REVIEW ARTICLE

CURRENT CONCEPTS

Hepatitis E

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Hepatitis E, the fifth known form of human viral hepatitis, is probably the most common cause of acute hepatitis and jaundice in the world.[1,2] Yet in the United States and other developed nations, hepatitis E is uncommon, and its role in causing liver disease is not well defined. This disease was initially identified in 1980 as "epidemic, non-A, non-B hepatitis," an infectious, waterborne illness similar to hepatitis A that was common in the developing countries but rare elsewhere.[3,4] Three years later, Mikhail Balayan visualized the hepatitis E virus (HEV) using immune electron microscopy to examine his own stool samples, which he collected prospectively after self-administration of infectious material.[5] The viral genome was subsequently isolated and sequenced with the use of bile samples obtained from experimentally infected cynomolgus macaques.[6]

The sequencing of HEV RNA allowed for its further characterization and development of assays for anti-HEV antibody. Sensitive enzyme-linked immunoassays showed that anti-HEV antibody was common in the United States and other developed countries,[2,7] and high rates of antibody positivity were observed in several mammalian species, particularly swine. In 1997, a swine strain of HEV was identified and classified as genotype 3.[8] Soon thereafter, cases of acute hepatitis due to genotype 3 HEV were reported in humans in the United States.[9] Cases were later reported in Europe,[10-13] New Zealand,[2] and Australia.[2] A different swine strain (genotype 4) was identified in Japan[14,15] and China.[16] In the past several years, sporadic "autochthonous" (locally acquired) cases of genotype 3 and 4 HEV infection have been increasingly reported in developed countries, including cases of acute liver failure,[17] chronic hepatitis,[18] cirrhosis,[19] and end-stage liver disease due to hepatitis E.[19]

Characteristics of HEV

HEV is a small, nonenveloped virus with a single-stranded RNA genome that is 7.2 kb in length and contains three partially overlapping open reading frames (ORFs) that are bracketed by short 5′ and 3′ nontranslated regions[1,20,21] (Fig. 1). ORF1 encodes the nonstructural, enzymatic activities required for viral replication, and ORF2 the structural, viral capsid that includes neutralizing epitopes. The function of ORF3 is unknown, but it appears to be necessary for cellular egress.[22] The genomic structure of HEV is unique and defines the Hepeviridae family, of which it was the first member to be identified (the genus hepevirus). HEV replicates in the cytoplasm, with a subgenomic RNA producing capsid proteins and the full genomic RNA encoding nonstructural proteins and serving as a template for replication.

The four genotypes of HEV that have been identified fall into two major groups. Genotypes 1 and 2 are human viruses that have been identified as causing epidemic hepatitis and are associated with waterborne and fecal–oral transmission. Genotypes 3 and 4 are swine viruses that are common in domestic and wild pigs

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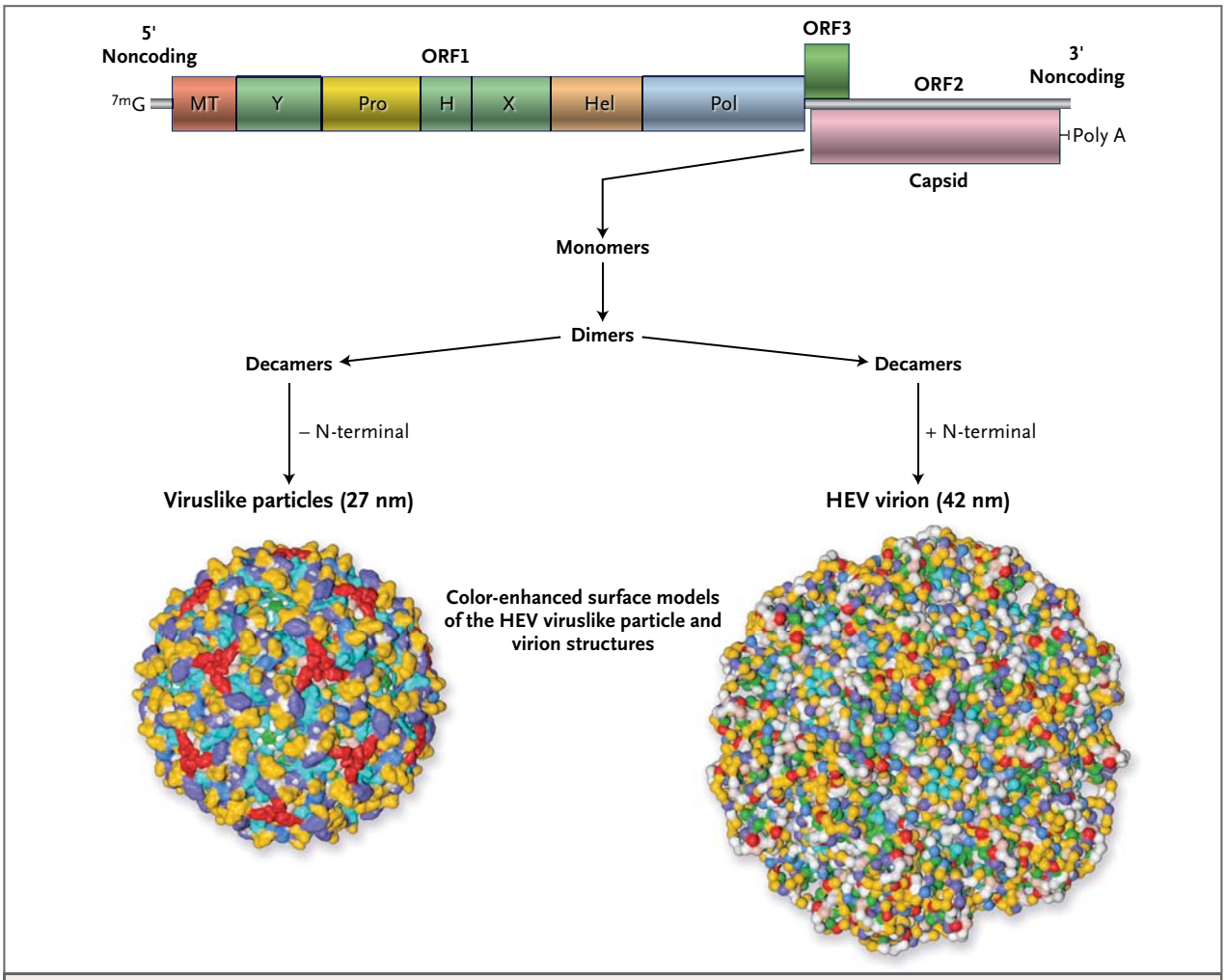

Figure 1. Structure of the Hepatitis E Virus (HEV) and Its RNA Genome.

The viral RNA is approximately 7.2 kb in length and has short 5′ and 3′ noncoding regions and three overlapping open reading frames (ORFs). ORF1 encodes the nonstructural proteins, including a methyl transferase (MT), cysteine protease (Pro), helicase (Hel), and RNA polymerase (Pol), as well as three regions of unknown function (Y, H, and X). ORF2 encodes the structural capsid protein. ORF3 encodes a small protein proposed to have multiple functions, including cellular egress. The 5′ end of the RNA genome is capped with 7-methylguanosine (^{7m}G), and the 3′ end is polyadenylated (poly A). Assembly of virions begins with the production of capsid monomers (with or without an N-terminal region), which self-assemble into dimers and subsequently decamers. Decamers lacking the capsid N-terminal assemble into small viruslike particles that are the source of HEV vaccines and serologic reagents. Decamers of full-length capsid monomers encapsidate the viral RNA to form full-size virions. (Adapted from Xing et al.[21])

and appear to infect humans as an accidental host; these viruses are thus zoonoses.[23] There is cross-neutralization among the four HEV genotypes, indicating that they belong to a single serotype despite clinical and epidemiologic differences.[24] HEV grows poorly in vitro, but recently, several cell-culture systems have been developed for genotypes 3 and 4.[25,26] An important finding was the identification of short human-sequence inserts in HEV RNA; these inserts facilitated tissue-culture adaptation. Remarkably, similar human-sequence inserts have been identified in HEV RNA isolated directly from patients with striking neurologic complications of hepatitis E.[26] These findings suggest that recombination events may alter the replicative capacity, tissue specificity, and pathogenicity of HEV and make this agent unique among human hepatitis viruses.

HEV strains have been detected in several

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mammalian species other than swine, including deer, elk, sheep, cattle, rats, and rabbits.[23,25-28] Some of these viruses may represent new HEV genotypes, but most resemble genotypes 3 and 4. Although several viruses have been shown to be infectious in pigs, the potential of these mammalian viruses to infect and cause disease in humans (i.e., their zoonotic potential) remains unclear. Most recently, other HEV-like agents have been identified in birds and fish, but they are probably different genera that are unlikely to infect humans.[29,30]

DIAGNOSTIC ASSAYS

As in other forms of viral hepatitis, viremia arises during the incubation period of hepatitis E, and antibodies (both IgG and IgM) appear at the time of clinical onset, just preceding elevations in serum aminotransferase levels and symptoms[2] (Fig. 2). Recovery is marked by viral clearance, an increase in IgG titers, and a decrease in IgM levels. HEV is also present in stool, usually during the incubation period, throughout active infection, and in the initial part of the recovery period.[31] The duration of viral shedding is variable, as is the presence of antibodies. IgM anti-HEV antibody remains detectable for only 3 to 12 months, whereas IgG anti-HEV antibody persists for years, if not for life.

Tests for anti-HEV antibody (including IgG- and IgM-specific assays) are available commercially, but none have formal Food and Drug Administration (FDA) approval. Unfortunately, the sensitivity and specificity of available assays vary widely; this may account for the discrepancies among published rates of anti-HEV antibody in various populations.[32] In studies from the United Kingdom, the prevalence of anti-HEV antibody in a blood-donor population was 3.6% with the use of one commercial assay and 16.2% with the use of another.[33] Similarly, serum samples obtained from patients with acute HEV infection (documented on the basis of detectable HEV RNA during the acute phase) were reactive in 44% of patients with one assay and in 98% with the other.

Until assays receive FDA approval, physicians must depend on whatever test is locally available. Patients with unexplained acute or chronic hepatitis should be tested for IgM anti-HEV antibody, with a positive result suggesting ongoing infection. Tests for HEV RNA in serum and stool are confirmatory but are currently still experimental. Serologic and virologic testing is available on a limited basis from the Centers for Disease Control and Prevention (www.cdc.gov/hepatitis).

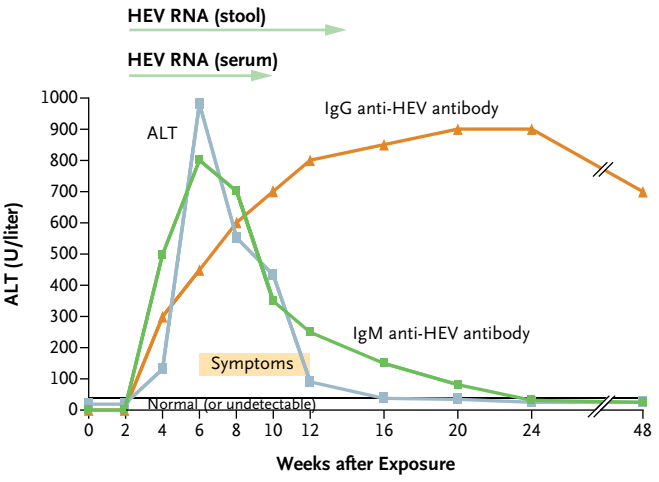

Figure 2. Course of Acute HEV Infection.
HEV RNA becomes detectable in stool and serum during the incubation period, with the subsequent appearance of the IgM and IgG anti-HEV antibodies. The level of IgM antibody peaks early and becomes undetectable during recovery, whereas the level of the IgG antibody continues to increase and persists in the long term. Clinical symptoms (fatigue, nausea, and jaundice) begin shortly after elevations in serum alanine aminotransferase (ALT) levels. HEV RNA disappears from serum with recovery, whereas detectable virus usually persists longer in stool (arrows).

EPIDEMIOLOGY

In developing countries, hepatitis E occurs both sporadically and as epidemic disease, affects a large proportion of the population, and is largely due to genotype 1 (with genotype 2 accounting for cases in Mexico and parts of Africa).[1,2] Published rates of anti-HEV antibody among adults in these areas range from 30 to 80%. In Bangladesh, the incidence of HEV infection was studied prospectively in cohorts of both the general population and pregnant women, who are especially prone to fulminant hepatitis E.[34] In the population at large, the incidence of HEV infection was 6.4% among approximately 1200 people across all ages. In two cohorts of pregnant women, the annual incidence of HEV infection was 4.6% and 5.6%. Assessment of the women's micronutrient status and serum cytokine levels suggested that nutritional and immunologic features played a

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role in the susceptibility to severe infection; these findings indicate potential inroads in efforts to reduce morbidity and mortality associated with HEV infection.

Rates of anti-HEV antibody in the general population are lower in Europe and the United States than in Asia and Africa. However, population-based surveys from 1988 to 1994 indicated that 21.0% of U.S. adults had anti-HEV antibody, a rate lower than that of anti-HAV antibody (38.3%) but higher than that of antibodies against hepatitis B (5.7%) or hepatitis C (2.0%).[7] Anti-HEV antibody rates increased markedly with age, from less than 10% among persons 6 to 19 years of age to more than 40% among those older than 60 years. Strikingly, specific risk factors for the presence of anti-HEV antibody were different from those for other forms of hepatitis. Age-adjusted rates of anti-HEV antibody were lower among blacks (14.5%) than among non-Hispanic whites (22.1%), among men who had sex with men (23.1%) than among those who did not (23.9%), among cocaine users (16.8%) than among nonusers (23.6%), and among people living in the southern United States (14.7%) than among people living in the Northeast (20.8%), Midwest (26.6%), or West (25.0%). Rates of anti-HEV antibody were minimally higher among men than among women (21.6% vs. 20.4%) and among persons who regularly ate liver or offal than among those who did not (26.5% vs. 20.4%). Finally, among men who had sex with men, rates of anti-HEV antibody were lower among men with human immunodeficiency virus (HIV) infection (12.8%) than among men without HIV infection (19.2%).[35] Preliminary results from more recent U.S. population–based surveys show a much lower rate of anti-HEV antibody overall, but a similar distribution according to risk factors.[36]

Cases of acute hepatitis E account for a large proportion of cases of acute liver disease in developing countries, with smaller (although unknown) proportions in Europe and the United States.[36] In developed countries, individual cases and small outbreaks have been linked to exposure to pigs and consumption of undercooked pork[2,12,13] or wild game.[12,14] Indeed, testing of samples of pig liver and sausage from commercial groceries in Europe[13] and the United States[37] identified HEV RNA in a high percentage of samples. Furthermore, laboratory analyses showed the presence of infectious HEV in rare and medium-rare meat. Case reports have also linked hepatitis E to consumption of shellfish[38] and to blood transfusions,[39,40] but the overall rate of these risk factors among unselected patients is low. Thus, most patients with autochthonous hepatitis E report no specific risk factors, such as exposure to pigs or consumption of undercooked pork or sausage.[2,15-18,20,22] Furthermore, secondary spread is rare, if it occurs at all. Only small numbers of cases have been reported in the United States, many of which were misdiagnosed as drug-induced liver injury.[41]

CLINICAL FEATURES

Acute hepatitis E has an incubation period of 3 to 8 weeks, a short prodromal phase, and a period of symptoms or jaundice lasting days to several weeks.[2,10,11,15,16] In published series, most cases were self-limited and none resulted in chronic hepatitis. The case fatality rate ranged from 0 to 10%, averaging approximately 5%, but the association of fulminant hepatitis with pregnancy (which is common with genotype 1 infection) has not been reported with autochthonous hepatitis E. Indeed, in large surveys of acute liver failure in the United States, cases attributable to HEV infection were rare, accounting for less than 1% of cases in adults.[42]

Autochthonous hepatitis E has distinctive clinical features that separate it from epidemic forms (Table 1), as well as from other types of viral hepatitis. Specific age and sex distributions are characteristic of autochthonous hepatitis E. In most case series, the average age was more than 60 years, and men outnumbered women by at least 3 to 1; these features were not shared by other forms of viral hepatitis and were not well explained by risk factors.[10,15,41] These differences may reflect variability in the rate of clinically apparent disease according to sex and age. In an outbreak of hepatitis E aboard a cruise ship, for instance, only 7 of 33 patients had jaundice (21%), and most cases occurred in elderly men.[38] Such findings suggest that autochthonous HEV infection is usually subclinical and mild, particularly in women and young persons; this may explain why 21% of adults in the United States have anti-HEV antibody, but few have a history of acute hepatitis.

Autochthonous hepatitis E also has a striking spectrum of serious complications, including

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Table 1. Clinical and Epidemiologic Characteristics of HEV Infections According to Genotype.

Characteristic	Genotypes 1 and 2 (Epidemic)	Genotypes 3 and 4 (Autochthonous)
Geographic distribution	Developing countries only	Both developing and developed countries
Pattern of spread	Epidemic and sporadic	Sporadic
Occurrence in United States	Travel-related, imported	Autochthonous
Species specificity	Human	Swine, human (humans are accidental host)
Major mode of spread	Fecal–oral, waterborne	Foodborne
Secondary spread	Uncommon	Extremely rare
Rate of icteric illness	High	Low
Age distribution	Disease rates highest among adolescents and young adults	Disease rates highest among older adults
Sex distribution	Similar disease rates among men and women	Higher disease rates among men
Mortality	High among pregnant women	High among older adults
Extrahepatic features	Few	Neurologic complications
Chronic infection	None	Common in immunosuppressed persons
Therapy	None known	Ribavirin, peginterferon (experimental)
Prevention	Vaccine*	Vaccine*

* An HEV vaccine has been approved in China but not elsewhere.

"acute-on-chronic" liver failure, neurologic disorders, and chronic hepatitis. Acute-on-chronic disease refers to hepatitis with a rapid appearance of signs of liver failure ascites and encephalopathy in a person with preexisting liver disease. The preexisting liver disease may be subclinical and unsuspected. HEV infection is a common precipitant of this clinical phenotype,[2,10,41] and most instances of severe autochthonous hepatitis E fit this clinical pattern rather than that of typical fulminant hepatic failure, which occurs with hepatitis A or B.[17]

Reported extrahepatic manifestations of hepatitis E include arthritis, pancreatitis, and aplastic anemia, as well as such neurologic complications as polyradiculopathy, the Guillain–Barré syndrome, Bell's palsy, peripheral neuropathy, ataxia, and mental confusion.[43] These neurologic findings can overshadow the liver injury, and hepatitis may not be suspected. Resolution of hepatitis E, either spontaneously or with therapy, is usually followed by remission of neurologic symptoms.

CHRONIC HEPATITIS E

HEV was initially thought to resemble hepatitis A virus, causing acute, self-limited infections only; thus, it came as a surprise when cases of chronic hepatitis E were described.[18] Chronic infection has been identified almost exclusively among immunocompromised persons, including organ-transplant recipients,[19] patients receiving cancer chemotherapy,[44] and HIV-infected persons.[45] HEV RNA has been detected in moderate-to-high levels in serum and stool and has persisted for years. Serum aminotransferase levels have also been abnormal, and some patients have had progressive liver disease with fibrosis or cirrhosis[19] (Fig. 3). Chronic HEV infection may also occur in adults without apparent immunodeficiency, although such cases are rare.[46] The source of infection is often unknown, but in a minority of cases, blood transfusions or the organ itself have appeared to be the source. The unreliability of antibody tests and the need for direct molecular assays to detect HEV infection pose diagnostic challenges in this population.

Studies in which patients were monitored after solid-organ transplantation showed that chronic infection developed in two thirds of those with acquired hepatitis E.[18,19] Reducing the level of immune suppression led to spontaneous viral clearance in one third of the patients. Chronic hepatitis E was also susceptible to antiviral therapy. Individual case reports and

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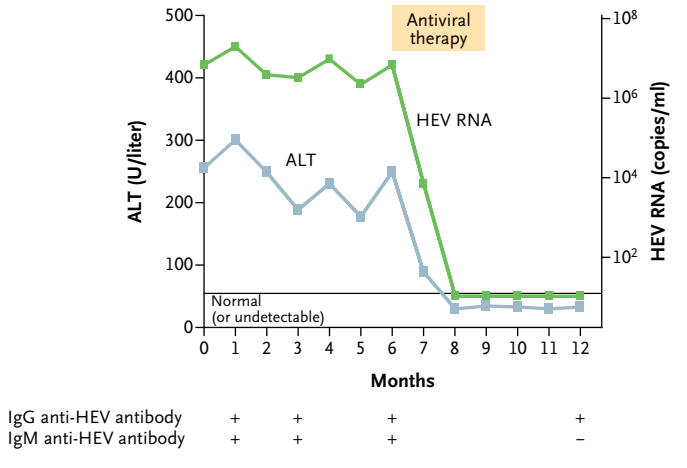

Figure 3. Chronic Hepatitis E and Response to Antiviral Therapy.

Chronic hepatitis E is characterized by the persistence of HEV RNA in serum and stool, generally accompanied by fluctuating, mild-to-moderate elevations in serum ALT levels and low or moderate titers of IgG and IgM anti-HEV antibodies. Antiviral therapy with peginterferon or ribavirin usually results in a rapid decrease in HEV RNA levels in serum, followed by decreases in serum ALT levels. In some instances, HEV RNA becomes and remains undetectable even once therapy has been discontinued (indicating a sustained virologic response), usually with long-term improvement in the liver disease and loss of the IgM anti-HEV antibody.

small case series have shown that peginterferon, ribavirin, or a combination of the two agents leads to viral clearance in most patients and a sustained response in a high proportion of patients.[2,19,47,48] Ribavirin alone in doses of 600 to 800 mg daily for 12 weeks yields sustained virologic responses in at least two thirds of patients with chronic hepatitis E.[2,19] The successes with ribavirin have led to its use for severe, acute hepatitis E, with promising results.[49] At present, however, treatment of hepatitis E is experimental, guidelines have not been formulated, and neither ribavirin nor peginterferon has been approved for this use.

PREVENTION

Because hepatitis E is a zoonosis, prevention might begin with its containment among animals. Surveys of pig farms indicate that a large proportion of herds have evidence of ongoing or prior infection.[8,23] Molecular evidence of HEV has been detected in waste-water runoff from swine farms. This runoff might reach drinking water or shellfish-harvesting areas.[50] At present, there are no regulations regarding prevention of HEV infection in commercial swine herds, isolation of infected animals, or monitoring of waste runoff for HEV. However, the possibility of transmission is justification for reinforcing recommendations for thorough cooking of pork (heating at 71°C [160°F] for at least 20 minutes),[51] and avoidance of raw shellfish, particularly on the part of immunocompromised persons.

Several cases of HEV transmission through blood transfusion have been reported.[39,40] HEV RNA testing of plasma pools suggests that 1 in 4000 to 1 in 8000 donors from Western countries harbor the virus.[52] In studies from the National Institutes of Health Clinical Center, testing of approximately 1000 blood donors showed 22% to be positive for anti-HEV antibody.[53] However, no donor had detectable HEV RNA, and no transfusion-transmitted HEV infections were detected among prospectively followed recipients. Thus, blood transfusion is a potential but rare route of HEV transmission.

Hepatitis E is preventable by vaccination. A controlled trial involving 1794 members of the Nepalese military showed 95% efficacy of a recombinant genotype 1 HEV vaccine in preventing infection and clinical disease.[54] More recently, a recombinant genotype 1 HEV vaccine produced in China similarly was shown to have more than 95% efficacy in a population-based, controlled trial involving more than 100,000 volunteers.[55] Both genotype 1 and 4 infections were prevented, so there was cross-protection against different HEV genotypes.

CONCLUSIONS

Hepatitis E occurs in two forms with different clinical and epidemiologic features. The epidemic form is common in developing countries and is associated with waterborne spread, severe acute disease, and infection with genotypes 1 and 2. The endemic, or autochthonous form, occurs in developed countries and is associated with foodborne and zoonotic spread, mild and typically subclinical disease, and infection with genotypes 3 and 4. The diagnosis of acute hepatitis E is made most readily by testing for IgM anti-HEV antibodies, although the reliability of currently available tests is not high. As a consequence, the frequency of autochthonous hepatitis E in the United States is unknown. However, this disease does oc-

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cur and can have striking clinical features, arising most frequently in older adults and men and sometimes manifested as acute-on-chronic liver failure or characterized by prominent neurologic complications. HEV can also cause chronic infection in immunocompromised persons, which may be progressive and severe but also potentially treatable with antiviral agents.

Hepatitis E research faces many challenges. The replicative cycle, cell-surface receptors, and tissue and species specificity of HEV are poorly understood. Reliable assays for IgG and IgM anti-HEV antibodies and molecular tests for HEV RNA are critically needed. The epidemiology and manner of spread of hepatitis E in developed countries are perplexing and not well described. Finally, approaches to the prevention and treatment of hepatitis E have been developed, but their applicability has yet to be defined. HEV is unlike any other human hepatitis virus, and it has created multiple challenges that have only recently been recognized.

Based in part on a workshop, "Hepatitis E in the United States," held on March 26, 2012, at the National Institutes of Health, Bethesda, MD. (The program book with the agenda, list of speakers, and full abstracts of the presentations is available at www3.niddk
.nih.gov/fund/other/HepE2012/index.htm.)

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