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 and oesophageal cancer, 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).1 We then performed the JAM assay to rule out the presence of a functional Fasl expression below the detection limit of our assays. 2 Although we found that gastric cancer cells were able to induce DNA fragmentation in the Fas sensitive T-cell 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 Fas protein (crmA), which inhibits activation of caspases 1 and 8 and thereby mediates resistance to Fas triggering (fig 1B).3

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

<table>
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<th>Cell line</th>
<th>Fasl mRNA(^1)</th>
<th>+TNF-α (100 ng/ml)(^2)</th>
<th>+IFN-γ (100 ng/ml)(^3)</th>
<th>Fasl expression(^4)</th>
<th>Control (%)</th>
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<td>RF-1</td>
<td>Negative</td>
<td>1.1/1.0</td>
<td>1.0</td>
<td>0.8</td>
<td>8.3</td>
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<td>RF-48</td>
<td>Negative</td>
<td>1.3/1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>6.1</td>
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<td>Kato-III</td>
<td>Not done</td>
<td>0.9/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>1.4</td>
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<td>SNU-1</td>
<td>Negative</td>
<td>1.1/1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>4.9</td>
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<td>SNU-16</td>
<td>Negative</td>
<td>1.0/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>1.1</td>
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<td>N-87</td>
<td>Not done</td>
<td>1.0/1.2</td>
<td>Not done</td>
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1RT-PCR analysis was done as follows: total RNA from about 1 x 10⁶ cells was extracted by the acid guanidinium thiocyanate-phenol-chloroform protocol described by Chomczynski and Sacchi.2 1 µg RNA together with 250 ng of oligo (dT)₃ 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 °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 °C (cycle 4-6), 50°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). The constitutive expression of Fasl protein was determined using two different monoclonal antibodies, NOK-1 (Pharmingen, San Diego, California, USA) and HI1 (Alexis, Läufelfingen, Switzerland). For detection of Fasl expression, 0.5 x 10⁶ cells were fixed with paraformaldehyde, permeabilized 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 control antibody for 30 minutes at 4°C. In the case of staining with NOK-I, 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.

2Time kinetics (1-3 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.

3For detection of Fasl expression 0.5 x 10⁶ cells were stained with 1 µg of a specific FITC labelled anti-Fasl monoclonal antibody (UB2, Immunotech, Marseille, France) or an isotype matched control. The mean value of MFI for three independent experiments is given.

4Cells 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. 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)).
tumour cells,cluded the possibility of lymphocytes being induced cell death. Although on morphologi-features that together characterise activation analyse Fas expression and sensitivity, fea-


2 Bennett MW, O’Connell J, O’Sullivan GC, et al. The Fas counterattack in vivo: apoptotic depletion of tumor-infiltrating lymphocytes associ-

they did not supported by our data (fig 1).

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tumour cell lines lose FasL expression during tumour induced apoptosis is unlikely for the fol-

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reviews, Notes

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 sublines 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 data. Authentic FasL mediated killing of Fas sensi-

defence?

2 Bennett MW, O’Connell J, O’Sullivan GC, et al. The Fas counterattack in vivo: apoptotic depletion of tumor-infiltrating lymphocytes associ-

insensitive towards Fas is usually an early example of co-culture of FasL expressing effector cells. Tinhofer et al performed a pro-

is needed.


Unfortunately, the presence of proliferating e-

See also the recent reviews by Bennett et al of the FasL gene or of its expression during and involves activation of wild-type Fas. J Clin Invest 1997;99:805–13.

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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 1998;44:476–82). 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 implications from a respiratory 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.1,2 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 would therefore be expected. Finally, there can be significant minute to minute variation in lower oesophageal sphincter tone. 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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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%.


Mycophenolate mofetil for Crohn’s disease

Editor,—On the basis of a study recently reported by Neurath et al (Gut 1999;44:625–628), commentators in Gut1 and the Lancet2 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 there are important differences between the groups that 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 commented 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 immunosuppressant drug that is often used in organ transplantation.1 It is an end produg of mycophenolic acid that inhibits inosine monophosphate dehydrogenase and potently suppresses lymphocyte proliferation.2 Furthermore various clinical trials have shown its efficacy in suppressing autoimmune and chronic inflammatory disorders, such as rheumatoid arthritis,3 pemphigus vulgaris,4 and psoriasis.5 There are several case reports6 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 compared 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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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 the Rome process, 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 the Rome criteria are now used for the choice 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-III) 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 has added much to 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 simplify important comparisons. 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 IBS gastroenterology, which summarises 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 distor-
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@ghc.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 Lammlé. 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 Wilanderselén, Örebro Medical Centre, Örebro, Sweden, on 19–20 April 2000. Further information from: Kurskansliet, Region sjukhuset, 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, University 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), 119 Castlemaine Street), MIlton, Queensland 4064, Australia.

Barrett 2000 The 6th World Congress on Barrett’s Oesophagus will be held in Paris, France, on 1–6 September 2000. Further information from: Michele Liegeon, A.O.S. O.E.S.O., 2 Boulevard Pershing, 75017 Paris, France. Tel: +33 1 55 37 90 15; fax: +33 1 55 37 90 04; email: michele.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: wejdg@public.bta.net.cn

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@ghc.med.uni-muenchen.de

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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, University 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), 119 Castlemaine Street), MIlton, Queensland 4064, Australia.

Barrett 2000 The 6th World Congress on Barrett’s Oesophagus will be held in Paris, France, on 1–6 September 2000. Further information from: Michele Liegeon, A.O.S. O.E.S.O., 2 Boulevard Pershing, 75017 Paris, France. Tel: +33 1 55 37 90 15; fax: +33 1 55 37 90 04; email: michele.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: wejdg@public.bta.net.cn
Gastric cancer cell lines lack Fas ligand (FasL) expression but kill T cells via a FasL independent pathway

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