Chapter 13
Complications of Liver Disease

A1a. Hold a research workshop on improvement and standardization of clinical measurements of cirrhosis and portal hypertension. A workshop entitled "Measurement of Hepatic Vein Pressure Gradient: Role in Management of Portal Hypertension" was held on June 16-17, 2006. A summary publication is being drafted that will include recommendations for future research. (2006 50%; Total 50%)

A1b. Define whether N-acetylcysteine is beneficial in acute liver failure. Two prospective randomized controlled trials of N-acetylcysteine (NAC) for non-acetaminophen induced acute liver failure have received NIH funding. The trial in adults has received been completed, and results are expected within the next year. The trial in children is still ongoing. (2006 10%; Total 30%)

A2. Better define the natural history of hepatopulmonary syndrome and whether early detection is beneficial. An NIH-funded National Network on Hepatopulmonary Syndrome continues to enroll patients in a prospective study of this syndrome. (2006 0%; Total 10%)

A3a. More fully elucidate the pathophysiology of portal hypertension. Patients with cirrhosis have a hyperdynamic state in the splanchnic bed that is caused at least in part by nitric oxide (NO). Vasodilation induced by NO may be mediated by vascular endothelial growth factor (VEGF) (Abraldes JG. Am J Physiol Gastrointest Liver Physiol 2006;290:G980). In the liver, the vasodilator response to NO is blunted, which in a rat model appears to be due to upregulation of endothelial phosphodiesterase-5, the enzyme which is responsible for degrading NO (Loureiro-Silva MR. J Hepatol 2006;44:886). Both phosphodiesterase-5 and VEGF may be targets for therapy of portal hypertension. (2006 10%; Total 20%)

A3b. Better characterize the cause of increased susceptibility to bacterial infections in cirrhosis. Elucidation of the basic mechanisms by which patients with cirrhosis are at increased risk for infections might lead to means of prevention. Infections remain a major cause of morbidity and mortality in patients with cirrhosis. (2006 0%; Total 0%)

B1. Define optimal nonspecific approaches to management of hepatic encephalopathy, hepatorenal syndrome, refractory ascites, prevention of bacterial infection, and coagulopathy in patients with cirrhosis. A clinical trial of terlipressin vs placebo for treating hepatorenal syndrome in cirrhotic patients has recently been completed, and results will be published in the next year. (2006 0%; Total 0%)

B2a. Define whether hypothermia is beneficial in acute liver failure for management of cerebral edema. An investigator-initiated trial of hypothermia for acute liver failure has been planned, but has yet to be funded. (2006 0%; Total 0%)

B2b. Define natural history and identify predictors of development and growth of varices.) Ultrasound elastography as a measure of liver stiffness may be a reliable and noninvasive means of following the development of varices (Kazemi F. J Hepatol 2006;45:230) (2006 10%; Total 30%)

B3a. Identify small molecule targets that would lead to better control of portal hypertension at different stages of disease. No new agents for portal hypertension have yet been approved for use. (2006 0%; Total 0%)

B3b. Develop a noninvasive means of measuring portal pressure. Studies from Europe have shown that ultrasonic elastography is accurate in defining the degree of liver stiffness associated with a raised portal pressure (Carrion JA. Liver Transpl 2006;12:1791). Thus, elastography may be an excellent means of monitoring patients with advanced fibrosis and identifying when endoscopic documentation and invention might be appropriate. This area of research is encouraged through a program announcement for small business (SBIR/STTR) grants: "New Technologies for Liver Disease" (PA-06-396/397). (2006 20%; Total 20%)

C1a. Elucidate the optimal approach to manage patients with varices that have not bled (primary prevention). Further studies are warranted comparing band ligation, beta blocker therapy, and more innovative approaches. (2006 0%; Total 10%)

C1b. Define whether monitoring portal pressure (HVPG) improves management of patients with chronic liver disease. The workshop on "Measurement of Hepatic Vein Pressure Gradient: Role in Management of Portal Hypertension" held on June 16-17, 2006 dealt directly with this issue. In studies of patients with hepatitis C after liver transplantation, HVPG was shown to be more predictive of clinical decompensation than liver biopsy, suggesting that it may be a reliable surrogate marker for progression of liver disease (Blasco A. Hepatology 2006; 43:492). (2006 10%; Total 10%)

C2a. Develop a noninvasive means to assess hepatic regeneration and reserve in liver failure. Efforts to assess regeneration and reserve function in cases of liver failure are encouraged by an NIH-funded initiative on "Development of Disease Biomarkers" (PA-07-052). (2006 0%; Total 0%)

C2b. Develop and evaluate better drugs for portal hypertension. Endothelin (ET)-1 is believed to contribute to portal hypertension in patients with cirrhosis. However, in investigational studies in 16 patients with cirrhosis, systemic and pulmonary but not portal pressures were decreased by inhibition of ET-A and ET-B receptor activity (Tripathi D. Gut 2006;55:1290). (2006 0%; Total 10%)

C3a. Develop an artificial or bioartificial hepatic support and demonstrate that it prolongs survival in acute liver failure. The status of hepatic assist devices as therapy of acute liver failure was considered at an NIH-sponsored meeting on "Acute Liver Failure" held December 4-5, 2006. At least five different bioartificial hepatic support devices are being evaluated in animal models and in phase 1 studies. In addition, several non-cell based hepatic assist devices are

being evaluated in acute liver failure and may become commercially available in the next few years. (2006 10%; Total 10%)

C3b. Develop noninvasive means to screen for large varices. Studies are ongoing in this area, focusing on developing noninvasive indicators of varices size, such as platelets and splenic size. Elastography may also be valuable as a tool to predict the presence of large varices. (2006 0%; Total 0%)

Figure 15. Estimated Progress on Complications of Liver Disease Research Goals, 2006 (Year 2) [Cross-hatching indicates recent year's progress.]