Back to the Future: A Backward Glance at the Forward Progress of Hepatitis Virus Research

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It has been 2408 years since Hippocrates bequeathed our medical oath of ethics and first described an epidemic form of yellow jaundice, later called hepatitis from the Greek word *hepar* for “liver” and the Greek suffix *itis* for “oy, I don’t feel so good.” For the next 2350 years, little more was learned about hepatitis than could be garnered from Hippocrates’ original description. Nonetheless, there were other post-Hippocratean epidemics described, perhaps the most significant of which was a large outbreak of jaundice in Bremen shipyard workers in 1885, traced to smallpox vaccine that was contaminated with human lymph [1]; this may represent the first description of “serum hepatitis.” After another long lull, interest in hepatitis was rekindled in World War II (WWII) when both infectious hepatitis, particularly in the North Africa campaign, and serum hepatitis from contaminated lots of yellow fever vaccine together resulted in over 100,000 cases of hepatitis among American soldiers. Clinical and epidemiological descriptions of these two forms of hepatitis, subsequently called hepatitis A and B, proliferated, but the agents themselves continued to defy characterization. Indeed, another 20 years transpired post-WWII before the serendipitous finding of a precipitin reaction between the serum of a patient with hemophilia and that of an Australian aborigine resulted in the discovery of the Australia antigen [2]. This precipitin reaction ushered in the modern age of hepatitis virus discovery. Unraveling the origin and meaning of the Australian antigen was a fascinating series of sometimes serendipitous events that over the course of 5 years culminated in the realization that this antigen was the major constituent of the hepatitis B virus (HBV) envelope protein [hepatitis B surface antigen (HBsAg)] [3]. It is a tribute to the value of undirected medical research that none of the investigators involved...
in this seminal discovery was either a hepatologist, a virologist or an infectious disease specialist and that none initially was seeking a hepatitis agent [4].

The Australia antigen and its link to HBV set in motion a chain of discoveries that accomplished more in 20 years than in the preceding two millennia. Hippocrates would have been proud of how astute observation set the course for major clinical benefit. Unraveling the structural significance of the Australia antigen led to the development of HBsAg assays that were used to screen blood donors beginning in 1970. Combining this assay with the adoption of an all-volunteer donor system resulted in a 70% decline in the overall incidence of post-transfusion hepatitis and the near eradication of clinical transfusion-related hepatitis B [5]. Of even greater significance, the ability to concentrate HBsAg and to separate it from the HBV virion (Dane particle) led to the first plasma-derived HBV vaccine in 1980 and subsequently to a highly efficacious and safe recombinant vaccine. HBV vaccination is now universal for children in the United States and is used increasingly throughout the world. True global utilization of this vaccine, particularly in Asia and Africa, could eradicate the scourge of hepatitis B and its devastating sequelae of cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC); an intense global effort is needed to make this occur.

The near eradication of post-transfusion hepatitis B led to the recognition in prospective studies that there was a second dominant form of transfusion-associated hepatitis (TAH) that was tentatively designated non-B. It was thought that these non-B cases would be due, at least in part, to the hepatitis A virus (HAV), the only other known virus at the time. However, in 1973, Feinstone et al. [6] discovered HAV using immune electron microscopy of stool isolates from an HAV epidemic. Following this discovery, serial sera from non-B TAH cases were tested and, surprisingly, not a single case was related to HAV infection [7]. Residual TAH cases were then designated non-A, non-B hepatitis (NANBH), a cautious term that reflected how little was known about this agent or agents. Despite intensive efforts to delineate the agent of NANBH over the course of 15 years, it eluded observation, isolation, and test development. However, using the chimpanzee infectivity model it was shown that NANBH was readily transmitted by blood [8], that there was an asymptomatic carrier state in donors and chronically infected patients, that the agent was between 30 and 60 nm in diameter and that it had essential lipid in its envelope. Clinical studies revealed that NANBH frequently resulted in chronic infection and that 20% of those infected developed cirrhosis [9]. Despite this mass of peripheral knowledge, it was not until the late 1980s that Houghton and colleagues, employing the emerging techniques of molecular biology, cloned the agent and designated it the hepatitis C virus (HCV) [10]. Using well-pedigreed cases of NANBH, it was then shown by anti-HCV seroconversion that almost all transfusion-associated NANBH cases were caused by HCV [11] This allowed the term NANBH to fade slowly from our lexicon and for HCV to emerge as the dominant agent of TAH and the leading cause of chronic hepatitis and its sequelae in the developed world. Although very sensitive serological and molecular assays for HCV have virtually eradicated TAH, the virus continues to be spread, primarily by intravenous drug use, and the reservoir of chronically infected individuals is estimated to number one million in the United States and 300 million throughout the world. Currently, HCV is the leading cause of cirrhosis and HCC in all areas of the world where HBV is not hyper-endemic. Treatments for HCV have improved considerably in the past decade, but the best current regimen, pegylated interferon plus ribavirin, results in only a 50% cure rate in patients with the prevalent genotype-1 infection. HCV-specific protease and helicase inhibitors are under development and should enhance therapeutic responses. HCV-associated end-stage liver disease is now the leading indication for liver transplantation in the United States and Europe, and the need for transplantable livers far exceeds supply. Because HCV exists as a highly mutable virus with a complex quasi-species, it has been extraordinarily difficult to develop a broadly effective vaccine. Development of a safe and efficacious vaccine is the holy grail of this field of investigation, but it has met many of the same pitfalls as human immunodeficiency virus (HIV) vaccine development and for many of the same virological reasons.

In the chapters that follow, first Christoph Seeger, Michael Lai, and William Mason brilliantly describe the complex molecular biology of each of the five known human hepatitis agents. It is astounding how much is known about these agents at the molecular level and how well, although not completely, understood are the intricate replication pathways. It is generally accepted that in most circumstances viral hepatitis is the result of immune attack upon virus-infected liver cells rather than direct viral damage. Carlo Ferrari and Mario Mondelli provide a comprehensive description of the critical role of CD8 and CD4 T-cells in the evolution of viral hepatitis and of the complex interplay between viruses and the mediators of innate and adaptive immunity that have varying degrees of success in viral eradication, being highly successful for the enterically transmitted agents HAV and HEV, and only marginally successful for HCV. Further understanding of these immune mechanisms and the intricate interplay between virus and host is central to the future development of immune therapies and an effective HCV vaccine. The field of HBV therapeutics is now burgeoning, with seven US Food and Drug Administration (FDA)-licensed agents, including an increasing array of nucleotide and nucleoside inhibitors of the HBV viral polymerase. Timothy Block, Ju-Tao Guo, and Thomas London describe HBV...
therapeutics within the context of the biological functions of each of the viral encoded proteins and the complex replication cycle of the agent. It is this basic understanding that has generated the existing anti-viral agents and that hopefully will lead to inhibitors of molecular targets other than the viral polymerase. Most needed for HBV are therapies that eradicate covalently closed circular DNA (cccDNA), the drug-resistant intranuclear intermediate that sustains chronic HCV infection.

Stanley Lemon, Patrizia Farci, and Marc Ghany describe the viral escape mechanisms that so frequently result in persistent HCV infection and that inhibit vaccine development. These involve not only viral quasi-species evolution, but also the ability of HCV proteins to inhibit directly various steps in the host innate and adaptive immune response. HCV is uniquely adapted for survival in a hostile immune environment, even without the ability to integrate into the host genome. This chapter also describes the deleterious consequences of persistent HCV infection. The vast majority of HCV-infected individuals fail to clear the virus spontaneously and, even though only 20–30% of those carriers evolve to decompensated cirrhosis and/or HCC, the absolute number of such lethal outcomes is enormous based on the sheer magnitude of the globally infected population.

Gary Davis and Jean-Michel Pawlotsky describe current therapies for chronic hepatitis B and C and their mechanisms of action. In addition, they describe the rationale for new therapeutic approaches directed at all aspects of the viral life cycle, including cell attachment and entry, RNA translation, post-translational processing, replication, and viral assembly and release. The therapeutic potential is expanding rapidly. However, current therapies frequently fail and in this instance liver transplantation has been remarkably successful. James Burton, Hugo Rosen, and Paul Martin comprehensively review the biological principles and clinical issues underlying liver transplantation for both HCV and HBV infections. Although the incidence of new hepatitis infections is diminishing, the cumulative mass of persons developing cirrhosis and HCC is increasing as cohorts infected in the 1940s through the 1970s reach durations of infection that place them at increasing risk for these insidious and delayed consequences of chronic viral hepatitis. Unless this mass of already infected patients with slowly progressive fibrosis and inoperable carcinoma are effectively treated, there will be an increasing demand for liver transplantation in the decades to come and an increasing shortage of transplantable livers. We need still better treatments, new strategies for liver regeneration, and perhaps artificial livers. The ultimate goal of prevention and treatment strategies will be to make the need for liver transplantation a mere historical note in future editions of this text.

So what would Hippocrates think about his “hepatitis” if he were here today. He certainly would be duly impressed with all the knowledge that has been gained and all the lives that have been saved. However, he might wonder, given these remarkable advances, why new cases of hepatitis continue to occur. As a philosopher, he would view hepatitis as much a social and economic disease as an infectious disease. He would see a near fully protective vaccine for HBV and realize that this disease could be eradicated if only there was the social will and the financial resources to vaccinate the global population. He would see HCV and realize that this is now almost wholly a disease spread by illicit drug use and other practices of percutaneous instrument sharing fostered by ignorance or avoidance of known infectious disease practices. He would not be naïve enough to think that we could rapidly resolve the problem of addiction, but he would favor needle-exchange programs and global education programs to make the risk of shared devices widely understood. He would invest heavily in development of an HCV vaccine which, together with existing HBV, HAV, and HEV vaccines and universal infant and childhood vaccination programs, could reduce the level of new hepatitis infections to that critical juncture where person-to-person spread would become very unlikely. Although Hippocrates had no experience with cost-effectiveness calculations, he would see hepatitis prevention strategies as highly cost-effective. In the final analysis, he would probably administer a new oath to physicians that stated, “First, do no harm, and second, use your enormous knowledge to engage the world in this battle because knowledge that is not applied is as futile and meaningless as no knowledge at all.”

REFERENCES