

# PostScript

## LETTERS

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

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

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

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

### Investigation of chronic diarrhoea

I congratulate the authors of the recently revised "BSG guidelines for the investigation of diarrhoea" for their excellent overview of this important clinical problem (*Gut* 2003; 52(suppl V):v1-15). I would however take issue with the suggestion that measurement of stool volumes in outpatients is impractical. In my experience such measurement is readily achievable and cheap, merely requiring a suitable container and some weighing scales. A three day stool collection should be considered early in the investigation of chronic diarrhoea, particularly if a factitious aetiology is suspected which is unfortunately often underdiagnosed and over investigated.<sup>1</sup>

R C G Pollok

Department of Gastroenterology, St George's Hospital, London SW17 0QT, UK; [rpollok@sghms.ac.uk](mailto:rpollok@sghms.ac.uk)

### Reference

- 1 Pollok RCG, Banks MR, Fairclough PD, *et al*. Dilutional diarrhoea: under-diagnosed and over-investigated. *Eur J Gastroenterol Hepatol* 2000;12:609-11.

### Authors' reply

We welcome Dr Pollock's comments on the use of a three day stool collection in the investigation of chronic diarrhoea. Our concern about its use in the outpatient setting, and particularly when factitious diarrhoea is suspected, is that collection is unsupervised and potentially susceptible to interference. It was for this reason that inpatient collection was suggested. Furthermore, we think there will be widespread doubt by clinicians about the acceptability of this approach. Excepting these caveats, we agree that it is a relatively simple and effective way to assess stool volume which may limit the need for other investigations in these patients.

P Thomas, A Forbes

St Mark's Hospital, Watford Road, Harrow HA1 3UJ, UK

Correspondence to: Dr A Forbes; [alastair.forbes@ic.ac.uk](mailto:alastair.forbes@ic.ac.uk)

### Interstitial pneumonia associated with autoimmune pancreatitis

We read with interest the article by Kamisawa *et al* reporting IgG4 positive plasma cells in peripancreatic tissue, extrahepatic bile duct, gall bladder, and salivary gland (*Gut* 2003;52:683-7). The association of retroperitoneal fibrosis and sclerosing pancreatitis with IgG4 bearing plasma cells in the tissues of both lesions has been also reported.<sup>1</sup>

We would like to report the first case of interstitial pneumonia associated with autoimmune pancreatitis and IgG4 positive plasma cells in the interstitium.

Hyperamylasemia was detected in a routine blood examination in a 63 year old man who had been treated for duodenal ulcer at a clinic. He was admitted to our hospital for further examination. He did not complain of epigastralgia or back pain. Serum amylase was 323 (39-130 IU/l), IgG was elevated to 2350 (800-1600 mg/dl), and IgG4 was 1690 (<80 mg/dl). Antinuclear antibody, anti-SS-A antibody, anti-SS-B antibody, rheumatoid factor, and antismooth muscle antibody were all negative. Abdominal ultrasonography and computed tomography (CT) showed swelling of the head and tail of the pancreas. Endoscopic retrograde pancreatography showed irregular narrowing of the main pancreatic duct in the head and tail. Magnetic resonance cholangiography showed extrinsic stenosis of the lower common bile duct. The patient was diagnosed with autoimmune pancreatitis but he refused steroid therapy and was followed as an outpatient.

Three months later, honeycombing of the bilateral lower lung field was detected in a follow up abdominal CT. Chest CT revealed ground glass attenuation in the middle and lower lobe, and honeycombing predominantly at the back of the lower lobe, bilaterally (fig 1A). (Figure 1 (A-D) is available for viewing online at <http://gut.bmjournals.com/cgi/eletters/52/5/683#127>.)

Retrospectively, a slight reticular shadow in the lower lung field was detected in the chest roentgenogram taken at the first admission but the lesion had progressed over three months. He was readmitted for further examination. He had a history of smoking 30-40 cigarettes a day for approximately 40 years. IgG was 3934 mg/dl, IgG4 was 2690 mg/dl, KL-6 was 1440 (<500 u/ml), serum amylase was 142, and lipase was 121 (0-49 IU/l). Schirmer's test indicated a decrease in lacrimal secretion. Swelling of the head and tail of the pancreas were not changed on abdominal ultrasonography and CT.

With gallium scintigraphy, uptake was observed bilaterally at the back of the lower lobe, suggesting active pneumonia. Histology obtained by transbronchial lung biopsy from segment 8a of the right lobe showed marked thickening of the alveolar septum with marked infiltration of plasma cells and lymphocytes (fig 1B).

Immunostaining with IgG4 was performed using the immunoperoxidase method (mouse antihuman IgG4; ICN Biomedicals, Inc, Ohio, Canada). Infiltration of IgG4 positive plasma cells was detected in the alveolar septum (fig 1C).

Macrophages in the alveoli are considered to be due to smoking which often coexists with interstitial pneumonia in smokers.<sup>2</sup>

Because interstitial pneumonia associated with autoimmune pancreatitis was strongly suggested, prednisolone (40 mg/day) was administered for two weeks and then the dose was tapered. Chest CT taken two weeks after treatment showed that the ground glass attenuation in the middle and lower lobe had disappeared whereas the honeycombing remained (fig 1D).

Abdominal ultrasonography performed two weeks after treatment showed a marked decrease in the swelling of the pancreas.

In the present case, infiltration of IgG4 positive plasma cells in the interstitium strongly suggests that the interstitial lung disease was associated with autoimmune pancreatitis. Interstitial pneumonia associated with Sjogren's syndrome is unlikely in this case although there was decreased lacrimal secretion. Sicca syndrome observed in autoimmune pancreatitis is distinctive from classical Sjogren's syndrome in that it is negative for anti-SS-A or anti-SS-B antibodies, serum IgG4 is elevated, and infiltration of IgG4 positive plasma cells in the salivary glands is observed.<sup>3</sup>

Autoimmune pancreatitis, in some cases, may be part of a systemic disease associated with IgG4.

T Taniguchi, M Ko, S Seko, O Nishida, F Inoue, H Kobayashi, T Saiga, M Okamoto

Department of Internal Medicine, Radiology, and Pathology, Ohtsu Red Cross Hospital, Ohtsu, Japan

T Fukuse

Department of Thoracic Surgery, Kyoto University Faculty of Medicine, Kyoto, Japan

Correspondence to: Dr T Taniguchi, Department of Internal Medicine, Ohtsu Red Cross Hospital, 1-1-35 Nagara, Ohtsu, Shiga Ohtsu, Japan

### References

- 1 Hamano H, Kawa S, Ochi Y, *et al*. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002;359:1403-4.
- 2 American Thoracic Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002;165:277-304.
- 3 Hamano H, Kawa S, Horiuchi A, *et al*. High serum concentration in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732-8.

### Author's reply

We thank Dr Taniguchi *et al* for the interesting presentation of interstitial pneumonia associated with autoimmune pancreatitis (AIP).

We have experienced 24 cases of AIP but no cases showed interstitial pneumonia clinically. Recently, we immunohistochemically examined the organs of eight patients with AIP using anti-IgG4 antibody. IgG4 positive plasmacytic infiltration was detected in the portal area of the liver, gastric mucosa, colonic mucosa, and bone marrow as well as in the pancreas, peripancreatic tissue, extrahepatic bile duct, gall bladder, salivary gland,

and lymph nodes of patients with AIP. However, few IgG4 positive plasma cells were observed in identical control specimens. From these findings, we proposed a new clinicopathological entity of IgG4 related autoimmune disease, and stressed that AIP is not simply pancreatitis but a pancreatic lesion involved in this systemic autoimmune disease.<sup>1,2</sup> As IgG4 positive plasmacytic infiltration was observed in the transbronchially biopsied pulmonary specimens of the patient with AIP (unpublished data), it is likely that interstitial pneumonia occurs in association with AIP.

**T Kamisawa, N Funata, A Okamoto**  
Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Correspondence to: Dr T Kamisawa, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan; kamisawa-k@komagome-hospital.bunkyo.tokyo.jp

## References

- 1 **Kamisawa T**, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. *Am J Gastroenterol* 2003;**98**:2811–12.
- 2 **Kamisawa T**, Funata N, Hayashi Y, *et al.* A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;**38**:982–4.

## The diagnostic dilemmas in discrimination between pancreatic carcinoma and chronic pancreatitis

In response to the letter of Harlozinska-Szmyrka and Strutyńska-Karpinska (*Gut* 2004;**53**:469–70) commenting on our study,<sup>1</sup> we agree with the remarks made in relation to the difficulties in discriminating between chronic pancreatitis and adenocarcinoma using currently employed diagnostic imaging and tumour marker analysis. Our study was aimed at determining the risk of cancer development in patients with proven chronic pancreatitis,<sup>1</sup> examining age and sex standardised incidence ratios calculated from the number of observed cases of pancreatic cancer in our cohort of 373 patients with predominantly alcohol related chronic pancreatitis to the number of cases expected in the National Cancer Registry. Our study design did not take into consideration diagnostic dilemmas and focused purely on cancer risk in our cohort of patients using defined stringent criteria. Indeed, we previously underlined the interest of biological markers in this situation (for example, CA19-9 and circulating K-ras)<sup>2,3</sup>; however these markers have problems with both sensitivity and specificity.

We acknowledge that given the difficulties in diagnosing cancer in this situation, the establishment of new tumour markers such as tissue polypeptide specific antigen (TPS)<sup>4</sup> with proven good sensitivity and specificity should provide for progress in the future. It has to be stressed however that TPS, a marker of proliferation activity, is not specific to pancreatic cancer, and other digestive and non-digestive cancers as well as benign chronic disorders may have high levels of this marker.<sup>5–7</sup> Thus validated data concerning tumour markers, either alone or in combination, in distinguishing pancreatic

cancer from chronic pancreatitis should prove important in diagnostic situations.

**P Ruzsniwski, D Malka, P Hammel, F Maire, P Rufat, I Madeira, F Pessione, P Lévy**  
Department of Gastroenterology, Beaujon Hospital, Clichy, France

Correspondence to: Professor P Ruzsniwski, Service de Gastroenterologie, Hôpital Beaujon, F-92118, Clichy, France; philippe.ruzsniwski@bjn.ap-hop-paris.fr

## References

- 1 **Malka D**, Hammel P, Maire F, *et al.* Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut* 2002;**51**:849–52.
- 2 **Nouts A**, Levy P, Voitot H, *et al.* Diagnostic value of serum CA 19-9 antigen in chronic pancreatitis and pancreatic adenocarcinoma. *Gastroenterol Clin Biol* 1998;**22**:152–9.
- 3 **Maire F**, Micard S, Hammel P, *et al.* Differential diagnosis between chronic pancreatitis and pancreatic cancer: value of the detection of KRAS2 mutations in circulating DNA. *Br J Cancer* 2002;**27**, **87**:551–4.
- 4 **Slesak B**, Harlozinska-Szmyrka A, Knast W, *et al.* Tissue polypeptide specific antigen (TPS), a marker for differentiation between pancreatic carcinoma and chronic pancreatitis. A comparative study with CA 19-9. *Cancer* 2000;**89**:83–8.
- 5 **Malamitsi-Puchner A**, Vazeou-Gerasimidi A, Sarandakou A, *et al.* Tissue polypeptide-specific antigen serum concentrations in children, adolescents, and young adults with type 1 diabetes. *Diabetes Care* 2002;**25**:240–1.
- 6 **Hrycek A**, Kokocinska D, Kosmider J, *et al.* Tissue polypeptide-specific antigen in SLE patients treated with low doses of quinagolide. *Lupus* 2003;**12**:149–52.
- 7 **Valik D**, Nekulova M. Serum tissue polypeptide-specific antigen (TPS): what is its diagnostic value? *Br J Cancer* 2000;**82**:1756–8.

## In search of the correct strategy for preventing the spread of HCV infection

Hepatitis C virus (HCV) infection is an emerging global healthcare issue. Apart from affecting approximately 3% of the world population, HCV is also a silent disease—the majority of incidences go unrecognised and serve unknowingly as sources of infection to others.<sup>1,2</sup> Add to that the scant information defining the transmission routes and rates of HCV, the programme presented by Skipper *et al* in their paper evaluating the diagnosis and prevention of HCV in a prison outreach clinic (*Gut* 2003;**52**:1500–4) seems a model that could significantly constrain a situation that appears to be reaching epidemic proportions, especially here in Southern Italy.

Studies on the epidemiology of HCV infection in Italy have shown that this infection represents a major health problem throughout Southern Italy, with a prevalence of up to 12.6% in the general population.<sup>3–5</sup> Also, HCV has been linked to the high incidence and mortality rates for liver cancer found in our region (standardised incidence rates per 100 000 inhabitants: 18.9 male, 13.2 female; mortality rates 15.2 male, 9.0 female).<sup>6</sup> Between January 2000 and December 2001, we performed a cross sectional study of 5844 individuals (4260 men; 1584 women) from the general population and from five select groups in the city of Naples, with the purpose of assessing the prevalence of HCV infection in select groups with different exposure

patterns in Southern Italy. Below are the preliminary data from this study:

- general population (n = 1972; prevalence 8.5%);
- imprisonment (n = 524; prevalence 37.4%);
- intravenous drug use (n = 1436; prevalence 31.8%);
- haemodialysis (n = 678; prevalence 2.9%);
- routine medical examination of patients (n = 453; prevalence 12.6%); and
- health care workers at the National Cancer Institute of Naples (n = 781; prevalence 6.4%).

Our findings confirm the high prevalence among drug users (31.8%) but the highest prevalence was found among male prisoners (37.4%), particularly those in the 30–49 year age range (47.3%). In fact, we concur with Skipper *et al* that “those involved with IDU frequently pass through the penal system and spend time in prisons” thus indicating a probable interrelationship between these two groups.

Our other findings from this study shed light on the unusually high prevalence of this disease in the general population of Southern Italy. Previous reports have shown that the prevalence of HCV infection is generally low in the general population of most industrialised countries (<5%).<sup>7</sup> In Southern Italy, the high prevalence of HCV infection may be the result of past iatrogenic transmission, aggravated by:

- (1) extensive use of glass syringes or non-sterile syringes<sup>8</sup>; and
- (2) social conditions which may indirectly favour the spread of infection:

- general poverty,
- poor education etc,<sup>9,10</sup> and
- especially among females, haemodialysis procedures.

Prisons do play a significant role in the hepatitis C epidemic, especially as the same social conditions mentioned above which may facilitate spread of infection also predict imprisonment.<sup>11</sup> In fact, a disproportionate share of the burden of HCV infection is found among those who pass through correctional facilities.<sup>12</sup> As stated previously, HCV seroprevalence is high among this group. A history of incarceration is one of the strongest associations with HCV seropositivity.<sup>13</sup> Yet despite these high levels, reports of HCV transmission in the prison setting are uncommon.<sup>14,15</sup> In fact, studies have revealed that an overwhelming number of these infections are being brought into prisons via inmates who are already previously infected; drug users are most likely to become infected with HCV at the beginning of their addiction—long before being imprisoned for the first time.<sup>16–18</sup> Yet it must be taken into account the fact that the dynamic movement of people in and out of prisons makes it very difficult to detect transmission.<sup>19</sup> While the available data do not prove that infections are acquired in prison, they do indicate prisons as high risk institutions for the spread of HCV.<sup>20</sup>

What is of great concern to us are the implications of the previous and following data:

- HCV is easily transmitted parenterally.

- Our prisons are overcrowded (the Secondigliano prison located in Naples, for example, has 1350 prisoners and only 750 beds).
- In Southern Italy, the health system in general is less efficient and less meticulous than that in the north of Italy (and in the rest of the EU and in the USA).<sup>8</sup>
- We have no harm reduction programmes in place.

The limited availability of prevention methods has been linked to the transmission of HCV infection.<sup>21</sup> This association, and its relation to inadequate management of a manageable problem, surely opens up our National Health System to costly retaliations. If it can be proven that an inmate contracted HCV while incarcerated, due to a lack of sufficient care and prevention on the part of the system, he then has the right to seek judicial indemnification—a costly process for all concerned.

How much more economical to initiate admission screening programmes in our overcrowded prisons where, as detailed above, there is an identifiable elevated risk. By so doing, we move one step closer to correcting a problem that is grossly out of control. As HCV is associated with different kinds of neoplasms (liver, possibly non-Hodgkins lymphoma) and with autoimmune diseases (cryoglobulinaemia, thyroiditis, Hashimoto thyroiditis), which develop after the virus has caused immune system alterations,<sup>22</sup> routine health screening on admission to prison presents a unique opportunity to identify health needs and plan health services at an early stage.<sup>23</sup> In fact, studies have found that screening provides a preventive function, as those who had previously presented for a hepatitis C test, regardless of the result, were less likely to have recently engaged in high risk behaviour (that is, sharing injecting equipment).<sup>24</sup>

How much more economical to initiate a good educational harm reduction programme such as that implemented by Skipper *et al.* Correctional interventions of this kind stand to benefit not only the inmates themselves and their families and partners, but also the public health of the communities to which the vast majority of inmates return.<sup>12</sup> By implementing such a programme, the health-care system would be doing its job, demonstrating efficient management of a crucial problem and sustaining the welfare of its people.

**M Montella, A Crispo, J Wynn-Bellezza**

National Cancer Institute, Naples, Italy

Correspondence to: Dr M Montella;  
epidemiologia.int@tin.it

## References

- Mohsen AH, Group TH, Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 2001;**48**:707–13.
- Thomas DL, Astemborski J, Rai RM, *et al.* The natural history of hepatitis C virus infection: host, viral and environmental factors. *JAMA* 2000;**284**:450–6.
- Guadagnino V, Straffolini T, Rapicetta M, *et al.* Prevalence, risk factors and genotype distribution of hepatitis C virus infection in the general population: a community-based survey in Southern Italy. *Hepatology* 1997;**26**:1006–11.
- Maio G, d'Argenio P, Straffolini T, *et al.* Hepatitis C virus infection and alanine transaminase levels in the general population: a survey in a southern Italian town. *J Hepatol* 2000;**33**:116–20.
- Raffaele A, Valentini M, Iovenitti M, *et al.* High prevalence of HCV infection among the general population in a rural area of Central Italy. *Eur J Epidemiol* 2001;**17**:41–6.
- Zanetti R, Gafà L, Pannelli F, *et al.* *Cancer in Italy: Incidence data from Cancer Registries, third volume: 1993–1998*. Rome: Il Pensiero Scientifico Editore, 2002.
- Touzet S, Kraemer L, Colin C, *et al.* Epidemiology of hepatitis C virus infection in seven European Union countries: a critical analysis of the literature. HENCORE Group (Hepatitis C European Network for Co-operative Research). *Eur J Gastroenterol Hepatol* 2000;**12**:667–78.
- Di Stefano R, Straffolini T, Ferraro D, *et al.* Endemic hepatitis C virus infection in a Sicilian town: further evidence for iatrogenic transmission. *J Med Virol* 2002;**67**:339–44.
- Sarbah SA, Younussi ZM. Hepatitis C: an update on the silent epidemic. *J Gastroenterol Hepatol* 2000;**30**:125–43.
- Geddes M, Berlinguer G. *La Salute in Italia, rapporto*. Rome: Ediesse Edition, 1998.
- McCarthy N. The legitimacy of punishment systems should be addressed. *BMJ* 2000;**321**:1406.
- Hammitt TM, Harmon MP, Rhodes W. The burden of infectious disease among inmates of and releases from US correctional facilities, 1997. *Am J Pub Health* 2002;**92**:1789–94.
- Crofts N, Jolley D, Kaldor J, *et al.* The epidemiology of hepatitis C virus infection among Australian injecting drug users. *J Epidemiol Community Health* 1997;**51**:692–7.
- Haber PS, Parsons SJ, Harper SE, *et al.* Transmission of hepatitis C within Australian prisons. *Med J Aust* 1999;**171**:31–3.
- Rosen HR. Acquisition of hepatitis C by a conjunctival splash. *Am J Infect Control* 1997;**25**:242–7.
- Lamden KH, Kennedy N, Beeching NJ, *et al.* Hepatitis B and hepatitis C virus infections: risk factors among drug users in Northwest England. *J Infect* 1998;**37**:260–9.
- Chang CJ, Lin CH, Lee CT, *et al.* Hepatitis C virus infection among short-term intravenous drug users in southern Taiwan. *Eur J Epidemiol* 1999;**15**:597–601.
- Rezza G, Sagliocca L, Zaccarelli M, *et al.* Incidence rate and risk factors for HCV seroconversion among injecting drug users. *Scand J Infect Dis* 1996;**28**:27–9.
- Dolan KA. Can hepatitis C transmission be reduced in Australian prisons? *Med J Aust* 2001;**174**:378–9.
- Allwright S, Bradley F, Long J, *et al.* Prevalence of antibodies to hepatitis B, hepatitis C, and HIV and risk factors in Irish prisoners: results of a national cross sectional survey. *BMJ* 2000;**321**:78–82.
- Butler TG, Dolan KA, Ferson MJ, *et al.* Hepatitis B and C in New South Wales prisons: prevalence and risk factors. *Med J Aust* 1997;**166**:127.
- Farci P, Shimoda A, Coiana A, *et al.* The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. *Science* 2000;**288**:339–44.
- Morrison DS, Gilchrist G. Prison admission health screening as a measure of health needs. *Health Bull (Edinb)* 2001;**59**:114–9.
- Cook PA, McVeigh J, Syed Q, *et al.* Predictors of hepatitis B and C infection in injecting drug users both in and out of drug treatment. *Addiction* 2001;**96**:1787–97.

## Cross reactivity due to positive canrenone interference

Canrenone is a selective competitive inhibitor of the aldosterone receptor and a diuretic drug commonly used in the treatment of cirrhotic patients both with and without ascites.<sup>1</sup> The aim of our observation was to determine if canrenone cross reacts with aldosterone in an immunoradiosorbent assay kit used for the hormonal scoring system according to the Child-Pugh classification for liver cirrhosis.<sup>2</sup> Canrenone, in vitro experi-

ments, was a gift from GiEnne Pharma (Group Therabel) Diagnostics. Canrenone, potassium canrenoate, and spironolactone are often used with digoxin in clinical practice and can cause falsely low readings in common assays for digoxin (that is, AxSym MEIA-Abbott) due to negative cross reactivity, and falsely elevated serum digoxin concentrations with the fluorescence polarisation immunoassay for digoxin.

Human hepatic stellate cells, isolated from wedge sections of normal human liver unsuitable for transplantation, were separated, after digestion with collagenase/pro-nase, from other liver non-parenchymal cells by ultracentrifugation over gradients of stractan. Cells were cultured on plastic culture dishes in Iscove's modified Dulbecco's medium, supplemented as described elsewhere.<sup>3</sup> Cells were plated ( $1 \times 10^5$  cells in well dishes) and incubated with increasing concentrations of canrenone or with no drug (SFIF or control conditions), after a 24 hour incubation period in serum free insulin free (SFIF) medium. After 24 hours, medium was removed and then lyophilised in a dry vacuum. Pellets were then resuspended in a total volume of 1 ml and aliquots of 200  $\mu$ l were processed for aldosterone assay (Radim kit, Italy: KS17CT, RIA method). The results showed increasing linearity (0.007 (0.003); 0.018 (0.004); 0.027 (0.003) nmol/l (mean (SD)); n = 3). As values obtained in SFIF samples were below the lower limit of the assay (0.009 (0.001)), it is conceivable that these cells do not produce aldosterone under basal conditions.<sup>4</sup>

To further validate this observation, we then spiked sera with increasing concentrations of canrenone (10, 50, 100  $\mu$ M) and, subsequently, aldosterone concentrations were determined. Sera were collected from patients with different degrees of liver disease (from acute hepatitis (n = 1), to non-alcoholic steatohepatitis (n = 1), or chronic active hepatitis with (n = 3) or without (n = 6) cirrhosis). Aldosterone concentrations were as follows: 0.32 (0.18), 0.63 (0.22), 0.85 (0.26), and 1.07 (0.35) nmol/l (n = 11). Comparing these concentrations with the increasing concentrations of canrenone spiked into sera, a statistically significance was found (from  $r = 0.874$  to  $r = 0.988$ ;  $p < 0.001$ ).

To date, only positive interferences leading to falsely high digoxin readings, including those due to spironolactone and canrenone, have been reported.<sup>5</sup> Negative interference is much more dangerous. Toxic concentrations may remain undetected. Less severe negative interferences or interferences from clinically less significant cross reactants have been reported. Assay manufacturers should assess potential cross reactivity in the presence of the primary ligand. This difficulty may apply to immunoassays and cross reactants other than digoxin and canrenone. Pathologists and clinicians should be aware of negative interference so that intoxication due to drug dosing guided by monitoring of its concentration in serum can be avoided. For positive interference of a low molecular weight substance, such as in our observation, false positive test results for hormonal and electrolyte disturbances during liver cirrhosis can be avoided.

These in vitro results can be considered effective in measuring aldosterone concentrations in plasma under in vivo conditions using a more cautious approach, as cross

reactivity could hardly affect biological determinations.

**R G Romanelli, P Gentilini**

Università degli Studi di Firenze, Dipartimento di  
Medicina Interna, Viale Morgagni, 85 50134  
Florence, Italy

Correspondence to: Dr R G Romanelli;  
r.romanelli@dmi.unifi.it

## References

- 1 **La Villa G, Barletta G, Romanelli RG, et al.** Cardiovascular effects of canrenone in patients with preascitic cirrhosis. *Hepatology* 2002;**35**:1441–8.
- 2 **Pugh RNH, Murray-Lyon IM, Dawson JL.** Transection of the esophagus for bleeding esophageal varices. *Br J Surg* 1973;**60**:646–9.
- 3 **Pinzani M, Failli P, Ruocco C, et al.** Fat-storing cells as liver-specific pericytes: spatial dynamics of agonist-stimulated intracellular calcium transients. *J Clin Invest* 1992;**90**:642–6.
- 4 **Caligiuri A, De Franco RMS, Romanelli RG, et al.** Antifibrogenic effects of canrenone, an antialdosterone drug, on human hepatic stellate cells. *Gastroenterology* 2003;**124**:504–20.
- 5 **Huffman DH.** The effect of spironolactone and canrenone on the digoxin radioimmunoassay. *Res Commun Chem Pathol Pharmacol* 1974;**9**:787–90.

## Responses to endothelin-1 in patients with advanced cirrhosis before and after liver transplantation

In response to Helmy's comments in his recent letter (*Gut* 2004;**53**:470–1), we wish to emphasise the following points, many of which were clearly stated in our original paper.<sup>1</sup>

In agreement with the comments on "generalised vasodilatation" in cirrhosis, we made it clear that basal forearm blood flow was normal in our patient cohort despite the presence of a vasodilated circulation, as evidenced by a reduced systemic vascular resistance index. As pointed out in our paper, this observation is consistent with findings of previous studies and suggests that beds other than the forearm circulation, such as those of the splanchnic and pulmonary circulation, were dilated in our patients.

With regard to the issues raised about the use of one arm plethysmography, our own results and those of others have shown that under well controlled circumstances the effects of external stimuli on results obtained using this approach are minimal.<sup>2</sup> Indeed, in our study, the results of forearm plethysmography were very consistent across both the control and cirrhotic patient groups.<sup>1</sup> However, we acknowledge that single forearm plethysmography could be affected by changes in systemic haemodynamics (due for example to the effects of drug infusions). However, as stated in the text, neither heart rate nor blood pressure altered significantly throughout the course of the experiment.

In forearm resistance arteries (and elsewhere), ET<sub>B</sub> receptors on vascular smooth muscle and endothelial cells mediate opposing effects on vascular tone.<sup>3</sup> Thus ET<sub>B</sub> blockade could result in either vasodilatation or vasoconstriction, depending on which receptor subpopulation is most affected. In our hands, preliminary experiments with the ET<sub>B</sub> blocker BQ788 yielded ambiguous responses, even in control subjects, causing vasoconstriction in some and vasodilatation

in others. Until a selective ET<sub>B</sub> receptor antagonist (for VSMC or endothelium) is available, interpretation of the results obtained using BQ788 remains difficult.

As for the concern that similar vasodilatation was observed with endothelin-1 (ET-1) and BQ123 (an ET<sub>A</sub> antagonist), we wish to re-emphasise these were two very different experiments in two separate groups of patients, asking two different questions. We observed:

- (1) that ET-1 infusion in these advanced cirrhotics produced mild vasodilatation; and
- (2) in similar patients, there was no difference between cirrhotics and controls in the effects of BQ123 on vascular tone.

We put these two results together to propose that it is likely that the abnormal response to ET-1 infusion reflects alterations in ET<sub>B</sub> mediated responses in cirrhotics (either via receptor changes or downstream pathways such as changes in nitric oxide synthesis, prostanoid production, or endothelium derived hyperpolarising factor).

As pointed out by Helmy, there was an early dilatory response following ET-1 infusion in cirrhotics. This is not totally unexpected as it has previously been demonstrated that ET-3 (an ET<sub>B</sub> receptor agonist) causes early vasodilatation in control subjects; similarly, a trend towards an early vasodilatory effect of ET-1 has been observed in healthy subjects.<sup>3</sup>

Regarding the use of concomitant drug therapy, all medications were ceased more than 24 hours prior to the experiments. While some residual effect of these agents is possible, more prolonged cessation of drug therapy in these decompensated patients was not considered safe or ethical. With regard to measurement of ET-1, as detailed in our paper, a commercially available assay with cross reactivity between big ET-1 and ET-1 was used. The study was not powered (nor was it designed to) to pick up small differences in brachial artery ET-1 levels.

**P W Angus, R B Vaughan, J P F Chin-Dusting**

Department of Gastroenterology, Austin Hospital,  
Heidelberg 3084, Australia

Correspondence to: Professor P W Angus;  
Peter.Angus@austin.org.au

## References

- 1 **Vaughan RB, Angus PW, Chin-Dusting JPF.** Evidence for altered vascular responses to exogenous endothelin-1 in patients with advanced cirrhosis with restoration of the normal vasoconstrictor response following successful liver transplantation. *Gut* 2003;**52**:1505–10.
- 2 **Duffy, SJ, Tran BT, Gishel N, et al.** Continuous release of vasodilator prostanoids contributes to regulation of resting forearm blood flow in humans. *Am J Physiol* 1998;**274**:H1174–83.
- 3 **Haynes WG, Strachan FE, Gray GA, et al.** Forearm vasoconstriction to endothelin-1 is mediated by ETA and ETB receptors in vivo in humans. *J Cardiovasc Pharmacol* 1995;**26**:S40–3.

## Cluster's last stand

Guthrie and colleagues (*Gut* 2003;**52**:1616–22) described the results of cluster analysis in a patient sample with severe irritable bowel syndrome (IBS). Their analysis investigated a broad range of factors in addition to symptoms; these included psychosocial measures (psychiatric involvement, health service

encounters, quality of life) and physiological parameters (rectal thresholds). The authors have demonstrated that severe IBS can be classified according to non-symptom characteristics and, in particular, according to the level of psychological distress, service encounters, and rectal sensitivity. They describe three groups which they labelled "distressed high utilisers," "distressed low utilisers", and "tolerant low utilisers." The authors defend their analysis on clinical grounds and point to treatment implications for each of these groups.

We feel that there are some fundamental points about the nature of cluster analysis that readers of this paper should not overlook. Cluster analysis was initially developed to create and/or evaluate classifications.<sup>1</sup> Its application to gastrointestinal research has followed this approach. In recent years, clustering techniques have been applied to confirm that IBS and functional dyspepsia exist as separate clinical entities, and to evaluate specific syndrome subgroups, as described by the current Rome criteria.<sup>2–4</sup> Following traditional clinical approaches, cluster solutions have generally been derived from symptom based parameters, including frequency, severity, and predominant complaint.

The term "cluster analysis" describes a range of procedures which use empirical methods to form groups of highly similar entities. While the notion that cluster analysis is solution seeking, operation of these techniques is essentially solution imposing; that is, clustering methods will *always* place objects into groups. Furthermore, as there are no formal statistical procedures to evaluate the resulting solution, the reasonableness of any solution is determined only on the basis of personal judgement. This is a problem. Indeed, critics of the approach have argued that cluster analysis encourages "naïve empiricism"—that is, inclusion of as many variables as possible in the hope that a meaningful structure will come out.<sup>1,5</sup> However, proponents of cluster analysis have suggested that careful selection of variables on theoretical grounds can overcome this limitation.<sup>1</sup>

It is intuitively obvious that any single entity can be classified according to a broad range of dimensions, and Guthrie *et al* have certainly demonstrated this with respect to IBS. However, we rarely classify any object or entity according to all possible dimensions simultaneously; this would lead to a complex set of descriptors which may be unwieldy and contain many redundancies. Rather, we tend to select out a subset of meaningful dimensions that best suit our purposes in forming a classification.

There are certainly theoretical grounds for considering psychological involvement when evaluating patients with IBS. The association of IBS with psychological disturbance and health care seeking has been well described, and our understanding of these factors has contributed greatly to current therapeutic approaches. However, we challenge the proposed classification of IBS according to psychological involvement on two grounds. Firstly, we view this as a step towards naïve empiricism; other researchers may be encouraged to replicate these analyses across a broader and even more diverse (yet irrelevant) range of dimensions. This is not likely to produce a parsimonious classification scheme that is useful in either clinical practice or the research setting. Secondly, classification of IBS according to psychological and/or psychiatric involvement

may stigmatise some patients with this complaint; one of the unfortunate consequences of classification is the tendency to attach labels to the subgroups that emerge.

#### S C Howell

School of Public Health, The University of Sydney,  
Nepean Hospital, Penrith, New South Wales,  
Australia

#### G D Eslick

Department of Medicine, The University of Sydney,  
Nepean Hospital, Penrith, New South Wales,  
Australia

#### N J Talley

Center for Enteric Neurosciences and Translational  
Epidemiological Research (CENTER), Mayo Clinic,  
Rochester, Minnesota, USA

Correspondence to: Mr S C Howell, School of Public  
Health, The University of Sydney, Nepean Hospital,  
Level 5, South Block, PO Box 63, Penrith, NSW 2751,  
Australia; HowellS@wahs.nsw.gov.au

## References

- 1 Aldenderfer MS, Blashfield RK. *Cluster analysis, Sage University paper series on quantitative application in the social sciences*. New Delhi: Sage Publications, 1984.
- 2 Eslick GD, Howell SC, Hammer J, et al. Empirically derived symptom sub-groups correspond poorly with diagnostic criteria for functional dyspepsia and irritable bowel syndrome. A factor and cluster analysis of a patient sample. *Aliment Pharmacol Ther* 2004;**19**:133–140.
- 3 Talley NJ, Holtmann G, Agreus L, et al. Gastrointestinal symptoms and subjects cluster into distinct upper and lower groupings in the community: a four nations study. *Am J Gastroenterol* 2000;**95**:1439–47.
- 4 Ragnarsson G, Bodemar G. Division of the irritable bowel syndrome into subgroups on the basis of daily recorded symptoms in two outpatient samples. *Scand J Gastroenterol* 1999;**34**:993–1000.
- 5 Everitt B. Unresolved problems in cluster analysis. *Biometrics* 1979;**35**:169–81.

## Small bowel carcinoma and coeliac disease

We thank Howdle *et al* for their comments on our study, detailed recently in their letter (*Gut* 2003;**53**:470). In their British Society of Gastroenterology (BSG) National Survey,<sup>1</sup> Howdle *et al* relied mainly on gastroenterologists and surgeons to report cases of small bowel carcinoma and whether they were associated with either coeliac or Crohn's disease. This may have resulted in underestimation of associated coeliac disease. In our series, we had two cases in which the original pathologist had failed to recognise the histological features of coeliac disease in mucosa adjacent to the adenocarcinoma.<sup>2</sup> The diagnosis of coeliac disease was made after review of the original

resections. This problem has been recognised previously<sup>3</sup> and results in the underdiagnosis of coeliac disease and further diagnostic delay for the patient with coeliac disease.

While the individual risk for patients with coeliac disease in developing adenocarcinoma of the small intestine is not great, poor survival should prompt rapid evaluation when symptoms occur. In addition, there should be a consideration of whether there is a subset of patients with coeliac disease who would benefit from screening for these cancers. Because patients with coeliac disease do not have a significantly increased risk of duodenal adenomas,<sup>4</sup> the role of video capsule endoscopy of the entire small intestine needs to be explored.

#### P H R Green, S D Rampertab

Columbia University College of Physicians and  
Surgeons, New York, USA

Correspondence to: Dr P H R Green, Columbia  
University College of Physicians and Surgeons, 161  
Fort Washington Ave, Room 645, New York 10032,  
USA; pg11@columbia.edu

## References

- 1 Howdle PD, Jalal PK, Holmes GK, et al. Primary small-bowel malignancy in the UK and its association with coeliac disease. *Q J Med* 2003;**96**:345–53.
- 2 Rampertab SD, Forde KA, Green PH. Small bowel neoplasia in coeliac disease. *Gut* 2003;**52**:1211–14.
- 3 MacGowan DJ, Hourihane DO, Tanner WA, et al. Duodeno-jejunal adenocarcinoma as a first presentation of coeliac disease. *J Clin Pathol* 1996;**49**:602–4.
- 4 Rampertab SD, Fleischauer A, Neugut AI, et al. Risk of duodenal adenoma in celiac disease. *Scand J Gastroenterol* 2003;**38**:831–3.

## RETRACTION

Due to an administrative error, one article has been published on two occasions. The journal would like to retract the paper by Lindsay *et al* in the July issue (*Gut* 2003;**52**:981–7) as it is a replicated version of a paper by the same authors in the March issue (*Gut* 2003;**52**:363–9). The journal apologises for this error.

## NOTICES

### British Society of Gastroenterology Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of

the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United Kingdom for specialist experience and training in endoscopy.

Specialist registrars who have not achieved their CCST are expected to have the approval of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applicants are expected to provide confirmation that they have been accepted for training in the unit that they wish to visit.

Successful applicants will be expected to provide a brief written report to the Endoscopy Committee of the outcome of their visit.

Application forms are available from the British Society of Gastroenterology Office, 3 St Andrew's Place, London NW1 4LB. Email: bsg@mailbox.ucl.ac.uk

### 14<sup>th</sup> International Workshop of Digestive Endoscopy, Ultrasonography and Radiology

The 14<sup>th</sup> International Workshop of Digestive Endoscopy, Ultrasonography and Radiology will be held in Marseille on 27–28 May 2004. For further information, please contact: Nathalie Fontant, Atelier Phenix, 41 rue Docteur Morruci, 13006 — Marseille (tel: (33) 04-91-37-50-83; fax: (33) 04-91-57-15-28; e-mail: nfontant@aphenix.com).

### European Postgraduate Gastro- surgical School (EPGS) Courses 2004

The EPGS at the Academic Medical Center of the University of Amsterdam will be holding the following courses during the year: 'Benign Hepato-Biliary Disorders' will be held on 22 & 23 April 2004, 'Endosonography live in Amsterdam' will be held on 2, 3 & 4 June 2004, and 'Update in Coloproctology' will be held on 28 & 29 October 2004. For further information, please contact: J Goedkoop (tel: (31) 566 3926; fax: (33) 267 5594; e-mail: j.goedkoop@amc.uva.nl; website: www.epgs.nl).

### 8<sup>th</sup> Southeast European Symposium of Paediatric Surgery

The 8<sup>th</sup> Southeast European Symposium of Paediatric Surgery will focus upon 'Infectious Problems in Paediatric Surgery.' The event will be held between 24–25 September 2004, at the University of Graz, Austria. For further information, please contact: Professor M E Höllwarth, Department of Paediatric Surgery, Medical University of Graz, Austria, Auenbruggerplatz 34, 8036 Graz; tel: + 43 316 385 3762; fax: tel: + 43 316 385 3775; e-mail: kinderchirurgie@uni-graz.at.