of the carbohydrate side chains. Thus, we feel that data obtained using different methods should be compared very cautiously. In our case, the use of formalin fixed tissues has given the most reproducible results.

As far as the persistence of changes in lectin binding patterns after gluten free diet, Barresi et al provide very interesting and exciting results. We agree that further studies on this matter are still needed, as the patients studied by Barresi after 12 months of gluten free diet still showed partial altered lectin glycoconjugates. The persistence of these changes observed by Barresi et al in these patients might in fact reflect the incompleteness of recovery rather than the expression of a primary defect.

M Vecchi
G Torgano
R de Franchis
D Agape
G Ronchi
Instituto di Medicina Interna
Università di Milano, Italy

regenerative hyperplasia of the liver exhibiting mild increase in alkaline phosphatase activity. In the report of McMahon et al there were no histological features consistent with primary biliary cirrhosis. Moreover it is well documented that nodular regenerative hyperplasia of the liver should be distinguished from needle biopsy, but this is not the case for primary biliary cirrhosis. Third, the presence of an antimitochondrial antibody is good evidence of primary biliary cirrhosis, especially when its titre is >1:1500. The titre of these antibodies, however, was not mentioned in the report discussed. Moreover, antimitochondrial antibodies can be found in sclerodermoid and in scleroderma in the absence of associated chronic liver disease. Antimitochondrial antibody is found in 18-27% of these patients with sclerodermoid even though only 3-4% of these patients had evidence of primary biliary cirrhosis. Finally, McMahon and colleagues have reported a new case of association between CREST syndrome and nodular regenerative hyperplasia of the liver, the basis of which was the positivity of an antimitochondrial antibody.

It is concluded for the reasons already discussed that an overlap syndrome between CREST syndrome nodular regenerative hyperplasia of the liver and primary biliary cirrhosis has not been fully demonstrated.

J F CADRANEL, P GRIFFON, D GARGOT, OPOLON
Service d’Hépatogastroentérologie, Hôpital de La Salpêtrière, 47 Bd de l’Hôpital, Paris 75013, France


Reply

Str,—We are pleased to note the interest expressed in our paper by Cadranel and colleagues, and are grateful to them for drawing attention to our omission of two further cases, the first reporting the association of nodular regenerative hyperplasia of the liver and CREST syndrome in a letter to Presse Medicae and the second describing the association of CREST, nodular regenerative hyperplasia of the liver, and primary biliary cirrhosis in the Czechoslovakian literature. The purpose of our paper was to highlight the histological features of overlap between the syndromes of nodular regenerative hyperplasia of the liver, CREST and primary biliary cirrhosis rather than to report an association or coincidental occurrence of the three conditions.

Although we agree that the biochemical abnormalities reported in our patient may be seen in nodular regenerative hyperplasia of the liver, as well as in primary biliary cirrhosis, the presence of anti-M2 antibodies and the severe depression of BSP-K, (50% of which have a normal serum bilirubin as did this patient at the time of testing), Cadranel et al correctly state that decreased bromosulfophthalain clearance has been reported in patients with nodular regenerative hyperplasia of the liver. We have, however, used a more detailed analysis of bromosulfophthalain kinetics and shown a severe impairment in hepatic excretory function (BSP-K%) in our patient which to our knowledge has not previously been reported in nodular regenerative hyperplasia of the liver. The mechanisms leading to a raised serum alkaline phosphate concentration in liver disease are complex and in primary biliary cirrhosis are thought to be related to damage to the bile duct system, which can be recognised easily morphologically. The mechanism of raised serum alkaline phosphatase in nodular regenerative hyperplasia of the liver, however, is unknown because the bile ducts appear normal at light microscopy. Our observation of reduced hepatic excretory capacity suggests that the raised alkaline phosphatase in nodular regenerative hyperplasia of the liver may be the result of an abnormality in the bile duct apparatus, presumably at the ultrastructural level.

The interpretation of the antimitochondrial antibody testing is more complex than outlined in the paper. Serologic testing by immuno-fluorescence and a sample was referred to Professor Berg's laboratory in Tubingen, FRG. The initial results by ELISA showed the presence of antibodies with an IgG (i.e. 1: 220) and IgG (1 in 320) type in addition to anti-M4 antibody of low activity, which have been stated to be characteristic of primary biliary cirrhosis. Further analysis by Western blotting, however, showed that these antibodies were of the recently described "naturally occurring type" and this is what we reported in the paper. Although these antibodies have been described in the sera of families and contacts of primary biliary cirrhosis patients, sera of some patients have shown the presence of primary biliary cirrhosis specific and non-primary biliary cirrhosis specific determinants in parallel. This raises the difficult question of the specificity of the serologic pattern of an antimitochondrial antibody testing with increasing scientific sophistication, and further studies on the relationship between these antibodies and primary biliary cirrhosis are awaited.

We do not claim in the paper that the patient reported had primary biliary cirrhosis as the histological features were those of nodular regenerative hyperplasia of the liver alone. The letter from Cadranel et al however, invites comment on the wider issue of the criteria for the diagnosis of primary biliary cirrhosis and what should be accepted as the gold standard. First, the clinical presentation of the disease can vary from the asymptomatic to the classical picture of pruritus followed by progressive jaundice but incorporates a subgroup of patients who develop severe portal hypertension and need surgical intervention. Second, it is well recognised that up to 20% of cases in major series have a negative antimitochondrial antibody by conventional methods. Third, antimitochondrial antibody positive patients with no evidence of biliary cirrhosis have been recently shown to have histological features of primary biliary cirrhosis. Finally, histological diagnosis of primary biliary cirrhosis may in extremely difficult conditions be missed by a clinician. In summary, we feel that the conclusion of our paper remains valid. The association of CREST syndrome with primary biliary cirrhosis is well recognized. Moreover, Cadranel et al. have shown that our case with CREST and nodular regenerative hyperplasia of the liver is further strengthened by our report, and nodular hyperplasia of the liver has recently been shown as a cause of portal hypertension in primary biliary cirrhosis. Our case brings together the clinical features of CREST syndrome, the histological features of nodular regenerative hyperplasia of the liver, and the biochemical and serological features of primary biliary cirrhosis, and highlights the overlap between these three syndromes.

R F T M MAHON
CABBS
T W WARNES
Department of Pathology, University of Manchester, The Liver Unit, Manchester Royal Infirmary


