Hepatitis C—a virus for all seasons

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Hepatitis C disease, currently enjoying unprecedented publicity, is spread by a potentially lethal blood-borne virus that can reside in the bloodstream for years without symptoms. While the cost of this new epidemic and the quest for a safer national blood supply escalate, the road to effective therapeutic agents and preventive vaccines will be bumpy.

Liver disease caused by the recently discovered hepatitis C virus (HCV) is an emerging infectious disease of growing concern. HCV is 1 of 6 identified viruses (A, B, C, D, E, and G) that together account for most cases of viral hepatitis (1, 2). First reported in the Wall Street Journal in 1988, HCV infection is a leading cause of cirrhosis and liver cancer and is now the major reason for liver transplantation in the USA.

Nearly 4 million Americans, or 1.8% of the US population, are infected with HCV. Recovery from infection is unusual, and between 70% and 85% of infected persons become chronic carriers of the virus. According to the Centers for Disease Control and Prevention, chronic hepatitis C causes 8000 to 10,000 deaths and leads to about 1000 liver transplants in the USA each year. Roughly 30,000 cases are diagnosed each year at an annual estimated cost of $600 million in medical expenses (excluding liver transplantation) and work loss (3, 4). Currently, it is estimated that at least 3% of the world's population is chronically infected with HCV.

HCV is known to enter through the patient's bloodstream and, in a relatively short time, settle in the liver. There the virus begins replicating, eventually causing scarring of the liver in many individuals. Most commonly, patients are infected through shared needles or syringes during intravenous drug use or through other exposures to contaminated blood, such as in tattooing, body piercing, blood transfusion, and possibly through unprotected sexual contact (5). The mode of transmission remains unknown in about 10% of HCV cases. Also, HCV is more common in minority populations (African Americans, 3.2%, and Mexican Americans, 2.1%) than in non-Hispanic whites (1.5%).

HISTORICAL SUMMARY

Hepatitis was first described by Hippocrates around 400 bc, and its ability to cause epidemics was recognized as early as the eighth century. Yet, while other diseases were recognized and even had yielded to vaccines—smallpox, yellow fever, and poliomyelitis
among them—hepatitis, in all its forms, remained unvanquished.

As late as 1956, Dr. Sheila Sherlock of the Royal Free Hospital in London taught that there were 2 major types of “viral hepatitis.” The one called infectious hepatitis (type A), with a short incubation period, was transmitted through feces and ingested orally; the other, called serum hepatitis (type B), with a longer incubation period, was transmitted by infected needles and blood transfusion. At that time, firm epidemiologic evidence clearly demonstrated the existence of at least 2 types of viral hepatitis but, hunt as they might, virologists could not isolate any hepatitis virus (1).

In 1964, Dr. Baruch S. Blumberg, searching for genetic variations in serum proteins, discovered an antigen in the blood of an Australian aborigine that reacted with an antibody in the serum of a hemophiliac. Blumberg called this protein “Australia antigen” and, through a series of experiments and observations, linked Australia antigen with hepatitis. His work was recognized 10 years later with the award of the Nobel Prize in Physiology and Medicine. In 1969, Dr. Alfred Prince of the New York Blood Center showed that Australia antigen was present in individuals who were infected with hepatitis B. One year later the virus itself was discovered by Dr. D. S. Dane of Middlesex Hospital in London; it was dubbed the “Dane particle” by his colleagues. Thus, with the isolation of the hepatitis B virus (HBV) and its antigenic components, sensitive serologic diagnosis was made possible by the early 1970s.

Detection methods for hepatitis A virus (HAV) or antibody lagged behind those for HBV because of the low magnitude of viremia and the short viremic phase of hepatitis A. In 1973, Feinstone and colleagues adapted immune-electron microscopy for visualization of the viruses in fecal preparations and modified the technique to detect antibodies in serum.

The successful transmission of both type A and type B viral agents to primates made possible the study of the disease's natural history. In 1977, anomalies observed by Mario Rizzetto while he examined HBV-infected livers led to the unexpected discovery of hepatitis delta agent, or hepatitis D virus. We are now aware that hepatitis D has a short RNA with a viroid-like circular structure and multiplies only in hepatocytes already infected by HBV. Also, hepatitis D causes acute hepatitis in people who are infected with HBV and furthers the progression to cirrhosis in hepatitis B surface antigen (HBsAg) carriers.

The discovery of HBV and the elimination of identifiable carriers of HBsAg from the US blood donor pool held great promise for the eradication of this common complication of blood transfusion. Only a slight reduction in posttransfusion hepatitis resulted because the newly available tests for hepatitis showed that most posttransfusion cases of hepatitis were not caused by HAV or HBV, but by unidentified viral agents. In 1975, the rubric “non-A, non-B hepatitis” (NANB) was coined to describe this disease. In the USA, despite serologic testing of blood donors for HBsAg, as many as 1% to 10% of patients developed NANB hepatitis after infusion of blood and blood components. Also, it became evident that NANB hepatitis could occur sporadically without percutaneous exposure or a history of blood transfusion. The NANB infection is generally mild, being anicteric in 75% of the cases and symptomatically mild in an even higher percentage. However, in 36% of all fulminant
hepatitis cases NANB infection was diagnosed, and the rate of survival was lower than for fulminant hepatitis A and B cases.

Following some controversy, blood banks in the USA began surrogate testing for NANB hepatitis in mid to late 1986 using alanine aminotransferase and antibody to hepatitis B core antigen. Studies prior to implementation projected that surrogate testing could reduce transfusion-associated NANB by 30% to 60%. However, many blood donors, despite having an abnormal surrogate test, were not infected with the NANB hepatitis virus and, therefore, could not transmit the disease.

By 1988, researchers had spent more than a decade trying to isolate the viruses that cause posttransfusion NANB hepatitis. Studies in primates at the Centers for Disease Control and Prevention showed the presence of a transmissible agent in the plasma of carrier blood donors and suggested that the NANB hepatitis agent was a small enveloped virus that was readily transmissible to chimpanzees, but the virus itself could not be isolated or visualized. Also, the principles that had worked well for hepatitis A and B could not be used in designing serological systems for the detection of the NANB hepatitis agents. What was particularly frustrating was that the resulting “tests” often appeared to respond to something in the suspect sera, but either were nonreproducible and nonspecific or were detecting normal liver antigens whose production was stimulated by the infection.

On May 11, 1988, the Wall Street Journal reported that scientists at the Chiron Corporation, a small California-based biotechnology company, had cloned the “proteins of an elusive virus responsible for blood-borne hepatitis.” Almost a year later, in April 1989, 2 papers in Science detailed the development and application of a test to detect HCV antibody. Using material isolated from a chimpanzee experimentally infected with NANB hepatitis, Chiron scientists produced a clone that expressed an HCV-specific epitope. Furthermore, evidence was presented that a radioimmunoassay test, using the expressed antigen, detected antibody in the serum of patients who developed NANB hepatitis after transfusion. Data were presented showing that anti-HCV was present not only in blood donors implicated in the transmission of NANB hepatitis, but also in individuals with a history of community-acquired NANB hepatitis. The validation of the immunoassay for antibody to HCV was established convincingly by its ability to distinguish under code between serum samples from pedigreed infectious cases of NANB hepatitis and appropriate control serum samples (1, 2).

A historical review would not be complete without a brief mention of hepatitis E virus. This single-stranded RNA virus, about 27 to 34 nm in diameter, gives rise to a fecally transmitted form of viral hepatitis and is usually seen in large epidemics in developing countries. One important feature is its high mortality rate (about 20%) in infected pregnant women. Hepatitis E can also be responsible for “sporadic” or “community-acquired” NANB hepatitis in endemic countries.

Finally, in 1995, hepatitis G virus was discovered independently by 2 different laboratories in the USA (6). At this time, hepatitis G, found in tamarin monkeys, has an uncertain pathologic role, but it has been proposed as a cause of mild human hepatitis.
REDUCING HCV SPREAD THROUGH THE BLOOD SUPPLY

In the past, blood transfusions were responsible for a substantial amount of HCV transmissions. To reduce the spread of HCV, the Department of Health and Human Services has worked to ensure the safety of our nation's blood supply. As a result of these efforts, the risk of blood transfusion–related HCV transmission has declined significantly since 1990, when the first test for HCV antibody was introduced. Since 1992, following the introduction of more sensitive and effective blood tests for the detection of HCV, the risk of transfusion-related hepatitis is now in the range of 1 in 100,000 units transfused, compared with 1 in 200 before screening (7).

To reach individuals who may have been infected by blood transfusions prior to testing, Secretary of Health and Human Services Donna E. Shalala announced in January 1998 that the Department of Health and Human Services would implement measures recommended by its Advisory Committee on Blood Safety and Availability (8). These measures (revised in March 1998) include a direct notification effort to reach individuals who received a transfusion from a donor who later tested positive for HCV and a public and provider education effort directed at all people at risk for hepatitis C. Shalala also pledged to go beyond the committee's recommendations by evaluating the initial efforts and identifying ways to address unmet needs. She has instructed the Centers for Disease Control and Prevention and the Food and Drug Administration to develop plans to carry out such an effort. These efforts are ongoing.

The instigation of the HCV “lookback” in March 1998 caused blood collection centers to identify blood donors who tested HCV-seropositive since initiating the second-generation anti-HCV test in 1992. (Currently, the Food and Drug Administration is considering a proposal that “lookback” be extended to include the first-generation HCV test in 1990.) Units of blood received from these donors before HCV testing would be identified retroactively for 10 years and traced to the transfusion services using them. The transfusion services (usually hospitals) would check their records to identify and notify primary physicians, patients, or both of possible transfusion-transmitted HCV infection and offer testing and counseling. Three separate attempts must be made to contact the recipient of the unit in question.

HCV/HIV TESTING IN 1999

Currently a “window period” exists between the time a blood donor contracts an infectious disease, such as hepatitis C, and its detection by standard serological tests that detect the presence of antibody. Because of this delay in antibody response, about 2 cases of human immunodeficiency virus transmission and 100 cases of HCV transmission occur every year in patients who are transfused in the USA. In an attempt to make the nation's blood supply even safer, a new test for the virus is being introduced. The nucleic acid test can detect minuscule amounts of HCV and human immunodeficiency virus present in blood even before the donor's body can recognize the infection and form antibodies (9). This test will help ensure fewer cases of blood-transmitted viral infections by identifying infected blood donors who may not have viral antibodies present.
Furthermore, the Food and Drug Administration has approved an improved supplemental test to confirm screening results for antibodies to HCV. The new test, called the RIBA HCV 3.0 Strip Immunoblot Assay, is used to test blood specimens that have already repeatedly tested reactive on licensed screening tests. This new test can detect one more type of antibody to HCV virus than the previous supplemental test and is better at distinguishing truly positive from falsely positive test results.

**NATURAL HISTORY AND PROGNOSIS OF HCV INFECTION**

The natural history and prognosis of HCV infection are still ill-defined. While approximately 15% to 20% of patients make a complete recovery, the remainder, many years later, eventually develop signs and symptoms of liver disease, which include fatigue, loss of appetite, abdominal pain, and nausea, as well as cirrhosis and hepatocellular carcinoma (10). The disease is also known to attack the heart, skin, kidneys, and body joints. Survival is decreased by cirrhosis, long disease duration, excessive alcohol consumption, a history of intravenous drug abuse, and proven blood transfusion–transmitted infection. Liver function tests such as alanine aminotransferase and bilirubin have no effects on survival; neither do sex and viral genotype. Significant progress has been hindered by the lack of an animal or cell culture model of HCV infection. Also, there is no complete in vitro model of HCV replication or translation. Finally, it has been observed that the clinical progression of chronic HCV disease is not uniform throughout the entire period of infection but is more rapid in patients with advanced histologic changes (11). Fortunately, several studies have shown that mother-infant vertical transmission is low (<8%) (12).

**CURRENT TREATMENT**

Until recently, interferon was the only treatment for HCV infection. Typically only 15% to 20% of patients treated with interferon are rid of the virus; most eventually relapse (13). Also, many patients cannot tolerate this drug because of complications such as fever, headache, myalgia, fatigue, anorexia, depression, and suicidal ideation. On June 3, 1998, Rebetron was approved by the Food and Drug Administration for the treatment of HCV infection. Rebetron is a treatment that comprises interferon injection and ribavirin capsules. The treatment cost is about $15,000 a year per patient. Studies have shown that Rebetron therapy results in a significant increase in the number of patients (up to 40%) showing a sustained loss of detectable HCV compared with patients receiving standard interferon monotherapy (14). A significant improvement was also noted in histologic response. However, since ribavirin is a known teratogenic agent, patients and their partners are advised to use 2 forms of contraception during and for several weeks after treatment. Even the most enthusiastic “treaters” concede that more effective, safer, and less discomforting therapies are sorely needed.

**FUTURE PROSPECTS FOR HCV MANAGEMENT**

Efforts are on the way to develop and commercialize ribozymes for the treatment of HCV infection. Ribozymes are based on a novel, Nobel Prize–winning technology and have the unique ability to act as molecular scissors. According to a conversation with W. C. Maddrey
(April 1999), a lead therapeutic candidate called Heptazyme has been developed that specifically targets the conserved region of the HCV RNA and is currently undergoing trials.

In Belgium, a new vaccine for hepatitis C appears to be effective in HCV-infected chimpanzees. Researchers, however, face several challenges in developing a human HCV vaccine. The first challenge is the genetic variation of the virus. HCV includes 11 genotypes and more than 85 subtypes. Subtype 1b is the usual disease-causing agent in the USA and the one most commonly targeted. Also, there is considerable variation within a subtype, so that the virus presents a constantly moving target. However, a subunit vaccine composed of recombinant conserved HCV proteins may prevent infection or chronic infection by different HCV genotypes (15).

This article is dedicated to the memory of Alexander Walker McCracken, MD, who stimulated my interest in virology.

References


