Editorial

HEPATITIS C VIRUS: WHERE IS IT LEADING US?

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In the alphabet of the hepatitis viruses, hepatitis C virus (HCV) is evoking considerable interest. Hepatitis A (HAV) and hepatitis B (HBV) viruses were visualized in 1973 and 1965 respectively. The study of these viruses was facilitated by the presence of high titer anti-viral antibodies in infected patients' sera or secretions, and the identification of virus-specific antigens in the case of HBV. An understanding of their replication cycle was made possible by studies using nonprimate animal models and in vitro infectious systems [1]. HCV, in comparison to other hepatitis viruses, has been an elusive infectious agent with difficulty in its identification, characterization, and visualization. Limitations in our knowledge of HCV structure can be attributed, to a great extent, to the presence of HCV in very low titers in infected tissue and sera, the lack of convenient models of HCV infection, and the absence of an in vitro replication system. However, molecular approaches, and impressive efforts by many investigators, led to its identification in 1989, representing a major success in the application of cloning techniques in the identification of new infectious agents [2].

HCV contains a positive-sense RNA genome approximately 10,000 bases in length. In overall genome organization it is very similar to members of the *Flaviviridae* family particularly in the coding for a single polyprotein that is then cleaved into a series of structural proteins (nucleocapsid protein, two membrane glycoproteins) and non-structural proteins, with presumed enzymatic role in virus replication [3]. HCV is currently considered as a separate genus within the *Flaviviridae*, a

group that contains the insect- and tick-borne flavivirus as its prototype genus, and includes the pestiviruses.

Interest in HCV has emerged because of its role as a major etiological agent in post-transfusion hepatitis and its ability to establish chronic infection and progressive disease in a large proportion of those exposed. Chronic hepatitis develops in 60 per cent or more of individuals after acute HCV infection. Based on clinical and biochemical follow-up, an estimated 50 per cent of cases of chronic hepatitis C have nonprogressive disease while the other half have insidiously progress to cirrhosis [4,5]. The mechanism for HCV persistence remains uncertain; most explanations are based on the concept of "immune escape" in which rapid change in envelope proteins alters the antigenicity of the outer viral surface sufficiently to avoid neutralization by the host's humoral immune system.

An association of this hepatotropic virus with hepatocellular carcinoma (HCC) has also been noted. In Japanese patients with transfusion-acquired chronic hepatitis C and cirrhosis there has been a marked increase in mortality from HCC [6]. HCC, a major cause of cancer related morbidity and mortality in many parts of the world, shows marked regional variation in incidence and natural history which is believed to be related in part to viral epidemiology. Although it is clear that HCV infection and HCC are strongly related the mechanism by which this virus causes HCC is speculative.

The diagnosis of hepatitis C is based on the

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detection of anti-HCV antibodies or the presence of HCV RNA in the serum. Successful molecular cloning of the genome of HCV has resulted in detailed analysis of the sequence and organization of the virus genome and expression of recombinant HCV antigens for use in diagnostic immunoassays. In the first generation immunoassays a portion of the nonstructural protein NS4 (termed C 100-3) was used as a target antigen to detect anti-HCV antibodies. However this assay showed a high level of nonspecificity and failed to detect anti-HCV in a number of infectious blood donor [7]. Later generation tests have used NS3 (C33) as well as core proteins (C22) in addition to C 100-3. In the third generation HCV enzyme immunoassays, wells are coated with synthetic peptides from core, NS3, NS4 and NS5 regions. PCR is also used for identification of HCV RNA in blood and other tissues.

In this context, the paper on page 3 of this issue of the journal is instructive. Ohri and colleagues applied a third generation recombinant immunoblot assay test system for anti-HCV testing [8]. Most of the earlier studies from our country have used a second generation test, by which positivity for anti-HCV is lower as compared to third generation tests. The anti-HCV positivity determined in the control population was 2.33 per cent. Although this is higher than that reported from other countries significantly, the anti-HCV prevalence in our patient population is also higher.

In order to develop a sound strategy against HCV infection in our country, it is important to

know the current status and the behaviour of HCV infection in our population. We also need to know more about the natural history of chronic hepatitis C and the clinical significance of finding anti-HCV in otherwise healthy individuals.

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