Is coeliac disease a confounding factor in the diagnosis of NASH?

EDITOR,—We read with great interest the paper by Wigg *et al* (*Gut* 2001;**48**:206–11) concerning the role of small intestinal bacterial overgrowth in the pathogenesis of non-alcoholic steatohepatitis (NASH) but we would like to comment on the enrolment criteria used for their study. We agree with Farrell (*Gut* 2001;**48**:148–9) that the Adelaide group's failure to characterise the variables of obesity and diabetes in their population might result in selection bias. Moreover, they made no attempt to exclude the possibility of coeliac disease (CD) which can also be associated with altered intestinal permeability even when the disease is subclinical.[1]

In approximately 40% of all adults with this disease, increased serum transaminase levels are found at diagnosis,[2] and such elevations may be the only abnormality in cases of "occult" CD.[3] In fact, in a study by Bardella *et al*, 9.3% of cases of unexplained chronic hypertransaminasaemia were ultimately diagnosed as CD.[4]

From December 1997 to December 1999, we observed 30 subjects (22 males, eight females; mean age 40 (9.3) years; mean weight 71.6 (7.9) kg) with clinical and laboratory pictures fully compatible with a diagnosis of NASH—that is, AST 56.3 (13.6) IU/l (normal 7–45); ALT 102 (36.8) IU/l (normal 7–45); histological findings of macrovesicular steatosis, inflammation, hepatic fibrosis, and Mallory's bodies; no history of alcohol consumption; and no other significant liver disease. All 30 patients had serum assays of IgG and IgA antibodies against gliadin and endomysium antibody (EMA), and duodenal biopsies were collected from those who were EMA positive. Four of these patients (one male and three females; mean age 30.6 (5.5) years) were thus diagnosed as having occult CD. The only clinical abnormalities were elevations in serum transaminase and sonographic evidence of fatty infiltration of the liver. All four were placed on a gluten free diet and followed with clinical examination and blood chemistry studies every three months. After three months on the prescribed diet, all patients presented decreases in serum transaminase levels (AST 30.2 (8.6) IU/l and ALT 45.2 (9.3) IU/l) and reduced steatosis on ultrasound. At one year from diagnosis, transaminase levels have normalised (AST 29.6 (9.7) IU/l and ALT 23.6 (2.5) IU/l), duodenal histology has improved considerably, and there is no sign of steatosis on sonography.

CD may cause increased intestinal permeability,[5] and its clinical, biochemical, and histological findings are similar to those of NASH.[6] The fact that elevated transaminase levels and EMA positivity can be documented even in the subclinical stages of CD suggests that the inflammatory process in this disease may be triggered by the same oxidative stress cited by Farrell as a cause of tissue damage in NASH. In a recent study, Lahat *et al* showed that CD is also associated with increased expression of inflammatory cytokines, including tumour necrosis factor α.[7]

In light of the findings reviewed here, we feel that all patients with unexplained hypertransaminasaemia should be screened for CD, and that CD must be excluded before the diagnosis of NASH is made.

A GRIECO
L MIELE
G PIGNATARO
M POMPILI
G L RAPACCINI
G GASBARRINI
Institute of Internal Medicine, Policlinico Universitario A Gemelli, Catholic University of Sacred Heart, Rome, Italy

Correspondence to: Dr A Grieco, Institute of Internal Medicine, Catholic University of Sacred Heart, Largo Gemelli 8—00168 Rome, Italy.
antgrieco@katamail.com

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Reply

EDITOR,—We thank Grieco *et al* for their important observation that NASH may be associated with occult coeliac disease (13% in their series). We have also been interested in the possibility of this association. Coeliac disease, like small intestinal bacterial overgrowth, can be associated with increased intestinal permeability. It is plausible therefore that they could also share a similar pathogenetic mechanism resulting in non-alcoholic steatohepatitis (NASH) (that is, translocation of gut bacteria, Kupffer cell stimulation, and production of tumour necrosis factor α (TNF-α), proinflammatory cytokine, and reactive oxygen species, resulting in liver inflammation).

In our series of 22 NASH patients, none had a prior diagnosis of coeliac disease or suggestive symptoms. We also tested for antigliadin IgA and IgG antibodies (unpublished data). Three patients had positive antibodies (one positive for both antibodies, and two positive for the antigliadin IgG antibody only). One of these patients has been further investigated and coeliac disease has been confirmed histologically.

Although further investigation is required in the remaining two patients to exclude coeliac disease, it is possible that three patients (14%) in our NASH series could have occult coeliac disease (a value similar to that reported by Grieco *et al*).

None of the possible coeliac disease patients however had positive breath tests and their mean TNF-α levels did not differ significantly from the mean of the other NASH patients. Coeliac disease is therefore unlikely to be a confounding factor in our important observation of a high prevalence of small intestinal bacterial overgrowth and elevated serum TNF-α levels in NASH patients.

In our study, small intestinal bacterial overgrowth was present in 50% of patients. We have always considered that the pathogenesis of NASH is likely to be multifactorial. Coeliac disease, with perhaps a similar pathogenetic mechanism to small intestinal bacterial overgrowth, could be another important contributing factor in the development of NASH.

A WIGG
Unit of Gastroenterology and Hepatology, Flinders Medical Centre, Bedford Park, Adelaide, SA, 5042, Australia

A CUMMINS
Department of Gastroenterology, Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, Adelaide, SA, 5011, Australia

Correspondence to: A Wigg.
alan.wigg@flinders.edu.au

Induction of multiple autoantibodies to islet cell antigens during treatment with interferon alpha for chronic hepatitis C

EDITOR,—Induction or augmentation of autoimmunity during the treatment of chronic hepatitis C with interferon alpha is a well known phenomenon and a matter of great concern to physicians involved in the field of viral hepatitis. In recent years there have been a number of reports suggesting a link between the antiviral therapy and the development of antibodies to multiple autoantigens. In a recent issue of *Gut*, Wesche *et al* (*Gut* 2001;**48**:378–83) described the appearance of antibodies to 21-hydroxylase, an autoantigen of the adrenal cortex, and autoantibodies to glutamate decarboxylase 65 (GAD65) and the tyrosine phosphatase IA2 (IA2), both important autoantigens with respect to the pathogenesis of autoimmune (type 1) diabetes. Autoantibodies to GAD65 and IA2 appeared during or after therapy with alpha interferon for chronic hepatitis C in 5/62 and 1/62 patients, respectively. However, none of these patients was positive for both antibodies.

Type 1 diabetes is regarded as a chronic autoimmune disease caused by selective destruction of the insulin producing β cells. The disease is mediated by T cells but autoantibodies are well established markers for an ongoing autoimmune process within the islets.[1] As these autoantibodies usually appear prior to the clinical onset of the disease, they may be used to predict type 1 diabetes in predisposed individuals. In recent studies it has been shown that only those individuals in whom more than one diabetes related autoantibody could be determined are at considerable risk of developing type 1 diabetes.[2] Overall, the risk increases with the number of positive autoantibodies.[3] Therefore, combined screening for diabetes related autoantibodies is suggested to increase the specificity and the positive predictive value of the autoantibody tests.

We studied 56 patients with chronic hepatitis C (defined by positive anti-HCV and positive HCV-RNA) for the appearance of diabetes related autoantibodies after interferon therapy. We first screened for islet cell antibodies (indirect immunofluorescene) and if positive additionally determined autoantibodies to GAD 65, IA2, and insulin (radioimmunoassay and ELISA, respectively). In case of positivity for any antibody we analysed a pretreatment serum sample to

Table 1 Characteristics of patients with diabetes related autoantibodies after interferon alpha therapy for chronic hepatitis C infection

Patient No/sex/age	Mode of infection/genotype of HCV	Date of interferon therapy	Diabetes related autoantibodies	Estimated risk for type 1 diabetes
No 1/male/52 y	Unknown/genotype 1	8/98–8/99	IAA, GAD 65	Moderate
No 2 /male/49 y	IV drug use/genotype 1	9/98–3/99	ICA, GAD, IA2	High
No 3/female/48 y	Blood transfusion/genotype 1	7/98–7/99	IAA	Low
No 4/male/41 y	Unknown/genotype 3	11/98–5/99	IAA	Low

ICA, islet cell antibodies; GAD65, autoantiodies to glutamate decarboxylase 65; IA2, autoantibodies to tyrosine phosphatase IA2; IAA, insulin autoantibodies.

exclude the existence of any of these autoantibodies prior to interferon alpha therapy.

We identified four patients with diabetes related autoantibodies after cessation of therapy with interferon alpha (table 1). None of the patients had any of these antibodies prior to antiviral therapy nor had they a positive family history for autoimmune diabetes. Patient Nos 3 and 4 only developed insulin autoantibodies at a low titre. Induction of antibodies to insulin is a known phenomenon during therapy with interferon alpha and is described in a frequent number of cases.[4] Overall, these patients seem to have a low risk of progressing to clinically overt diabetes. Patient No 1 was found to be positive for insulin and GAD65 autoantibodies. Based on prospective clinical studies, this patient has an intermediate risk of developing diabetes.[5] We have now followed the patient for 16 months after interferon therapy and he has not developed an abnormal fasting glucose so far. The most striking example for induction of diabetes related autoantibodies was found in patient No 2. He developed three major autoantibodies during interferon therapy (GAD65, IA2, and ICA). Based on the predictive value of three positive autoantibody tests, this patient has a considerable risk of developing clinical overt diabetes over the next years. To date (follow up for 12 months) he has not developed an abnormal fasting glucose or an abnormal glucose tolerance test. The situation in this patient is further complicated as he did not respond to the antiviral therapy and another course of interferon might further increase his risk of developing autoimmune diabetes.

In summary, different diabetes related autoantibodies can be induced during interferon therapy for chronic HCV infection. However, we propose that only those patients with more than one autoantibody are at a considerable risk of progressing to clinically overt disease. Therefore, if one autoantibody appears during antiviral therapy, follow up should include screening for all other diabetes related autoantibodies. Furthermore, the question of whether patients with multiple autoantibodies should be retreated with interferon remains unsolved. Here the physician has to weigh possible progression of liver disease against the possibility of inducing autoimmune diabetes.

H E WASMUTH
C STOLTE
A GEIER
C GARTUNG
S MATERN
Medical Department III,
Technical University of Aachen, Germany

Correspondence to: H E Wasmuth, Medical Department III, Technical University of Aachen, Pauwelsstraβe 30, D-52074 Aachen, Germany. hwasmuth@hotmail.com

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ERCP training

EDITOR,—The leading article "ERCP training —time for change" by Hellier and Morris (*Gut* 2000;**47**:459–60) addresses important issues. Views as to how endoscopic retrograde cholangiopancreatography (ERCP) training should change may vary considerably between those in the average district general hospital (DGH) serving 220 000–250 000, and those in larger units, frequently serving populations of around 500 000.

Firstly, those without ERCP training but additional skills elsewhere will soon find themselves a favoured species. What price a skilled ultrasonographer? Advertising recently for a third consultant gastroenterologist to join two who undertook ERCP, we specified that ERCP was a skill *not* required. We felt an additional ERCP practitioner would dilute experience and eventually skill. Many DGH trusts are in a similar position with two consultants already in post who can provide sufficient ERCP cover and they do not want a third.

Secondly, the quality of training is largely dependent on two factors: the skill of the trainer, both in relation to ERCP and as an educationalist, and the case exposure available to the trainee. Frequently in a DGH there is only one trainee and case exposure is high. In a larger centre, while the number of ERCPs undertaken may be twice as great, there are frequently 3–5 trainees wanting to gain experience and "hands on" case experience is unavoidably less.

I am sure that I am not alone in finding that some attached SpRs have improved rapidly when exposed to a regular weekly list, an exposure that they were unable to achieve at their main teaching centre where teaching was otherwise excellent, simply because of pressure of the number of trainees on lists.

If the final decision is that units undertaking less than an arbitrary number of procedures (currently 250) are not to train SpRs, there are obvious consequences for training beyond further loading of the teaching centres which are already overstretched. It means that if an SpR is attached to a DGH at a late stage of training, when she is competent to undertake procedures independently, as judged by the main teaching centre, she will be unable to consolidate her skill at the DGH during the attachment. This is because it would be unwise from the clinical governance and medicolegal standpoint for a consultant or trust to allow anyone still defined as being a "trainee" near an ERCP if the unit is not a Joint Advisory Group (JAG) approved training centre.

The top centres in the country have practitioners the skill of which we all admire but few of us working elsewhere could ever approach. They provide excellent live demonstration teaching days and at times informal and friendly one to one advice from which we greatly benefit. Attendance at such live demonstration days should be a required component of all trainees' training and regularly considered for CPD by trainers.

Finally, my recent experience of SpR applicants for a consultant post had its illuminating aspects. The stated experience of some was such that they had apparently undertaken ERCPs independently on the equivalent entire average clinical load for a DGH for a three year period and this was for a post where ERCP was not required. I did wonder how trainers were maintaining any skill at all.

D BULLIMORE
Barnsley DGH Trust, Gawber Road,
Barnsley, South Yorkshire S75 2EP, UK
dwwbullimore@compuserve.com

Reinnervation after childbirth—a new paradigm for sensory bowel symptoms?

Visceral hypersensitivity has been identified as a significant feature in a proportion of patients with irritable bowel syndrome.[1] Reinnervation following a difficult intrapartum episode may be an important contributory factor. Many benign pelvic symptoms may be interpreted as pain or discomfort in response to touch (allodyniae or hyperalgesiae), including chronic pelvic pain, deep dyspareunia, urinary urgency, tampon discomfort, dysmenorrhoea, etc. Premature and prolonged maternal voluntary efforts in the second stage of labour appear to be significant aetiological features in women presenting with these clusters of sensory pelvic symptoms that include laparoscopically-negative pelvic pain.[1] Malpresentations, big babies, operative vaginal delivery, and excessive uterine activity may also contribute to the primary visceral denervation. Reinnervation has been demonstrated in the uterus, though an interval of five to ten years precedes the onset of sensory pelvic symptoms.[2] Similar patterns of reinnervation have been demonstrated in the vulva[3] and may occur in other pelvic viscera.

Anecdotal reports suggest that women treated with tolterodine tartrate (Detrusitol, Pharmacia, New Jersey) for irritative bladder symptoms, experience some improvement in sensory bowel symptoms—for example, faecal urgency and incomplete emptying. Precise questions about a woman's intrapartum history, medium term reinnervation, and different receptor systems may help to account for the neuropathic hypersensitivity that is such a feature of some forms of irritable bowel syndrome.

MARTIN QUINN
Department of Obstetrics & Gynaecology,
Hinchingbrooke Hospital,
Huntingdon, PE29 6NT, UK
martin.quinn@hbhc-tr.anglox.nhs.uk