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MASTER'S PERSPECTIVE

Progress in Hepatitis B: A 30-Year Journey Through Three Continents

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Natural Choice for a Career Path

Being asked to contribute a Master Perspective article in HEPATOLOGY is a great honor that I accepted with trepidation. In preparation for this article, I reviewed the previous ones and realized each tells a different story. I hope this article will illustrate how much progress we have made in our understanding of hepatitis B in the last 30 years. I also hope that my personal journey will inspire young readers to believe in their dreams and to strive towards their goals even when the path is tortuous and riddled with hurdles.

I grew up in Hong Kong in a family where there had never been a physician. In fact, I was the first in my family to choose a science track in high school (we were forced to choose between science and humanity tracks at the end of 8th grade). My father cautioned that science is not for girls. When I got a "C" for my first physics test, I thought I should have listened to the old man. Fortunately, history did not repeat itself. After my "O Level" exam (an exam that kids from all schools take at the end of 11th grade), I applied to a boys' school with a reputation in science (a move from an all-girls' school strong in language and humanities) and was accepted as the only girl in a class of 31 boys. Being the odd person out, the boys were super nice and polite, and the teachers were so sympathetic that I ended up ranking top of the class 2 years in a row. When I announced that I would be applying for medical school at the end of 13th grade (college was an unnecessary waste of time), my father advised that nursing would be more appropriate for girls but he was delighted when I was accepted into medical school.

The 5 years of medical school flew by quickly. After a year of internship, I was offered a lecturer position in the Department of Medicine, University of Hong Kong. There were very few faculty then and residents like myself were drafted to teach medical students (on top of all the clinical duties, there were no work-hour limits). Salaries were the same as other residents with no teaching duties but the perk was university sponsorship of overseas fellowship training. I fell in love with hepatology during my first rotation as a resident. Two people had a big influence on my decision to be a hepatologist. Dr. K.C. Lam[1] was my attending and Dr. Rudi Schmid (Chief of Gastroenterology and Hepatology at University of California-San Francisco) was a visiting professor. Both were inspiring teachers who asked a lot of questions on rounds and made me think and want to know more. It is amazing how our lives are shaped by fate or chance encounter.

As I mentioned earlier, the perk of taking on additional teaching duties as a resident was sponsorship of overseas fellowship training. Being a freebie made it easier for me to get into the best program. The Royal Free Hospital in London, headed by Dame Sheila Sherlock, was the mecca of hepatology at that time. My 2 years at the Royal Free were some of the best times in my life. The training and experience at the Royal Free provided solid foundations for my academic career. Just as important, if not more, I became a member of the Sherlock Hepatology Family (Fig. 1) and the Sherlock brand name was a major reason how I landed with a faculty position in the United States despite never having any training in the country.

Hepatology was a fairly new specialty in the early 1980s (the Journal HEPATOLOGY was inaugurated in January 1981). Coming from Hong Kong, it was

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; anti-HBe, hepatitis B e antibody; ARA-AMP, adenine arabinoside monophosphate; FDA, Food and Drug Administration; HBeAg, hepatitis B e antigen; HBRN, hepatitis B research network; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases.

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Fig. 1. Dame Sheila Sherlock and the Sherlock Hepatology Family at the Royal Free Hospital in London on the occasion of Dame Sheila's retirement celebration in September 1983. Photo provided by Antonio Ascione.

natural for me to choose hepatitis B as the research focus. Figuring out what topic to study was more difficult. I knew very little about hepatitis B (still don't know enough), had no research experience, and was not familiar with the research ongoing at that time. My first meeting with Professor Howard Thomas, my research mentor, did not go well. I was not able to articulate what topic I wanted to research on and how I would go about doing it. It took time, patience, and perseverance to prove that I was trainable.

Hepatitis B Was Simple Back Then

Hepatitis B in the early 1980s was fairly simple. Hepatitis B virus (HBV) had been established as a DNA virus that causes chronic hepatitis and cirrhosis but an etiological association with hepatocellular carcinoma (HCC) was still debated. Assays for HBV DNA were in its infancy. The assays used hybridization with limit of detection ~1 million IU/mL. The results were usually scored from 0 to 4+. The natural history of chronic HBV infection was thought to comprise two distinct phases: hepatitis B e antigen (HBeAg)-positive when virus replication and liver inflammation are active and HBeAg-negative when virus replication ceases and liver inflammation subsides. Seroconversion from HBeAg to HBe antibody (anti-HBe) was thought to be an irreversible process. There was no approved treatment for hepatitis B.

Hepatitis B Research: The Early Days at the Royal Free

Although the tools were crude, the early 1980s was a golden era for HBV research. Molecular diagnostic tests were rapidly developing and there were few distractions. The latter changed by mid 1980s with the AIDS epidemic and the realization that it was caused by a virus. Because of the high rate of mortality and devastating complications affecting mainly young people, a lot of funding and resources were earmarked for human immunodeficiency virus (HIV) research and many HBV investigators defected. Of those who stayed, many left in the early 1990s when the elusive non-A, non-B hepatitis virus was found.

One of my first projects at the Royal Free was to study the use of interferon (IFN) in the treatment of chronic hepatitis B. In 1976, Tom Merigan and his colleagues at Stanford reported promising results in a study of four patients treated with IFN.[2] The IFN we used was produced by a human lymphoblastoid cell line (recombinant DNA technology was not available yet) and administered as an intravenous infusion in doses of up to 100 million units/m^2. Because of the intensity of the adverse reactions, the infusion had to be administered by a physician (yours truly) who would stay by the patient's bedside for the next few hours in case a catastrophic reaction occurred. This early experience spurred the evaluation of lower, better-tolerated doses. In a study of six patients given daily (n = 2), alternate day (n = 1), or thrice weekly (n = 3) intramuscular injections of IFN at 7.5-10 million units/m^2, we found that thrice weekly administration of IFN was as effective as daily injections in inhibiting HBV replication, were associated with fewer side effects, and could be continued for up to 3 months.[3] The rationale for thrice weekly (Monday, Wednesday, and Friday) versus alternate day administration was simply a matter of convenience because alternate day would require working over the weekend. Until pegylated IFN became available, thrice weekly administration of IFN was the norm for hepatitis B. I have always wondered why no one questioned the irregular spacing. In hindsight, we would not be able to tell whether HBV DNA levels crept up during the weekend gap because the HBV DNA assay used was not sensitive enough to detect <2-3 log changes. An "n" of 3 would be considered grossly inadequate nowadays but the concept of "sample size" had not been introduced into clinical trial designs in the early 1980s and a schedule designed to make the life of a young fellow easy was adopted worldwide with no questions asked.

Following on the heels of the success of IFN, I led a randomized trial comparing IFN to another antiviral: adenine arabinoside monophosphate (ARA-AMP), which had been shown to inhibit HBV replication by

Jay Hoofnagle at the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) and Tom Merigan at Stanford.[4,5] The intention of our trial was to compare the safety and efficacy of 12 weeks of IFN versus 4 or 12 weeks of ARA-AMP; however, during the course of the trial some patients in the 12-week ARA-AMP group developed peripheral neuropathy and the duration of treatment had to be shortened.[6] A similar trial at Stanford was terminated early because of similar adverse events. Seeing young otherwise healthy patients came back to the clinic limping in severe pain is a sight that I would never forget. I am pretty certain we did not mention neuropathy was a possible adverse event in the consent forms and were lucky none of the patients pursued legal action. This experience taught me to be very cautious in reviewing everything that is known about an experimental drug before agreeing to be an investigator in any clinical trial and to have my eyes and ears open for unexpected events. This trial did show a benefit of IFN and was one of the studies that laid the foundation for subsequent multicenter trials leading to approval of IFN as treatment for hepatitis B. I presented the results of this trial during my debut at The Liver Meeting in 1983. The meeting was held in the Hyatt Hotel in Chicago with fewer than 1,000 participants.

After a slow start, I was quickly swarmed. My 2-year fellowship at the Royal Free resulted in a total of 23 papers and book chapters, the meager support (one-third of my salary in Hong Kong while living in an expensive city, London) from the University of Hong Kong no doubt boosted my productivity. It was a lot more fun and relaxing to stay late at work than to return to a 90-sq. ft. room that I called home. One of the most interesting papers was in collaboration with Stephanos Hadziyannis in Greece. Stephanos was a Sherlock fellow and had observed that some HBeAg-negative patients continued to have elevated alanine aminotransferase (ALT) levels in serum and active inflammation in liver biopsies. He also found a high percent of these patients had detectable HBV DNA in serum (despite the insensitivity of the assays at that time). Unfortunately, reviewers and editors were not convinced. After the paper was rejected several times, Stephanos turned to Howard Thomas for advice. Howard in turn asked me (a rookie) to salvage the paper. We decided to add a control group of British patients and to retest all samples with the Royal Free (branded) HBV DNA assay. The paper was accepted by *Gut* on first submission.[7] Perhaps the editors and reviewers recognized the significance of the finding—one of the earliest descriptions of the clinical entity "HBeAg-negative chronic hepatitis."

As I was planning my trans-Atlantic trip to my first American Association for the Study of Liver Diseases (AASLD) meeting, I thought I should take the opportunity to visit some of the famous hepatologists and academic centers that I read so much about. Within 3 weeks I received return mail (this was before faxes and emails) from NIDDK, Massachusetts General Hospital, Mayo Clinic, Albert Einstein Medical Center, and Rockefeller University inviting me to visit and to present my research findings. There was no doubt the Sherlock brand contributed to the warm responses.

Hepatitis B Research: Continuing the Journey in Hong Kong

In December 1983, I returned to Hong Kong and was eager to apply everything I learned in London. The first equipment I requested was a −70°C freezer. Together with C.L. Lai, we established a Hepatitis B Clinic and assembled a database and serum repository and I replicated the dot-blot hybridization assay for HBV DNA. Ready access to a large number of patients and the lack of an approved treatment for hepatitis B provided a golden opportunity to study the natural history of chronic hepatitis B. We described the different phases of chronic HBV infection, the rates of spontaneous HBeAg seroconversion and seroreversion, and frequency and causes of exacerbations of chronic hepatitis B. In one of the early articles we described that young Chinese with chronic hepatitis B have normal ALT despite high levels of HBV DNA. One of the reviewers commented that this clinical phenotype (immune tolerance) does not exist in Caucasian patients and the authors should verify these atypical findings. As Baruch Blumberg mentioned in his book, "Hepatitis B: The Hunt for a Killer Virus," when one challenges the dogma, one has to be prepared that it would be met with skepticism and be willing to stand by our own data. Another lesson I learned was that when you are an unknown entity it takes more effort to convince others that you and your data can be trusted. Our description of the "immune tolerance" phase complemented and confirmed findings of Yun-Fan Liaw in Taiwan, whose group made some of the most important contributions to our understanding of the natural history of chronic hepatitis B.

Following the success of IFN in my London patients, we conducted two randomized controlled trials of IFN in HBeAg-positive adults and children, but only 15% of adults and 8% of children lost HBeAg.[8,9] These disappointing results led some experts to conclude that the poor response in Chinese patients was

genetically related and Asian patients should not be considered for IFN therapy. Because IFN was the only available treatment at that time, I felt a moral obligation to untie the knot I created. A detailed look at the patients enrolled in these two trials revealed that most had normal ALT and were in the immune tolerance phase. This led us to launch another trial in which HBeAg-positive patients with normal and those with abnormal ALT were separately randomized to receive IFN with or without prednisone priming. The notion of prednisone priming must seem irrational to our young readers but this was the fad in the late 1980s when it was realized that, while corticosteroids enhance HBV replication, abrupt withdrawal of steroids is often followed by an ALT flare and in some instances HBeAg seroconversion. The prevailing belief was that antiviral treatment might be more effective if it was started when there is a rebound in immune response triggered by withdrawal of a preceding short course of steroids. We demonstrated that Chinese patients with elevated ALT had significantly better response to IFN than those with normal ALT and their responses were on par with that of Caucasian patients, illustrating that the phase of HBV infection/host immune responsiveness to HBV and not genetic factors account for the low response rates we reported in our earlier trials, and prednisone priming had a marginal benefit on antiviral response.[10] High pretreatment ALT remains an important predictor of response not only to IFN but also nucleos(t)ide analog therapy to this day. While none of our patients had serious ALT flares, liver failure and death were observed in some studies that tested the concept of prednisone priming.[11]

The risk of liver failure associated with withdrawal of immunosuppressive therapy was first reported in the mid-1970s. After witnessing several patients who died of HBV-related liver failure despite being cured of their underlying malignancies, I launched a prospective study on HBV reactivation in patients receiving chemotherapy. This was the first prospective study on HBV reactivation and it was possible because the oncologists at the University of Hong Kong recognized the gravity of the problem and facilitated the study.[12] Sadly, awareness of the risk of HBV reactivation in patients receiving immunosuppressive therapy remains low 40 years after the initial case reports, although this once fatal condition can now be easily prevented by screening of patients for HBV infection prior to start of immunosuppressive therapy and initiating prophylactic antiviral therapy in those with moderate-high risk of HBV reactivation.[13]

Bold Move or Professional Suicide

In April 1992, I left Hong Kong—my home, my family, and friends, for the U.S. I was advised to take it easy after I was promoted to Reader in Medicine (equivalent to full Professor in the U.S.). Promotion was based on seniority back then: after being promoted ahead of some more senior colleagues I was advised to slow down. The notion that I had reached an academic ceiling when I was still in my 30s motivated the move. I have no family and had never had any training in the U.S. and took the first position that offered me a Green Card and a medical license. I had looked at several positions in the U.S. in the late 1980s but none of those worked out either because I was not doing basic science research and had never and likely would never have a publication in *Science* or I was not worth the trouble (of securing a Green Card and a medical license). Some friends were impressed by my courage while others thought the move was akin to professional suicide; indeed, many well-intended hepatologists warned that with the availability of safe and effective HBV vaccines, hepatitis B would soon be eradicated and the prevalence of hepatitis B in the U.S. is so low that that it would not be possible to secure any funding for hepatitis B research, nor would there be enough patients to sustain my practice.

Settling in the U.S., a Eureka Moment, and a Lesson From the Fellowship Days

My first job in the U.S. was in New Orleans at Tulane University. Two people were pivotal in that decision: Atilla Ertan, chief of Gastroenterology and a foreign medical graduate himself who solved the logistical hurdles, and the late Michael Gerber, Chair of Pathology and a renowned hepatic pathologist provided opportunities for collaboration. With the discovery of the hepatitis C virus (HCV), the focus of hepatology research rapidly shifted to hepatitis C. Not only was there a shift in research priorities and funding, there was also an exodus of hepatitis B investigators. It was tempting to defect but my commitment to hepatitis B research is deeply rooted. Hepatitis B is a complex disease with many nuances and therefore intellectual challenges. More important, hepatitis B affects Asians disproportionately and I have always felt a moral obligation to find solutions that would decrease the burden of hepatitis B among Asians.

Earlier on, I mentioned that one of my first articles was on "HBeAg-negative chronic hepatitis." In 1989, Bill Carman, working with Howard Thomas, found

that patients with HBeAg-negative chronic hepatitis often harbor a variant of HBV with a stop codon mutation in the precore region of the HBV sequence, which prevents HBeAg production.[14] This finding solved the mystery how HBV can continue to replicate and express hepatitis B core antigen despite not being able to secrete HBeAg, but it did not explain why HBeAg-negative chronic hepatitis was more common in southern Europe and Asia. One evening I stumbled on an article describing the role of a cis-acting sequence (ε) in the precore region as a signal for encapsidation of the HBV pregenomic RNA.[15] After staring at one of the figures for half an hour, I experienced a Eureka moment and realized that the precore region folds back as a stem-loop structure and while the G1896A (stop codon) mutation stabilizes ε when the opposing nucleotide at position 1858 is a T, as in the case of HBV genotypes B, D, and some subtypes of C, it destabilizes ε when there is a C at position 1858, as in the case of HBV genotypes A and some subtypes of C.[16] It turns out that the prevalence of precore HBV variant in different parts of the world is related to the prevalence of its associating HBV genotype and whether the nucleotide opposite 1896 is a C or T. We published this revelation around the same time as Shuping Tong (with whom I collaborated in recent years), who was working with Christian Trepo in France.[17]

The 1990s was an exciting period of antiretroviral drug development for HIV. The resources and expertise in HIV drug development spilled over to HBV which replicates through reverse transcription of the pregenomic RNA. In 1994, I was asked to participate in a multicenter trial of fialuridine, which was shown to have potent antiviral activity against HBV in preliminary studies. After reviewing the Investigators' Brochure, I declined participation because some of the preclinical and pharmacological data reminded me of ARA-AMP. When news broke that fialuridine caused mitochondrial toxicity, lactic acidosis, and liver failure,[18] I was relieved that the lesson I learned from ARA-AMP spared me and my patients from being exposed to this drug.

Settling in the U.S. was not as difficult as I had imagined but it took some time to transition from a national health system where I never had to bill any patients to a fee-for-service health system in the U.S. Having published more than 100 papers before I moved to the U.S. helped launch my research program but there were times when I had to prove myself again. Fortunately, there were more believers than skeptics.

Continuing the Journey in Michigan and Finally a Hepatitis B Research Network in North America

After 3.5 years in New Orleans, I accepted a position as the Director of Clinical Hepatology at the University of Michigan in October 1995. Michigan had a strong luminal gastroenterology program but hepatology received very little attention. Having spent most of my life in tropical climates, many friends predicted I would not last more than 1-2 winters. The Michigan Hepatology Program has grown from 5 to 14 full-time faculty members with expertise in diverse areas of liver diseases and many faculty and former trainees have become independently successful investigators with national and international recognition. It has been a lot of hard work and there have been many trials and tribulations but this has been an enjoyable and rewarding journey and I feel like a proud mother with every right to brag about my kids.

By the mid-1990s, it was shown that several antiretroviral drugs for HIV are safe and have antiviral activity against HBV. In 1998, the U.S. Food and Drug Administration (FDA) approved the first oral antiviral drug for HBV, lamivudine.[19,20] This was an exciting time. Finally, we were able to treat patients with hepatitis B with one pill a day. Not only were serum HBV DNA levels suppressed, ALT levels normalized and liver histology improved. In patients who presented with liver failure, jaundice abated and ascites disappeared, allowing some patients who were initially listed for liver transplantation to be taken off the transplant waiting list. The initial excitement about lamivudine as a miracle drug was quickly dampened by the realization that drug resistance occurs quickly. Nonetheless, lamivudine saved the lives of many hepatitis B patients. In most parts of the world, lamivudine has been replaced by tenofovir and entecavir, which have higher barriers to resistance.

Fifteen years after approval of the first nucleos(t)ide analog for hepatitis B, we now have evidence that antiviral therapy improves clinical outcomes including reversal of cirrhosis, prevention of liver failure and HCC, and the need for liver transplantation.[21-23] The availability of well-tolerated potent oral antiviral drugs not only decreased the need for liver transplantation they also revolutionized the prevention of recurrent hepatitis B after liver transplantation. In the late 1980s and early 1990s, hepatitis B was considered a contraindication to liver transplantation because HBV reinfection occurred in 80% of patients and recurrent hepatitis B was associated with rapidly progressive liver

failure, resulting in >50% mortality within 2-3 years of transplant. Although the findings of Didier Samuel and his colleagues in Europe showed that long-term intravenous infusion of hepatitis B immune globulin starting from the anhepatic phase significantly decreased the incidence of HBV reinfection and mortality from recurrent HBV,[24] this approach was very expensive and ineffective in patients who were viremic (serum HBV DNA detected by hybridization assay, roughly >5 $\log_{10}$ IU/mL) at the time of transplant. This field changed so much in the last 15 years that my attempt in leading an NIDDK-funded multicenter study in early 2000 to examine the most cost-effective strategy to prevent recurrent hepatitis B after liver transplantation was repeatedly derailed when successive new antiviral drugs and more sensitive HBV DNA assays became available during the course of the study. We ended up abandoning the notion of completing the planned randomized trials for a pragmatic study which showed that when appropriate oral antiviral drugs were administered before and after liver transplantation and rescue therapy was available for virologic breakthrough, HBV recurrence can be kept below 10% regardless of the dose and duration of hepatitis B immune globulin used.[25]

Implementation of HBV vaccination programs and universal precautions in healthcare settings have resulted in a marked decline in the incidence of acute HBV infection as well as a decrease in the prevalence of chronic HBV infection in children and adolescents in the U.S.; however, the prevalence of chronic HBV infection in adults has remained relatively stable because of the immigration of chronically infected persons from endemic countries. The U.S. is known to be a melting pot. In the case of hepatitis B, it is not just a mix of persons of different races and ethnicities but also a mix of HBV genotypes (A-H), age at infection (perinatal, childhood, and adult), and lifestyle and environmental factors (alcohol, smoking, obesity, etc.). Thus, data on the natural history of HBV infection from studies conducted in other countries may not be applied in the U.S. Similarly, because of changes in immigration pattern over the years, epidemiological data of HBV infection in the U.S. in the past may not apply to the present.

In early 2000, with the recognition that responses to antiviral treatment of HBeAg-negative chronic hepatitis differ from that of HBeAg-positive chronic hepatitis, pharmaceutical sponsors began to have separate protocols for treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B. In several instances, U.S. sites were excluded from the trials for HBeAg-negative chronic hepatitis because it was thought that HBV genotype A predominated and HBeAg-negative chronic hepatitis is rarely seen in the U.S. As a physician who sees patients in the clinic, it was obvious that these dogmas were incorrect. To rectify these myths, I led a 17-center study in 2002 to determine the prevalence of HBV genotypes, precore and basal core promoter variants in the U.S. This study showed that genotype A was present in 35% of patients and genotypes B and C (that predominate in Asian countries) in 53% of patients, supporting data from other studies that 50-70% of patients with chronic HBV infection in the U.S. are Asians.[26] This study also showed that precore variants were present in 27% and basal core promoter variants in 44% of patients, confirming that HBeAg-negative chronic hepatitis was not a rare entity in the U.S.

Table 1. Milestones in Hepatitis B Development

1965	Discovery of Australia antigen
1970	WHO recommendation to screen blood donors for Australia antigen
1981	FDA approval of HBV vaccine
1992	FDA approval of interferon as treatment of chronic hepatitis B
1998	FDA approval of first oral antiviral – lamivudine as treatment of chronic hepatitis B
2000	U.S. Medicare approval of liver transplantation for hepatitis B

WHO, World Health Organization; FDA, U.S. Food and Drug Administration.

Twenty years after I moved to the U.S. and was told that hepatitis B will soon be eradicated, it is estimated as many as 2.2 million persons living in the U.S. have chronic HBV infection,[27] and many questions regarding immunopathogenesis, natural history, and optimal treatment of hepatitis B remain. It was very gratifying that in 2008 NIDDK established the Hepatitis B Research Network (HBRN) which includes 21 adult and 7 pediatric clinical sites in the U.S. and in Toronto, Canada. The HBRN has enrolled more than 2,000 adults and children with chronic HBV infection in the observational cohort studies and launched three clinical trials of antiviral therapy. The diverse race/ethnicity of the patients and entire spectrum of HBV genotypes from A to H provide a unique opportunity to examine the impact of host, virus, and environmental factors on the outcomes of HBV infection that is not possible with studies in countries where most patients are of the same race and only one or two HBV genotypes prevail. It has been an honor and a privilege to chair the HBRN Steering Committee. Data from the HBRN are beginning to emerge and we expect these data will improve our understanding of the epidemiology and natural history of HBV

Table 2. Progress in Hepatitis B During the Last 3 Decades

Then	Now
• HBV as a cause of HCC was still in debate	• HBV is a potent carcinogen and an unequivocal cause of HCC
• HBV vaccines (plasma derived) were just approved by FDA	• HBV vaccines not only prevent HBV infection but also HCC
• Seroconversion from HBeAg to anti-HBe was thought to be an irreversible event, associated with cessation of HBV replication and remission of liver disease	• HBV persists after HBeAg seroconversion and even after HBsAg clearance
• Hybridization assays (with limit of detection ~1 million IU/mL) were developed for semi-quantitation of HBV DNA	• Real-time PCR assays with limit of detection ~10 IU/mL are available for quantification of HBV DNA
• No approved drugs for treatment of hepatitis B	• Seven drugs are approved for treatment of hepatitis B: 2 formulations of IFN and 5 nucleos(t)ide analogs
• Liver transplantation (for any indication) was an experimental therapy	• Outcomes of liver transplantation for hepatitis B are better than that for other liver diseases

infection not only in the U.S. but worldwide because ~80% of the participants were foreign-born.

Looking Back and Looking Forward

As the first and only (so far) physician in the family, this has been a remarkable journey. There were many hurdles along the way but also a lot of triumphs personally and professionally.

Over the years, I have made many friends, traveled to many parts of the world, and experienced many cultures. Through participation at hundreds of meetings and collaboration on multiple projects, I got to know many iconic figures in hepatology who have inspired and helped me in my professional development and made many friends who share not just research ideas and data but also life experiences and lasting friendship. I have also mentored many fellows and junior faculty, many of whom have risen through the ranks and have become internationally recognized leaders: Bob Fontana, Jorge Marrero, Henry Chan, just to name a few. My proudest accomplishment is being the matriarch of the Lok Hepatology Family witnessing the growth and success of the kids who stay in touch through an annual family reunion during The Liver Meeting.

I have been fortunate to be recognized by my peers and to have received many awards including a Distinguished Scientist Award and an autographed book "Hepatitis B: The Hunt for a Killer Virus" by the late Nobel laureate Baruch Blumberg from the Hepatitis B Foundation in 2008, and a Distinguished Service Award from AASLD in 2011—it meant a lot to be recognized by the society that I am most closely affiliated with and to be placed among other giants in hepatology whom I admire and respect. After serving as Councilor at Large of AASLD in 2001-2003, I was honored to be selected as Councilor again in 2013 and will serve as President in 2017. I look forward to the challenges and opportunities of leading the premier society of our specialty.

As a researcher, being part of the growth of the field of hepatology and hepatitis B has been an amazing journey. Table 1 shows the major milestone in HBV progress and Table 2 shows how far we have come in the last three decades. As a co-author of the AASLD guidelines on HBV (with Brian McMahon) for a decade, I appreciate the opportunity to shape the care of hepatitis B worldwide.

During the last 30 years, there have been drifts of investigators and funding from HBV to HIV and then HCV. With the imminent prospect of HCV cure, it is gratifying to see a shift back to HBV and a commitment from the scientific community and the pharmaceutical industry to find a "cure" for HBV.

In closing, I want to thank the HEPATOLOGY editors for the honor to contribute this Master's Perspective. Many important milestones in HBV progress and many people who have contributed to the progress and who have helped me along the way could not be included due to space constraints. There are a few people I must acknowledge: my mother, who believed girls can be doctors, my father, who told me I need to work harder (when I was 9), and my brothers, who bear the brunt of taking care of our elderly parents allowing me to pursue my dreams guiltlessly. Professionally, I would not be where I am without the inspirations and support from Sir David Todd and Rosie Young in Hong Kong, the late Dame Sheila Sherlock in London, and Jay Hoofnagle in the U.S.

References

1. Lam KC, Lai CL, Trepo C, Wu PC. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. N Engl J Med 1981;304: 380-386.
2. Greenberg HB, Pollard RB, Lutwick LI, Gregory PB, Robinson WS, Merigan TC. Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. N Engl J Med 1976; 295:517-522.

3. Lok AS, Weller IV, Karayiannis P, Brown D, Fowler MJ, Monjardino J, et al. Thrice weekly lymphoblastoid interferon is effective in inhibiting hepatitis B virus replication. Liver 1984;4:45-49.
4. Smith CI, Kitchen LW, Scullard GH, Robinson WS, Gregory PB, Merigan TC. Vidarabine monophosphate and human leukocyte interferon in chronic hepatitis B infection. JAMA 1982;247:2261-2265.
5. Hoofnagle JH, Minuk GY, Dusheiko GM, Schafer DF, Johnson R, Straus S, et al. Adenine arabinoside 5'-monophosphate treatment of chronic type B hepatitis. HEPATOLOGY 1982;2:784-788.
6. Lok AS, Novick DM, Karayiannis P, Dunk AA, Sherlock S, Thomas HC. A randomized study of the effects of adenine arabinoside 5'-monophosphate (short or long courses) and lymphoblastoid interferon on hepatitis B virus replication. HEPATOLOGY 1985;5:1132-1138.
7. Lok AS, Hadziyannis SJ, Weller IV, Karvountzis MG, Monjardino J, Karayiannis P, et al. Contribution of low level HBV replication to continuing inflammatory activity in patients with anti-HBe positive chronic hepatitis B virus infection. Gut 1984;25:1283-1287.
8. Lai CL, Lok AS, Lin HJ, Wu PC, Yeoh EK, Yeung CY. Placebo-controlled trial of recombinant alpha 2-interferon in Chinese HBsAg-carrier children. Lancet 1987;2:877-880.
9. Lok AS, Lai CL, Wu PC, Leung EK. Long-term follow-up in a randomised controlled trial of recombinant alpha 2-interferon in Chinese patients with chronic hepatitis B infection. Lancet 1988;2:298-302.
10. Lok AS, Wu PC, Lai CL, Lau JY, Leung EK, Wong LS, et al. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. Gastroenterology 1992;102:2091-2097.
11. Perrillo RP, Schiff ER, Davis GL, Bodenheimer HC Jr, Lindsay K, Payne J, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. N Engl J Med 1990; 323:295-301.
12. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100:182-188.
13. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. Nat Rev Gastroenterol Hepatol 2013 [Epub ahead of print].
14. Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, et al. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. Lancet 1989;2:588-591.
15. Junker-Niepmann M, Bartenschlager R, Schaller H. A short cis-acting sequence is required for hepatitis B virus pregenome encapsidation and sufficient for packaging of foreign RNA. EMBO J 1990;9:3389-3396.
16. Lok AS, Akarca U, Greene S. Mutations in the pre-core region of hepatitis B virus serve to enhance the stability of the secondary structure of the pre-genome encapsidation signal. Proc Natl Acad Sci U S A 1994; 91:4077-4081.
17. Tong SP, Li JS, Vitvitski L, Kay A, Treepo C. Evidence for a base-paired region of hepatitis B virus pregenome encapsidation signal which influences the patterns of precore mutations abolishing HBe protein expression. J Virol 1993;67:5651-5655.
18. McKenzie R, Fried MW, Sallie R, Conjeevaram H, Di Bisceglie AM, Park Y, et al. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. N Engl J Med 1995;333:1099-1105.
19. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998;339:61-68.
20. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341:1256-1263.
21. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468-475.
22. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-1531.
23. Kim WR, Terrault NA, Pedersen RA, Therneau TM, Edwards E, Hindman AA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. Gastroenterology 2009;137:1680-1686.
24. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993;329:1842-1847.
25. Degertekin B, Han SH, Keeffe EB, Schiff ER, Luketic VA, Brown RS Jr, et al. Impact of virologic breakthrough and HBIG regimen on hepatitis B recurrence after liver transplantation. Am J Transplant 2010;10:1823-1833.
26. Chu CJ, Keeffe EB, Han SH, Perrillo RP, Min AD, Soldevila-Pico C, et al. Hepatitis B virus genotypes in the United States: results of a nationwide study. Gastroenterology 2003;125:444-451.
27. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. HEPATOLOGY 2012;56:422-433.