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.

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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.

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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