Chapter 11
Genetic Liver Disease

A1a. More fully define the frequency of disease expression associated with *HFE* C282Y and define major modifying factors. In the Hemochromatosis and Iron Overload Screening (HEIRS) Study of approximately 100,000 North Americans, C282Y homozygosity was identified in 0.44% of whites, but only 0.12% of African-Americans and less than 0.1% of Asian Americans. Among persons with C282Y homozygosity identified in screening studies who undergo liver biopsy, hepatic iron overload is common and significant fibrosis is found in 13% of women and 29% of men (Powell LW. Arch Intern Med 2006;13:294). Modifying factors for disease expression include viral hepatitis, alcoholism, and possibly nonalcoholic steatohepatitis (Walsh A. Clin Gastroenterol Hepatol 2006;4:1403). (2006 20%; Total 40%)

A1b. Identify a cohort of patients with congenital hepatic fibrosis to study its natural history and optimal management. Studies from cohorts seen at a major medical center between 1961 and 2004 identified 65 cases of autosomal recessive polycystic kidney disease (ARPKD), 10 of whom had isolated congenital hepatic fibrosis (CHF) with no or minimal renal involvement. Mutations in the *PKHD1* gene were found in 81% of cases and did not correlate with clinical phenotypes (Adeva M. Medicine 2006; 85:1). (2006 10%; Total 30%)

A2a. Establish DNA evaluation centers of excellence for Wilson disease, the porphyrias, and hemochromatosis. No such centers have yet been established. (2006 0%; Total: 0%)

A2b. Develop a reliable animal model for the liver disease of cystic fibrosis. Studies in a mouse model lacking the *CFTR* gene to assess therapies for CF suggest that chronic therapy with docosahexaenoic acid (an omega-3 fatty acid) is beneficial in decreasing inflammatory liver disease (Beharry SA. Am J Physiol Gastrointest Liver Physiol 2006;9: epub). These results have yet to be extended to humans. (2006 10%; Total 30%)

A3. Fully elucidate the molecular mechanisms of intestinal absorption, hepatic metabolism, and biliary excretion of copper. Copper absorption is largely accomplished by the human intestinal copper transport protein 1 (Ctr1), which is closely regulated by copper status (Kuo YM. J Nutr 2006;136:21); mice lacking the *Ctr1* gene develop severe copper deficiency (Nose Y. Cell Metab 2006;4:235). The crystallographic structure of human CTR1 has been defined, revealing a novel channel structure. Similarly, NMR spectroscopy of the Wilson ATPase (ATP7B) has defined the structure of the ATP-binding N-terminal domain, which is affected by at least 30 of the known Wilson disease mutations (Dmitriev O. Proc Natl Acad Sci USA 2006;103:5302). (2006 10%; Total 20%)

B1a. Develop and apply practical and accurate screening methods for identifying hemochromatosis before significant tissue injury has occurred. Potential screening tests for hemochromatosis include transferrin saturation, unsaturated iron-binding capacity, and serum ferritin, all of which have shortcomings in terms

of biological variability. The practicality of genetic testing for *HFE* gene mutations remains to be shown. (2006 0%; Total 0%).

B1b. Define the role of heterozygosity for Wilson ATPase and *HFE* mutations in other liver diseases. Persons heterozygous for Wilson ATPase and classical *HFE* mutations (C282Y and H62D) appear healthy and without tissue injury from copper or iron overload. Heterozygosity for *HFE* mutations is associated with mild increases in hepatic iron, but is not associated with worsening of hepatitis C (Bonkovsky HL. Gastroenterology 2006;131:1440) or alcoholic hepatitis (Gleeson D. Am J Gastroenterol 2006;101:304). (2006 10%; Total 20%)

B2a. Fully define the normal molecular pathways of iron metabolism in humans with specific definition of the roles of *HFE* and hepcidin. Major advances continue to be made in the elucidation of the role of hepcidin and other molecules in iron metabolism (Nemeth E. Blood 2006;107:328). Targeted disruption of hepcidin results in severe hemochromatosis (Lesbordes-Brion JC. Blood 2006; 108:1402), and chronic overexpression of hepcidin causes iron deficiency and iron retention in macrophages (Viatte L. Blood 2006;107:2952). The mechanisms by which hemojuvelin mutations result in iron overload (juvenile hemochromatosis) have been elucidated. Hemojuvelin is a co-receptor for bone morphogenetic protein (BMP) and disruption of BMP signaling results in lowering of hepcidin expression and consequent iron overload (Babitt JL. Nat Genet 2006;38:531). Multiple other factors regulate hepcidin production by the liver including inflammatory signals through interleukin 6 (IL-6), which leads to STAT3 activation, hepcidin promoter engagement, and increased hepcidin expression (Wrighting DM. Blood 2006;108:3204). Inflammation and IL-6 also induces increases in the plasma membrane transporter Zip14, which mediates uptake of zinc and non-transferrin bound iron into hepatocytes (Liuzzi JP. Proc Natl Acad Sci USA 2006;103:13612). (2006 10%; Total 30%)

B2b. Define the role of liver iron levels in the course of NASH, alcoholic liver disease, chronic hepatitis C, and porphyria cutanea tarda. Both serum and hepatic iron levels are often high in patients with chronic liver disease and they often correlate with more advanced fibrosis and poor response to therapy. The cause of iron overload is likely due to deficient hepcidin production. Defining the possible role of iron depletion in ameliorating the course of chronic liver diseases awaits further study. (2006 0%; Total 10%)

B3a. Identify the major genetic causes of inherited iron overload among African Americans, Asian Americans, and Hispanics. Despite low rates of *HFE* mutations among African Americans, Asian Americans, and Hispanics, elevations in iron saturation and serum ferritin are not uncommon. In these groups, iron overload and serum aminotransferase elevations are frequently associated with high rates of hepatitis C (18-33%) and hepatitis B (2.5-5%) (Adams PC. Clin Gastroenterol Hepatol 2006; 4:918). The prevalence of actual iron overload has not been well defined in non-Caucasian populations, and may be low. Genetic causes for iron overload in the absence of co-existing liver disease in these cohorts have not been identified. (2006 10%; Total 10%)

B3b. Define the molecular basis of the increase in HCC risk among persons with the porphyrias. Links between the molecular abnormalities of porphyrin metabolism in the inherited porphyrias and pathways of carcinogenesis have not yet been defined. (2006 0%; Total 0%)

C1. Develop rapid metabolic screening test for Wilson disease that could also be applied to newborns or infants and assess test for efficacy and risk-benefit ratio. Until there is a more complete understanding of copper metabolism and its control, there is unlikely to be a rapid metabolic screening test for Wilson disease. More than 200 different mutations in ATP7B have been associated with Wilson disease, and testing for the most common mutations would identify less than half of cases. (2006 0%; Total 0%)

C2a. Define specific genetic modifiers of Wilson disease and porphyrias using animal models and clinical cohorts of patients. In large patient cohorts from Europe and the United States, no genetic modifiers of Wilson disease have been identified. (2006 0%; Total 0%)

C2b. Develop an improved therapy for amelioration of acute crises in porphyria. A preparation of recombinant porphobilinogen deaminase is now in phase I/II human trials for acute intermittent porphyria. (2006 0%; Total 0%)

C3a. Develop noninvasive means of accurately defining total body and hepatic iron and copper, either using imaging studies or mathematical models and serum levels of related molecules. Special MRI algorithms have been approved for clinical use in detecting marked iron overload. At present, however, accurate determination of mild and moderate iron or copper overload requires quantitative analysis of liver biopsy tissue. (2006 0%; Total 20%)

C3b. Develop practical gene or stem cell therapy for AIP and EPP. Sequential liver and bone marrow transplantation has been found to reverse EPP (Rand EB. Pediatrics 2006;118:1896). Gene therapy research is promoted by NIH-funded Molecular Therapy Core Centers. (2006 10%; Total 10%)

Figure 13. Estimated Progress on Genetic Liver Disease Research Goals, 2006 (Year 2)
[Cross-hatching indicates recent year's progress.]