THE GORDON WILSON LECTURE

THE ABC'S OF VIRAL HEPATITIS

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NEW YORK

It is a great honor to be asked to present the 1991 Gordon Wilson lecture and a privilege to have my name added to the distinguished list of previous lecturers.

The disease that is called viral hepatitis today has an ancient history. Reports of epidemic jaundice were described by Hippocrates in Greece during the 5th century B.C., and many outbreaks were reported during the 19th and 20th centuries.

Epidemics of so-called "campaign jaundice" were prevalent during various wars. For example, more than 70,000 cases occurred among Union troops during the Civil War, and many hundreds of thousands cases occurred among American, British and French troops during World War II. In retrospect, it is likely that these outbreaks were caused by hepatitis A virus (HAV). The outbreak that was associated with contaminated lots of yellow fever vaccine during the 1940's was caused by hepatitis B virus (HBV).

When the late Dr. Joseph Stokes, Jr. discussed viral hepatitis during his 1952 Gordon Wilson Lecture, the epidemiological evidence indicated that there were two types of hepatitis, A and B. At that time, neither HAV nor HBV had been identified. However, there has been a virtual revolution in our knowledge of viral hepatitis during the past four decades. Today, during the course of my discussion, evidence will be presented to confirm the existence of at least five immunologically distinct viruses: HAV, HBV, hepatitis C (HCV), hepatitis D (HDV) and hepatitis E (HEV).

HEPATITIS A

This disease was formerly known as infectious hepatitis, epidemic jaundice, acute catarrhal jaundice and other designations. The causative agent, HAV, is a 27 nm particle that has the physical, chemical and biologic characteristics of an enterovirus. It is a simple non-enveloped virus with a nucleocapsid that contains a single-stranded molecule of

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RNA. HAV can be cultivated in various cell cultures and its genome has been cloned (1).

Prior to the mid-1950's, the presence of jaundice was essential for a diagnosis of hepatitis A. The existence of anicteric hepatitis was suspected but it could not be confirmed. Today, highly sensitive and specific tests are available to identify viral hepatitis with and without jaundice. They include serum enzymes such as alanine aminotransferase (ALT) and assays for hepatitis A antibody (anti-HAV). The availability of these tests has provided the technology needed to make a specific diagnosis of hepatitis A and to determine the immune status of an individual. The detection of IgM anti-HAV in the serum of a person with acute hepatitis is indicative of hepatitis A infection. The test for IgG anti-HAV is useful to determine susceptibility or immunity to HAV infection.

The clinical, epidemiologic and immunologic features of hepatitis A as compared with types B, C, D and E are listed in Table 1. The clinical picture is variable. In children, the acute disease is generally milder and its course is shorter than in adults. In both children and adults, jaundice may be inapparent or transient, or it may persist for many weeks.

The incubation period is about 30 days with a range of 18 to 40 days. The following observations have been confirmed by various investigators: 1) large quantities of HAV can be detected in stool specimens during the latter part of the incubation period; 2) ALT values become abnormal several days before onset of jaundice if present, and 3) jaundice, if present, is observed at the time of peak transaminase (2).

The duration of illness is variable, ranging from several weeks to several months. The degree of morbidity and the duration of jaundice correlate directly with age. Complete resolution of hepatitis usually occurs. Unlike hepatitis B, C and D, hepatitis A does not cause chronic liver disease. Viremia is transient and a chronic carrier state does not occur. Although the outcome of HAV infection is favorable usually, fulminant hepatitis may occur but it is very rare.

Epidemiologic Aspects. The geographic distribution of hepatitis A is worldwide. It is endemic in Africa, South and Central America and the Orient. Susceptible travelers to these areas are at risk of infection. Although no person of any age is immune, the highest incidence in civilian populations occurs among persons younger than 15 years.

Transmission of HAV is via the fecal-oral route as indicated previously. HAV is detectable in the blood and stools during the latter part of the incubation period. Viremia is not detectable when anti-HAV appears shortly after onset of jaundice. Fecal shedding of HAV persists for about one week after onset of jaundice.

Explosive water-borne, milk-borne and food-borne epidemics have been reported. Ingestion of raw shellfish from polluted waters has been

TABLE 1

Viral hepatitis types A, B, C, D, and E—comparison of clinical, epidemiologic, and immunologic features

Features	Hepatitis A	Hepatitis B	Hepatitis D	Hepatitis C	Hepatitis E
Virus	HAV	HBV	HDV	HCV	HEV
Family	Picornavirus	Hepadnavirus	Satellite	Flavivirus	Calcivirus
Genome	RNA	DNA	RNA	RNA	RNA
Incubation period	15–40 days	50–180 days	21–90 days	1–5 months	2–9 weeks
Type of onset	Usually acute	Usually insidious	Usually acute	Usually insidious	Usually acute
Prodrome: arthritis and rash	Not present	May be present	Unknown	May be present	Not present
Mode of transmission					
Oral (fecal)	Usual	No	No	No	Usual
Parenteral	Rare	Usual	Usual	Usual	No
Other	Food or water-borne	Intimate (sexual) contact perinatal	Intimate (sexual) contact less common	Intimate (sexual) contact less common	Water-borne transmission in developing countries
Sequelae carrier	No	Yes	Yes	Yes	No
Chronic hepatitis	No cases reported	Yes	Yes	Yes	No cases reported
Mortality	0.1%–0.2%	0.5%–2.0% in uncomplicated cases; may be higher in complicated cases	2%–20%	1%–2% in uncomplicated cases; may be higher in complicated cases	20% in pregnant woman; 1%–2% in general population
Immunity					
Homologous	Yes	Yes	Yes	Yes	Yes
Heterologous	No	No	No	No	No

the cause of many epidemics. In 1988, an epidemic of hepatitis A in Shanghai, China involved more than 300,000 persons who had eaten raw hairy clams. HAV was isolated from the gills and digestive tracts of the contaminated clams.

Seroepidemiological surveys have provided valuable information about the distribution of anti-HAV in various population groups. A striking correlation between the presence of anti-HAV and socioeconomic status has been observed. Persons from lower socioeconomic groups are more likely to have detectable anti-HAV (past hepatitis A infection) than those from middle or upper socioeconomic groups.

It is likely that continued improvement of socioeconomic conditions will decrease the probability of exposure to hepatitis A, thereby changing a predominantly childhood infection to one that is more apt to occur in adults.

Prophylaxis Aspects. Immune globulin is the only licensed product available for the prevention of hepatitis A. This passive immunizing agent can be used for postexposure and/or preexposure prophylaxis. In the future the use of immune globulin will be replaced by active immunization with hepatitis A vaccine. Studies currently in progress are very encouraging. Experimental inactivated hepatitis A vaccines have proved to be safe, highly immunologic and effective. It is likely that this vaccine will be licensed by 1993.

HEPATITIS B

Hepatitis B is synonymous with serum hepatitis, a disease with a more recent history. The first known outbreak occurred in 1883 among a group of shipyard workers who were vaccinated against smallpox with glycerinated lymph of human origin. Later, an increased incidence of the disease was observed among patients attending venereal disease clinics, diabetic clinics, and other facilities where multiple injections were given with inadequately sterilized syringes and needles contaminated with the blood of a carrier. The most extensive outbreak occurred during 1942 when yellow fever vaccine containing human serum caused 28,585 cases of hepatitis B infection with jaundice among United States military personnel. It was unknown at the time of vaccination that the human serum component of the vaccine was contaminated with HBV. The various aliases of hepatitis B recorded in the literature include serum hepatitis, homologous serum jaundice, transfusion jaundice, syringe jaundice, and postvaccinal jaundice.

The Agent. The hepatitis B virus, a complex 43-nm virion, is a member of a new class of viruses, designated "hepadna." Unlike HAV, HBV has not been successfully propagated in cell cultures. Nevertheless, its bio-

physical and biochemical properties have been well characterized, and the HBV genome has been cloned and sequenced. The virus is a double-shelled particle; its outer surface component, the hepatitis B surface antigen (HBsAg) is immunologically distinct from the inner core component, the hepatitis B core antigen (HBcAg). The core contains the genome of HBV, a single molecule of partially double-stranded DNA. Additional components of the core include DNA-dependent DNA polymerase and hepatitis B e antigen (HBeAg).

Clinical Aspects. The incubation period of hepatitis B may range between two and six months. The detection of HBsAg in the blood of a patient who has acute hepatitis is indicative of HBV infection. Hepatitis B surface antigen may be detected about 1 week to 2 months before the appearance of abnormal levels of ALT and jaundice. In most patients who have acute hepatitis B, HBsAg is present consistently during the latter part of the incubation period and during the preicteric phase of the disease. The antigen may become undetectable shortly after onset of jaundice.

After an incubation period of approximately 50 days, the serum ALT values become abnormal, rising gradually over a period of several weeks. The duration of abnormal ALT activity may be prolonged, usually exceeding 30 to 60 days.

The first antibody to be detectable is anti-HBc; it appears approximately 1 week or more after onset of hepatitis. The anti-HBc titers, predominantly IgM, are usually high for several months. Thereafter, IgM values decline to low or undetectable levels, but anti-HBc persists for many years.

The anti-HBc IgM assay should be useful for differentiating recent from past HBV infections and identifying acute hepatitis B in patients whose HBsAg has declined to undetectable levels before appearance of anti-HBs (window-phase). Antibody to HBsAg (anti-HBs) usually appears late, approximately 2 weeks to 2 months after HBsAg is no longer detectable. Anti-HBs is detected in approximately 80% of patients with hepatitis B who eventually become HBsAg-negative. In the remainder, the antibody levels are too low to be detected. Anti-HBs may be detected in about 5% to 10% of HBsAg carriers.

Progression to chronic infection has been reported in 3% to 13% of adults. However, in infants born to mothers who are HBsAg- and HBeAg-positive the risk may exceed 60%. Other serious consequences of hepatitis B infection include fulminant hepatitis, cirrhosis and hepatocellular carcinoma. In addition, it is well recognized that HBV infections may be associated with a variety of extrahepatic manifestations. The underlying pathology is usually a diffuse and widespread immune-complex-type vasculitis. The following syndromes have been identified: serum sickness-

like syndrome, polyarteritis nodosa, chronic membranous glomerulonephritis, essential mixed cryoglobulenemia, and papular acrodermatitis.

Epidemiological Aspects. Early epidemiologic concepts indicated that hepatitis B virus was transmitted exclusively by the parenteral route. It now is clear, however, that the following modes of transmission play an important role in the dissemination of HBV: (1) oral-oral, (2) sexual, (3) perinatal and (4) intimate physical contact of any type. The antigen has been detected in saliva, in semen, and in many other body fluids.

The major reservoir of HBV is chronic carriers. The infection is transmitted to susceptible persons by transfusion of blood, plasma, or other blood products or by the use of inadequately sterilized needles and syringes. Medical, dental, paramedical and paradental personnel may be infected by accidental inoculation or ingestion of contaminated materials. Outbreaks have occurred among drug addicts using unsterilized equipment. Tattooing and acupuncture have been responsible for transmitting the infection. Patients and personnel in the following areas have been shown to be at high risk: renal dialysis, intensive care, and oncology units, as well as various laboratories in which potentially contaminated blood and tissues are examined.

Seroepidemiologic surveys to detect the presence of HBsAg and anti-HBs have confirmed the worldwide distribution of the disease. The antigen has been detected in all populations, even in those living in the most remote areas devoid of parenteral modes of transmission. The antigen is most prevalent among persons living under crowded conditions and with poor hygienic standards. This accounts for the endemicity of the disease in institutions for mentally retarded persons and in certain developing countries of the world.

The HBsAg carrier rate may range from 0.1% to more than 10%; it is dependent on such factors as geographic location, age, and sex. The carrier rate is higher in tropical, underdeveloped areas than in temperate developed countries; it is higher in urban than in rural communities, and higher among males than among females. The prevalence of anti-HBs in various populations may range from a low of 5% to 80%.

The period of infectivity of patients with hepatitis B is dependent on the presence or absence of a carrier state. HBsAg is detectable in the blood during the latter part of the incubation period and for a variable period after onset of jaundice. Infectivity also has been associated with the presence of HBeAg and a high titer of HBsAg. For example, perinatal transmission of hepatitis B infection from HBsAg-positive mothers to their infants is highly likely if they are HBeAg-positive. On the other hand, HBsAg-positive and HBeAg-negative mothers are much less likely to transmit infection.

Immunoprophylaxis. Hepatitis B vaccine. Two types of hepatitis B

vaccine are licensed in the United States: plasma-derived and yeast recombinant. Extensive experience to date has confirmed the safety, immunogenicity and efficacy of these vaccines in adults and in infants (3, 4). Plasma-derived vaccine is no longer produced in the United States.

Primary vaccination consists of three intramuscular doses of vaccine given at 0, 1 and 6 months. An alternate schedule of four doses at 0, 1, 2 and 12 months also has been recommended. Because various hepatitis vaccines are not generic, the age-specific doses may be variable.

All hepatitis B vaccines are inactivated (non-infective) products. There is no evidence of interference with other vaccines administered simultaneously. There has been no evidence of risk to the fetus following vaccine given during pregnancy. In contrast, HBV infection in a pregnant woman may cause a severe disease in the mother and chronic infection of the newborn infant. Therefore, pregnancy and lactation are not a contraindication for use of the vaccine in women who are at high risk of contracting hepatitis B.

Hepatitis B vaccine is recommended for the following individuals who are at increased risk: health care professionals exposed to blood or blood products, patients who have hemophilia or thalassemia, children or staff at institutions for the developmentally disabled, promiscuous homosexual males, intravenous drug abusers, and household contacts of chronic carriers (5).

Prevention of Neonatal Hepatitis B. Postexposure prophylaxis of perinatal hepatitis B infection with hepatitis B immune globulin and hepatitis B vaccine has proved to be effective because (1) intrauterine infection is rare (about 5%), 2) most infants are exposed at the time of birth, and 3) the incubation period of hepatitis B may range between six weeks and six months. Consequently, active immunization with hepatitis B vaccine can induce an antibody response before onset of infection.

Several studies have confirmed the efficacy of combined passive (hepatitis B immune globulin) and active (hepatitis B vaccine) immunization for the prevention of perinatally acquired infection (4). The results of these studies revealed that the following regimen should prevent 85% to 90% of chronic infections in infants born to mothers whose blood is positive for HBsAg and HBeAg: 1) Hepatitis B immunoglobulin, 0.5 mL given intramuscularly within the first few hours after birth, and 2) hepatitis B vaccine, given intramuscularly before the baby leaves the hospital. Combined hepatitis B immune globulin and hepatitis B vaccine prophylaxis is recommended for all infants whose mothers are HBsAg positive, regardless of their HBeAg status. It is essential that HBsAg-positive pregnant women be identified during the prenatal period. Notification of the obstetric staff will enable them to protect themselves and other patients from infectious blood or secretions. Notification of the

pediatric staff will alert them to institute therapy immediately after birth.

During 1988, the U.S. Public Health Service recommended that all pregnant women in the United States should be tested routinely for HBsAg. However, routine screening of all pregnant women is neither feasible nor recommended for those living in developing areas of the world where HBV infection is hyperendemic. Under these circumstances, routine immunization of all newborn infants who have hepatitis B vaccine is indicated. This strategy should prevent perinatally or postnatally acquired vaccine infection.

Universal Immunization of Infants. Hepatitis B vaccine has been used extensively throughout the world since its licensure in November 1981. Experience involving many millions of vaccinees has confirmed its safety and efficacy. Hepatitis B vaccine currently is being incorporated into the Expanded Program on Immunization of the World Health Organization. The first dose of vaccine is given to all infants soon after birth. Additional doses are given at subsequent routine visits.

Universal immunization of all infants in the United States is now recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and the Committee on Infectious Diseases of the American Academy of Pediatrics. The preferred schedule is to give 1) the first dose of vaccine at birth before discharge from the hospital; 2) the second dose at the first routine visit 1–2 months later, and 3) the third dose at a routine visit between 6 and 18 months of age. An alternative schedule would include the first dose at 2 months of age, the second dose at 4 months of age and the third dose at 6 to 18 months of age. It is anticipated that in the future multiple antigen preparations will include hepatitis B, diphtheria-tetanus-pertussis (DPT), polio, Haemophilus influenzae type b, and hepatitis A.

HEPATITIS C

Studies using chimpanzees revealed the presence of a transmissible agent in blood products that caused NANB hepatitis (6). The agent was sensitive to organic solvents, and it was less than 80 nm in diameter as assessed by filtration. Using large quantities of well characterized highly infectious plasma as a source of virus, Choo *et al.* cloned the genome of this NANB agent that has been designated hepatitis C virus (HCV) (7). The physical characteristics of HCV indicate that it is a flavivirus-like agent; it contains a positive single-stranded RNA molecule.

Hepatitis C was formerly designated "parenterally transmitted non-A, non-B hepatitis" (PT-NANB). Non-A, non-B hepatitis was recognized as a clinical entity during the 1970s when specific tests for the identifi-

cation of HAV and HBV infections became available. Absence of HAV and HBV serologic markers of infection suggested the presence of NANB hepatitis. The identification of HCV as the most common cause of PT-NANB hepatitis was reported during 1989 (8). Extensive serologic studies have revealed that HCV is a cause of sporadic as well as posttransfusion hepatitis.

Most patients with HCV infection are anicteric, especially those who have the contact-acquired sporadic form. The incubation period may range between 1 and 5 months. The clinical signs and symptoms of the acute illness are milder than HAV and HBV infections. However, biochemical evidence of chronic liver disease develops in about 50% of patients with posttransfusion hepatitis C. Serum alanine aminotransferase levels may fluctuate over prolonged periods of time.

The interval between exposure to HCV or onset of illness and detection of anti-HCV by serum enzyme immunoassay may be prolonged. In recipients of transfusions, the mean interval from onset of hepatitis to detection of anti-HCV may be 15 weeks (range 4 to 32 weeks). In general, anti-HCV persists in patients who have chronic disease; it may disappear in those who have acute resolving hepatitis C. Long-term prospective studies of patients contracting posttransfusion NANB hepatitis (HCV disease) have revealed evidence of progression to cirrhosis and to hepatocellular carcinoma.

The availability of a specific serological test to detect anti-HCV has clarified the epidemiology of parenterally transmitted and sporadic HCV infection. The distribution of the disease is worldwide with an estimated 100 million HCV carriers. In the United States, hepatitis C may be the cause of 20% to 40% of all acute hepatitis cases. Persons at high risk of contracting HCV infection include: transfusion recipients, intravenous drug users, hemodialysis patients, and health care workers with frequent blood contact. Unlike hepatitis B, promiscuous homosexual and heterosexual persons have a low risk of contracting HCV infection. Perinatal transmission of HCV has not been well documented.

HEPATITIS D

Hepatitis D virus is a defective RNA virus that can replicate only in the presence of acute or chronic hepatitis B infection. The genome for HDV codes for an internal antigen but the virus is encapsulated by HBsAg of the helper HBV (9).

Clinical Aspects. The clinical manifestations and course of type D hepatitis resemble acute or chronic hepatitis B. In general, however, hepatitis D is a more severe disease. The mortality rate of acute HDV hepatitis has ranged from 2% to 20%, as compared with less than 1% for

acute hepatitis B. In addition, cirrhosis and complications of portal hypertension occur more often and progress more rapidly in hepatitis D.

Acute delta hepatitis occurs as either a coinfection or superinfection of hepatitis B. In the case of coinfection, there is simultaneous onset of acute HBV and HDV infection. In the case of superinfection, a chronic HBV carrier is infected with HDV.

The course of acute delta coinfection is as follows: During the latter part of the incubation period, HBsAg followed by HDV RNA appears. Thereafter, serum ALT levels begin to rise followed by the development of clinical symptoms and jaundice. Serum ALT activity is often biphasic. Resolution of acute liver disease follows clearance of HBsAg and cessation of HDV replication. The antibody to HDV (anti-HDV) that appears shortly after onset of clinical disease is transient.

The course of acute delta superinfection is often followed by the development of chronic delta hepatitis. At the end of the incubation period there is 1) a rise in serum ALT values; 2) appearance and persistence of HDV RNA; 3) followed by appearance of IgM anti-HDV, which is transient; and 4) a rise of IgG anti-HDV to high levels, which persist.

Epidemiological Aspects. The epidemiology of hepatitis D is characterized by striking similarities to and certain differences from hepatitis B (Table 1). The modes of transmission are the same except that HDV perinatal infection is rare. In general, the prevalence of HDV correlates with the prevalence of HBV in the following high risk groups: intravenous drug users, hemophiliacs, and institutionalized mentally retarded patients. In contrast, HDV has not been reported to be prevalent in the following HBV high risk groups: homosexual men and chronic carriers in such highly endemic areas as southeast Asia, southern Africa, and Alaska.

Superinfection of chronic HBV carriers has been responsible for epidemics of HDV-associated fulminant hepatitis in Venezuela, Colombia and Brazil. In the United States and northern Europe, HDV is most common among drug abusers.

Prophylactic Aspects. Persons who are immune to hepatitis B are protected against HDV infection. Consequently, immunoprophylaxis of hepatitis B will prevent hepatitis D infection.

HEPATITIS E

Hepatitis E was previously called "enterically transmitted NANB" (ET-NANB) (10). Serologic studies of various outbreaks of ET-NANB hepatitis revealed no evidence of HAV or HBV infection. In retrospect,

it is clear that these outbreaks were caused by HEV, an agent that was cloned in 1990.

The clinical manifestations and course of hepatitis E are essentially the same as hepatitis A. However, there are several striking differences. During various epidemics, the disease has been rare in children and common in adolescents and young adults.

Hepatitis E virus, like HAV, does not cause chronic liver disease. In most patients the illness is self-limiting, and there is no evidence of a chronic carrier state. However, unlike hepatitis A, hepatitis E can be a devastating disease in pregnant women. Whereas the mortality from hepatitis A in pregnancy is less than 1%, it has ranged between 10% and 20% in outbreaks of hepatitis E. The deaths are caused by fulminant hepatitis. Mortality is highest during the third trimester and lowest during the first trimester. The mortality rate in non-pregnant women is the same as that among men, less than 1%.

At the present time, a practical serologic test to confirm a diagnosis of hepatitis E is not available. Immune electronmicroscopy was the first generation test to be used by investigators. Second generation tests such as RIA and EIA are being evaluated for their sensitivity and specificity.

The epidemiology of hepatitis E is characterized by certain similarities to and many differences from hepatitis A (Table 1). Both hepatitis E and hepatitis A are enterically transmitted diseases that are spread via the fecal-oral route.

Hepatitis E has occurred predominantly in certain developing areas of the world during the course of water-borne outbreaks. Hepatitis E has been most common in adults, rare in children and the secondary attack rate in household contacts has been relatively low, less than 3%. Epidemics have occurred in China, southeast and central Asia, northern and western Africa, Mexico and Central America. With the exception of a few imported cases, hepatitis E has not occurred in the United States.

Prophylactic Aspects. Outbreaks of hepatitis E have not occurred in the United States. Travelers to areas of the world where epidemics may occur are at risk. There is no evidence that U.S. manufactured immune globulin will prevent this infection. The best means of preventing HEV infection is to avoid potentially contaminated food and water.

CONCLUSION

In the May 1991 issue of Seminars in Liver Disease, Dr. Jules Dienstag summarized the present status of hepatitis research. "Progress in hepatitis research has continued at a frenzied pace. Hepatitis virology has become the province of molecular biologists, molecular and immunological approaches have been joined to elucidate virus and host responses

during acute and chronic infection, work on non human examples of hepadnaviruses and on transgenically created models of HBV infection have taught us important lessons about HBV replication and pathogenesis, and both hepatitis C and hepatitis E viruses have been identified and characterized. Our understanding of the epidemiology of hepatitis B has become more sophisticated, prevention of hepatitis B with vaccine has become a routine part of preventive medicine, and chronic viral hepatitis is now considered a treatable disease!"

The extraordinary progress in hepatitis research during the past 35 years was achieved by the contributions of many, many investigators. It has been an exciting and stimulating experience for me to be one of the participants in the studies of the natural history and prevention of viral hepatitis.

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