

# VECTOR

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## SCREENING FOR HEPATITIS C

Some countries, including the USA, already screen blood donors for Hepatitis C. This test is being introduced to the UK. Dr John Barbara assesses the implications.

**H**epatitis C was first discovered in 1989 and its clinical significance is now becoming clearer.

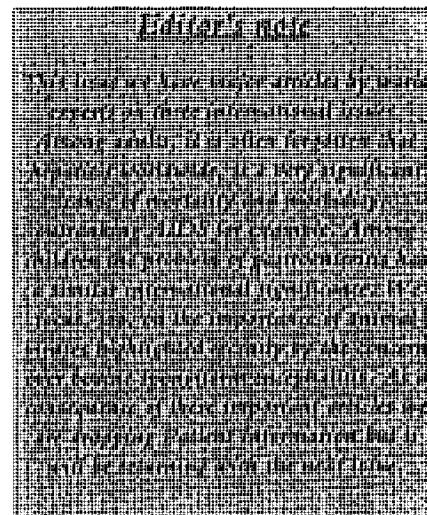
For many years a relatively common form of viral hepatitis could only be diagnosed by exclusion of hepatitis A and hepatitis B viruses. It was therefore known by the accurate but rather clumsy name 'non-A, non-B hepatitis' or NANBH for short. In 1989 after more than a decade of vain attempts to devise tests for identification of this virus (or

viruses), the scientific world - with natural scepticism at first - learned of the cloning of an antigen of hepatitis C virus (HCV)<sup>1</sup>, probably the major cause of NANBH. This major achievement extended the already growing 'hepatitis alphabet' of viral hepatitis (Table 1).

Once a viral antigen had been cloned, an assay to detect antibody to that antigen (anti-HCV) could be developed<sup>2</sup>. In persistent infections, detection of antibody does not necessarily reflect immunity, but may indicate continuing infectivity. Most transfusion-transmissible infections are, therefore, detected by appropriate antibody screening.

### How prevalent is HCV?

The first international symposium



on the newly discovered HCV (which has, however, still not been isolated or even verifiably visualised in the electron microscope) was held in Rome in 1989<sup>3</sup>. Prevalence of reactivity in blood donors (as detected by

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The Hepatitis Alphabet	
Type	Description
Hepatitis A HAV	Faecal-oral infectious hepatitis
Hepatitis B HBV	Serum hepatitis
Hepatitis C HCV	Principal or only cause of NANBH
Hepatitis D HDV	The defective delta agent (requires HBV a helper virus)
Hepatitis E HEV	Epidemic/enteric form of hepatitis
Hepatitis F	Possible minor cause of NANBH

Table 1.

ELISA) ranged from 0.2% to 2% in different parts of Europe and the USA, and the virus was shown to be prevalent worldwide. Rates in parts of Africa were higher, but the extent of false-positivity due to high serum levels of IgG (e.g. due to parasitic infestation) is unclear although likely to be very high. Despite indications from supplementary testing that up to 3/4 of ELISA reactive sera may be false-positive, the virus is obviously prevalent worldwide.

NANBH is characterised by the asymptomatic nature of the acute phase in most infections. Classically it was recognised in prospective studies in recipients of blood transfusion by detection of defined elevations in serum alanine aminotransferase (ALT), as an index of liver damage. The rate of post-transfusion hepatitis (PTH) in recipients of blood and blood components ranged from 2% in the UK to 20% in Japan. In the USA, 90% of PTH was subclinical and only detectable by estimation of ALT levels in the recipient. Naturally, a firm diagnosis of non-A, non-B viral hepatitis was often open to question and specific assays were constantly but until now, unsuccessfully sought.

Using the first generation anti-HCV assay in a recent prospective study of PTM in North London, HCV seroconversion associated with PT-NANBH only occurred in 0.25% of transfusion recipients<sup>4</sup>.

#### Chronic liver disease

The incubation period of NANBH varies from a few weeks to up to 4 months. Although the acute infection is mild or inapparent, 50% of individuals may progress to chronic liver disease, 10% of whom may develop cirrhosis which may even lead to primary hepatocellular carcinoma in some cases. Haemophilia patients who received untreated pooled clotting factor concentrates (derived from plasma from up to 20,000 donors) invariably showed liver function

Artist's impression of the Hepatitis C virus.

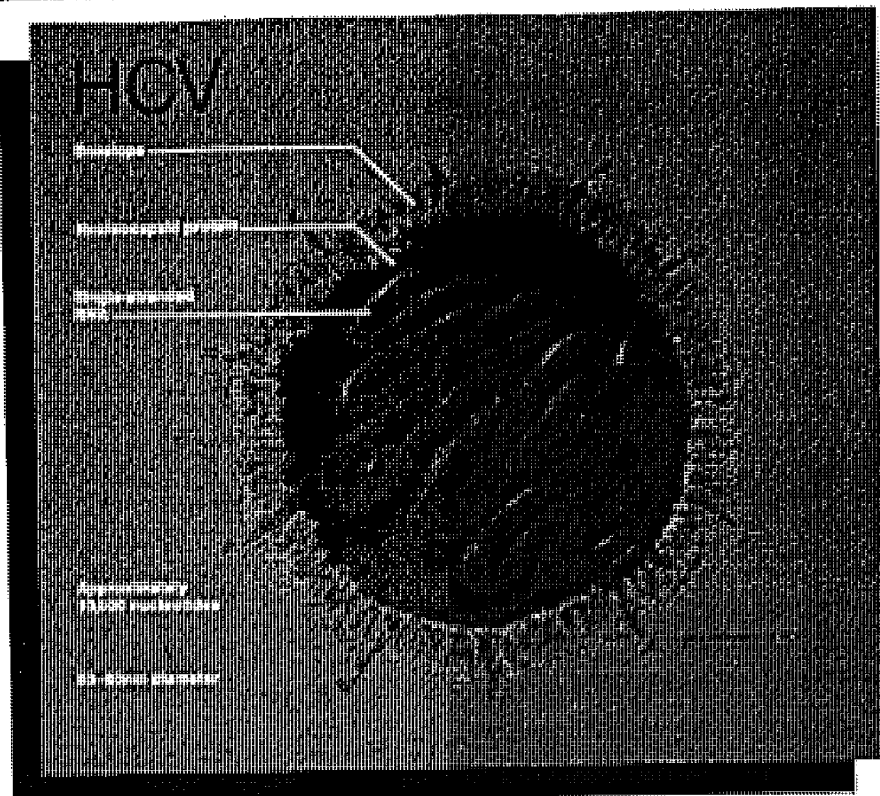
evidence of NANBH infection. Sporadic NANBH has also been reported in untransfused individuals but follow up studies are not as extensive as for PT; clinical cases (the minority) therefore underestimate the extent of NANBH in the community.

The concern as regards the safety of the blood supply is therefore of chronic liver disease (CLD) associated with transfusion. Little research data on this topic is available, but in the UK, Wood *et al*<sup>5</sup> failed to find a significant association between CLD and a history of blood transfusion. More data is required before the morbidity due to NANBH following transfusion in the UK are validated.

NANBH has long been recognised as a persistent infection because the extent of PTH suggests a relatively high carrier rate in blood donors and because sera taken from individuals at long intervals show continuing infectivity for humans<sup>6</sup> and chimpanzees. This persistence of NANBH, with the often asymptomatic nature of the infection, explains why it can be

transmitted by transfusion. It is noteworthy that the rate of PTH has fallen in the USA<sup>7</sup> and Canada following the exclusion of donors at risk of contracting HIV infection.

The high risk of NANBH from earlier clotting factor concentrates is reflected in the 60 to 80% prevalence of anti-HCV worldwide in haemophilia patients who have been treated with commercial Factor VIII. This high HCV prevalence made patients receiving heat treated British Factor VIII (Factor VIII Y) an ideal group in which to validate both the heat treatment and the anti-HCV assay, at the same time. Skidmore *et al*<sup>8</sup> showed that haemophiliacs who had exclusively received Factor VIII Y were HCV seronegative, whereas those receiving uninactivated material were uniformly seropositive. Similar results have since been reported elsewhere. Although this indicates the safety of suitably treated Factor VIII and shows that the test is genuinely detecting anti-HCV, it tells us nothing about the predictive value of the assay in low-prevalence populations.



Haemodialysis patients also show increased prevalence of anti-HCV. The extent varies around the world<sup>9</sup> and is possibly related to the stringency of measures to exclude HBV. Higher than background prevalence of anti-HCV, reminiscent of those for HBV, have been reported in mentally handicapped patients. Unlike HBV however, HCV does not appear to be sexually transmitted to any great extent<sup>3</sup>, although the evidence is conflicting and a low level of transmission cannot be excluded.

Further evidence for lack of sexual transmission comes from a Danish study of a group of homosexual men<sup>10</sup>. During several years of follow-up, HBV and HIV seroconversions were noted, in the absence of significant HCV infection. In contrast, intravenous drug (IVD) use has been overwhelmingly incriminated as a mode of HCV transmission, with sero-prevalences as high as 80% or more in IVD users.

#### Where will the assay be used?

In the UK screening for anti-HCV is being introduced this autumn. As yet, the methods for confirming reactivity and differentiating 'infectious' from 'immune' seropositive donors are still experimental and expensive. Indeed donor reinstatement may be difficult in the absence of a range of markers, since fluctuating infectivity may be common at least in certain seropositive individuals.

One approach to predicting the infectivity of an HCV seropositive donor utilises the polymerase chain reaction (PCR). In this test, a sequence of the genome of a virus is made detectable by amplifying the number of copies of that viral sequence in the sample<sup>8</sup>. This is achieved by using a heat stable DNA polymerase enzyme mixed with excess DNA nucleotides and the appropriate oligonucleotide primers that flank the sequence to be amplified. The test is potentially

sensitive enough to detect a single genome (and hence the presence of virus) in a sample.

Areas of uncertainty for diagnostic laboratories, counsellors and general practitioners still remain, although in individuals at high risk of infection (eg. IVD users) and in patients suffering from hepatitis, the screening test and the growing number of supplementary assays are increasingly clarifying the situation.

Although the patent situation may require resolution, new assays based on synthetic peptides, in addition to the improved tests from Ortho and Abbott, are appearing on the market. Because of these new assays, together with advances in molecular biological techniques to increase sensitivity and detection of the full range of HCV strains by PCR,<sup>8,11</sup> the extent of false-negativity in screening assays can now be more accurately assessed.

#### The significance of anti-HCV screening for GP's

In the UK, approximately 1 in 1500 previously untested blood donors are likely to be capable of transmitting HCV by transfusion<sup>4</sup>. With approximately one million donors tested in the first six months of screening, GP's must expect notification by the Transfusion Service of an appreciable number of HCV carriers for referral to hepatologists where appropriate. The number of carriers will, however, fall as the donor panel is screened. Hepatitis C screening in UK Transfusion Services is likely to cost £8 million per annum, largely due to the current high prices for reagents. Despite the high cost, no additional central funding has been made available to cover the screening test or the associated activities of counselling donors and performing assessments of liver function in those identified as possible carriers. The necessary funding will therefore, have to be found from existing resources.



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