

A B C D E F G ...

Early this century, two types of acute hepatitis were defined epidemiologically: one characterized by person-to-person transmission, particularly related to poor hygienic conditions; and the other transmitted parenterally, particularly via blood products and shared needles or syringes. Accordingly, the first type was called infectious hepatitis and the second was called serum hepatitis. In the early 1970s, hepatitis A virus (HAV) and hepatitis B virus (HBV) were discovered. HAV is transmitted by the fecal-oral route and can cause outbreaks, whereas HBV is transmitted parenterally, sexually and vertically, and causes sporadic disease. It was initially believed that the discovery of these two agents solved the hepatitis puzzle. In the mid-1970s when serological testing for both HAV and HBV become available it was immediately evident that a substantial portion of cases of acute hepatitis were due to neither HAV nor HBV and thus the term non-A, non-B (NANB) hepatitis was coined.

Subsequently, a number of researchers took interest in NANB hepatitis. It was once again noted that there were at least two epidemiological types of NANB hepatitis: a fecal-oral type (NANB, like A) and a parenteral type (NANB, like B). In the late 1980s, two new viruses were discovered: hepatitis C virus (HCV) and hepatitis E virus (HEV). HCV has been shown to be responsible for over 90% of cases of transfusion-associated NANB hepatitis (1) and HEV causes sporadic and epidemic NANB hepatitis in third-world countries and is somewhat distinct in being particularly virulent in pregnant women (2).

However, the hepatitis alphabet continues to evolve. After the discovery of HCV and HEV, approximately 10% to 20% of cases of acute hepatitis are still due to none of HAV, HBV ± hepatitis D virus, HCV, HEV, Epstein-Barr virus or cytomegalovirus (3,4). Such cases of hepatitis have been referred to as non-A-E hepatitis and, once again, both parenteral and enteral forms are recognized.

In the past two years, at least one enteral and three parenteral non-A-E hepatitis viruses have been described, two of which are referred to as hepatitis F virus (HFV) and hepatitis G virus (HGV).

HEPATITIS F

Isolated cases of nonparenterally acquired non-A-E hepatitis have been reported from western Europe, the United States and India. In several of these outbreaks, virus-like particles were observed in stool samples by electron microscopy. Researchers at the National Institute of Immunology in New

Delhi have been able to passage the fecally excreted non-A-E virus serially in rhesus monkeys by intravenous injection (3,4). Infected monkeys demonstrate histological hepatitis and are immune to reinfection. The feces of infected humans and monkeys contain 27 to 37 nm viral particles that consist of double-stranded DNA of approximately 20 kb (4). This agent is now called HFV and it is substantially different from HAV and HEV, both of which consist of single-stranded RNA of approximately 7.5 kb.

The epidemiology of HFV is not yet determined. In a small study, six of 10 stool samples from cases of sporadic NANB hepatitis were positive for HFV compared with four of 10 that were positive for HEV (4). No serological test is available for the diagnosis of HFV, but electron microscopy of stool may be useful in cases of acute hepatitis in whom the etiology of the hepatitis is not determined by testing for other viruses.

HEPATITIS G

In the mid-1960s, Deinhardt and colleagues (5) were the first to demonstrate the transmission of human viral hepatitis in nonhuman primates. Specifically, these researchers worked with tamarins, also known as marmosets, a South American squirrel-like monkey. In one of their experiments, they demonstrated that serum collected during the third day of jaundice from a 34-year-old surgeon with the initials GB produced hepatitis in the tamarin that could be serially passaged. Subsequently, the putative agent(s) contained in this inoculum has been referred to as the 'GB agent'. A variety of experiments in different primates as well as cross-challenge experiments indicated that the GB agent was distinct from the human hepatitis viruses A to E (6).

A team of researchers at the Virus Discovery Group at Abbott Laboratories in North Chicago recently unravelled the GB mystery. Their work was made possible by a novel polymerase chain reaction (PCR) technique referred to as representational difference analysis (RDA), which amplifies unique DNA sequences present in one source (called the tester) that are absent in a highly related source (called the driver). It is hypothesized that the only qualitative nucleic acid difference between pre-inoculation plasma and infectious plasma from a GB-infected monkey is the presence of the GB-agent genome. Therefore, RDA of infectious plasma from a GB-inoculated monkey (tester) and pre-inoculation plasma (driver) from the same monkey was postulated to amplify segments of the GB-agent genome. This technique revealed the presence of two flavivirus-like genomes with positive sense RNA of approxi-

mately 10 kb (7). These two agents were called GB virus A (GBV-A) and GB virus B (GBV-B). The existence of two viruses in the GB inoculum is supported by studies demonstrating that the two RNA species can be filtered, diluted and passaged separately in tamarins. It is of interest that only GBV-B inoculation in tamarins results in elevation of liver enzymes, antibody production and protection from reinfection, whereas infection with GBV-A does not result in elevated liver enzymes, antibody production or protection from reinfection (8). Studies of the open reading frames demonstrated that GBV-A and GBV-B exhibit approximately 27% amino acid sequence identity to each other and 28% identity to HCV type 1 (9). Thus, GBV-A and GBV-B each represent new genera within the *Flaviviridae* family. Subsequently, the same group of researchers isolated a novel virus from the serum of several patients with non-A-E hepatitis (10). This agent had a high degree of identity with GBV-A (59% at the nucleotide level and 64% at the amino acid level) and thus this virus was termed GBV-C (10). Genetic analyses have demonstrated that GBV-C is an additional member of the *Flaviviridae*, distinct from GBV-A, GBV-B and HCV, but it is more closely related to GBV-A than to either GBV-B or HCV (11).

In January 1996, Linnen et al (12) independently described a virus isolated from the plasma of a patient with chronic hepatitis, which they called HGV. Analysis of the polyprotein sequences of HGV compared with those of GBV-C show 95% amino acid sequence identity and thus these two viruses are considered to be independent isolates of the same virus (13). Although the official name of this virus has not been established by the Committee on Viral Taxonomy and Nomenclature, it is likely that it will be called HGV.

Limited data regarding the epidemiology of HGV are available. Among 769 consecutively screened American volunteer blood donors with normal alanine aminotransferase (ALT) values, 13 (1.7%) were HGV-RNA-positive by PCR (12). Among 709 individuals excluded from donation because of an ALT level exceeding 45 IU/mL, 1.5% were HGV-RNA-positive (12). HCV and HGV co-infection may be relatively common. Of 107 patients with acute hepatitis C, 19 (18%) were also HGV-RNA-positive (12). Several cases of prospectively studied post-transfusion hepatitis in which hepatitis A-E had been excluded were found to be HGV-RNA-positive (12, 14).

It has been noted by several groups that HCV is rarely implicated in fulminant hepatitis. In a small study of six patients from Japan, three patients with fulminant non-A-E hepatitis were found to be GBV-C (HGV) RNA-positive (14).

WHERE ARE WE HEADED?

At least two new causes of viral hepatitis in humans have been identified: HFV and HGV. The role of GBV-A and GBV-B in human disease is less well defined. Seroprevalence studies for HGV are underway. Given that the seroprevalence of HGV in 1478 volunteer blood donors in the United States was similar to that of HCV, it seems likely that HGV serological testing will be incorporated into blood banking and organ donation programs once a reliable screening test that is suit-

able for large numbers of samples, such as an enzyme immunoassay, is available. As with HCV testing of donated blood, this will add to both the safety and the cost of the blood transfusion system, but is undoubtedly more useful than the recent decision to add human immunodeficiency virus p24 antigen testing, which was based more on public relations than on science.

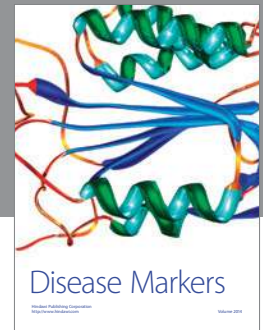
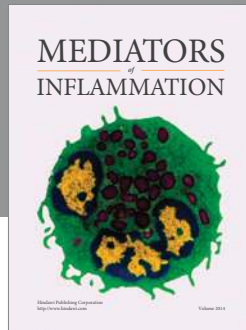
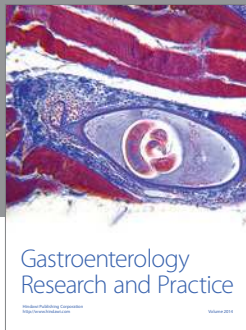
The availability of HGV diagnostics will also aid in the diagnosis of individual cases of hepatitis. We will also need to assess the recurrence rate of HGV in individuals who undergo liver transplantation following HGV infection in order to learn whether transplantation is appropriate in this setting. Preliminary evidence from the somewhat related flavivirus HCV suggests that transplantation may well be appropriate (15).

These are exciting times in the field of viral hepatitis. Thank goodness the alphabet has 26 letters.

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SD Shafran MD FRCP
Edmonton, Alberta
JM Conly MD FRCP
Toronto, Ontario



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