tissue[15] using colorimetric[16] or atomic absorption spectrophotometry[17] based methods. A semi-quantitative grading of iron deposition and cellular distribution can be accomplished using histological assessment of sections stained for iron using Perls' Prussian blue method.[18]

It has long been known that serum and non-heme hepatic iron parameters can be increased in chronic liver diseases of diverse aetiologies excluding hereditary haemochromatosis and other secondary iron overload disorders.[19] Blumberg and colleagues described abnormal iron studies in patients with hepatitis B.[20,21] Interest in the role of iron in chronic hepatitis C commenced in 1992 when Di Bisceglie *et al.*[22] noted that up to 36% of patients with chronic hepatitis had elevated serum iron parameters, but only 5% had elevated HICs in the order generally seen in haemochromatosis. Similar observations have also subsequently been reported by other groups.[23,24] Following this Van Thiel *et al.*[25] reported that in a group of patients with chronic viral hepatitis of varying aetiologies, the HIC of responders was less than that of non-responders and that HIC predicted response to interferon. Olynyk *et al.*[26] studied the effect of HIC on response to interferon therapy of chronic hepatitis C. This study demonstrated that the HIC was higher in non-responders to IFN therapy compared with responders. More specifically, an HIC > 1100 μg/g predicted non-response in nearly 90% of patients (Fig. 1). In contrast, HICs ranging up to 700 μg/g were also frequently seen in responders. In keeping with the biochemical measurements of HIC, more patients demonstrated low-grade stainable hepatic iron in the non-responder group. Additionally, the HIC was similar in cirrhotic and non-cirrhotic patients, suggesting that hepatic iron was not related to histological severity of disease. Serum ferritin concentrations were significantly higher in the 'high' iron non-responder group than in the 'low' iron non-responder and the responder groups. However, the marked overlap of ferritin concentrations between these groups precluded using an increased serum ferritin concentration to predict response (Fig. 2). The overlap in ferritin concentrations may be due to the acute-phase reactant properties of ferritin in the setting of chronic inflammatory liver disease. The responders and non-responders had similar HCV RNA levels (Fig. 3). There were no significant relationships between HCV RNA levels and the HIC, the presence of an elevated serum ferritin levels, or the alanine aminotransferase (ALT) level. In the last 4 years many additional studies have been published regarding the role of iron in chronic hepatitis C.[27–41] Most have confirmed that increased serum and/or hepatic iron parameters are associated with a lower likelihood of response to interferon therapy.

Several studies have indicated that the distribution of iron within the liver lobule and the cell type effected by the iron may be important in determining the effect which iron has on chronic hepatitis C. Iron deposition within zone 1, portal tracts and sinusoidal lining cells is associated with a higher likelihood of non-response to interferon therapy.[27–34] In our study,[26] we noted that 18 of 24 responders had no stainable iron in hepatocytes or Kupffer cells. The remaining 6 responders had grade I stainable iron distributed equally between hepatocytes and Kupffer cells. However, 19 of 34 non-responders showed grade I stainable iron distributed equally between hepatocytes and Kupffer cells. Banner *et al.*[32] conducted a study of the frequency with which stainable iron occurred in sections of liver biopsies from patients with chronic hepatitis C. These investigators noted that non-responders to treatment had greater accumulation of iron in the sinusoids and portal tracts. Ikura *et al.*[31] found that the presence and degree of portal iron deposition correlated inversely with the response to interferon treatment. The presence of stainable iron has been shown to correlate with inflamma-

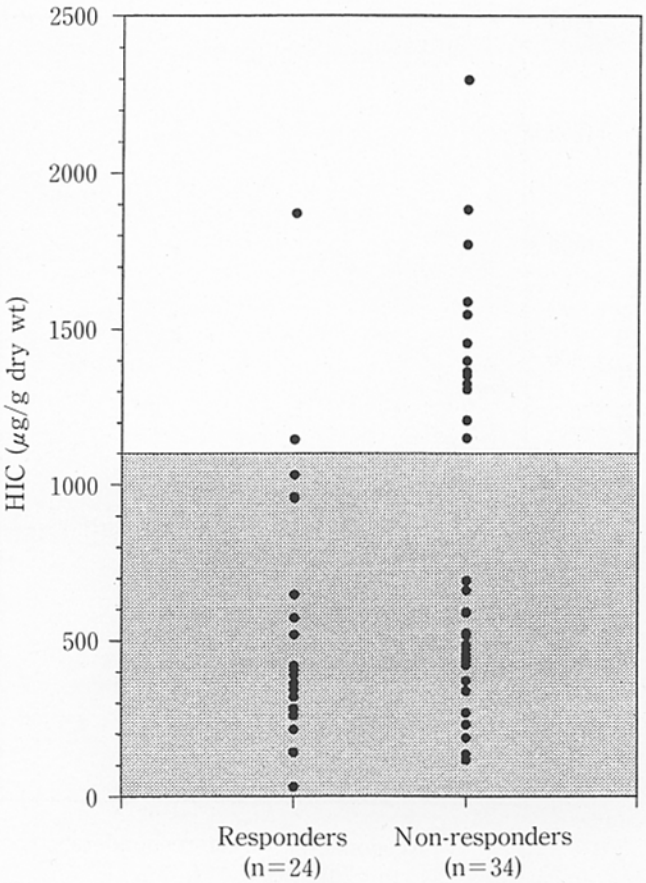

Fig. 1 Hepatic iron concentration in responders and non-responders to interferon α therapy in chronic hepatitis C. The shaded region represents HICs of <1100 μg/g. *P < 0.05, non-responders vs responders. (Reproduced from 24).