toxins has been previously described. Iron has been shown to be a synergistic factor in the pathogenesis of alcohol and carbon tetrachloride induced liver diseases.[53–55] It is generally accepted that iron increases the formation of reactive oxygen intermediates which can result in lipid peroxidation which can result in oxidative damage to proteins and nucleic acids. This can result in organelle dysfunction, fibrosis and eventually hepatocellular carcinoma. Whilst these findings were initially based on studies in iron overload, lipid peroxidation products have been shown in the plasma[56] and liver biopsies[57–58] of patients with chronic hepatitis C. Farinati *et al.*[57] studied whether HCV may have a direct cytopathic effect on hepatocytes through the occurrence of iron-dependent lipid peroxidation. Patients with chronic hepatitis C had significantly greater lobular inflammation, steatosis, serum ferritin levels and transferrin saturation, tissue iron, glutathione and malondialdehyde levels compared with patients with other forms of chronic hepatitis nor related to HCV infection. These results suggested that altered iron metabolism and iron accumulation in chronic hepatitis C may be related to a specific effect of the virus on parenchymal or non-parenchymal cell function. In liver tissue, lipid peroxidation products are mainly observed in portal tract macrophages.[58] Lipid peroxidation products have been shown to stimulate collagen production in activated hepatic stellate cells and cultured human fibroblasts.[59,60] Alternatively, lipid peroxidation products may increase production of transforming growth factor (TGF)-β or other profibrogenic substances by Kupffer cells which might then stimulate hepatic stellate cell activation.[61,62]

It is well known that the risk for development of hepatocellular carcinoma is substantially increased in both hereditary hemochromatosis and chronic hepatitis C.[63] The mechanisms responsible for the development of hepatocellular carcinoma in chronic liver disease are not clear but several potential mechanisms exist. Chronic infection with HCV may be directly oncogenic.[64] Alternatively, HCV-induced chronic liver injury may culminate in cirrhosis and an increased risk for hepatocellular carcinoma.[65] As cirrhosis develops, hepatocyte necrosis is followed by an attempted secondary proliferative response of mature hepatocytes.[66–69] However, this proliferative response is often impaired in chronic liver disease. An alternative mechanism for hepatocyte regeneration in chronic liver disease involves stem cell proliferation and differentiation into hepatocytes. In humans, oval cells have been reported in hepatitis B-associated hepatocellular carcinoma and chronic liver disease associated with ductular proliferation.[70,71] We have recently shown that oval cells are present in patients with hereditary hemochromatosis and chronic hepatitis C.[72] Furthermore, oval cell numbers increase significantly with progression of disease severity in each of the groups studied, suggesting that oval cell proliferation is not disease specific but occurs in response to progressive liver injury and fibrosis. The association between severity of liver disease and increasing number of oval cells is consistent with the hypothesis that oval cell proliferation is associated with the increased risk for development of hepatocellular carcinoma with advancing liver disease, particularly when cirrhosis is present. Finally, iron could contribute to the increased risk of hepatocellular carcinoma in chronic hepatitis C through DNA damage from iron-induced adduct formation and chromosomal damage.[73,74]

The pathophysiological mechanisms whereby iron exerts its effects in chronic hepatitis C are unknown. Much evidence has accumulated supporting an immunopathological mechanism which underlies liver injury in chronic hepatitis C.[75–77] Virus specific T cells are present in the liver tissue and peripheral blood of patients with HCV infection and are able to contribute to hepatocellular injury, but are not able to eliminate viral infection.[78,79] Previous studies have shown that persistent hepatitis B virus infection is associated with iron overload.[20,21,80] It is also known that patients with iron overload are more susceptible to bacterial infections.[81] Iron has been shown to impair antigen-specific immune responses and generation of cytotoxic T-cells, decrease functional T-helper precursor cells, and enhance T-suppressor activity.[82,83] Natural killer cell activity has also been reported to be decreased in iron overload conditions.[84–86] Lymphocyte proliferation is inhibited by ferritin.[87,88] Ferritin molecules, particularly those rich in heavy (H) subunits, bind to activated T-cells[89] and H-ferritin receptors are expressed by T-cell lines.[90,91] These data suggest that iron could impair host lymphocyte-dependent clearance of HCV virus. Interferon α possesses multiple actions including direct antiviral effects and enzyme modulation.[92] The actions of IFN are not known to be dependent on intracellular iron although it is possible that iron might also interfere in some way with these actions resulting in a reduced antiviral activity. It has been suggested that transferrin and non-transferrin-bound iron-uptake pathways may be affected in necro-inflammatory conditions.[93] As a result, non-responders might have increased iron uptake and hepatic iron deposition when compared with responders. Increased hepatic iron deposition in hepatitis C may then result in increased oxidative stress in the liver, decreased glutathione levels and lipid peroxidation and formation of malondialdehyde adducts.[29,32,39,40,56–58] The type of storage molecule from which iron is released could modulate these effects. It is well known that ferritin and hemosiderin release iron to different degrees, a property which may