

Hepatology at Mount Sinai:

The Present and the Future

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Abstract

The Division of Liver Disease at Mount Sinai, now into its fifth decade, has evolved through two remarkable periods in its development and is on the cusp of a third exciting era. The first, extending from the division's creation in 1957 to the retirement in 1988 of its first division chief, Fenton Schaffner, was characterized by brilliant clinical and pathophysiologic insights derived from the unique collaboration of Schaffner, a master clinician, with Hans Popper, a world renowned pathologist widely acknowledged as the father of the modern discipline of hepatology. The second, extending from the appointment in 1988 of Paul D. Berk as Schaffner's successor to the present day, has witnessed enormous growth in the clinical and scientific activities of the division, together with the emergence of a world-class liver transplant program at Mount Sinai. During this recent period, an extensive program of formal clinical research was established; the basic research program then expanded into the areas of hepatic transport, molecular virology, and the cellular and molecular pathogenesis of hepatic fibrosis; and both the clinical and research productivity of the division increased dramatically. A major undertaking, now in its second year, has been the creation of the Center for the Study of Primary Biliary Cirrhosis; Mount Sinai has contributed important advances toward the understanding of this disease. Funding for the Center, from the Artzt Family Foundation Trust, supports a series of interrelated basic studies on the immunology and pathobiology of the disease, as well as creation of a unique clinical database, a serum and tissue bank, and a program of clinical studies. This integration of basic and clinical research in pursuit of new methods of diagnosis and treatment serves as a model for the division's continued leadership role.

Key Words: Hepatology, history, Mount Sinai, primary biliary cirrhosis, Popper, H., Schaffner, F., hepatitis B, hepatitis C.

Origin

A LONG HISTORY OF CLINICAL EXPERIENCE and outstanding scientific investigation that extends from bench to bedside has made Mount Sinai synonymous throughout the world with the study and treatment of liver disease. The foundations of its reputation in modern hepatology were laid in the thirty years between the creation of the Division of Liver Disease in the late 1950s, with Fenton Schaffner as its first chief, and his retirement in 1988. Some of the divi-

sion's seminal contributions include: the identification of the clinical and pathophysiologic significance of cholestasis; recognition of the importance of fibrosis as the final pathway leading from different inciting injuries to the common end result of cirrhosis; elucidation of the nature of chronic viral infections of the liver; and delineation of the clinical spectrum and natural history of primary biliary cirrhosis. Fundamental though they were, these landmark contributions were made with little more than sharp bedside observation, a light microscope, and keen human intellect. The use of special stains to enhance the diagnostic power of light microscopy, or — on occasion — the application of transmission electron microscopy, were the principal inroads made at Mount Sinai by high technology during this period. This was a multidepartmental effort, involving hepatologists, surgeons, pathologists, anatomists, and clinical chemists. Few would dispute, however, that the driving force for more than 30 years came from Hans Popper and Fenton Schaffner, friends and colleagues. Schaffner held joint

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professorships in both Medicine and Pathology. In a coincidence of almost poetic symmetry, Dr. Schaffner's death, on January 24, 2000, occurred on the very day that the January 2000 issue of *The Mount Sinai Journal of Medicine*, containing his last published article, "History of Liver Disease at the Mount Sinai Hospital" (1), was distributed, bringing to a close an extraordinary era.

The Post-Schaffner Era

By the time of Dr. Popper's death in 1988, followed shortly thereafter by Dr. Schaffner's retirement as chief of the division, winds of change had already begun to transform Mount Sinai's liver disease program. The first liver transplant at this institution, performed by Dr. Charles Miller (Mount Sinai School of Medicine [MSSM] class of 1978) in September 1988, initiated a massive, clinical enterprise combining the talents and dedications of the Liver Transplant Surgery Team and the Division of Liver Disease. The appointment of Dr. Paul D. Berk, then chief of Hematology, to succeed Dr. Schaffner as Mount Sinai's second chief of Liver Disease initiated a strategy to complement the outstanding clinical research enterprise with a laboratory program exploring basic mechanisms of liver disease.

In 1988 the Division of Liver Disease had two faculty members, two small NIH grants, and clinical revenues of less than \$150,000 annually (Figure). Its faculty roster now stands at sixteen, eleven M.D.s, an M.D./Ph.D., and four Ph.D.s, and its annual clinical faculty practice activity has increased more than ten-fold. The

division now carries out diverse research projects supported by five grants from the NIH, extensive support from private, nonprofit foundations, and clinical trial funding from the pharmaceutical industry. The research budget has grown steadily since 1988, and is approaching \$3 million annually.

Clinical Investigation

Over the past 12 years, the Division of Liver Disease has been a model of "translational research." Dr. Henry Bodenheimer, a Schaffner trainee, was recruited from Brown University to become the division's clinical director in 1992. A figure known nationally for his participation in important clinical trials, including those establishing a role for interferon in the treatment of chronic hepatitis C, he has spearheaded the development of a clinical research program that has kept Mount Sinai at the forefront of evolving medical therapies for chronic liver diseases. Most recently, he was named medical director of the Recanati-Miller Transplantation Institute. Dr. Bodenheimer has also played a critical role in the development of training programs in liver disease for both the medical house staff and fellows. This commitment to our training environment was recently highlighted by the awarding of three fellowships from the American Association of the Study of Liver Disease (AASLD)/Schering Advanced Hepatology to divisional trainees, the most of any institution in the country. In addition, Dr. Efsevia Albanis, a 1994 MSSM graduate and currently Senior Research Fellow in the laboratory of Dr. Scott Friedman, won the highly prestigious AASLD/AMGEN Physician Development Award.

In addition to Drs. Bodenheimer and Berk, the clinical staff of the division currently includes Drs. Nancy Bach, Scott Friedman, David Jaffe, Leona Kim-Schluger, Albert Min, Thomas Schiano, Michael Schilsky, and Samuel Sigal. All of them participate in a cooperative enterprise that combines the care of a large and challenging population of patients with liver disease, along with close collaboration with investigators in other departments, such as Drs. Swan Thung and Isabel Fiel from Pathology and Drs. Charles Miller, Myron Schwartz, Patricia Sheiner, Sucru Emre, and other members of the liver transplant surgical team. A selection of recent publications from this clinical program is included in the reference list of this article (2–17).

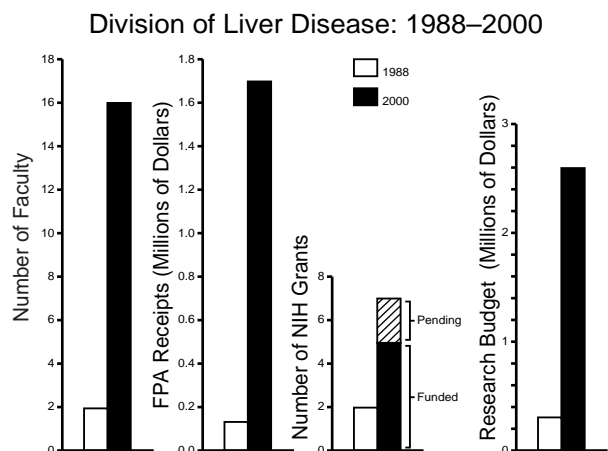


Figure. a. Number of faculty and clinical practice income in 1988 vs 2000. b. Number of NIH grants and total research expenditures in 1988 vs 2000.

The investigative interests of the Liver Disease faculty reflect the breadth of Mount Sinai's patient population and the diverse venues in which these patients are seen, including the Faculty Practice suite, The Mount Sinai Hospital Liver Clinic, clinics associated with the liver transplant program, and a satellite office in New Jersey. Shared clinical research interests include: the diagnosis and management of chronic hepatitis, especially that resulting from infection with the hepatitis B and C viruses (2–4); other complications of these infections, including the development of hepatocellular carcinoma (5) and B-cell lymphomas (6); and the utility of various diagnostic studies used in screening for specific complications of liver disease (7). At the same time, faculty members have evolved their own areas of special expertise, on which they have focused both their patient care activities and their clinical investigative programs. Thus, Dr. Albert Min has a strong interest in hepatocellular carcinoma in the setting of chronic liver disease (5). In addition, Dr. Min is currently involved in various Phase II and III clinical trials of novel therapies for hepatitis B and C. Along with Dr. Henry Bodenheimer, he is involved in assessing the efficacy of long-acting interferon in combination with ribavirin for chronic hepatitis C, both in previously untreated patients and in those unresponsive to prior antiviral therapy. With his interest in pretransplant evaluation of patients with end-stage liver disease in the setting of a severe scarcity of donor livers, he has attempted, along with Dr. Thomas Schiano, to find additional prognostic factors for identifying the most suitable pretransplant candidates (7). He is currently analyzing the long-term outcomes of patients transplanted at Mount Sinai for various forms of chronic viral hepatitis.

Dr. Nancy Bach, another Schaffner trainee, supervises a productive office-based program focused on clinical investigation in primary biliary cirrhosis (8). Dr. Bach is also involved in a study assessing the efficacy of combination antiviral treatment in patients with chronic hepatitis C and normal liver enzymes.

Although all the physicians in the division are actively involved in the evaluation and preoperative care of liver transplant candidates, Drs. Leona Kim-Schluger and Thomas Schiano have primary responsibility for postoperative care of transplanted patients, and for identifying specific medical complications that arise in the post-transplant setting (9–11). Dr. Kim-Schluger is also participating in clinical trials of

new immunosuppressive agents in liver transplant patients, and is spearheading a pilot study of the long-term efficacy of liver or kidney transplantation in patients infected with human immunodeficiency virus. Dr. Schiano has a particular clinical interest in the treatment of recurrent viral hepatitis after liver transplantation. In this regard, he is involved in studies of passive immunoprophylaxis to prevent recurrent disease in patients undergoing transplant for hepatitis C-related, end-stage liver disease. Having been trained in clinical nutrition, he is also exploring the association between nutrition and the health of the liver, and in the use of herbal and complementary medications for the treatment of liver disease.

Dr. David Jaffe, an outstanding biliary endoscopist, has become a regionally recognized authority on biliary tract disease. His interests include assessing the outcome of patients transplanted for primary sclerosing cholangitis, and screening these patients for possible development of cholangiocarcinoma. Dr. Samuel Sigal's long-standing interest in hepatic regeneration (12) translates into a clinical focus on managing complications of end-stage cirrhosis, such as ascites, electrolyte disturbances, hepatorenal syndrome, portal hypertension, and hepatic encephalopathy. Dr. Sigal's particular interests include managing and evaluating patients who have undergone transjugular intrahepatic portosystemic shunts (TIPS), and caring for patients with hepatocellular carcinoma, especially those who are candidates for percutaneous ethanol injection therapy (PEIT). Dr. Michael Schilsky, recruited from the Albert Einstein College of Medicine in 1999, is a recognized expert on disorders of metal metabolism, including hereditary hemochromatosis and Wilson's disease (13–17). Dr. Schilsky is currently participating in an FDA-sponsored pharmacologic trial with Dr. George Brewer of the University of Michigan, to determine the best initial therapy for the treatment of patients with Wilson's disease and neurologic symptoms. This study is being conducted in Mount Sinai's General Clinical Research Center in collaboration with the Department of Neurology. Dr. Schilsky is also a co-investigator in the National Hemochromatosis Transplant Registry, which is designed to determine the outcome of patients with hemochromatosis who undergo liver transplant. Along with staff from the surgical intensive care unit (SICU) and colleagues from the Transplant Institute, he is initiating a trial of an extracorporeal liver assistance device (ELAD) for patients with

fulminant hepatic failure. Depending on the clinical situation, this device will be used either to provide a bridge to liver transplant or to support the patient during recovery of the native liver. Dr. Berk, an authority on jaundice and the hereditary hyperbilirubinemias (18), also has clinical and research interests in primary biliary cirrhosis, hemochromatosis, the porphyrias, and hepatitis C. Thus, the division has broadened both its clinical expertise and clinical research interests over the past twelve years. It is moving toward a goal of having virtually every patient participate in one of its multifaceted clinical research programs.

Bench Research

The last dozen years have witnessed an explosive growth in the discipline of hepatology, as measured by a tripling of attendance at major national and international meetings devoted to the liver, an increase in the number of books and journals devoted to the specialty, and increased emphasis on training in liver disease within the framework of fellowship programs in gastroenterology. The enormous growth in this field is largely a consequence of two major phenomena: the dramatic increase in liver transplantation and the worldwide epidemic of hepatitis C. What is sometimes overlooked is the equally dramatic growth in the application of such basic disciplines as cellular and molecular biology to the study of liver disease, and the increased basic science content of the entire field, as is clearly reflected both at its meetings and within its published literature. The prominence of basic science within the discipline of hepatology, both nationally and internationally, is reflected in parallel changes within the Division of Liver Disease at Mount Sinai. The division currently conducts four major basic science efforts.

Fatty Acid Transport

When the Berk laboratory moved from Hematology to Liver Disease in 1998, it brought with it a well-established program in hepatic metabolism and hepatic transport. While the focus had for many years been on bilirubin (18), the laboratory's interests were evolving, and by 1988 at least half of the effort was focused on the plasma membrane transport of long chain free fatty acids (LCFFA). LCFFAs are increasingly recognized as important intracellular modulators of gene expression, suggesting that con-

trol of their intracellular concentrations through regulation of their cellular uptake and efflux would be of great value. However, cellular uptake of LCFFA was long considered an entirely passive, and therefore unregulated, process of relatively little intrinsic interest. Over the past 15 years, studies in the Berk laboratory, which have included research assistant professors Drs. Michael Bradbury and Shengli Zhou, as well as Dr. Xinqing Fan; Decherd Stump, and Chih-Li Kiang, have established that LCFFA uptake under physiologic conditions is mainly a facilitated transport process (19). The laboratory also identified the first putative LCFFA transporter, initially designated "plasma membrane fatty acid binding protein" (FABPpm). Tissue-specific regulation of the expression of this protein and of facilitated LCFFA transport occurs in several cellular and animal models of human disease. In particular, LCFFA uptake is selectively up-regulated in adipocytes, but not in other critical tissues such as liver and cardiac muscle, in a variety of rodent models of obesity and non-insulin-dependent diabetes mellitus (20, 21). The net effect of this change is to divert LCFFA from skeletal and cardiac muscle, where they would be consumed for energy production, into adipose tissue, where they are stored as fat. Thus, the observed changes in LCFFA disposition contribute to perpetuation of the obese phenotype. Conversely, ethanol was found to up-regulate LCFFA uptake selectively in hepatocytes, contributing to alcohol-induced fatty liver (22). Somewhat surprisingly, FABPpm proved to be identical to mitochondrial aspartate aminotransferase (mAspAT) (reviewed in reference 19). Molecular modeling studies of mAspAT, carried out in collaboration with Dr. Frank Guarnieri of the Department of Physiology and Biophysics, have identified a previously unrecognized hydrophobic cleft of suitable size to be an LCFFA-binding site. His laboratory has shown that the plasma membrane and mitochondrial components of mAspAT are both derived from a single message; sorting of the protein to different sub-cellular sites does not involve alternative splicing of the mRNA (23). Ongoing cell biologic studies are elucidating the complex route by which mAspAT traffics to the plasma membrane and is exported from the cell.

Studies of the Hepatitis C Virus

The hepatitis C virus (HCV), now recognized as the principal causative agent of non-A,

non-B hepatitis, was first discovered in 1989. Its ~9 kb RNA genome encodes a single polyprotein that is subsequently cleaved by both host and virally encoded enzymes to the various recognized structural and nonstructural proteins characteristic of HCV. Of approximately 4 million Americans who have antibody evidence of having been infected with HCV, only some 15% appear to clear the virus spontaneously. The remainder experience chronic hepatitis of variable severity that persists for decades. Approximately 20% eventually develop cirrhosis and, ultimately, the complications of end-stage liver disease. Chronic HCV infection is now the most frequent indication for liver transplantation in the United States and Western Europe.

The biology of the virus remains poorly understood. Because of the division's growing clinical involvement with hepatitis C, Dr. Andrea Branch, an outstanding authority on plant viroids and on the delta agent (hepatitis D virus, HDV), was recruited from Rockefeller University in 1994 to develop a program of basic studies of the HCV virus. Her highly reasoned critical reviews of what is known about hepatitis C (e.g., reference 24), and of the potential strengths and weaknesses of conventional approaches to both antisense therapy (25–28) and gene therapy (29, 30), have very quickly established her as an important and creative contributor to the field. Recognizing that viral genomes often have overlapping genes, Dr. Branch and her associates, in particular Dr. Jose Walewski and Decherd Stump, developed software that has facilitated their comparative sequence analyses of published HCV isolates, in an effort to identify overlapping, dual-use regions. Their strategy for identifying such regions is based on the degeneracy of the genetic code. Thus, the code for a number of amino acids is fully specified by the first two bases of a codon. Since the third base in this situation is of no consequence for defining the encoded amino acid, it would be anticipated that, over time, random mutations would have resulted in the given amino acid being encoded by any of four sequences, with the same bases in positions 1 and 2, and A, T, G or C in position 3. This variability in position 3 would have no effect on the amino acid sequence of the encoded polypeptide. However, if there were an overlapping reading frame, an insignificant change in base position 3 in one reading frame could produce a significant alteration in the amino acid composition of a polypeptide encoded in an overlapping, alternative reading frame. Based

on these theoretical considerations, diverse HCV sequences were obtained from GenBank (Bethesda, MD), and aligned. The proximal portion of the main open reading frame (ORF) was found to contain a region of highly constrained sequence, in which the third base in numerous codons was far more restricted than would be anticipated by chance. When read in the alternative 1+ reading frame, nearly 90% of the retrieved sequences contained at least 124 codons without a stop codon, representing a candidate second or alternate ORF. By contrast, within the same region of HCV RNA, the 2+ reading frame was riddled with stop codons. To determine if this alternate ORF (A-ORF) was biologically significant, two peptides, representing different regions of the encoded A-ORF polypeptide, were synthesized and used to develop assays to detect antibodies against the A-ORF protein. Analysis of sera from patients with chronic HCV demonstrated that an appreciable proportion of them contained antibodies to the A-ORF protein (31), indicating that the protein must be synthesized during chronic HCV infection. Efforts are now ongoing to identify the protein itself in liver samples from infected patients. The identified protein may be of value in improved HCV diagnostics. Moreover, the new protein, as well as the uniquely conserved region of the HCV genome that encodes it, are potential targets for a variety of new anti-HCV therapeutic strategies. It is likely that therapies developed on the basis of these observations will eventually undergo clinical evaluation within our program at Mount Sinai.

Mechanisms, Diagnosis and Treatment of Hepatic Fibrosis

Dr. Scott Friedman, a graduate of the MSSM (class of 1979), returned as a faculty member and director of research in the Division of Liver Disease in November 1997. His return followed an absence of 18 years, which included 15 years at the University of California San Francisco (UCSF), first as a gastroenterology fellow and then as a faculty member. During his tenure at UCSF, he did pioneering research into the underlying causes of scarring, or fibrosis, associated with chronic liver disease. Dr. Friedman was the first to isolate and characterize the hepatic stellate cell, which is the key cell type responsible for scar production in liver (32). This work has led to major insights into how the liver responds to injury, and points the way toward new treatments.

Dr. Friedman's interest in liver disease can be traced directly to Mount Sinai's founding fathers of hepatology, Drs. Schaffner and Popper, whose lectures planted the seeds of interest that led to his specialty. Remarkably, his experimental studies have followed directly from earlier observations by Drs. Popper and Schaffner, who emphasized the stellate cell's potential importance in liver disease. From this initial finding, Dr. Friedman's research has expanded into a comprehensive program exploring the cellular and molecular basis of liver fibrosis, which has spawned parallel efforts in dozens of laboratories and pharmaceutical companies throughout the world (33–38). Liver fibrosis, leading ultimately to cirrhosis, is a serious consequence of excessive alcohol consumption (39), and has assumed major importance as a potential treatment target for the millions of patients infected with hepatitis C (40). In addition to continuing an in-depth exploration of molecular mechanisms of hepatic fibrosis, he is collaborating with Dr. Frank Eng and several other colleagues, in the clinical realm, with the testing of novel diagnostic agents and therapies for hepatic fibrosis. Much of the current excitement about the potential benefits of anti-fibrotic therapy in these important liver diseases can be traced to Dr. Friedman's contributions.

The Pathobiology of Primary Biliary Cirrhosis

Mount Sinai has had a major and productive interest in primary biliary cirrhosis (PBC) for nearly 50 years, with important studies by Drs. Popper and Schaffner illuminating its clinical spectrum, natural history, and histopathologic evolution, as well as the nature and significance of cholestasis. This interest led to the accumulation of a large group of PBC patients, who have participated in numerous trials of medical therapies, and have provided many candidates for Mount Sinai's liver transplant program. Mount Sinai is currently following as many as 600 patients with this uncommon disease, including more than 100 who have received liver transplants and a similar number with advanced disease, who are currently being followed in the pretransplant clinic. The remainder, at earlier stages in their disease, are being followed in either the Liver Disease Associates FPA suite or the Liver Clinic.

As a result of this unique experience, the Artzt Family Foundation Trust recently provided the division with a three-year grant to ini-

tiate the Center for the Study of Primary Biliary Cirrhosis at Mount Sinai. The Center will support both clinical and basic science initiatives related to PBC. A major component of the clinical program is the development of a unique patient database, which will eventually contain patient data not only from Mount Sinai, but also from collaborating centers around the world. The database, under development with the assistance of Computer Associates (Islandia, NY), will incorporate *neugents*, a unique artificial intelligence tool capable of identifying previously unrecognized trends and correlations in very large data sets and using them for the formulation of new hypotheses. This database will also support future clinical trials, some of which, we anticipate, will be designed to test hypotheses developed with the *neugents* technology. A serum and tissue bank, linked to the database, will be an important resource for laboratory investigations. The Center is already supporting basic studies in several laboratories, including those of Drs. Berk, Branch, Friedman and Thung. For the most part, these studies represent an extension of ongoing work, such as studies of mitochondrial protein trafficking and hepatic fibrosis, as well as relevant aspects of PBC. A critical component of the program, however, is the creation of a new laboratory devoted specifically to the immunology of PBC. Dr. Joseph Odin, an alumnus of Mount Sinai's M.D./Ph.D. program, has been recruited back to his alma mater from the Johns Hopkins School of Medicine to create this new program. Dr. Odin has had a long interest in the immunology of PBC and most recently has been investigating the role of apoptosis of biliary epithelial cells in the generation of the antimitochondrial antibodies that are characteristic of this disease.

Hepatology in the New Millennium

The Mount Sinai Division of Liver Disease, by virtue of its long tradition and extraordinary recent development, is perfectly positioned to exploit the explosive growth in biomedical research now being witnessed worldwide. This era of science, driven in part by the impending completion of the sequencing of the human genome, is a "golden age of biology," much as the 1940s and 1950s were a golden age for physics, with the harnessing of nuclear energy. Moreover, the trajectory of anticipated divisional growth is aligned perfectly with the institutional commitment to translational research, as articulated in Dean Arthur Rubenstein's Strategic Plan.

What new advances can we expect in the field — at Mount Sinai and elsewhere? New computer technologies, such as the unique patient database described above, will allow investigators to gather and analyze data from patients with PBC and other liver diseases, with a level of sophistication not even dreamed of only 5 years ago. Laboratories within the Division of Liver Disease at Mount Sinai will make major contributions to improvements in molecular diagnostics and imaging for viral hepatitis and its fibrotic complications. This will reduce the need for invasive methods of assessing liver disease. Antiviral therapies for the treatment of hepatitis B and C will be continually refined, and will include new therapeutic tools such as ribozymes, in addition to improved versions of conventional antiviral drugs. Along with better characterization of genetic and host factors that influence prognosis and response to therapy, these will lead to improved outcomes for medical treatment of these serious illnesses. Improved understanding of the immunopathogenesis of PBC will permit the development of rational, successful medical therapy for this disorder as well. Basic studies of the membrane transport of fatty acids will provide insights that will foster specific therapies for steatohepatitis, as well as for disorders such as obesity and non-insulin-dependent diabetes mellitus, which are not primarily diseases of the liver. Antifibrotic therapies, already in early clinical trials, will be refined on the basis of still further understanding of the fibrotic process, and will delay the evolution of cirrhosis across a wide spectrum of liver diseases, even those for which the underlying pathogenesis is incompletely understood. These advances, in all of which Mount Sinai scientists will play a major role, will reduce the need for liver transplantation for many patients, thereby bringing into more reasonable balance patient needs and the limited supply of donor organs.

The progressive maturation of gene therapy will overcome current obstacles and achieve safe, targeted delivery and sustained function of a variety of genes. Isolated hepatocyte transplantation will also find a role in the treatment of genetic diseases of the liver and, perhaps, of some acquired forms of liver failure. These complementary modalities have the ability either to replace genetically deficient gene function or to augment acquired deficiencies of function, for a spectrum of disorders from fulminant liver failure to malignancy. These efforts will be informed by the knowledge of the

human genome sequence in ways that cannot be predicted, and totally new paradigms of cellular and integrative biology are sure to emerge. Equally certain is that growth in biological understanding and therapy will dramatically enhance collaboration among Mount Sinai's programs in liver disease, neoplastic diseases, pediatrics, and genetics. Although these medical advances will decrease the need for liver transplantation, transplants will remain a crucial therapy of last resort. Transplantation biologists from the Immunobiology Center and the Transplantation and Gene Therapy Institutes, working in collaboration with the Division, will discover the optimal modes of immunosuppression that can prevent liver rejection and minimize complications. For desperately ill patients awaiting liver transplantation, new modalities will be developed as a bridge to liver transplantation, using either extracorporeal devices or molecular reconstitution of liver function. The Transplantation Institute will continue its pioneering role in creating new surgical options for patients requiring liver transplantation, as exemplified by the recent growth in living-related-donor transplantation surgery.

Underlying all these efforts will be the sustained growth in interdisciplinary science that is so vital to success in this golden age of biology, combining the expertise of basic scientists and clinicians in divisions and departments throughout the institution. This critical ingredient will create synergy in all aspects of science and clinical care. These activities, in turn, will continue to rely on the support of the NIH and other federal agencies, pharmaceutical partners, grateful patients and generous patrons. Now, as much as ever, the Mount Sinai Division of Liver Disease — together with its many institutional partners — is on course to maintain its role as a world leader in understanding and treating patients with liver diseases.

References

1. Schaffner F. The history of liver disease at The Mount Sinai Hospital. *Mt Sinai J Med* 2000; 67:76–83.
2. Fiel MI, Schiano TD, Guido M, et al. Increased hepatic iron deposition resulting from treatment of chronic hepatitis C with ribavirin. *Am J Clin Pathol* 2000; 113:35–39.
3. Schiff ER, Karayalcin WS, Grimm JS, et al, and the International Lamivudine Investigator Group. Lamivudine and lamivudine/interferon combination therapy in patients with hepatitis B who previously failed interferon: An international controlled trial. *JAMA* (In press).
4. Schiano TD, Fiel MI, Abe K, et al. Absence of hepatitis G virus within liver tissue of patients undergoing liver transplantation for cryptogenic cirrhosis. *Transplantation* 1999; 67:1193–1197.

5. Gambarin-Gelwan M, Wolf DC, Shapiro R, et al. Sensitivity of commonly available screening tests in detecting hepatocellular carcinoma in cirrhotic patients undergoing liver transplantation. *Am J Gastroenterol* 2000; 95:1535–1538.
6. Ye MQ, Suriawinata A, Black C, et al. Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type in a patient with primary biliary cirrhosis. *Arch Pathol Lab Med* 2000; 124:604–608.
7. Schiano TD, Bodian C, Schwartz ME, et al. Accuracy and significance of CT scan assessment of hepatic volume in patients undergoing liver transplantation. *Transplantation* 2000; 69:545–550.
8. Bach N, Bodian C, Croen E, et al. Methotrexate therapy for primary biliary cirrhosis [abstract]. *Hepatology* 2000; 32:A1398.
9. Fiel MI, Schiano TD, Klion FM, et al. Recurring veno-occlusive disease in liver allografts. *Am J Surg Pathol* 1999; 23:734–737.
10. Fiel MI, Schiano TD, Bodenheimer HC, et al. Hereditary hemochromatosis in liver transplantation. *Liver Transpl Surg* 1999; 5:50–56.
11. Schluger LK, Sheiner PA, Thung SN, et al. Severe recurrent cholestatic hepatitis C following orthotopic liver transplantation. *Hepatology* 1996; 23:971–976.
12. Sigal SH, Rajvanshi P, Gorla GR, et al. Partial hepatectomy attenuates proliferative capacity in remnant hepatocytes with polyploidy and other changes suggesting induction of cell aging-type processes. *Am J Physiol* 1999; 276:G1260–G1272.
13. Schilsky ML, Tavill AS. Wilson's disease. In: *Diseases of the liver*. Editors: Schiff ER, Sorrell MF, Maddrey WC. Philadelphia: Lippincott-Raven; 1999. pp. 1091–1106.
14. Schilsky ML, Sternlieb I. Management of Wilson's disease. In: Krawitt EL, editor. *Medical management of liver disease*. New York: Marcel Dekker; 1999. pp. 397–406.
15. Tavill AS, Schilsky ML. Wilson's disease. *Current Treatment Options in Gastroenterology* 1999; 2:68–71.
16. Schilsky ML. Inherited metabolic disease. *Current Opinion in Gastroenterology* 1999; 15:200–207.
17. Bacon BR, Schilsky ML. New knowledge of the genetic pathogenesis of hemochromatosis and Wilson's disease. *Adv Intern Med* 1999; 44:91–116.
18. Berk PD, Wolkoff AW. Bilirubin metabolism and the hyperbilirubinemias. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. *Harrison's principles of internal medicine*. 15th ed. New York: McGraw Hill; 2000 (In press).
19. Berk PD, Stump DD. Mechanisms of cellular uptake of long chain free fatty acids. *Mol Cell Biochem* 1999; 192:17–31.
20. Berk PD, Zhou S-L, Kiang C-L, et al. Uptake of long chain free fatty acids is selectively upregulated in adipocytes of Zucker rats with genetic obesity and non-insulin dependent diabetes mellitus. *J Biol Chem* 1997; 272:8830–8835.
21. Berk PD, Zhou S-L, Kiang C-L, et al. Selective up-regulation of fatty acid uptake by adipocytes characterizes both genetic and diet-induced obesity in rodents. *J Biol Chem* 1999; 274:28626–28631.
22. Zhou SL, Gordon RE, Bradbury M, et al. Ethanol up-regulates fatty acid uptake and plasma membrane expression and export of mitochondrial aspartate aminotransferase in HepG2 cells. *Hepatology* 1998; 27:1064–1074.
23. Bradbury MW, Berk PD. Mitochondrial aspartate aminotransferase: Direction of a single protein with two distinct functions to two subcellular sites does not require alternative splicing of the mRNA. *Biochem J* 2000; 345:423–427.
24. Branch AD. The RNA of hepatitis C virus. *Semin Liver Dis* 2000; 20:57–68.
25. Branch AD. A hitchhiker's guide to antisense and nonantisense biochemical pathways. *Hepatology* 1996; 24:1517–1529.
26. Branch AD. A good antisense molecule is hard to find. *Trends Biochem Sci* 1998; 23:45–50.
27. Branch AD. Antisense drug discovery: Can cell-free screens speed the process? *Antisense Nucleic Acid Drug Dev* 1998; 8:249–254.
28. Branch AD. Antisense RNA. In: Lederberg J, editor. *Encyclopedia of microbiology*. 2nd ed. San Diego (CA): Academic Press; 2000.
29. Kresina TF, Branch AD. Molecular medicine and gene therapy: An introduction. In: Kresina T, editor. *An introduction to molecular medicine and gene therapy*. New York: Wiley-Liss. (in press)
30. Branch AD, Klotman PE. Optimizing ribozymes for somatic cell gene therapy. *Exp Nephrol* 1998; 6:78–83.
31. Walewski JL, Stump DD, Keller TR, Branch AD. HCV-infected patients produce antibodies against a protein encoded in a second reading frame [abstract]. *Hepatology* 1998; 28:A278.
32. Li D, Friedman SL. Liver fibrogenesis and the role of hepatic stellate cells — new insights and prospects for therapy. *J Gastroenterol Hepatol* 1999; 14:618–633.
33. Okuno M, Sato T, Kitamoto T, et al. Increased 9,13-di-*cis*-retinoic acid in rat hepatic fibrosis: A potential link between retinoid loss and TGF- β mediated fibrogenesis via RARA activation. *J Hepatol* 1999; 30:1073–1080.
34. Whalen R, Rockey DC, Friedman SL, Boyer TD. Activation of rat hepatic stellate cells leads to loss of glutathione-S-transferases and enzymatic activity against products of oxidative stress. *Hepatology* 1999; 30:927–933.
35. Nieto N, Friedman SL, Greenwel P, Cederbaum A. CYP 2E1 mediated oxidative stress stimulates collagen gene expression in rat hepatic stellate cells. *Hepatology* 2000; 30:987–996.
36. Kojima S, Hayashi S, Suzuki Y, et al. Transcriptional activation of urokinase-type plasminogen activator by the Krüppel-like factor Zf9/COPEB activates latent TGF- β 1 in vascular endothelial cells. *Blood* 2000; 95:1309–1316.
37. Friedman SL. Cytokines in fibrogenesis. *Semin Liver Dis* 1999; 19:129–140.
38. Friedman SL. Molecular regulation of hepatic fibrosis: An integrated cellular response to tissue injury [mini-review]. *J Biol Chem* 2000; 275: 2247–2250.
39. Friedman SL. Stellate cell activation in alcoholic fibrosis. *Alcohol Clin Exp Res* 1999; 23:904–911.
40. Friedman SL. The evaluation of fibrosis and hepatitis C. *Am J Med* 1999; 107(6B):27S–30S.