t(10;14) translocation for *HOX11* or a *SIL-SCL* fusion *(Tal1d)* for *SCL*, expression of the proto-oncogene was monoallelic. However, about half of the patients who had activated *SCL* or *LMO2* showed biallelic expression, suggesting that inappropriate activation of an upstream transcription regulatory molecule could be the cause of proto-oncogene activation. Moreover, they demonstrated that *SCL* and *LMO2* were normally expressed in the most primitive double-negative (DN1, DN2, and DN3) thymocytes and down-regulated to undetectable levels as thymocytes matured to the double-positive (DP) and single-positive (SP) stages. Therefore, it is feasible that aberrant expression of these genes is caused by a lack of normal down-regulation in the maturing thymocytes, perhaps due to the absence of a normal silencing molecule or the inappropriate persistence of a positive transcription regulator. Taken together, these findings suggest that genes critical for the development of T-ALL ("genes of interest") might lie upstream of *SCL* or *LMO2* in a transcriptional cascade.

—Peter D. Aplan
National Cancer Institute

1. Ferrando AA, Neuberg DS, Staunton J, et al. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. Cancer Cell. 2002;1:75-87.
2. Lowsky R, DeCoteau JF, Reitmair AH, et al. Defects of the mismatch repair gene MSH2 are implicated in the development of murine and human lymphoblastic lymphomas and are associated with the aberrant expression of rhombotin-2 (Lmo-2) and Tal-1 (SCL). Blood. 1997;89: 2276-2282.

A silent epidemic in survivors of hematopoietic cell transplantation

The field of hematopoietic cell transplantation is now 35 years old, and many complications seen in the early days have been consigned to the historic record. One complication, however, was never anticipated. Cirrhosis caused by chronic hepatitis C infection has a cumulative frequency in transplantation survivors of 2% to 4% after 20 years. Chronic hepatitis C and progression to cirrhosis are usually clinically silent until falling platelet counts, jaundice, bleeding varices, and fluid accumulation herald end-stage liver disease.

The study by Peffault de Latour and colleagues (page 1618) provides important insights into this problem by careful follow-up of 96 hepatitis C virus (HCV)–infected survivors for up to 28 years. The cumulative incidence of cirrhosis was 24% at 20 years after transplantation, a remarkably high figure in comparison to the progression of HCV infection in nontransplantation patients. While genotype 3 and the presence of extrahepatic manifestations of HCV infection were related to development of cirrhosis, the hazard ratios were less than 2 for both factors. Other studies have shown that progression of HCV to cirrhosis is HLA restricted, that is, not a matter of bad luck but of biologic determinism. Why progression to cirrhosis should be so rapid in one fourth of this cohort of transplantation survivors is not clear from the data, but as the authors point out, a similar situation obtains in other patients with depressed T-cell immunity, for example, after renal transplantations and with HIV infection. Although immunity after transplantation often returns to normal after one year, during that year there is opportunity for unfettered viral replication and infection of more hepatocytes than would ever occur naturally.

As many as 35% of survivors from transplantation surgeries before 1992 may be infected with HCV. All survivors, particularly those from transplantation surgeries before 1992, must be tested for anti-HCV and staged by biopsy for extent of liver disease if infected. This is easier said than done. Some people are lost to follow-up. Others do not want their history of transplantation known to anyone. Some are uninsured and cannot bear the costs of liver biopsy and lengthy therapy. In the absence of a contraindication to therapy with interferon-α (IFNα) and ribavirin, all patients who have evidence of progressive liver disease on a biopsy should be treated, albeit with limited expectations, as the clearance of HCV following pegylated IFNα and ribavirin therapy is achieved only half of the time. One note of caution about using IFNα in transplantation survivors: our experience has been that platelet and granulocyte counts in some transplantation survivors may be very sensitive to IFNα. Use of ribavirin and pegylated IFNα as initial treatment poses the risk of profound depression of blood counts because of the long half-life of pegylated IFNα. It may be safer to initiate therapy with ribavirin and IFNα daily or 3 times a week until patient tolerance is demonstrated. Better, less toxic therapy for HCV infection is urgently needed. The first step toward preventing the development of cirrhosis, however, is to emulate the practice of the Paris group by tracking all transplantation survivors and determining who is infected by HCV.

—George B. McDonald
Fred Hutchinson Cancer Research Center; and University of Washington School of Medicine

Hyperfibrinogenemia and vascular disease: does it matter?

Elevated plasma levels of fibrinogen are strongly associated with human vascular disease. The Northwick Park Heart Study, which prospectively followed more than 1500 men for a mean of 10 years, found that elevated plasma fibrinogen at recruitment was independently associated with subsequent cardiovascular risk, with an increase in baseline plasma fibrinogen of approximately 0.7 g/L (70 mg/dL) being associated with a 39% increase in cardiac death and a 60% increase in nonfatal myocardial infarction.[1] However, it is unknown whether elevated plasma fibrinogen plays a causal role in vascular disease progression. On the one hand, elevated plasma fibrinogen may promote vascular disease by increasing blood viscosity, by promoting fibrin formation, by enhancing platelet-platelet interactions, or by other mechanisms. On the other hand, elevated plasma fibrinogen could