percentages of gastric cell mediated target cell killing. The bars represent mean (SEM) specific killing (n=8). Statistical analysis of the blocking experiments showed the following: untreated v anti-FasL monoclonal antibody treated effectors (RF-1, p=0.5; RF-48, p=0.5; SNU-1, p=0.2); untreated v anti-tumour necrosis factor (TNF) α treated effectors (RF-1, p>0.07; RF-48, p>0.15; SNU-1, p>0.5). (B) CrmA expressing CEM-C7H2 (C7H2/crm) cells were used as target cells. Experimental conditions were as for (A). Statistical analysis did not reveal any significant reduction in mean specific killing of the crmA expressing C7H2 cells by the gastric cancer cell lines (RF-1, p>0.3; RF-48, p>0.8; SNU-1, p>0.5).*

*Table 1 Expression of FasL and Fas in gastric cancer cell lines and their sensitivity toward Fas triggering by the CH11 monoclonal antibody*

| | | *Expression of FasL protein*[2] | | | | *Responsiveness toward Fas triggering*[5] | |
|---|---|---|---|---|---|---|---|
| *Cell line* | *FasL mRNA*[1] | *Constitutive NOK-1/H11* | *+TNF-α (100 ng/ml)*[3] | *+IFN-γ (100ng/ml)*[3] | *Fas expression*[4] | *Control (%)* | *CH11 (%)* |
| RF-1 | Negative | 1.1/1.0 | 1.0 | 0.8 | 8.3 | 1 | 6 |
| RF-48 | Negative | 1.3/1.0 | 0.9 | 0.9 | 6.1 | 3 | 10 |
| Kato-III | Negative | 0.9/1.2 | Not done | Not done | 1.4 | 7 | 9 |
| SNU-1 | Negative | 1.1/1.0 | 0.9 | 0.9 | 4.9 | 8 | 16 |
| SNU-16 | Negative | 1.0/1.2 | Not done | Not done | 1.1 | 21 | 21 |
| N-87 | Not done | 1.0/1.2 | Not done | Not done | 2.2 | Not done | |

[1]RT-PCR analysis was done as follows: total RNA from about $1 \times 10^6$ cells was extracted by the acid guanidinium thiocyanate-phenol-chloroform protocol described by Chomczynski and Sacchi[3]; 1 μg RNA together with 250 ng of oligo $(dT)_{15}$, primer was diluted in a.d. to a final volume of 14 μl, denatured by heating up to 70°C for five minutes and immediately chilled on ice. To each reaction, 6 μl RT mixture containing 4 μl 5× buffer, 2 pmol each of dATP, dCTP, dGTP and dTTP, and 200 units Moloney-murine leukaemia virus reverse transcriptase, was added (all reagents from Promega, Wisconsin, USA). For cDNA synthesis all samples were incubated at 37°C for 60 minutes. The reaction was stopped by heating the sample to 80°C for two minutes; 100 ng cDNA obtained was amplified by 50 cycles with 1 unit Taq polymerase (Promega). The reaction conditions were: denaturation, 60 seconds at 95°C; annealing, 60 seconds each at 63°C (cycle 1-3), 59°C (cycle 4-6), and 56°C (cycle 7-50); and extension, 45 seconds at 72°C. The oligonucleotide primers used were: TTC TTC CCT GTC CAA CCT CTG TGC (sense) and TCA TCT TCC CCT CCA TCA TCA CCA (antisense).[4] PBMC of a healthy individual served as a positive control.

[2]Constitutive expression of FasL protein was determined using two different monoclonal antibodies, NOK- 1 (Pharmingen, San Diego, California, USA) and Hl1 (Alexis, Läufelfingen, Switzerland). For detection of FasL expression, $0.5 \times 10^6$ cells were fixed with paraformaldehyde, permeabilised with a buffer containing 0.05% saponin and 1% bovine serum albumin and stained with 1 μg of the respective specific monoclonal antibody or a relevant isotype matched negative control antibody for 30 minutes at 4°C. In the case of staining with NOK- 1, cells were incubated for 20 minutes at 4°C with a secondary fluorescein isothiocyanate (FITC) labelled rabbit anti-mouse antibody (Dako, Vienna, Austria; dilution 1 in 10). Cells were washed and immediately analysed by flow cytometry for their specific fluorescence signals. Mean specific fluorescence intensities (MFI) were calculated as the ratio of mean fluorescence intensity achieved with the specific antibody/isotype matched control antibody. A ratio ⩾ 1.5 was considered positive. The mean value of MFI for three independent experiments is given.

[3]Time kinetics (l-3 days' stimulation) were performed and values are given for day 3. Tumour necrosis factor (TNF) α and interferon (IFN) γ were purchased from R&D Systems (Minneapolis, Minnesota, USA). Flow cytometric analysis was performed using the NOK- 1 monoclonal antibody.

[4]For detection of Fas expression $0.5 \times 10^6$ cells were stained with 1 μg of a specific FITC labelled anti-Fas monoclonal antibody (UB2, Immunotech, Marseille, France) or an isotype matched control. The mean value of MFI for three independent experiments is given.

[5]Cells were incubated with the CH11 monoclonal antibody (250 ng/ml) for 24 hours and the proportion of apoptotic cells was determined using the propidium iodide assay.[4] Even after 72 hours' incubation, there was only a very small increase in the percentages of apoptotic cells (e.g. in the SNU-1 cell line the increase was from 3% (control) to 5% (CH11)).

differences between in situ and in vitro results be explained?

Bennett *et al* mention that CD45+ TIL express FasL mRNA, but they did not analyse Fas expression and sensitivity, features that together characterise activation induced cell death. Although on morphological examination of slides the authors excluded the possibility of lymphocytes being killed by infiltrating neutrophils potentially attracted by the expression of FasL on the tumour cells,[7] it is possible that lymphocytes succumbed to apoptosis owing to either fratricide or suicide. This mechanism could well be under the (cytokine) control of the tumour as has been discussed for other diseases.[8] Alternatively, lymphocytes could indeed be killed by the tumour cells but by a mechanism independent of the Fas system, a hypothesis supported by our data (fig 1).

Bennett *et al* did not use the standard Lauren classification system.[9] It has been shown that gastric carcinoma cells of the intestinal and diffuse type (according to Lauren[9]) differ in morphology, growth pattern and risk factors, and also in their expression of molecules involved in apoptosis such as Fas or p53.[10] There is evidence that at least in some tumour models Fas and FasL expression are under transcriptional control of p53.[11] Loss-of-function mutations or deletions of p53 have been reported to be involved in gastric carcinogenesis[11] and the frequency of these events differs between intestinal and diffuse gastric cancers.[12] Also, a correlation between p53 mutation, Fas expression and gastric carcinoma cell differentiation has been demonstrated.[10] Further studies of the impact of differentiation and p53 functional status on FasL expression are therefore mandatory in gastric carcinoma cells.

Insensitivity towards Fas is usually an early step in tumour development, allowing tumour cells to resist the attack of the immune system and to avoid suicide when FasL expression is acquired.[13] Furthermore, a sequence of Fas resistance and FasL expression has been demonstrated for hepatocellular carcinogenesis.[14] Secondary loss of the FasL gene or of its expression during continuous culture of gastric adenocarcinoma cells is unlikely for the following reasons: (I) the cell lines were resistant to Fas and thus loss of FasL expression does not seem to be a prerequisite for their survival, and (ii) to our knowledge, no data are available from other cell (line) systems that tumour cell lines lose FasL expression during long term culture.

In conclusion, we think that Bennett *et al*'s data suggest that CD45+ lymphocytes die in the immediate proximity of neoplastic cells. Although their data are compatible with Fas induced TIL cell death, our functional data from cell lines suggest that other tumour mediated mechanisms of killing immunocompetent cells might also exist in gastric cancer. Further work clarifying the sequence of Fas/FasL expression and function during the transformation and metastatic processes is needed.

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## Reply

EDITOR,—We concur with the view expressed by Tinhofer *et al* that Fas ligand (FasL) mediated "counterattack" against antitumour lymphocytes is not the sole mechanism of immune evasion in gastric, or indeed any other form of cancer. Tumours evolve multiple immune evasive strategies. However, there is ample in vitro and in vivo evidence that constitutive expression of FasL enables cancers to promote apoptosis of antitumour immune effector cells.[1] For example, FasL has been significantly associated with apoptosis and loss of tumour infiltrating lymphocytes in human oesophageal cancer[2] and depletion of antitumour natural killer cells in a mouse model.

In stomach cancer, apart from our finding of FasL expression at the mRNA and protein level in vivo in all 30 gastric adenocarcinomas examined,[3] Rudi and colleagues[4] also showed FasL mRNA in all three gastric carcinoma cell lines examined—including one cell line, KATO III, in which Tinhofer *et al* failed to detect FasL mRNA. This poses serious questions regarding the sensitivity of the FasL RT-PCR performed by Tinhofer *et al*. In fact, appropriate positive controls have not been shown to verify that their negative findings are not merely owing to the insensitivity of their assays for detecting FasL mRNA and protein in adherent cells.

Successful use of the JAM assay depends on using target cells that exhibit good sensitivity to FasL mediated apoptosis. Even different cultures of cell lines that are regarded as Fas sensitive, such as Jurkat E6 cells, can vary in their Fas sensitivity for reasons which are unclear, and Fas resistant subclones are easily generated. Tinhofer *et al* need to demonstrate that their cultures of CEM-C7H2 target cells were indeed susceptible to apoptosis via Fas in order to validate their negative JAM results. Authentic FasL mediated killing of Fas sensitive target cells is normally detectable after eight hours of co-culture with FasL expressing effector cells.[5] Tinhofer *et al* performed a prolonged co-culture of 72 hours. It is more likely that the cell death detected in target cells at this late stage was from non-specific effects, such as exhaustion of nutrients or growth factors in the presence of proliferating effector cells, rather than a specific killing mechanism. Tinhofer *et al* should repeat their JAM assay for a shorter length of time with highly Fas sensitive target cells and include a proved FasL expressing effector cell line as a positive control.

Tinhofer *et al*'s findings that gastric carcinoma cell lines are relatively resistant to Fas mediated apoptosis is consistent with findings for several other types of cancer cell. Fas resistance is a prerequisite for expression of FasL. Colon adenocarcinoma cell lines, for example, are also Fas resistant, enabling most colon adenocarcinoma cell lines to coexpress Fas and FasL without undergoing Fas mediated suicide.[5 6] We agree with Tinhofer *et al* that the sequence of Fas/FasL expression and function during gastric carcinogenesis merits further investigation. Their suggestion that these molecules should also be investigated in metastases of gastric cancer is also pertinent as recent evidence suggests that FasL contributes to the invasion of Fas sensitive organs, such as the liver, by colonic adenocarcinoma cells.[7 8]

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## Vector manometry and LOS dynamics

EDITOR,—We read with interest the recent paper by Kahrilas *et al* on the effect of hiatus hernia on gastro-oesophageal junction pressure (*Gut* 1999;**44**:476–482). These authors used a novel technique that combined vector manometry, fluoroscopy, and endoscopic tagging of anatomical landmarks to map the differences in pressure profile between patients with and without hiatus hernia. Analysis of the vector profiles, taken at end expiration, revealed two distinct high pressure zones in each of the seven patients with hiatus hernia. These were thought to represent an axial separation of the internal and external components of the lower oesophageal sphincter (LOS). When these high pressure zones were repositioned to represent a simulated reduction of the hernia, the vector profile took on the appearance of a normal sphincter. This study drew some interesting conclusions regarding the effect of hiatal herniation on LOS pressure dynamics. We would like to raise two issues with the authors—the method of analysis used and the reproducibility of vector manometry.

With regard to the methodology of this paper, the numerical vector pressure analysis used an end expiratory gastric baseline whereas the vector profiling was referenced using an oesophageal pressure baseline. This is in contrast with previous studies which have uniformly used a gastric baseline in vector analysis and profiling.[1–3] If a gastric baseline had been applied to this study, the distal 'crural' high pressure zone (3 mm Hg) would have been less evident. These authors have thus presented a fundamental change in the methodology of vector profiling.

Our own experiences with vector manometry of the LOS have shown that this technique has poor reproducibility. We have performed rapid pull-through vector manometry (8 channel catheter, 0.5 ml/min perfusion, 0.5 cm/s pull-back speed) 10 times each on 17 volunteers. Using a gastric baseline we found a median coefficient of variance of 42% for LOS vector volume and 19% for LOS pressure with widely differing three dimensional vector profiles in individual patients (unpublished observation; fig 1).

We believe that three factors contribute to the poor reproducibility of vector manometry. Firstly, the point at which respiration is suspended is critical in defining vector volume. It is likely that the point at which respiration is suspended varies from patient to patient and from pull-through to pull-through—that is, not all patients suspend respiration at the end tidal point. Secondly, it is unlikely that the diaphragm is completely relaxed during a 15 second expiratory breath hold. It is speculated that crural activity

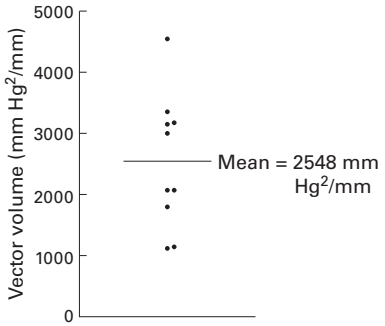


*Figure 1 Variation of lower oesophageal sphincter (LOS) vector volume from 10 pull-throughs at end tidal expiration in a single normal volunteer. Coefficient of variance=43%.*

would therefore be expected. Finally, there can be significant minute to minute variation in lower oesophageal sphincter tone.[4]

The poor reproducibility of vector manometry has been described previously by Bemelman *et al* using rapid pull-through vector manometry (8 channel catheter, 0.7 ml/s pull-back speed). They showed that mean LOS pressure varied from 20 to 80 mm Hg in 20 pull-throughs performed in one hour in the same patient.[3]

Kahrilas *et al* did not mention the number of pull-throughs for each patient or the reproducibility of vector profiling. It is therefore difficult to draw accurate conclusions on the size and position of high pressure zones, particularly when the study population is limited to seven patients.

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## Mycophenolate mofetil for Crohn's disease

EDITOR,—On the basis of a study reported recently by Neurath *et al* (*Gut* 1999;**44**:625–628), commentaries in *Gut*[1] and the *Lancet*[2] suggested that mycophenolate mofetil (MMF) should be used in patients with Crohn's disease who have either not responded to or are intolerant of azathioprine or 6-mercaptopurine. This advice is premature: firstly, because the study was flawed and, secondly, because it examined only management of acute inflammation, not the place of MMF in maintaining remission and in steroid sparing (a fact acknowledged in both commentaries).

The study by Neurath *et al* compared the effect of MMF 15 mg/kg daily with azathioprine 2.5 mg/kg daily, both with high dose steroids, in the treatment of active chronic Crohn's disease (six months' follow up). The main conclusions were that activity, as measured by the Crohn's disease activity index (CDAI), dropped further at one month in patients given MMF plus steroids than in those given azathioprine plus steroids, and that this was as a result of a faster effect in more severe disease. The major drawbacks of the study were as follows. As pointed out by the authors, neither patients nor investigators were blinded. Four (11%) of 35 patients in the MMF group were lost to follow up compared with none in the azathioprine group: thus results may have looked different if analysed on an intention to treat basis. The MMF group had higher starting CDAIs: if the levels of CDAI reached at one month were compared between groups, rather than the fall of CDAI, the groups may not have been significantly different. The division of patients into those with moderate and severe activity was retrospective: thus conclusions based on this division should be regarded as hypothesis generating only, especially as differences between the groups do not reach formal statistical significance if adjustments for multiple comparisons are made. Finally, steroid usage in the two groups is not recorded: one can imagine a scenario where a poor early response would lead to more steroids being given and so to a better overall result.

I agree with the authors and commentators that alternatives to azathioprine/6-mercaptopurine are needed. I also agree that the therapeutic effect of MMF in chronic active Crohn's disease should be assessed in properly performed trials, and perhaps more importantly that its effect in maintaining remission and in steroid sparing should be assessed. However, until then, MMF should be considered to have no clear indications for use in Crohn's disease.

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## Reply

EDITOR,—Mycophenolate mofetil (MMF) is an immunosuppressive drug that is often used in organ transplantation.[1] It is an ester prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase and potently suppresses lymphocyte proliferation.[2–4] Furthermore various clinical trials have shown its efficacy in suppressing autoimmune and chronic inflammatory disorders, such as rheumatoid arthritis,[5] pemphigus vulgaris,[6] and psoriasis.[7] There are several case reports[8 9] and also our controlled study indicating that MMF can be successfully used in patients with Crohn's disease. In our study treatment of patients with moderately active Crohn's disease with MMF/cortisone led to a significant reduction in clinical activity scores comparable with treatment with azathioprine/cortisone. These data suggested that treatment of chronic active Crohn's disease with MMF/cortisone would be effective in inducing remission. As corticosteroids were given to patients in addition to

MMF, the data available do not show unequivocally that MMF alone is effective in the maintenance of remission in Crohn's disease. This question is currently under study in a double blind, randomised controlled trial in Europe and the USA, in which the effects of MMF on maintenance of remission will be analysed.

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# BOOK REVIEWS

**Emergency Abdominal Surgery.** Edited by Jones PF, Krukowski Z, Youngson GG. (Pp 556; illustrated; £45.00) UK: Chapman & Hall, 1998. ISBN 0412819503 (HB).

The clear track record of success of *Emergency Abdominal Surgery* is proved by the publication of a third edition. The authors, who are all from Aberdeen, classify themselves as general surgeons and the book is dedicated to the general surgeons of the future. As we enter the millennium, general surgery is still vital to the management of unclassified surgical emergencies, and surgeons of all disciplines need to be trained in triage. Yet, ultimately, it is probable that few of the subjects in this book will remain the province of the general surgeon and many will be within the auspices of specialist service groups. However, although the days of the general surgeon who dealt with ruptured aneurysms may be over, but there is still a role for a surgeon to identify the physical signs and to direct the patient along the right route.

This book tackles emergencies in children as well as adults. Furthermore, the emergency presentation of vascular disease, and gynaecological and urological disorders is also discussed and the entire spectrum of general surgery as seen in the accident and emergency department of a district general hospital is comprehensively reviewed. Whether surgery in the future will follow the same pattern is open to speculation but there is currently a need for an up to date general surgical text for trainees and consultant surgeons.

The text is well illustrated and referenced, and I found the chapter devoted to the acute abdomen in pregnancy and the puerperium to be particularly valuable as this information is not readily available in other general surgical texts. The book achieves a good balance of guidance on when a generalist can tackle a problem safely and when it is best to stop; complex liver injuries are acknowledged as a problem best managed in a tertiary referral centre where all the available support facilities are operational.

I congratulate the authors of this book for bringing together a third edition of this text and they are to be applauded for using specialists in the areas that they no longer feel comfortable tackling themselves—that is, emergencies in children, urological emergencies, vascular emergencies, gynaecological disorders, and medical aspects of the acute abdomen. They are also to be praised for acknowledging in their preface that, nowadays, vascular surgery should be performed by specialists as should colorectal emergency surgery. Nevertheless, the emphasis in this book is on the clarity of decision making, by generalists where appropriate, and by specialists when indicated; it will continue to be a valuable resource for surgeons in training as well as those in practice.

M R B KEIGHLEY

**Gastroenterology. 2nd edition.** Edited by Travis SPL, Taylor RH, Misiewicz JJ. (Pp 505; illustrated; £29.25.) UK: Blackwell Science, 1998. ISBN 0632048875.

The first edition of this handbook was a valuable resource to both junior hospital staff and family doctors for its practical coverage of basic gastroenterology. In the seven years since it was first published, there have been many advances in gastroenterology and these have been included in the new edition, which is a rapid reference book which the authors hope will be of interest to doctors and health professionals in clinics, accident and emergency departments, and wards.

Covering a wide range of topics, including the various aspects of hollow organ gastroenterology, liver, biliary, and pancreatic disease, the book also contains chapters on nutrition and the gut in systemic disease, areas of interest to the more experienced reader. There are also sections on essential procedures for those involved in the preparation of patients, and a comprehensive chapter on gastroenterological emergencies which should prove invaluable in accident and emergency departments.

The breadth of coverage is impressive for such a small book although some parts lack depth. However, the authors live up to their promise to include recent advances in all areas and supply a comprehensive selection of further reading for those requiring more detailed information.

The style is dogmatic and didactic and, in conjunction with clear algorithms, presents information in the clear, concise manner essential to a rapid reference text. There are few radiological and pathological illustrations but they are of good quality and are accompanied by line diagrams to aid their interpretation.

The book aims to be a rapid and comprehensive reference tool for a wide audience of health professionals. This new edition easily achieves this and will undoubtedly continue to be useful in surgeries and wards for those who work in gastroenterology but have limited practical experience of the specialty.

R A HARRY

**Rome II: the Functional Gastrointestinal Disorders. Diagnosis, Pathophysiology and Treatment: a Multinational Consensus**. 2nd edn. Edited by Drossman DA, Corazziari E, Talley J, *et al.* (Pp 800; illustrated; $79.95) USA: Degnon Associates, 2000. ISBN 0965683729 (PB).

While medical students can confidently hold forth on the mechanisms of the Zollinger-Ellison syndrome, a condition affecting one in a million of the population, they rarely have much to say about functional GI disorders (FGIDs), which can affect up to a quarter of the population at some stage in their life. Part of the reason is that this is a complex area, which requires the integration of pathophysiology with psychology, and even sociology. FGIDs also suffer from having no objective measurable abnormalities, so that classifications must of necessity be symptom based. The Rome process is a valiant attempt to make this area of study less confused, more consistent, and scientifically respectable. As such, it undoubtedly has had a major impact, and Rome criteria are now used for the entry into most clinical trials and studies in this area. The senior chairman claims that this process has "done for functional gastrointestinal disorders what the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IIII) has done for psychiatry". While this may appear grandiose, I think it just might be true.

This book provides an overview of many years' work, which have seen major advances in our understanding of functional gastrointestinal disease (FGID). This is due in no small part to the "Rome" process, which is described in detail in the book. The challenge was to create order out of chaos by agreeing criteria for the diagnosis of FGIDs. The major advantage of such a classification is that studies using agreed definitions become comparable and the next study can build on the results of the last. The major disadvantages, which the authors constantly remind the reader of, are that uncritical readers may accept these definitions as fixed in stone. This would of course stultify inquiry and progress. We need to be constantly reminded that the new Rome criteria (for example, for irritable bowel syndrome), in reality excludes as many as 60% of the patients diagnosed as having IBS in clinical practice. This has the advantage of producing closely comparable patients for studies, but the disadvantage of reduced generalisability to normal clinical practice.

The excellent introductory chapter outlines the ideas behind the Rome process and emphasises the importance of the "bio-psycho-social model for IBS" for understanding how sufferers become patients. I much enjoyed the next chapter on the basic science for neurogastroenterology, which simplifies much work and renders it in a form readily understandable to clinicians with only vague memories of neuroanatomy. There then follows a section on motility and sensation measurements, again comprehensive but suitably cautious. There are sections on psychological assessments, and a good account of the weaknesses and strengths of various psychological rating scales for the non-psychiatrist. Specific functional disor-

ders are then dealt with by distinguished coauthors and, as would be expected, these chapters form a comprehensive, well referenced account of current understanding of these conditions. There is also a detailed account of how the new criteria differ from the old ones, and what evidence has been used to make these changes. One disappointment for me, was to see how sparse the new evidence was and what a long way there is to go before we understand the pathophysiology of most of these conditions.

One example of the dangers of classification, if it replaces true inquiry, is the lack of any mention in the definition of irritable bowel syndrome of the response to food. Exaggerated defecation after eating and remission of abdominal pain on fasting is a very common feature in IBS, and yet it is not part of the definition. The danger is that this will lead the response to food to be ignored and not subject to the same detailed study as it might otherwise justify.

Although reviews are meant to be critical, I do believe that this book is essential reading for gastroenterologists, particularly those entering research in the important field of functional gastrointestinal diseases. There is a useful chapter on the design of treatment trials and appendices including some sample questionnaire forms that would be useful to examine before setting up a study. My main caveat is to ensure that readers do listen carefully to the words of wisdom of W G Thompson, who clearly states that this document "does not represent the end but rather the end of the beginning". It is important to test these criteria and to alter them as new evidence accumulates on the underlying mechanisms. They are a vital staging post in the route to increased understanding, however the more we understand mechanisms, the less important these symptom based definitions will become. Once the importance of hypertension was recognised and effective treatment became available, we no longer focused on symptoms such as headaches and blurred vision, but simply measured the blood pressure. It seems likely that the Rome process has the seeds of its own destruction inbuilt, but, given the enormity of the problem, not any time soon!

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# NOTES

### 11th Annual International Colorectal Disease Symposium

The 11th Annual International Colorectal Disease Symposium will be held at the Marriott Harbor Beach Resort, Fort Lauderdale, Florida, USA, on 17–19 February 2000. Further information from: Cleveland Clinic Florida, Department of Continuing Education, 2950 West Cypress Creek Road, Fort Lauderdale, Florida 33309, USA. Tel: +1 954 978 5056; fax: +1 954 978 5539; email: jagelms@ccf.org

### 5th World Congress on Trauma, Shock, Inflammation, and Sepsis

The 5th World Congress on Trauma, Shock, Inflammation, and Sepsis will be held in Munich, Germany, from 29 February to 4 March 2000. Further information from: Prof Eugen Faist, Department of Surgery, Ludwig Maximilians University Munich, Klinikum Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany. Tel: +49 89 7095 5461/2461; fax: +49 89 7095 2460; email: faist@gch.med.uni-muenchen.de

### Second Annual Gastrointestinal Cancer Update: A Multidisciplinary Approach

The Second Annual Gastrointestinal Cancer Update conference will be held at the Yarrow Hotel and Conference Centre, Park City, Utah, USA, on 15–19 March 2000. Further information from: Rosalie Lammle. Tel: +1 801 581 8664; fax: +1 801 581 3647; email: rosalie.lammle@hsc.utah.edu

### European Courses on Laparoscopic Surgery

The European Courses on Laparoscopic Surgery will be held at the University Hospital Saint Pierre, Brussels, Belgium, on 4–7 April 2000 and 21–24 November 2000. Further information from: Conference Services S.A., Drève des Tumuli, 18, B-1170 Brussels, Belgium. Tel: +32 2 375 1648; fax: +32 2 375 3299; email: conference.services@skynet.be

### Third Scandinavian Course on Inflammatory Bowel Diseases

The Third Scandinavian Course on Inflammatory Bowel Diseases will be held at the Wilanderselen, Örebro Medical Centre, Örebro, Sweden, on 12–14 April 2000. Further information from: Kurskansliet, Regionsjukhuset, S-701 85 Örebro, Sweden. Tel: +46 19 15 37 05; fax: +46 19 15 37 95.

### XVIIIth European Workshop on Gastroenterology and Endotherapy

The XVIIIth European Workshop on Gastroenterology and Endotherapy will be held in Brussels, Belgium, on 26–28 April 2000. Further information from: Administrative Secretariat, Ms Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 4900; fax: +32 2 555 4901; email: beauprez@ulb.ac.be

### Digestive Disease Week

The Digestive Disease Week will be held at the San Diego Convention Centre, San Diego, California, USA, on 21–24 May 2000. Further information from: DDW Administration, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814, USA. Tel: +1 301 272 0022; fax: +1 301 654 3978; website: www.ddw.org

### International Hepato-Pancreato-Biliary Association 4th World Congress

The International Hepato-Pancreato-Biliary Association 4th World Congress will be held in Brisbane, Australia, from 28 May to 1 June 2000. Further information from: Intermedia Convention and Event Management. PO Box 1280 (Intermedia House, 11/97 Castlemaine Street), Milton, Queensland 4064, Australia. Tel: +61 (0)7 3369 0477; fax: +61 (0)7 3369 1512; email: hpb2000@im.com.au

### 7th Southeast European Symposium of Paediatric Surgery: Intestinal Motility Disorders

The 7th Southeast European Symposium of Paediatric Surgery will be held at the University of Graz, Austria, on 2 and 3 June 2000. Further information from: Prof Günther Schimpl, Department of Paediatric Surgery, Auenbruggerplatz 34, A-8036 Graz, Austria. Tel: +43 316 385 3762; fax: +43 316 385 3775; email: kinderchirurgie@kfunigraz.ac.at

### Courses from the European Postgraduate Gastro-Surgical School

The Board of Directors of the European Postgraduate Gastro-Surgical School announce the following events for 2000:

- 3rd Course in Endoscopy Live will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 8 and 9 June 2000. Registration fee: NLG 350.
- 9th Course in Digestive Endoscopy will be held at the Academic Medical Centre, Amsterdam, The Netherlands, from 31 August to 1 September 2000. Registration fee: NLG 500.
- Functional Disorders of the Colon and Rectum will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 19 and 20 October 2000. Registration fee: NLG 450.
- Diagnostic and Therapeutic Endoscopic Intervention in Paediatric Gastroenterology will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 16 and 17 November 2000. Registration fee: NLG 450.
- The 3rd Amsterdam International Update on Hepatology will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 14 and 15 December 2000. Registration fee: NLG 450.

Further information from: Helma Stockmann, Managing Director, European Postgraduate Gastro-Surgical School, G-4-zuid, Academic Medical Centre Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3926; fax: +31 20 566 6569/691 4858; email: w.j.stockmann@amc.uva.nl

### Barrett 2000

The 6th World Congress on Barrett's Oesophagus will be held in Paris, France, on 1–6 September 2000. Further information from: Michèle Liegeon, Administrative Assistant, O.E.S.O., 2 Boulevard Pershing, 75017 Paris, France. Tel: +33 1 55 37 90 15; fax: +33 1 55 37 9040; email: michèle.liegeon@utopia.eunet.fr

### Second World Conference on Digestology

The Second World Conference on Digestology will be held in Beijing, China, on 8–11 September 2000. Further information from: Second World Conference on Digestology, PO Box 2345, Beijing 100023, China. Tel: +86 10 6589 1901; fax: +86 10 6589 1893; email: wejd@public.bta.net.cn