Editorial

The Alphabet Soup of Viral Hepatitis: Is G a New Flavi(or) in the Mix?

VIRAL HEPATITIS in humans has a long past but a short history. Illnesses resembling those produced by hepatitis A and B infections were described in antiquity; clearer references are found in the medical literature of the past two hundred years. Landmark epidemiological and transmission studies, showing beyond doubt the existence of at least two forms ("infectious" and "serum") of hepatitis, were not carried out until the middle of this century.[1] Even then, simple, reliable tests suitable for screening and follow-up of patients at risk did not become available until 1965, when Blumberg, Alter, and Visnich published their seminal—albeit serendipitous—observations of a new antigen.[2] They identified the serum as a novel antigen in an Australian aborigine, in the context of a study focused not on hepatitis, but on genetic polymorphisms of components of human serum. Indeed, Blumberg at first did not believe he had identified a new viral antigen. He later (wisely) modified his views and was awarded the Nobel Prize for Physiology and Medicine for discovering what we now call hepatitis B surface antigen.

Identification of the viral cause of infectious hepatitis, the hepatitis A virus (HAV), followed a few years later, and highly sensitive and specific tests for antibodies to both HAV and HBV are now widely available. Use of these tests in patients with acute or chronic hepatitis showed that there must be at least one other viral cause of hepatitis. In the late 1970s and 1980s, evidence for several candidate "viruses" was presented, but confirmation proved elusive.

It was not until 1989 that the hepatitis C virus was identified, leading to an explosion of new knowledge about this flavivirus that produces relatively mild acute hepatitis (only about one patient in three develops jaundice) but usually leads to chronic infection (~85% of those infected), with evidence of chronic hepatitis (~70–80% of those infected).

The delta agent (HDV) and the hepatitis E virus (HEV) were also described during the past 20 years, and their roles in liver disease have been defined (Table 1). Fortunately, infections with these agents are now relatively rare in the US. HAV, HBV, HCV, HDV, HEV, and other known viruses (such as cytomegalovirus, coxsackie virus, Epstein-Barr virus, and herpes simplex virus [HSV]) clearly are responsible for a substantial majority of acute and chronic hepatitis everywhere in the world. The viruses capable of causing chronic hepatitis and cirrhosis (HBV, HCV, HDV) are the major etiological agents for hepatocellular carcinoma as well.

Even though hepatitis viruses A–E have been identified, it is clear that at least one other viral cause of hepatitis must exist, because patients continue to have clinical illnesses (posttransfusion hepatitis; fulminant hepatic failure; cryptogenic hepatitis and cirrhosis; aplastic anemia following acute hepatitis) that seem to be due to viruses, yet have no evidence for infection with HAV, HBV, HCV, HDV, or HEV.

In this issue of THE WESTERN JOURNAL OF MEDICINE, Cheung, Keeffe, and Greenberg provide a summary of information regarding the "newest kid on the block," hepatitis G or GBV-C.[3*] As summarized in their paper and in Table 1 on the next page, HGV, like HCV, is a positive-stranded RNA virus of the flaviviridae family, independently isolated, cloned, sequenced, and characterized by investigators at Abbott Laboratories and Genelabs. HGV certainly is associated with hepatitis, and many of those infected with the virus become chronic carriers.

However, as also summarized by Cheung et al., there is scant evidence that HGV is an important player causing serious forms of acute hepatitis, and there is no evidence at all that it causes chronic hepatitis, cirrhosis, or hepatocellular carcinoma. Furthermore, chronic infection with this remarkably ubiquitous virus does not appear to affect the course, severity, or outcome of liver disease due to other causes (such as HBV or HCV), although data are few from patients with diverse causes of disease (alcohol, autoimmune causes, metabolic causes). The most striking association to cause concern is that between HGV and aplastic anemia following acute hepatitis.[4–6] Indeed, HGV was first identified and isolated from a patient with aplastic anemia.[4] The two other cases of aplastic anemia and HGV infection described thus far were both in young men who developed severe acute hepatitis followed in 3–5 weeks by pancytopenia.[5,6] Both were found to be HGV RNA–positive by polymerase chain reaction early in their illnesses, before receiving any blood products, and both were negative for HAV, HBV, HCV, EBV, and CMV. One was tested, and found negative, for infection with HEV, coxiella, and leptospira; the other had only IgG antibodies to parvovirus B19, indicating remote infection. Neither had evidence for autoimmune disease or other known causes of hepatitis. Neither patient had serum available from before the onset of illness—unfortunate, but not surprising—and we cannot be sure whether they were already carriers of HGV and developed acute hepatitis from another cause. This is a possibility in view of the high prevalence of HGV RNA–positive people in the general population (1–10%) (see Table 1 of Cheung et al., page 26[3]).

In a careful report that appeared too recently to be included in the review of Cheung et al., the role of HGV in transfusion-associated hepatitis was described.[7] Seventy-nine of 357 recipients of transfusions (22%) at the National Institutes of Health between 1972 and 1995

*See also the Review by Ramsey C. Cheung et al, "Hepatitis G Virus: Is it a Hepatitis Virus?," on pages 23–33 of this issue.

Table 1.—*Summary of Known Major Human Hepatitis Viruses*

Name	Genomic nucleic acid	Size of genome (kb)	Viral family	Major routes of transmission	Cause of chronic hepatitis or cirrhosis	Comments
A	RNA	7.5	Picorna	Fecal-oral	No	Rarely causes fulminant hepatitis
B	DNA	3.2	Hepadna	Parenteral; sexual	Yes (5–10%)	Rarely causes fulminant hepatitis
C	RNA	9.4	Flaviviridae	Parenteral	Yes (70–80%)	Major indication for liver transplantation in the US
D	RNA	1.7	Unclassified	Parenteral	Yes	Requires co-infection with HBV
E	RNA	7.5	Calici- or alpha-like	Fecal-oral	No	Mainly Third World countries; high fatality rate in pregnant women
G	RNA	9.1	Flaviviridae	Parenteral	Unknown	Role in causing liver disease unclear

developed hepatitis. Sixty-three of the 79 (80%) had acute HCV infection, and three had pre-existing HCV. Ten (13%) were infected with unidentified agents, and only three (4%) developed acute HGV infection alone with hepatitis. All three developed mild, anicteric hepatitis with mean peak serum alanine aminotransferase (ALT) 198 U/l, and there was poor correlation between levels of ALT and HGV RNA. Evidence for acute HGV infection occurred with similar frequency in patients who developed acute hepatitis C (5/53), those with minor elevations in ALT (so slight that they did not fulfill criteria for acute hepatitis) (12/100), and those with no evidence of posttransfusion hepatitis whatsoever (14/181) (P = 0.26). (In contrast, out of 157 controls, HGV infection developed in only one patient who was also hospitalized but did not receive transfusions.) Thus, 89% of all acute HGV infections were associated with no or minimal evidence of hepatitis. The authors concluded that "no causal relation between HGV and hepatitis has been established." These results throw additional doubt on the notion that HGV is the cause of aplastic anemia. Perhaps both the severe hepatitis and the anemia that occasionally occur in patients transfused with HGV-positive and HAV-, HBV-, HCV-negative blood are due to another, still uncharacterized, virus or viruses.

HGV clearly is a new flavivirus that infects humans, often chronically, and is associated with acute and chronic hepatitis. The type and severity of hepatitis that it causes (if it does so at all) is so minor as to cast doubt on the appropriateness of its being classified as a hepatitis virus at all. It may have a role in development of aplastic anemia, but in that regard, too, Koch's postulates remain unmet. Current evidence does not support a need to screen all blood products for HGV—a good thing, since no practical screening assay exists. The search for other viral causes of acute and chronic hepatitis, fulminant hepatic failure, cryptogenic cirrhosis, and aplastic anemia must continue. HGV is not the culprit.

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