

# The History of Liver Disease at The Mount Sinai Hospital

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## Abstract

Diseases of the liver and biliary tract interested the physicians of The Mount Sinai Hospital from the time the hospital started until the present. Indeed, the institution has become a well-recognized center for the study of the liver and its diseases. During the first 75 years of the hospital, there were many admissions for hepatobiliary diseases, resulting in many case reports. The evolution of the hospital into a teaching hospital brought with it a more systematic method of studying diseases, not only in Pathology under Paul Klemperer, but in Clinical Chemistry and Microbiology as well. Liver biopsy was also attempted. With the arrival of Hans Popper in 1957, the emphasis shifted to coordinated studies of both normal and abnormal liver structure and function in diseases. Soon, Liver Diseases (Hepatology) was split from Gastroenterology, with Fenton Schaffner as the first chief. Over the next 30 years, more than 1000 papers, chapters and books were published. The main areas of research were fibrosis, cholestasis (especially morphology and bile salt metabolism), toxic liver injury, metabolic transformations and carcinogenesis. Primary biliary cirrhosis and viral hepatitis were and continue to be special interests. Fellows from all over the world were trained and many moved on to leadership positions. Although he was active in the development of the liver transplant program, Popper did not live to see its start. A new generation of hepatologists maintains the interest and position of The Mount Sinai Hospital in this important field of medicine. **Key Words:** Liver disease, history, The Mount Sinai Hospital.

LIVER DISEASE had been an uncommon reason for admission to The Mount Sinai Hospital in the first one hundred years of its existence, but this has changed in the last fifty years. The Mount Sinai 100th anniversary issue of the *American Journal of Medicine*, published in November 1952 with George Baehr as guest editor, contained reprints of what were considered the most significant contributions to medicine from the hospital. None was related to the liver. Included in this issue of the *American Journal of Medicine* were an informative forward by Baehr and an article on the founding and the early days of Mount Sinai, written by Eli Moschcowitz.

The first recorded death from liver disease at Mount Sinai was in 1861 from primary hepatocellular carcinoma. The decade 1897–1907 saw a total of 67 patients with such tumors admitted to

the hospital, while in 1986–1995, 183 were admitted. However, 890 patients with hepatobiliary diseases were hospitalized from 1897–1907, while in the recent last decade, 4347 were admitted. During the 19th century, contributions from Mount Sinai to the medical literature concerning liver diseases consisted of case reports of unusual conditions or unusual presentation of common diseases, mainly cysts and abscesses. Two were in the newly established *Mount Sinai Hospital Reports*, which first appeared in 1899 (1, 2). This became the *Journal of the Mount Sinai Hospital* in 1933. Between 1900 and 1904, four cases of rapidly fatal liver disease, termed acute yellow atrophy, were seen in young women (3, 4). Despite careful study and autopsy examination, no cause was found, although pregnancy may have been a factor in two. Such individual case reports of unusual cases of liver diseases have continued to appear, albeit less frequently. Series of cases were reported soon after the turn of the century (5, 6). Now very large series, natural history studies, controlled trials and experimental

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data related to the liver make up the bulk of publications, in addition to books, book chapters and periodicals.

Many factors contributed to the shift in direction of the role of Mount Sinai in hepatology. The first was that the institution became a teaching hospital at the turn of the 20th century, with the start of an intern training program. Medicine, surgery and pediatrics were established as separate disciplines, with the development of the “giants” of the hospital’s history, including Albert Berg in Surgery, Emanuel Libman in Medicine and Abraham Jacobi in Pediatrics, to name just a few. Chronic jaundice in those days was considered to be obstructive in nature and mainly a surgical condition (7).

Shortly after World War I, Paul Klemperer was appointed as the first full-time chairman of the Department of Pathology. This was a second factor in the development of interest in liver diseases at Mount Sinai. Klemperer and his coworker, Sadao Otani, began to describe hitherto unrecognized conditions, first in the innovative clinical pathological conferences published in the *Journal of the Mount Sinai Hospital* or its predecessor. Collections of some of these unusual cases led to the establishment of lupus erythematosus, thrombotic thrombocytopenia, giant follicular lymphoma and regional enteritis as disease entities. Klemperer described chronic intrahepatic obliterating cholangitis but did not connect this condition with inflammatory bowel disease (8). Rare tumors of the liver like primary sarcoma were reported (9) and primary hepatocellular carcinomas were the subject of clinical pathological conferences (CPCs) reported in the *Journal of the Mount Sinai Hospital* (10). Numerous cases of parasitic diseases of the liver and abscesses also were published in *The Journal* in the form of case reports or CPCs. Jaundice in heart failure was ascribed largely to hepatic anoxia (11), but three years earlier pulmonary infarction with excess bilirubin production was blamed (12). Arthur Sohval wrote an extensive review of hepatic complications of polycythemia vera, including descriptions of hepatic and portal vein thromboses, and the appearance of cirrhosis in some cases (13). Adverse hepatic drug reactions were beginning to be recognized, especially with cinchophen (14) and arsenicals (15) and experimental production of these in laboratory animals was attempted (15, 16). Reuben Ottenberg and Rose Spiegel compiled a detailed description of jaundice due to various chemicals, which served as the standard reference on the subject for many years (17).

A third factor contributing to the establishment of hepatology at Mount Sinai was the utilization of the clinical chemistry and later, the microbiology laboratories, in a systematic fashion. This was part of the global trend of moving away from empiricism to scientific medicine. Nitrogen metabolism was studied at various stages of medical and surgical hepatobiliary diseases (18) and in the hepatorenal syndrome (19, 20). Early attempts were made to investigate bilirubin and bile salt metabolism (21). New laboratory tests for assessing liver function were evaluated (22). One interesting test detected benzoyl glucuronide after administration of hippuric acid (23). This was devised by Isidore Snapper, who arrived from China in the early years of World War II. He had previously described the test for and significance of direct and indirect bilirubin with van den Bergh in Amsterdam just before the First World War. Snapper never associated glucuronide formation with bilirubin metabolism, although he lived to see direct bilirubin discovered to be bilirubin glucuronide. Mount Sinai joined the debate about whether catarrhal jaundice was the result of inflammation of bile ducts or necrosis of liver cells (24). The role of medications such as arsphenamine (25) and cinchophen (26) in causing jaundice that resembled hepatitis was explored. Just prior to World War II, attempts were made to biopsy the liver percutaneously by Edgar Baron (27) and just after the war by punch at surgery by Edward Jemerin (28). Percutaneous needle biopsy at this time did not succeed because bleeding could not be adequately predicted or controlled. The war itself offered the opportunity for the many Mount Sinai physicians in military service to see numerous cases of hepatitis, no longer called catarrhal jaundice and recognized to be either infectious or transmitted via serum. The heightened interest in liver disease resulted in the publication of the first large American textbook on diseases of the liver by Solomon Lichtman, which appeared shortly after the war. It went through three editions and was the standard mid-century text on the subject (29). A liver clinic was started as an adjunct to the GI clinic, with Alexander Richman as chief and Albert Parets as his associate.

### The Popper Era

The next important factor in the growth of interest in liver disease at Mount Sinai was the appointment in 1957 of Hans Popper as chairman of the Department of Pathology after Klemperer’s retirement. A few months later, Popper brought

Fenton Schaffner to New York to provide the clinical arm for a growing liver team forming in Pathology. The aim of the group was to correlate structure and function in the various liver diseases. Popper had been investigating many clinical and pathologic aspects of liver diseases for more than 20 years, first in Europe under Hans Eppinger in Vienna and then in Chicago where he was the pathologist for the Cook County Hospital. Schaffner was first a Fellow in Pathology at Cook County under Popper and then a part-time colleague while in full-time internal medical practice. Together they had just published a new type of text on liver, *Liver: Structure and Function* (McGraw-Hill, 1957), which emphasized structure as a guide to function.

The liver team was assembled and functioning, and research grants began to be received. Areas developed included histochemistry with recruitment of Tibor Barka (who became the first editor of the *Journal of Histochemistry*), biochemistry with Edward Singer and Ferenc Hutterer, immunocytochemistry with Fiorenzo Paronetto, and electron microscopy with Schaffner, under the tutelage of the Cell Research Laboratory headed by Leonard Ornstein. The number of liver biopsies performed in the hospital increased dramatically to about 600 a year with the introduction of the Terry Needle, brought from Chicago. The biopsy specimens were processed with great care by Hendrika van der Noen, who also trained many technicians in preparing truly beautiful histologic slides that remain the mainstay of teaching and research as well as diagnosis.

The Popper years saw an explosion in description and discovery, and in the number of papers published, which amounted to more than 1000 in a period of 30 years. The main topics were hepatic fibrosis, cholestasis with special emphasis on morphology and bile salt metabolism, toxic liver injury, metabolic transformations, and carcinogenesis. The early work of the team was described in annual progress reports from 1960–1963, which appeared in volumes 27–30 of the *Journal of the Mount Sinai Hospital*. These reviews dealt mainly with our work in hepatic fibrosis and the development of chronicity of liver disease. Later reviews were published in each volume of *Progress in Liver Diseases*.

The studies of fibrosis revealed that as collagen increased, it was distributed around portal tracts, proliferating ductules, and sinusoids in the spaces of Disse (30). The perisinusoidal fibrosis was associated with the formation of a basement membrane, resulting in capillarization of the sinu-

soids (31). The fibrosis of schistosomiasis was found to be periductal (32) and resulted in presinusoidal portal hypertension (33). Detail of the structure of the ductule was described, including how it acted as a trellis for the deposition of collagen (34, 35). Various aspects of alcoholic (36, 37), autoimmune (38, 39), and later, viral chronic liver disease (40, 41), were explored, including clinical and chemical correlations. Drug-induced liver disease was classified as hepatic or cholestatic (42), and many publications followed, ranging from case reports to large series and reviews. Ultrastructural and histochemical aspects of Wilson's disease were detailed (43) and experimental copper intoxication was studied (44). Involvement of the liver in AIDS was investigated as the epidemic progressed (45, 46). Much attention was devoted to cholestasis (47). The morphology of the condition was examined in patients in whom a bile duct had been ligated (48, 49) and in animals to which lithocholate was administered (50), as well as in those given cholestatic drugs (51) and alpha naphthylisothiocyanate (52). The site of the initial injury in primary biliary cirrhosis (53) and the stages of the disease (54) were described. Immunologic markers of the disease were studied (55). A large series of patients with primary biliary cirrhosis was accumulated, enabling description of the natural history (56), serum bilirubin as a prognostic indicator (57), and the effects of treatment in trials including penicillamine (58), colchicine (59) and later ursodiol and methotrexate. The serum bilirubin level also proved to be a prognostic marker for sclerosing cholangitis (60). The role of the bile acids in causing cholestasis and in producing hepatocellular injury (61) was examined. The state of the art facilities assembled also permitted a search for a no-effect level of toxic substances (62) and the earliest indications of hepatic injury and malignant transformation (63). The substances examined had either military (intravenous fat emulsions [64] and space cabin atmospheres [65]) or environmental importance (pesticides [66], vinyl chloride [67]).

A steady stream of foreign fellows and visitors began arriving, beginning with Perez from Argentina, Pang from Indonesia, Scheuer from England, and many more. Giorgio Menghini visited Mount Sinai in 1958 at the time the first meeting of the International Association for the Study of the Liver was held in Washington. Popper was a founding father of this society, which was modeled after the American Association for the Study of Liver Diseases (AASLD), which Popper founded a decade earlier

in Chicago. Menghini brought his newly-invented aspiration liver biopsy needle and performed the first such biopsy at Mount Sinai. He left one of his needles and Schaffner performed the second such one-second biopsy on a young diabetic girl in ketoacidosis who suddenly developed massive hepatomegaly and ascites. This was reported as a case of excessive glycogen deposition in the liver, visualized by electron microscopy (68). Albert Parets reviewed our early experience with the needle (69), which we continue to use to this day. The team and the visitors began producing a torrent of more than 500 papers, as well as frequent presentations at national and international meetings which continued for more than 30 years. The work continued even while Popper was Dean and President of our new medical school; he was the main driving force in its foundation.

Popper and Schaffner edited a special issue of *Gastroenterology* devoted to liver diseases in November 1959. As a result of this special issue, the series, "Progress in Liver Diseases," was begun in 1961, published by Grune and Stratton. It went through nine volumes, the last published by Saunders. One volume appeared every three years, until after Popper died in 1988. Other books appearing were *Clinico-Pathological Conferences of The Mount Sinai Hospital* by Schaffner and Popper, published by Grune and Stratton in 1963; *Cirrosis Hepática* by Anibal Latuff (from Venezuela) and Schaffner, published by Editorial Científico Médico, Barcelona in 1966; and *The Liver and Its Diseases*, put together as a festschrift for Popper's 70th birthday by Schaffner, Sheila Sherlock (of London) and Carroll Leevy of (New Jersey), published by Intercontinental Medical Books in 1983. Popper and Schaffner contributed chapters to the third and fourth editions of Bockus' *Gastroenterology*, Schaffner being an associate editor in the fourth edition and a senior co-editor in the fifth. Popper was an associate editor for the first two editions of *The Liver: Biology and Pathobiology*, published by Raven Press, with Irwin Arias as senior editor. Popper also served as an associate editor for *Gastroenterology* and for *Hepatology*.

During the Popper era, a program project grant was awarded by the National Institutes of Health (NIH) to Pathology to cover much of the research activity. A training grant for liver fellows was also awarded and Alexander Gutman, the chairman of the Department of Medicine, split Liver Diseases from Gastroenterology in 1965 and created a separate division with Schaffner as the first chief. One or two Liver fellows were

trained each year and when the grant ended, the hospital funded the fellowship and continues to do so. Several fellows elected to stay at Mount Sinai for varying periods of time. Franklin Klion remained as a full-time clinician for several years and then went into private practice. He continues to maintain close ties to the Division of Liver Diseases and when Richman retired as chief of the Liver Clinic, Klion was his successor. He also takes a very active role in the transplant program, and wrote a book, *Guide to Liver Transplantation*, with Thomas Fabry, published by Igaku-Shoin in 1992. Popper trained many pathologists from all over the world and several have become chairmen of their own departments, including Stephen Geller, Michael Gerber and Emanuel Rubin in the United States, Peter Scheuer and Helmut Denk in Europe, Zilton Andrade in Brazil and Goroku Ohta in Japan. They have all achieved international reputations and retain an active interest in the liver. Swan Thung was also a Popper student and she inherited the job of being responsible for all the liver biopsies as well as immunologic studies involving the liver, which she is still doing. Several internists from abroad also spent time learning about liver disease in the Department of Pathology and then returned home to become chiefs of their medical departments. These included Massimo Colombo in Italy, Whan Kook Chung and, later, Boo Sung Kim from Korea, and Hiroshi Sasaki from Japan. Many specimens of liver tissue were sent to Mount Sinai for second opinions and a very large collection of slides with accompanying histories was accumulated. After Popper died, these were donated to the Armed Forces Institute of Pathology in Washington.

Popper received many honors, including several honorary doctoral degrees. One was from the University of Vienna, his alma mater, on the 600th anniversary of the founding of the institution. The school also renamed the pathology department the Hans Popper Institute of Pathology. The Hans Popper Primate Center in Orth, a suburb of Vienna, was dedicated in 1992 for the study of viral diseases, including hepatitis. He received numerous honors in the United States. The Friedenwald Medal was bestowed on him in 1971 by the American Gastroenterological Association (70). Popper was elected to the Academy of Arts and Sciences. He spent the year 1974 as a Fogarty Scholar in residence at the NIH in Bethesda after he stepped down as dean and president. During his year away, he was able to organize a meeting on nomenclature chaired by Carroll Leevy of New Jersey. The meeting

resulted in a book on standardization of nomenclature, diagnostic criteria and diagnostic methodology (71).

Mount Sinai named the department of pathology the Popper and Stratton Department of Pathology, Lillian and Henry Stratton being major benefactors and close friends. Dr. Popper was awarded the Jacobi Medallion in 1973. Thomas Chalmers, Popper's successor as dean and president of the Medical Center, received the medallion in 1981, while Schaffner received it in 1992 (Fig. 1). Popper was very active in the national and international liver associations, having served as president of both the American and international societies. Chalmers (before he came to Mount Sinai), Schaffner and Paul Berk also were AASLD presidents. Berk, Schaffner and Rudi Schmid of California produced a book honoring Popper entitled *Hans Popper, a Tribute*, published by Raven Press in 1992. This was also translated into German as *Hans Popper, Freunde Erinnern Sich*, published by Schattauer. Herbert Falk, who founded the pharmaceutical firm devoted mainly to hepatological and gastrointestinal medications, paid for and distributed the book. Falk and Popper were close friends, and Popper served as an important advisor to Falk. For forty years, Falk sponsored many of Popper's symposia and other teaching activities that promoted interest in liver diseases. Falk has honored this relationship by creating the Hans Popper Prize for outstanding work in the field; it is awarded during the triennial Basal Liver Week.

Chalmers, who succeeded Popper as dean and president in 1974, was responsible for introducing the liver team to randomized, double-blind, con-



**Fig. 1.** Hans Popper, Thomas Chalmers, and Fenton Schaffner (l to r), together at a Mount Sinai School of Medicine conference in 1973.

trolled trials of therapy for liver diseases. Berk came to Mount Sinai as chief of Hematology, from NIH, where he was Chalmers's successor as chief of the liver program. He put together a team and laboratories dedicated mainly to bilirubin and membrane transport in the liver. During the Popper era, in 1980, two journals devoted to the liver were founded in the United States. AASLD gave birth to *Hepatology*, with a big push by Popper. Many of the Mount Sinai team served on the editorial board. The second journal, *Seminars in Liver Diseases*, began and still is at Mount Sinai, with Berk as editor and Chalmers, Charles Lieber, Popper and Schaffner constituting the original editorial board. Both journals continue to flourish and Berk has just completed a six-year term as editor of *Hepatology*. Lieber, who works at the Bronx Veterans Administration Hospital, has been editor of *Alcoholism*. When Schaffner became emeritus in 1991, Berk became the second chief of the division and the laboratories he established in the Division of Hematology came with him to Hepatology.

### The Transplantation Era

The year 1988 marked the end of the Popper era with his death at the age of 83 from pancreatic cancer. It also marked the introduction of liver transplantation at Mount Sinai. Within a few years, under Charles Miller, the institution became the third largest transplant center in the country. Both Popper and Chalmers pushed hard to have a transplant program at Mount Sinai. They did this, with the help and blessing of Arthur Aufses, Jr., the chairman of the Department of Surgery (Fig. 2). The trustees and the administration of the medical center gave their enthusiastic support for the program.

The first liver transplantation at Mount Sinai occurred on September 3, 1988, involving a patient with sclerosing cholangitis. The 1000th transplantation was done on October 9, 1995 and the 1000th patient was transplanted on September 18, 1996. As of September 1996, 2868 patients had been evaluated for transplantation and 254 were on the waiting list. The youngest surviving patient at transplant was not quite six months old and the oldest was 75 years. Several living-related and split-liver transplants have been performed. These data were obtained from the Fall 1996 issue of *Transplantation Update*, a publication of the Division of Liver Transplantation of the Department of Surgery.

After transplantation was begun, the need for more help from the Division of Liver Diseases



**Fig. 2.** The original Mount Sinai Liver Transplant team. First row (l to r): Fenton Schaffner, Arthur Aufses, Charles Miller, Paul Berk; Second row (l to r): Nancy Bach (medical Liver Fellow), Elizabeth Harrington, Myron Schwartz, Margaret Kadian (first coordinator), Martin Harrington (transplant Surgical Fellow) and Angelina Korsun (first administrator).

became obvious. Nancy Bach, then the liver fellow when transplantation began, was the one who set the tone for the cooperation of the division with the transplant team. Bach remains a full-time clinician with the division. Not only were more fellows needed, but more supervision and training had to be provided. To supervise the training as well as the clinical activity of the division, Henry Bodenheimer was invited to return to Mount Sinai. He had been an intern, medical resident and liver fellow at the hospital from 1975 to 1979, after which he went to Providence to finish his training in gastroenterology and then join the Brown Medical School faculty. More fellows and several full-time faculty members were recruited. During his fellowship and while he was in Rhode Island, Bodenheimer participated with Schaffner in clinical trials of therapy for primary biliary cirrhosis and conducted multi-center investigations including Mount Sinai. He participated in national trials of interferon treatment of chronic viral hepatitis, work he continues to this day.

Increasing clinical responsibilities, mainly related to the active transplant program, and a decrease in funding from government and other sources have curtailed some of the research activity. Nevertheless, studies of primary biliary cirrhosis (72, 73), chronic viral hepatitis (74, 75), nonalcoholic fatty liver (76), and acquired immunodeficiency syndrome (77) continue, as do investigation of various aspects of transplantation (78) and pathologic (79) and immunologic changes (80) in different liver diseases. An

important goal of the Division of Liver Disease is making transplantation unnecessary by curing and ultimately preventing liver diseases.

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