regenerative hyperplasia of the liver exhibiting mild increase in alkaline phosphatase activity.[6] In the report of McMahon *et al*[1] there were no histological features consistent with primary biliary cirrhosis. Moreover it is well documented that nodular regenerative hyperplasia of the liver can be misdiagnosed by needle biopsy,[4 5] 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 >1/500.[7 8] The titre of these antibodies, however, was not mentioned in the report discussed. Moreover, antimitochondrial antibodies can be found in sclerodermia[9 11] and in other collagenous disorders even in the absence of associated chronic liver disease. Antimitochondrial antibody is found in 18-27% of these patients with scleroderma even though only 3·4% of these patients had evidence of primary biliary cirrhosis.[11] 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 antimitochondiral 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.

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1 McMahon RFT, Babbs C, Warnes TW. Nodular Regenerative Hyperplasia of the liver CREST Syndrome and primary biliary cirrhosis: an overlap syndrome? *Gut* 1989; **30**: 1430–3.
2 Cadranel JF, Grippon P, Wechsler B, Bidegaray E, Karkouche B, Opolon P. CREST Syndrome et Hyperplasie nodulaire regenerative du foie – 1 observation. (letter). *Presse Med* 1987; **16**: 1656.
3 Hauftova D, Jezdinska V, Fischer J, Rehulka M. Primary biliary cirrhosis, CRST Syndrome, sjogren's syndrome and Nodular Regenerative liver Hyperplasia. *Cesk Gastroenterol Vyz* 1982; **8**: 429–36.
4 Wanless IR, Dogwin TA, Allen F, Feder A. Nodular Regenerative hyperplasia of the liver in hematologic disorders: a possible response to obliterative portal veinopathy. A morphometric study of nine cases with an hypothesis on the pathogenesis. *Medicine* 1980; **59**: 367–79.
5 Stromeyer FW, Ishak KG. Nodular Transformation (Nodular "regenerative" hyperplasia) of the liver. A clinicopathologic study of 30 cases. *Human Pathol* 1981; **12**: 60–71.
6 Capron JP, Degott C, Bernuau J, *et al.* L'hyperplasie nodulaire regenerative du foie. Etude de 15 cas et revue de la littérature. *Gastroenterol Clin Biol* 1983; **7**: 761–9.
7 Triger DR, Charlton CAC, Milford Ward A. What does the antimitochondrial antibody mean? *Gut* 1982; **23**: 814–8.
8 Cales P, Cales V,, Oksman F. Vinel JP, Pascal JP. Signification des anticorps antimitochondries dans une population de 111 malades issus de la région Midi-Pyrénées – *Presse Med* 1988; **17**: 742–5.
9 Allen BR, Sneddon IB. Scleroderma and primary biliary cirrhosis. (letter). *Br Med J* 1970; **3**: 526.
10 Buffet C, Husson JM. Foie et sclerodermie généralisée. *Nouv Presse Med* 1974; **3**; 2701–2.
11 Gupta RR, Siebold JR, Krishnan MR, Steigerwald JC. Mitochondrial antibodies in progressive systemic sclérosis (abstract). *Clin Res* 1983; **31**: 863 A.

Reply

SIR,—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 Medicale*[1] and the second describing the association of CREST, nodular regenerative hyperplasia of the liver, and primary biliary cirrhosis in the Czechoslovakian literature.[2] The purpose of our paper however, was to highlight the 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, the combination of results is, in our experience, typical of primary biliary cirrhosis. In our unit, which has a special interest in primary biliary cirrhosis, 96% of patients have had a raised serum IgM, 94% a raised serum alkaline phosphatase and 70% a severely depressed BSP-K_2 (50% of whom have a normal serum bilirubin as did this patient at the time of testing). Cadranel *et al* correctly state that decreased bromosulphthalein clearance has been reported in patients with nodular regenerative hyperplasia of the liver.[4] We have however, used a more detailed analysis of bromosulphthalein kinetics and shown a severe impairment in hepatic excretory function (BSP-K_2) in our patient, which to our knowledge has not previously been reported in nodular regenerative hyperplasia of the liver.[4] The mechanisms leading to a raised serum alkaline phosphatase concentration in liver disease are complex but in primary biliary cirrhosis are thought to be related to damage to the bile duct system, which can be recognised easily morphologically.[5] 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. Serum was negative by immunofluorescence and a sample was referred to Professor Berg's laboratory in Tubingen, FRG. The initial results by ELISA showed the presence of anti-M2 antibodies of IgM (1 in 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.[6] 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.[7] 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.[8] This raises the difficult question of the specificity and interpretation of anti-mitochondinal 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 do not become jaundiced.[9] Second, it is well recognised that up to 20% of cases in major series have a negative antimitochondrial antibody by conventional methods[10]. Third, antimitochondrial antibody positive patients with otherwise normal liver function tests have recently been shown to have histological features of primary biliary cirrhosis.[11] Finally, histological diagnosis of primary biliary cirrhosis may be extremely difficult in the absence of the florid duct lesion and may be mimicked by other conditions such as chronic active hepatitis, sarcoidosis, and lymphoma.[12] On this last point, we would disagree with Cadranel *et al* and suggest that primary biliary cirrhosis can be misdiagnosed on needle biopsy.

In summary, we feel that the conclusion of our paper remains valid. The association of CREST syndrome with primary biliary cirrhosis is well recognised, the association of CREST with 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 early stage 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.

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1 Cadranel JF, Grippon P, Wechsler B, Bidegaray E, Karkouche B, Opolon P. CREST syndrome et hyperplasie nodulaire regenerative du foie – 1 observation. (letter). *Presse Med* 1987; **16**: 1656.
2 Hauftova D, Jezdinska V, Fischer J, Rehulka M. Primary biliary cirrhosis., CRST syndrome, Sjogren's syndrome and Nodular Regenerative Liver Hyperplasia. Gastroenterol Vyz 1982; **8**: 429–36.
3 Capron JP, Degott C, Bernau J, *et al.* L'Hyperplasie Nodulaire Regenerative du Foie. *Gastroenterol Clin Biol* 1983; **7**: 761–9.
4 Hacki W, Bircher J, Preisig R. A new look at the plasma disappearance curve of sulfobromophthalein (BSP): correlation with the BSP transport maximum and the hepatic plasma flow in man. *J Lab Clin Med* 1976; **88**: 1019–31.
5 Warnes TW. Progress report – alkaline phosphatase. *Gut* 1972; **13**: 937–62.
6 Berg PA, Klein R, Lindenborn-Fotinos J. Anti-mitochondrial antibodies in primary biliary cirrhosis. *J Hepatol* 1986; **2**: 123–31.
7 Klein R, Berg PA. Demonstration of naturally occurring mitochondrial antibodies (NOMA) by Western blotting in families of patients with primary biliary cirrhosis (PBC) [Abstract]. *Hepatology* 1988; **8**: 1419.
8 Berg PA, Klein R. Heterogeneity of anti-mitochondrial antibodies. *Semin Liver Dis* 1989; **9**: 103–16.
9 Zeegan R, Stansfield AG, Dawson AM, Hunt AH. Bleeding oesophageal varices as the presenting feature in primary biliary cirrhosis. *Lancet* 1969; ii: 9–13.
10 Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histological features in asymptomatic and symptomatic primary biliary cirrhosis. *N Engl J Med* 1983; **308**: 1–7.
11 Mitchison HC, Bassendine MF, Hendrick A, *et al.* Positive antimitochondrial antibodies but normal alkaline phosphatase: is this primary biliary cirrhosis? Hepatology 1986; **6**: 1279–84.
12 Scheuer PJ. *Liver biopsy interpretation.* London: Bailliere Tindall, 1988: 53–65.