DNA test for hypolactasia premature

I write in response to the article by Rasinpera and colleagues (Gut 2004;53:1571–6) in which a DNA test was proposed for "adult-type hypolactasia". The ability to digest the milk sugar lactose as an adult (lactase persistence) is a variable genetic trait in human populations, lactase persistence being the most frequent phenotype in Northern Europe, while lactase non-persistence or "adult-type hypolactasia" is more frequent in most other populations. In sub-Saharan Africa for example, lactase persistence is found only at low frequency in the majority of populations that have been tested, but in some populations, particularly pastoralist groups, it is significantly more frequent.

A CT polymorphism located 13.9 kb upstream of exon 1 of the lactase gene (LCT) was previously shown in a Finnish population to be tightly associated with the lactase persistence phenotype and it is this change that is proposed as a DNA test for both Europeans and Africans. We agree that presence of a T at this polymorphic site is indeed a fairly good predictor of lactase persistence in Northern Europeans, and there is evidence that this nucleotide resides in a functional element. However, the presence of the alternative allele C at this site is not a good predictor of lactase non-persistence or "adult hypolactasia" in many non-Northern Europeans.

I particularly draw readers' attention to our recent study. We typed this polymorphism in 1671 individuals from seven African countries, which included 20 distinct cultural groups. In seven cases it was possible to match the groups tested with groups from the literature for whom phenotypic information was available. In five of these groups the published frequencies of lactase persistence were 88–25%. We found the T allele in Cameroon but it was so rare elsewhere that it cannot explain the frequency of the lactase persistence phenotype throughout Africa and we devised a statistical test to show that these results were unlikely to have been obtained by chance.

Our ongoing results support this published information and we urge the community to refrain from using DNA tests on Africans and probe other non-Northern Europeans until an appropriate DNA change has been identified.

D M Swallow

Correspondence to: Professor D M Swallow, The Galton Laboratory, Biology Department, University College London, Woburn House, 4 Stephenson Way, London NW1 2HE, UK, dmswallow@hmgp.mrc.ac.uk

Conflict of interest: None declared.

References


Authors' reply

Dr Swallow raises a question about another DNA variant underlying adult-type hypolactasia in sub-Saharan populations and does not recommend analysis of the C/T-13910 variant as a genetic test in African and non-Northern European populations. Although the studies performed by us and others do not support the existence of another variant, we agree with Dr Swallow that well conducted studies are needed to confirm this. The significance of the C/T-13910 variant underlying adult-type hypolactasia was questioned in the article by Mulcare. Their doubt is based on several assumptions that make it difficult to evaluate the significance of the findings. These assumptions can be listed as following:

1) It is not known whether or not the study subjects presented with adult-type hypolactasia. Thus there is a risk of wrong conclusions being drawn. It is well documented that the clinical diagnosis of adult-type hypolactasia is difficult to assess due to inaccurate diagnostic tests and variable, usually mild, symptoms. The diagnosis is usually based on indirect tests (lactose tolerance test or breath hydrogen test) whose specificity has been reported to range from 77% to 96% and sensitivity from 69% to 100%. There is evidence that the breath hydrogen test may be an indicator of bacterial overgrowth rather than lactose malabsorption.

2) Definition of ethnic origin was based on self definition and spoken language. As the authors themselves clarified, African populations have complex demographic histories. Many of the analysed groups were very small, and hence chance may have played a role. In contrast with the findings of Mulcare, our genotyping data in nomadic pastoralists Fulani-Sudanese were in agreement with the previously published figures of lactase persistence in this population.

3) There was no statistics shown against the C/T-13910 variant, only speculation presented in Mulcare’s paper.

When conducting phenotype-genotype correlation studies in lactase persistence/non-persistence, detailed clinical studies are essential. The studies are difficult as it is unethical to take an intestinal biopsy from a healthy subject that would give the most reliable diagnosis. Measurement of lactase activity from hospitalised patients with a clinical indication for intestinal biopsy may reflect a disease in the gut and the result obtained may not correlate with the genotype. These uncertainties should be taken into account when interpreting the genotyping results in adult-type hypolactasia.

K-L Kolho

Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

I Järvellä

Department of Medical Genetics, University of Helsinki and Laboratory of Molecular Genetics, Helsinki University Central Hospital, Helsinki, Finland

Correspondence to: Dr K-L Kolho, Hospital for Children and Adolescents, Box 281, FIN-00029, Finland; kajvi-lea.kolho@helsinki.fi

Conflict of interest: None declared.

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Abdominal symptoms leading to dehydration, in combination with repetitive bathing behaviour (Gut 2004;53:1566–70). They have concluded that these symptoms are due to cannabis use.

Cannabis has been consumed for many centuries and is currently used by millions of people in many countries. It is hard to believe that a distinctive syndrome caused by cannabis has never been noted before by users or clinicians.

The authors assert that cannabis laws are particularly liberal in South Australia. Four Australian jurisdictions now have a cannabis expiation notice system which South Australia first introduced in 1986. The other four Australian jurisdictions have variations on a bond system. Several European countries have far more lenient legislative arrangements. After over a generation of liberalisation of cannabis laws in many countries around the world, there is little evidence of a subsequent increase in cannabis use.

In a comparative study using the same methodology, the prevalence of cannabis use in more “liberal” Amsterdam was lower than in the more “punitive” San Francisco.

The title of the paper, “Cannabinoid hyperemesis” is unduly presumptive. Some of these cases appeared to improve with abstinence and were later rechallenged with cannabis, but neither the patients nor the authors appear to have been blinded to the rechallenge. The proposed biological explanation is weak.

We suggest that alternative explanations need to be sought for these cases. This syndrome should not be accepted as being caused by cannabis without additional reports and other evidence.

A Byrne, R Hallinan
Byrne Surgery, Sydney, Australia
A Wodak
St Vincent’s Hospital, Darlinghurst, New South Wales, Australia

Authors’ reply
We would like to thank Byrne et al for their interest in our paper (Gut 2004;53:1566–70).

The title of the paper, “Cannabinoid hyperemesis” is unduly presumptive. Some of these cases appeared to improve with abstinence and were later rechallenged with cannabis, but neither the patients nor the authors appear to have been blinded to the rechallenge. The proposed biological explanation is weak.

We suggest that alternative explanations need to be sought for these cases. This syndrome should not be accepted as being caused by cannabis without additional reports and other evidence.

A Byrne, R Hallinan
Byrne Surgery, Sydney, Australia
A Wodak
St Vincent’s Hospital, Darlinghurst, New South Wales, Australia

IL-1 gene cluster and TNFA–307 polymorphisms in the risk of perforated duodenal ulcer

Helicobacter pylori virulence markers have been associated with duodenal ulcer (DU) but there are few studies evaluating host factors such as cytokine polymorphisms and, to the best of our knowledge, no study has evaluated these polymorphisms as risk factors for perforated DU.

We investigated associations among interleukin 1 (IL-1) cluster and tumour necrosis factor α (TNFA)–307 polymorphisms, and DU and perforated DU in a non-Caucasian population. We included 223 patients with DU, 29 patients with perforated DU, and 541 blood donors. H pylori status was investigated by culture, preformed urease test, stained smear, polymerase chain reaction (PCR), and the 13C-urea breath test. cagA status was assessed by PCR. In the blood donors, H pylori status and cagA status were determined by serology, IL-1β–511T, IL-1β–31C, and TNFA–307 polymorphisms were genotyped by PCR. PCR restriction fragment length polymorphism in IL-1β–511T and IL-1β–31C polymorphisms were in almost complete linkage disequilibrium in all three groups (p<0.05).

We thus restricted further analyses to IL-1β–31C. No polymorphism remained associated with non-complicated DU predicting for age and sex, but the IL-1RN2 carrier showed a trend towards increasing DU risk (p=0.06; odds ratio (OR) 1.43 (95% confidence interval (CI) 0.99–2.05)). Regarding perforated DU, in the multivariate analysis, IL-1β–31C and TNFA–307A alleles remained inversely associated with the disease, even after inclusion of confounding factors (table 1). cagA status was the strongest factor associated with either uncomplicated (p=0.00; OR 4.29 (95% CI 2.63–6.98)) or perforated DU. The other polymorphisms were not associated with perforated DU (table 1).

Although morbidity from peptic DU has greatly decreased since early studies on H pylori infection,2 little change was observed
regarding perforated DU, as measured by surgical interventions in emergency services. Knowing who, among all H pylori infected subjects, will develop a perforated DU is therefore an important issue in treatment.

Garcia-Gonzales and colleagues’ and Zambon and colleagues,’ evaluating Spanish and Italian populations, respectively, did not find associations between single H pylori polymorphisms and DU. Conversely, Funuta and colleagues’ found that IL-1RN allele 2 and IL-1B–511T/T were protective factors for DU in a Japanese population.

In this investigation, in accordance with previous studies,’ no role could be established for IL-1B–511T or IL-1B–31C alleles in non-complicated DU. However, IL-1B–31C and TNFA–307A carriage was negatively associated with perforated DU. Thus the same IL-1B and TNFA polymorphisms which were associated with atrophy and increased gastric carcinoma risk in Caucasian populations’ were found to be inversely associated with perforated DU.

The mechanism by which overproduction of IL-1B and TNF-a due to IL-1B–31 and TNFA–307 polymorphisms protects from DU perforation may not differ from that associated with gastric carcinoma. The prevailing mechanism is probably inhibition of gastric acid production. Consequently, bacteria spread to the corpus where they accentuate the inflammation, lowering acid production, with the net effect of diminishing the risk of DU perforation.

Even though our results are biologically plausible, several factors may contribute to geographical specificities, as already seen in studies on other gastrointestinal diseases.’ Also, we have previously demonstrated’ in our population that the distribution of the inflammatory alleles at IL-1 loci is intermediate between Asians and Caucasians.

In conclusion, one of the questions that motivated the studies associating host cytokine polymorphisms with H pylori associated diseases was the possibility of explaining why some infected individuals develop gastric carcinoma, others peptic ulcer, and the majority remain otherwise without complications. These polymorphisms may play a role in the genesis of H pylori associated diseases but are probably insufficient to completely answer this question. Our study demonstrated independent inverse associations between IL-1B–31C and TNFA–307A polymorphic alleles and perforated DU, but no association with non-complicated DU.

Table 1 Univariate and multivariate analysis of the cytokine loci between patients with perforated duodenal ulcer (n = 29) and all blood donors (n = 539), and between patients with perforated duodenal ulcer (n = 29) and Helicobacter pylori positive blood donors (n = 369)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>H pylori positive subjects</th>
<th>Uni</th>
<th>Multivariate</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>cagA status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IL-1B–31</td>
<td>1/1 Ref.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>0.04</td>
<td>0.42</td>
<td>0.20–0.90</td>
<td>0.05</td>
<td>0.33</td>
<td>0.15–0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/2 Ref.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1RN</td>
<td>1/1 Ref.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/2</td>
<td>0.60</td>
<td>0.70</td>
<td>0.27–1.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFA–307</td>
<td>C/C Ref.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>0.03</td>
<td>0.21</td>
<td>0.05–0.88</td>
<td>0.03</td>
<td>0.21</td>
<td>0.05–0.96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

J B Guerra, A M C Rocha, C M de Castro Mendes, I E B Saavedra, C A de Oliveira, D M Queiroz Laboratory of Research in Bacteriology, Faculty of Medicine, UFMG, Belo Horizonte, Brazil and Hospital University of Medicine, UFMG, Belo Horizonte, Brazil; dqueiroz@medicina.ufmg.br doi: 10.1136/gut.2005.077362

Conflict of interest: None declared.

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Cryptic gluten intolerance in type 1 diabetes: identifying suitable candidates for a gluten free diet

Long term exposure to gluten in coeliacs,’ and coeliac disease (CD) after 16 years of age may induce type 1 diabetes (T1D) and other autoimmune disorders. Increased prevalence of CD among diabetes and their relatives is well documented.’ Early introduction of gluten to children at high risk for T1D produces T1D associated islet autoantibodies.’ Similarly, in the absence of overt clinical symptoms of T1D, some coeliac children produce diabetes autoantibodies in a gluten dependent manner. Handled with mild intestinal challenge with gluten produces mucosal recruitment of lymphocytes,’ similar to that in CD patients.’ In diabetes, however, there is no production of CD related anti-tissue transglutaminase antibodies (anti-tTG).

We have used a phage display assay’ to show that in CD patients, production of anti-tTG is limited to the intestine. Here, we monitored the effects of a gluten free diet (GFD) on anti-tTG antibody synthesis in the intestinal mucosa of a diabetic adult and a boy at high risk of diabetes, both carrying HLA DQ2/DQ8, but lacking serum anti-tTG. Intestinal specimens from both subjects and samples of peripheral blood lymphocytes were used to make phage-antibody libraries’ to look for lymphocytes synthesising anti-tTG antibodies.

Patient No 1 was a 35 year old man who had T1D for 20 years. During 1998–2001, serum anti-tTG responses were negative, and clinical control of T1D was good (mean glycosylated haemoglobin 6.8% (range 8.1–5.6%) in the patient despite the patient deviating from the treated diabetic retinopathy and microalbuminuria, with an average albumin excretion rate (AER) of 230 μg/min, despite treatment with angiotensin converting enzyme inhibitors. In 2001, ‘burning’ epigastric pain appeared with abdominal distension. Duodenal biopsy and number of intraepithelial lymphocytes were normal.

Patient No 2 was a two year old boy at risk of CD and T1D (diabetic father and coeliac brother) who tested positive (CD) for two out of five HLA T1D specific genotypes (DR1 *0301, DQA1*0501, DQB1*0201 and DRB1*0401, DQA1*0301, DQB1*0302). Tests for anti-tTG serum antibodies were negative while anti-islet cell antibodies (ICA) became positive at 20 months. Informed of the potential risks, the child’s parents consented to intestinal biopsy to detect possible silent CD. Duodenal biopsy and number of intraepithelial lymphocytes were normal.

In both subjects, positive tTG antibody clones (table 1) were isolated only from the intestinal lymphocyte libraries. Two control subjects aged 10 and 45 years, suffering from Helicobacter pylori gastritis and with no family history of CD or T1D, tested negative for intestinal anti-tTG clones. The diabetic adult and the child’s parents agreed to a GFD for 12 months, after which laboratory tests and biopsies were repeated. In the adult, control of diabetes was unchanged but AER was markedly improved (20 μg/min). The boy tested negative to ICA. In both subjects, biopsies were normal, and analysis of new phage antibody libraries showed complete elimination of anti-tTG clones in the adult and 90% reduction in both positivity and diversity in the child (table 1). Both patients remain on a

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GFD; AER is still normal in the diabetic adult and the child is still negative for ICA.

In the context of genetic predisposition to gluten intolerance, in line with Makì’s data on the gradual development of CD in diabetics, we found a gluten dependent immunological response, apparently only in the intestine. In the boy, reduced response to tTG and elimination of ICA after GFD may have been due to very early intervention, indicating temporary protection from the disease. In the diabetic adult, reduction of microalbuminuria may have indicated that while a GFD is of little benefit to the intestine. In the boy, reduced response to immunological response, apparently only in other organs.

In conclusion, at risk subjects with HLA DQ2/8 may develop intestinal anti-tTG antibodies on extended exposure to gluten. Similar larger scale studies are needed to prove that gluten is harmful in these subjects and confirm the benefits of a GFD.

Acknowledgements

The paper was founded in part by MURST COFIN 2004060237/5 and RIFI 149/03 IRCSS “Burlo Garofolo”.

D Sblattero
Department of Biology, University of Trieste, Trieste, Italy

A Ventura, A Tommasini
Department of Reproductive and Developmental Science, University of Trieste and IRCSS “Burlo Garofolo”, Trieste, Italy

F Florian, R Marzari
Department of Biology, University of Trieste, Trieste, Italy

A Bradbury
Bioscience Division, Los Alamos National Laboratory, Los Alamos, NM, USA

T Not
Department of Reproductive and Developmental Science, University of Trieste and IRCSS “Burlo Garofolo”, Trieste, Italy

Correspondence to: Dr T Not, Clinica Pediatria, Istituto per l’Infanzia “Burlo Garofolo”, via dell’Istria 65/1, 34100 Trieste, Italy; not@burlo.trieste.it

doi: 10.1136/gut.2005.077511

Conflict of interest: None declared.

Table 1 Clones isolated from intestinal biopsies and number of anti-transglutaminase positive clones before and after 12 months of a gluten free diet in the adult diabetic, in the at risk child, and in the controls.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (y)</th>
<th>HLA</th>
<th>ICA</th>
<th>% of tTG positive clones</th>
<th>Different antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>35</td>
<td>DQ2/8</td>
<td>–</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Adult during GFD</td>
<td>2</td>
<td>DQ2/8</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Child</td>
<td>10</td>
<td>DQ2/8</td>
<td>–</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Child During GFD</td>
<td>45</td>
<td>DQ2</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GFD, gluten free diet; ICA, in-tet-cell antibodies; anti-tTG, anti-transglutaminase antibodies; Different, number of different clones determined by sequencing.

References


Acquired factor V inhibitor associated with valproic acid use in a cirrhotic patient

Acquisition of factor V inhibitor is a rare event. The inhibitor most frequently encountered in clinical practice is directed against human factor V in vivo. Other noteworthy causes are blood transfusion, cancer, treatment with betalactam antibiotics or streptomyacin, major surgery (usually in patients having received transfusions or betalactam agents), and autoimmune disorders (coeliac disease, bullous pemphigoid, Sjogren’s syndrome, Hashimoto thyroiditis) associated with congenital factor V deficiency. No cause was found in nearly 20% of cases.7 To date, no cases have been linked to dental extraction or other minor surgeries. Anti-factor V antibodies can appear at all ages but most commonly occurred after age 65 years.8 The inhibitor was discovered fortuitously in nearly 40% of cases following an isolated increase in prothrombin time. Bleeding was the main presenting sign in 60% of cases, and was life threatening in 22%.9

To our knowledge, this is the first reported case of factor V inhibitor associated with valproic acid therapy. It is noteworthy that valproic acid inhibits fatty acid beta oxidation, potentially leading to life threatening microvesicular steatosis.10 However, our patient had no clinical or biological signs of hepatitis. Rare cases of cutaneous vasculitis or lupus-like syndrome have been linked to valproic acid or its prodrug valproamide. Factor V inhibitors have occasionally been detected in patients with such syndromes, but our patient had no clinical or biological signs of an autoimmune process. Factor V inhibitor appeared after three years of treatment with valproic acid, and prothrombin...
level improved partially after drug withdrawal. In previously reported cases, the inhibitor disappeared in 88% of patients overall, after a mean of 10 weeks. In patients with no identified cause, the inhibitor only disappeared in 62% of cases after a mean of 23 weeks, although this did not affect outcome. Bleeding is difficult to treat in patients with factor V inhibitor. Various approaches have been tried, such as infusion of fresh frozen plasma or, better, platelet concentrates. Plasmapheresis has been used to lower antibody titre and high dose immunoglobulin to neutralise the antibodies. Steroids and immunosuppressants (azathioprine, cyclophosphamide), alone or in combination, have been used for long term inhibition of factor V inhibitor synthesis. However, the results are difficult to interpret as the studies were small and included patients with heterogeneous manifestations. There is no consensus treatment.

In conclusion, the onset of hypocoaguability linked to a decline in factor V level in a cirrhotic patient should not be systematically attributed to hepatocellular insufficiency; in the absence of marked cytology, the presence an acquired factor V inhibitor and a possible drug related cause should be sought.

References


Acylated ghrelin stimulates food intake in the fed and fasted states but desacylated ghrelin has no effect

We were interested to read the article of Asakawa et al (Gut 2005;54:18–24) which reported that intracerebroventricular and peripheral administration of desacylated ghrelin inhibited food intake in mice in the fasted state. Acylated ghrelin (AG) has a unique biological structure with an acyl side chain on the third amino acid residue. AG is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a) and stimulates feeding and growth hormone release. In contrast, desacylated ghrelin (DAG), which does not have the acyl side chain, has no affinity for the GHS-R1a. As the authors suggest, their results might indicate the presence of an alternative receptor through which desacylated ghrelin acts.

We were interested in investigating whether DAG would modulate feeding. We injected saline, 0.3 mmol/kg AG, and 0.3 mmol/kg DAG into male mice intraperitoneally on two occasions, firstly in the fed state and secondly following a 20 hour fast, and measured food intake at 1, 2, 4, and 24 hours post injection (fig 1). In the fasting experiment, we also injected 0.03 mmol/kg PYY3–36 as a positive control. All animal procedures were approved by the British Home Office Animals (Scientific Procedures) Act 1986 (project license No 70/5281). Results were analysed using a one way repeated measures ANOVA. As previously reported, AG stimulated feeding in the fed state. However, DAG had no significant effect on food intake in the fed state. In the fasting study, PYY3–36 significantly inhibited feeding. AG stimulated cumulative food intake in fasted mice for up to six hours post injection although the percentage increase compared with saline was less than in the fed state (per cent increase two hours following ghrelin injection: fed state 32%, fasted state 30%). In contrast with the findings of Asakawa et al, DAG had no effect on food intake at any time point examined. We used a higher dose of DAG than that administered by Asakawa et al (approximately 2.5 nmol s 3 mmol per mouse) and therefore the absence of a feeding effect associated with DAG is unlikely to be explained by differences in dosing.

In conclusion, we have observed that acylated ghrelin stimulated food intake in the fasting as well as in the fed state. In contrast with the findings of Asakawa et al, there was no alteration in feeding in either the fed or fasting state following desacylated ghrelin. Our results suggest that circulating acylated ghrelin stimulates feeding independently of desacylated ghrelin.

Acknowledgements

We thank the Wellcome Trust for programme grant support and for clinical training fellowships for NMN and MRD.

ACR Neary, MR Druce, CJ Small, S R Bloom
Department of Metabolic Medicine, Hammersmith Hospital, Imperial College London, London, UK

Conflict of interest: None declared.

References


Future use of the Glasgow alcoholic hepatitis score

We read with interest the findings of Forrest and colleagues (Gut 2005;54:1174–9) regarding their prognostic algorithm for alcoholic hepatitis, the Glasgow alcoholic hepatitis score (GAHS). The study uses robust clinical endpoints to develop an algorithm. It has diagnostic advantages over the modified discriminant function score (DFS). We would like to discuss some of the future implications of this important study.

The overall death rate in the study was 23% at 28 days and the death rate of patients with a DFS >32 was 29% at 28 days in the derivation population. The latter figure is lower than the placebo arms of many of the randomised controlled trials of alcoholic hepatitis that range between 35% and 50%,1,2 This difference compared with the published literature may be attributable to case definition. It is possible that there were a fewer number of patients in the derivation cohort for GAHS with true alcoholic hepatitis. Some of the previous studies of alcoholic hepatitis have required liver biopsy evidence of alcoholic hepatitis as part of the case definition. This was not the case for entry into the derivation cohort for the GAHS study and the case definition was based solely on clinical and biochemical evidence of liver dysfunction in patients with heavy alcohol consumption. In the validation population there was biopsy evidence of alcoholic hepatitis in only 33%.

While this may invalidate the GAHS as a means of identifying cases of alcoholic hepatitis, it does not invalidate its use in identifying patients at risk of death when admitted to hospital with liver dysfunction on a background of heavy alcohol use. This makes it far more pragmatic than tests based on biopsies as many hospitals do not have access to specialised services to perform transjugular liver biopsies in the acute setting. Furthermore, there are published
randomised controlled trials which have not required histological evidence of alcoholic hepatitis before allocating treatment. The corollary to this is that although alcoholic hepatitis often presents with clinical features of fever, leucocytosis, and hyperbilirubinemia, there remains a differential diagnosis which may require a biopsy to resolve.

It is important to differentiate between true alcoholic hepatitis and severe liver dysfunction in patients with heavy alcohol consumption because it will influence the choice of intervention. Randomised controlled trials that use GAHS to identify patients with alcoholic hepatitis might be greatly underpowered if the therapy (for example, steroids) is effective in alcoholic hepatitis but ineffective or harmful in other clinical conditions where abnormal clinical parameters might be associated with heavy alcohol consumption. Selection of risk stratification models should be determined by the severity of the adverse effects of the therapy under trial. Those with more severe adverse effects will warrant models with high specificity whereas drugs with minimal side effects will benefit from a model with a high sensitivity. Compared with the DFS, the GAHS has an increased specificity, decreased sensitivity, and improved accuracy, making it suited to the selection of subjects in studies using more toxic therapies.

The utility of the GAHS will depend on the effect of its use in the care of patients. We suggest that the next step in the evaluation of GAHS should be a clinical trial to see if patients randomised to risk stratification with GAHS followed by appropriate interventions have a better outcome than those managed conventionally.

We believe this is an excellent study using robust clinical end points. It is a practical model which can be used easily at the bedside to give valuable prognostic information. Success of future therapeutic trials in alcoholic hepatitis will not only depend on the efficacy of the drug but also the appropriate selection of patients by models and their respective cut off points.

Scientific Officer for HepCGen. Roche, Gilead, Bayer, and Pfizer. He is the Chief W M Rosenberg is a consultant for Schering-Plough, IN Guha received grant support from Pfizer. W M Rosenberg is a consultant for Schering-Plough, Roche, Gilead, Bayer, and Pfizer. He is the Chief Scientific Officer for HepCGen.

Conflict of interest: None declared.

References


A proof of concept study establishing Necator americanus in Crohn’s patients and reservoir donors

The emergence of autoimmunity, including Crohn’s disease (CD) where the immune relationship with commensal bacteria is corrupted, has been linked to hygiene. However, repeated inoculation was required and concern has been raised that aberrant migration could occur. The haematophasogous hookworm, Necator americanus (NA), is proposed as an alternative. We have tested if CD patients tolerate hookworm infection, and the practical issues associated with establishing reservoir donors (RDs).

Over 700 million people remain infected with hookworms. Infective larvae (L3i) are acquired through skin contact with contaminated soil. Auto-reinfection, direct person to person infection, aberrant migration, and hypobiosis do not occur. Adult worms live in the host small intestine for an average of five years. Infection can be easily terminated with an anthelminthic. Anaemia is the only disease of consequence but is an unusual outcome in properly nourished individuals. Using L3i originally obtained from Madang, Papua New Guinea, but maintained in a healthy researcher in the UK, five CD subjects with longstanding but mostly inactive disease and three RDs each received a carefully measured inoculum (table 1). Subsequently, four additional CD subjects with chronic and mostly active disease were inoculated with L3i cultured from faeces provided by an RD, and the original CD cohort were reinoculated from week 27 to week 30. Ethics approval was granted by the Townsville Health Service District Institutional Ethics Committee. Haematological and clinical measurements are expressed as mean (95% confidence interval).

The inoculation caused a mild itch within five minutes that disappeared after a few days in eight CD subjects and a pruritic rash that lasted two weeks in the RDs, who also developed a painful transient enteropathy. Neither respiratory symptoms nor detectable aberrant migration occurred. In the CD cohort, blood eosinophilia developed from week 5 (mean 2.60 x 10^9/l (1.89) v week 1 0.18 x 10^9/l (0.10) v week 20 0.39 (0.20)). Patent infection had established by week 20 in all cases. CD activity index (CDAI) remained unchanged until week 17, possibly in part due to a hookworm related enteropathy recognisable because of blood eosinophilia and faecal Charcot-Leyden crystals. Over 20 weeks, the IBD questionnaire was improved (mean 141 (31) v week 20 129.3 (4.1) g/l). Reinooculation of the five CD subjects first inoculated were in remission at week 45 (fig 1).

Our pilot study has established a potential for NA, already a fact of life for many millions, as a candidate parasite to inoculate those with autoimmune disease. The natural advantages are lifecycle and migration predictability, ability to control the size of and eliminate a colony, and the parasite’s longevity. Inoculation proved safe, even in immune suppressed patients. Our hope that NA would suppress auto-reactivity sufficiently to allow immune suppressive therapy to be stopped was unrealistic. Recent and compelling evidence has shown that IBD is self sustaining. It may be that after remission is achieved, endoparasites will offer an alternative or adjunct to immune suppressive therapy, a priority for some people with CD.

J Croese
Department of Gastroenterology, Townsville Hospital, Townsville, Australia

J O’Neil
Department of Gastroenterology, Royal Brisbane Hospital, Brisbane, Australia

J Masson, S Cooke
Department of Gastroenterology, Townsville Hospital, Townsville, Australia

W Melrose
School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Australia

D Pritchard
Boots Science Building, School of Pharmacy, University of Nottingham, Nottingham, UK

R Speare
School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Australia
Table 1

<table>
<thead>
<tr>
<th>Initial inoculation trial</th>
<th>Re inoculation trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID, age [y], sex</td>
<td>Time (weeks)</td>
</tr>
<tr>
<td></td>
<td>0-4 5-8 9-12 13-16 17-20</td>
</tr>
<tr>
<td>CD1 55 M Inoculum therapy</td>
<td>25 L3i 79 60 89 77 68</td>
</tr>
<tr>
<td>CD2 46 M Inoculum therapy</td>
<td>25 L3i 38 114 20 68 48</td>
</tr>
<tr>
<td>CD3 41 F Inoculum therapy</td>
<td>25 L3i P5 M15 46 71 53 M7.5 53</td>
</tr>
<tr>
<td>CD4 54 M Inoculum therapy</td>
<td>50 L3i P38 M30 260 230 232 264 260</td>
</tr>
<tr>
<td>CD5 21 F Inoculum therapy</td>
<td>50 L3i P10 M20 144 151 103 79 70 P7.5 100</td>
</tr>
<tr>
<td>CD6 33 F Inoculum therapy</td>
<td>50 L3i P15 M20 49 32 6 49 29</td>
</tr>
<tr>
<td>CD7 33 M Inoculum therapy</td>
<td>50 L3i A150 260 114 96 125 118</td>
</tr>
<tr>
<td>CD8 46 M Inoculum therapy</td>
<td>50 L3i M20 145 159 171 152 186</td>
</tr>
<tr>
<td>CD9 44 F Inoculum therapy</td>
<td>100 L3i P5 M20 173 127 106 76 125</td>
</tr>
</tbody>
</table>

L3i, n 3rd stage N americanus larvae inoculated percutaneously; P, prednisone n mg/day; A, azathioprine n mg/day; M, methotrexate n mg/week.

Strong BCL10 nuclear expression identifies gastric MALT lymphomas that do not respond to H pylori eradication

Approximately 75% of gastric mucosa associated lymphoid tissue (MALT) lymphomas can be cured by _Helicobacter pylori_ eradication. It would be very useful to identify, at the time of diagnosis, the 25% of cases of gastric MALT lymphoma that will not respond to _H pylori_ eradication. In general, lymphomas at stage IA or above do not respond to _H pylori_ eradication. However, the prognostic value of staging in stage IA cases is very limited, although tumours that involve the muscularis propria or submucosa (stage IA) show a higher failure rate than those restricted to the mucosa and submucosa (stage IA). Paradoxically, the majority of gastric MALT lymphomas at diagnosis are at stage IA, but 20% of these cases will not respond to _H pylori_ eradication.

In a previous study, we have examined the value of t(11;18)(q21;q21) in prediction of the response of gastric MALT lymphomas to _H pylori_ eradication. Among the 111 cases of gastric MALT lymphomas studied, t(11;18)(q21;q21) was present in 42/63 (67%) non-responsive cases, including 26/43 (60%) at stage IE. In contrast, translocation was detected in only 2/40 responsive cases and the two translocation positive cases showed a temporary response to _H pylori_ eradication. Based on the same series of cases, we examined the value of t(1;14)(p22;q32) in prediction of the response of gastric MALT lymphomas to _H pylori_ eradication. Of the 111 cases examined, 75 including 35 from the complete regression group and 40 from the non-responsive group, had adequate tissue specimens for evaluation of BCL10 staining. Two cases showed strong BCL10 nuclear staining in virtually all tumour cells (fig 1), similar to that seen in t(1;14)(p22;q32) positive cells, while the remaining cases displayed either weak cytoplasmic or weak nuclear staining. Both cases with strong BCL10 nuclear staining were from the _H pylori_ eradication non-responsive group; one case (case No 1) had stage IIA disease and showed no response 12 months after _H pylori_ eradication while the other (case No 2) had stage IIA disease and showed no response eight months after _H pylori_ eradication. As shown in our previous study, both cases were t(11;18)(q21;q21) negative.

To ascertain whether the two cases that showed strong BCL10 nuclear staining were positive for t(1;14)(p22;q32) or variant, interphase fluorescence in situ hybridisation (FISH) with _BCL10_ break-apart dual colour probes, IGH break-apart probes, IgG break-apart probes, and _BCL10IGH_ dual colour dual fusion translocation probes were performed. Both cases failed to show evidence of _BCL10_ gene break or amplification. Case No 2 showed an _IGH_ break, but FISH with _BCL10IGH_ dual colour dual fusion translocation probes failed to show evidence of _BCL10IGH_ translocation. To further investigate these cases, we performed real time quantitative reverse transcription-polymerase chain reaction of _BCL10_ mRNA. Unfortunately, adequate tissue materials were available only in case No 2. The level (AC1 = 3.4) of _BCL10_ mRNA expression in this case was compatible with that in MALT lymphomas with t(1;14)(p22;q32) (mean 1.60 (SD 2.37)), well above that in those without the translocation (6.94 (1.72)).

To further assess the impact of t(1;14)(p22;q32) on the clinical behaviour of MALT lymphoma, we retrospectively reviewed the clinical presentation of 11 cases, including six from the stomach with known _BCL10_ involved translocation (table 1). Of these cases, nine including all those from the stomach, were at stage II or above. Although clinical presentation and follow up data were not available in each case, three cases (Nos 1, 2 and 7) presented unusual wide dissemination.

References

including pleural effusion, and blood and bone marrow involvement (table 1).

Taken together, our results suggest that gastric MALT lymphomas with strong BCL10 nuclear expression or t(1;14)(p22;q32) are mostly likely resistant to *H pylori* eradication.

**Acknowledgements**

This study was supported by research grants from Leukaemia Research Fund, UK and Deutsche Krebshilfe. The authors thank J Audouin, L Bedenne, O Bouché, Marie-Christine Copin, Y Bouhnik, J Fournet, A De Mascarel, Ph Moreau, J Lafon, A Parientie, and F Piard of the Groupe d’Étude des Lymphomes Digestifs (GELD), France; T. Thomas and P. Zinzani of Università degli Studi di Bologna, Italy; and M Stolte of Institut fur Pathologie, Klinikum Bayreuth, Germany, for contribution of part of the specimens used for this study.

**Figure 1** BCL10 immunohistochemistry. Both cases 1 and 2 show strong BCL10 nuclear staining in virtually all tumour cells, similar to that seen in tumour cells with t(1;14)(p22;q32).

**Table 1** Clinical feature of mucosa associated lymphoid tissue (MALT) lymphoma with t(1;14)(p22;q32) or variants

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Sex</th>
<th>Primary site</th>
<th>Genetic investigations</th>
<th>BCL10 involved chromosomal translocation</th>
<th>BCL10 IHC</th>
<th>Staging*</th>
<th>Dissemination</th>
<th>Clinical follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>Strong nuclear staining</td>
<td>IV</td>
<td>Perigastric lymph nodes, omentum, spleen, pleural effusion, blood</td>
<td>4 cycles of MCP chemotherapy, partial remission, alive at two year follow up</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>n/a</td>
<td>IV</td>
<td>Perigastric and splenic lymph nodes, pleural involvement, bone marrow involvement?</td>
<td>Chemotherapy with chlorambucil, complete remission in three year follow up</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>M</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;2)(p22;q12)</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>Perigastric and mesenteric lymph nodes, pleural effusion</td>
<td>Low dose chlorambucil chemotherapy, complete remission at 1.5 year follow up</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>F</td>
<td>Stomach</td>
<td>Interphase FISH</td>
<td>Yes</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>Lung</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>n/a</td>
<td>n/a</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q12)</td>
<td>Strong nuclear staining</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>F</td>
<td>Lung</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>Blood, bilateral pulmonary involvement, pleural and ascitic effusion, non-germinal lymph node</td>
<td>8 year low grade B cell lymphoma, then presented an aggressive clinical course presenting with lymphocytosis, pleural and ascitic effusions, partially responsive to chemotherapy, died of disease</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>F</td>
<td>Lung</td>
<td>Interphase FISH</td>
<td>t(1;14)(p22;q12)</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>No clinical evidence</td>
<td>Data on treatment not available, but patient alive without evidence of disease for 16 years</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>F</td>
<td>Lung</td>
<td>Interphase FISH</td>
<td>IGH-BCL10 fusion</td>
<td>Strong BCL10 nuclear staining</td>
<td>IIE</td>
<td>No clinical evidence</td>
<td>Data on treatment not available, but patient alive without evidence of disease for 16 years</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>F</td>
<td>Lung</td>
<td>Interphase FISH</td>
<td>IGH-BCL10 fusion</td>
<td>Strong BCL10 nuclear staining</td>
<td>IIE</td>
<td>No clinical evidence</td>
<td>Data on treatment not available, but patient alive without evidence of disease for 16 years</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>F</td>
<td>Breast</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q12)</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>Axillary lymph nodes</td>
<td>6 cycles of CHOP chemotherapy followed by surgery, complete remission in two year follow up</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>F</td>
<td>Breast</td>
<td>Interphase FISH</td>
<td>IGH-BCL10 fusion</td>
<td>Strong BCL10 nuclear staining</td>
<td>IIE</td>
<td>No clinical evidence</td>
<td>Data on treatment not available, but patient alive without evidence of disease for 16 years</td>
</tr>
</tbody>
</table>

*Ann Arbor-Musshoff staging system for extranodal lymphoma; the clinical stage was likely to have been underestimated as appropriate staging was unlikely to be carried out in each of these archival cases.

IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation; n/a, not available.
Conflict of interest: None declared.

References


Interferon-β plus ribavirin for patients with hepatitis C virus genotype 1: a randomised pilot trial

The rate of sustained eradication of hepatitis C virus (HCV) in response to a combination of interferon-α and ribavirin remains unsatisfactory in patients with genotype 1 infection.1 No effective alternative treatment is currently available for non-responders. Interferon-β is also a type 1 interferon commonly used to treat chronic HCV infection in Japan. A previous study showed that a 24 week course of therapy with interferon-β plus ribavirin resulted in sustained loss of HCV in three of nine patients with chronic hepatitis C.2 However, the efficacy and safety of interferon-β combined with ribavirin has yet to be fully evaluated.

We report the results of a randomised pilot trial comparing interferon-β plus ribavirin with interferon-α plus ribavirin in patients with HCV genotype 1 who poorly responded to interferon-α plus ribavirin. A total of 28 patients with HCV genotype 1 were given 6 MU of recombinant interferon-2b (Schering-Plough, Kenilworth, New Jersey, USA) by intramuscular injection daily for four weeks. Twenty seven patients (16 men and 11 women; mean age 47 ± 8 years) in whom HCV RNA was detected in serum on polymerase chain reaction at week 2 were included in this study and randomly assigned to receive one of two regimens from week 5. Fifteen patients continued to receive 6 MU interferon-2b intramuscularly, given daily from week 5 to week 8, and three times weekly from week 9 to week 24 (interferon-α group). The other 12 patients were assigned to 6 MU natural interferon-β (Toray Industries Inc., Tokyo, Japan), given by intravenous injection daily from week 5 to week 8, and three times weekly from week 9 to week 24 (interferon-β group). Ribavirin (Schering-Plough) was concurrently administered at a daily dose of 400 mg to patients who weighed 60 kg or less and 800 mg to those who weighed more than 60 kg. At the time of this study, a 24 week course of interferon-α plus ribavirin was commonly used in Japan. The data were analysed according to intention to treat.

Baseline characteristics of the patients in the treatment groups were similar. At week 4 of therapy, when treatment was randomly assigned, the proportion of patients without detectable HCV RNA in serum did not differ between the interferon-α group and interferon-β groups (table 1). The proportion of patients with HCV RNA in serum was higher in the interferon-β group than in the interferon-α group at week 12, but did not differ between the groups at the end of treatment (week 24). However, 24 weeks later (week 48), the proportion of patients with a sustained virological response was significantly higher in the interferon-β group than in the interferon-α group. During treatment, neutralising antibodies to interferon were detected in two patients in the interferon-α group and no patients in the interferon-β group (table 1). The proportion of patients with HCV RNA in serum was higher in the interferon-β group than in the interferon-α group at week 12, but did not differ between the groups at the end of treatment (week 24). However, 24 weeks later (week 48), the proportion of patients with a sustained virological response was significantly higher in the interferon-β group than in the interferon-α group. During treatment, neutralising antibodies to interferon were detected in two patients in the interferon-α group and no patients in the interferon-β group. Leucopenia, neutropenia, and platelet counts and haemoglobin concentrations were similar in two groups. Therapy was discontinued because of serious adverse events (including depression) in three patients in the interferon-α group and all 12 patients in the interferon-β group completed 24 weeks of treatment. The dose of ribavirin was reduced because of anaemia in eight patients in the interferon-α group and in four in the interferon-β group. We enrolled patients who did not have a favourable early response to treatment with interferon-α and ribavirin. Antibodies to interferon, which sometimes develop in

| Table 1 Proportions of patients without detectable hepatitis C virus RNA in serum |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Interferon-α group | Interferon-β group | p Value (z test) |
|                                | (n = 15)           | (n = 12)         |                 |
| Week 4                          | 4 (27%)           | 3 (25%)         | 0.92            |
| Week 12                         | 7 (47%)           | 10 (83%)        | 0.049           |
| Week 24 (end of therapy)        | 10 (67%)          | 9 (75%)         | 0.64            |
| Week 48                         | 0 (0%)            | 3 (25%)         | 0.040           |

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patients given recombinant interferon-α, can cause resistance to therapy. Both interferon-α and -β bind to a common type I interferon receptor but utilise different regions of the receptor subunits for specific signalling pathways, potentially leading to distinct biological responses. An oligonucleotide array study has shown that some interferon stimulated genes are preferentially induced by interferon-β, but not by interferon-α. We thus believe that interferon-β might be beneficial for some patients who are resistant to interferon-α. A large randomised trial of peginterferon-α plus ribavirin versus interferon-β plus ribavirin for 48 weeks is being conducted in patients with HCV genotype 1 who do not have a virological response to 12 weeks of treatment with peginterferon-α and ribavirin.

In summary, a combination of interferon-β and ribavirin produced a significantly better sustained virological response than a combination of interferon-α and ribavirin in patients with HCV genotype 1 who were resistant to interferon-α plus ribavirin. Although the overall safety profiles of the two regimens were similar, the rates of treatment discontinuation and of reduction in the dose of ribavirin were lower in patients receiving interferon-β and ribavirin than in those receiving interferon-α and ribavirin.

Acknowledgement
Grant support was received from Ministry of Health, Labour, and Welfare, Japan.

M Enomoto, A Tamori, N Kawada, H Jomura
Department of Hepatology, Osaka City University Medical School, Osaka, Japan

S Nishiguchi
Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

T Saibara, S Onishi
Department of Gastroenterology and Hepatology, Kochi Medical School, Kochi, Japan

S Mochida, K Fujwara
Division of Gastroenterology and Hepatology, Internal Medicine, Saitama Medical School, Saitama, Japan

Correspondence to: Dr S Nishiguchi, Division of Hepatobiliary and Pancreatic Diseases, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan; nishiguchi@hyo-med.ac.jp
doi: 10.1136/gut.2005.081935

Conflict of interest: None declared.

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EDITOR’S QUIZ: GI SNAPSHOT

Answer
From explorative laparotomy, the pancreatic tumour involving the head and proximal body of the pancreas was judged to be resectable. Pylorus preserving proximal pancreaticoduodenectomy was performed. Histology of the tumour was consistent with a diagnosis of renal cell cancer (RCC). Metastases were not detected in periampullary lymph nodes. The patient did not receive any further adjuvant therapy and was discharged from hospital without any serious perioperative morbidity.

The vast majority of pancreatic carcinomas are primary, and among these, more than 90% are of ductal origin. Solitary pancreatic masses can be classified as secondary tumours to the pancreas in only 2% of all cases. In the latter group, RCC seems to be the most common cancer. Within the last three years, 43 new cases of RCC metastases to the pancreas (fig 2). Metastases were not detected in periampullary lymph nodes. The patient did not receive any further adjuvant therapy and was discharged from hospital without any serious perioperative morbidity.

The vast majority of pancreatic carcinomas are primary, and among these, more than 90% are of ductal origin. Solitary pancreatic masses can be classified as secondary tumours to the pancreas in only 2% of all cases. In the latter group, RCC seems to be the most common cancer. Within the last three years, 43 new cases of RCC metastases to the pancreas have been reported (Medline review). Median interval from nephrectomy to diagnosis of pancreatic metastases is 83 months, but time intervals as long as 10–20 years were also reported. Complete resection of pancreatic metastases from RCC are associated with long term survival, particularly in cases of single tumours and/or a long disease free interval.

References
Future use of the Glasgow alcoholic hepatitis score

I N Guha and W M Rosenberg


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