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 Fas mRNA or protein in any of the six cell lines analysed by RT-PCR and by flow cytometry (table 1).4 We then performed the JAM assay to rule out the presence of a functional FasL expression below the detection limit of our assays. 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 virus protein ccrmA, which inhibits activation of caspases 1 and 8 and thereby mediates resistance to Fas triggering (fig 1B).

Owing to the discrepancy between our results (all cell lines were FasL negative), those of Bennett et al (all 30 primary neoplastic gastric adenocarcinomas), and those of Bennett et al (30 paraffin wax specimens), we studied the expression of Fas in these cell lines.

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

<table>
<thead>
<tr>
<th>Cell line</th>
<th>FasL mRNA1</th>
<th>+TNF-α (100 ng/ml)1</th>
<th>+IFN-γ (100 ng/ml)1</th>
<th>Fas expression1</th>
<th>Control (%)</th>
<th>Responsiveness toward Fas triggering2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF-1</td>
<td>Negative</td>
<td>1.1/1.0</td>
<td>0.8</td>
<td>8.3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>RF-48</td>
<td>Negative</td>
<td>1.3/1.0</td>
<td>0.9</td>
<td>6.1</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Kato-III</td>
<td>Negative</td>
<td>0.9/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>1.4</td>
<td>7</td>
</tr>
<tr>
<td>SNU-1</td>
<td>Negative</td>
<td>1.1/1.0</td>
<td>0.9</td>
<td>4.9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>SNU-16</td>
<td>Not done</td>
<td>1.0/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>1.1</td>
<td>21</td>
</tr>
<tr>
<td>N-87</td>
<td>Not done</td>
<td>1.0/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>2.2</td>
<td>Not done</td>
</tr>
</tbody>
</table>

1RT-PCR analysis was done as follows: total RNA from about 1×10⁶ cells was extracted by the acid guanidinium thiocyanate-phenol-chloroform protocol described by Chomczynski and Sacchi;1 1μg 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×RT buffer, 2 pmol each of dATP, dGTP, dCTP and dUTP, 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 each at 94°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 CCA TGA CCC TGG TAC TCA (antisense).1 PBMC of a healthy individual served as a positive control.

2Constitutive 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, 0.5×10⁶ 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 fluorescent 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 controls. The mean value of MFI for three independent experiments is given.

3Mean killing (%). For detection of Fas expression, 0.5×10⁵ 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.

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)).
differences between in situ and in vitro results be explained?

Bennett et al mentioned that CD45+ TIL express FasL mRNA, but they did not analyse Fas expression and sensitivity, features that together characterise activation induced cell death. Although an immunological 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,11 it is possible that lymphocytes succumbing to apoptosis owe it to either tricuside or suicide. This mechanism could well be under the (cytokine) control of the tumour as has been discussed for other diseases.12 Alternatively, lymphocytes could indeed be killed by the tumour cells but by a mechanism independent of the Fas system, a hypothesis Bennett et al did not use the standard Lauren classification system.13 It has been shown that gastric carcinomas of the intestinal and diffuse type (according to Lauren) differ in morphology, growth pattern and risk factors, and also in their expression of molecules involved in apoptosis such as Fas or p53.14 This evidence that at least in some tumour models Fas and FasL expression are under transcriptional control of p53.15 Loss-of-function mutations or deletions of p53 have been reported to be involved in gastric carcinogenesis16 and the frequency of these events differs between intestinal and diffuse gastric cancers.17,18 Also, a correlation between p53 mutation, Fas expression and gastric carcinoma cell differentiation has been demonstrated.19 Further studies of the impact of differentiation and p53 functional status on FasL expression are therefore mandatory in gastric carcinoma cells.

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 line 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

EVRON—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 esophageal cancer2 and depletion of antitumour natural killer cells in a mouse model.3

In stomach cancer, apart from our finding of FasL expression at the mRNA and protein level in vivo in all 30 gastric adenocarcinomas examined,4 Rudi and colleagues5 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 subtypes can readily be 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 results.5

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 unlikely 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 or rather than a specific Fas mediated apoptosis.5 Tinhofer et al should repeat their JAM assay for a shorter time length 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 resistant 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 apoptosis.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

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4 Rudi J, Kuck D, Strand S, et al. Involvement of the CD95 (APO-1/Fas) receptor and ligand system in Helicobacter pylori-induced gastric
EDITOR,—We read with interest the recent Vector manometry and LOS dynamics

Figure 1 Variation of lower oesophageal sphincter (LOS) pressure with a mean pull-through of 10

Letters, Book reviews, Notes

sure (hernia on gastro-oesophageal junction pres-
et al paper by Kahrilas took on the appearance of a normal sphinc-
ters. Using a gastric baseline we found a

man et al using rapid pull-through vector manometry (8 channel catheter, 0.7 mls/pull-back speed). They showed that mid-LOS pressure varied from 20 to 80 mm Hg in 20 pull-throughs performed in one hour in the same patient. 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.


Myoclonic epileptic convulsions (MECs) are an idiopathic disorder characterized by recurrent, paroxysmal episodes of rhythmic muscle contractions and relaxation. These episodes are often triggered by sensory stimuli or emotional factors. While the exact cause of MECs is unknown, various factors such as sleep deprivation, stress, and certain medications can exacerbate symptoms. Treatment typically involves antiepileptic drugs, which can effectively control most cases. However, some patients may require more invasive interventions like surgical procedures when medical management fails. It is important for healthcare providers to be aware of the intricacies of MECs to ensure timely and appropriate diagnosis and treatment.
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


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 trauma. 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, 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 should continue to be a valuable resource for surgeons in training as well as in practice.

R A HARRY


While medical students can confidently hold forth on the mechanisms of the Zollinger-Ellison syndrome in a consultation 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 diagnosis, 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 subjective boundaries. 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 entire field of gastroenterology into the 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’ research, which have now finally become widespread 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 agreed criteria for the diagnosis of FGIDs. The major advantage of such a classification is that studies using agreed definitions become comparable and the next step can build on the results of the last. These criteria, which are constantly verified by independent researchers, are now also included in the majority of journals. 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 IBS/gastroenterology, which I found to be full of 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 non-psychiatric 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 engaged 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 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 hyperventilation 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 33304, USA. Tel: +1 954 978 5056; fax: +1 954 978 5539; email: jgelmis@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@ch.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 1468; 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 13–16 March 2000. Further information from: Kurksankiet, Regionssjukhuset, 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 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: International 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@iim.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.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-uuid, Academic Medical Centre Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3925; fax: +31 20 566 6591 4858; email: wj_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: Michele Liegeon, Assistant, O.E.S.O., 2 Boulevard Pershing, 75017 Paris, France. Tel: +33 1 55 37 90 15; fax: +33 1 55 37 90 40; 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: wejd@public.bta.net.cn
Vector manometry and LOS dynamics

AD JENKINSON, SM SCOTT and SS KADIRKAMANATHAN

Gut 2000 46: 740
doi: 10.1136/gut.46.5.740

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