



HEPATITIS C — PROGRESS AT LAST

The term "non-A non-B hepatitis" was coined to describe cases of hepatitis which gave negative results in tests for hepatitis A and B and the other known viruses that affect the liver. It was recognised by the mid-70s that most post-transfusion hepatitis falls into this category and that the infection is also common in intravenous drug users.

Transmission of the disease was achieved by inoculating chimpanzees but conventional viral cultures and serological tests failed to identify the agent.

Hepatitis diagnosis and control have taken a great step forward with recent cloning of this elusive non-A non-B (NANB) hepatitis virus and the development of an assay which can be used to detect infected individuals.

A group of scientists from the Chiron Corporation in the United States applied recombinant DNA techniques to extract and clone the nucleic acid from a large pool of infectious chimpanzee plasma derived from the experiments which first demonstrated that NANB hepatitis was indeed caused by a virus.

This was followed by further molecular work which showed that the clone hybridises with RNA but not DNA in liver and serum from infected animals (confirming that the NANB agent must be an RNA virus) and does not react with uninfected human or chimpanzee controls. The best guess is that the new agent is probably similar to the flaviviruses (a group including yellow fever, and related to Ross River fever and Murray Valley encephalitis) because of its RNA and its size and sensitivity to organic solvents.

Chiron has managed to express a protein derived from its ("C-100") DNA clone, and has licensed this material to two well-known manufacturers of diagnostic kits whose first tests are now available. When serial samples from 20 patients who acquired post-transfusion NANB hepatitis were tested in an American series, 18 showed seroconversion.

As this particular panel from the National Institute of Health blood bank has been the downfall of many previous NANB tests, the results give powerful support to the company's claims. Most hepatitis scientists have readily translated NANB hepatitis as hepatitis C and the old name is fast disappearing from the literature.

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Correspondence

Please address all correspondence and potential contributions to:

The Editor,
NSW Public Health Bulletin,
Public Health Division,
Department of Health, NSW
Locked Bag
P.O. Box 961,
North Sydney NSW 2059
Telephone: (02) 391 9219
Facsimile: (02) 391 9293

Hepatitis C — Progress at Last

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The new test measures antibody against a viral protein which appears to be derived from a non-structural part of a genome — it is not part of the virus particle but is an enzyme needed for the growth of the virus inside the infected cell. It is perhaps not surprising that this test should have some serious limitations. First, the antibody measured by the current method rises rather slowly and seroconversion was delayed — on average anti-HCV appeared 15 weeks after the onset of hepatitis. This limits its diagnostic power at the time the patient presents with clinical illness.

Persistence of the antibody is also variable. Only 60 to 80 per cent of patients believed to have chronic hepatitis C have tested positive in reported studies. Preliminary analysis of tests on donated blood suggests that continuing viraemia may persist in the face of C-100 antibody production.

It is reasonable to expect that both the specificity and sensitivity of the tests will be greatly improved by future work, particularly if the glycoproteins of the viral envelope can be used as antigens. At present a high proportion of low-level and false positive results are encountered and better confirmatory tests are urgently needed.

What can be done with the test we now have? Blood banks throughout the world are introducing the new screening test for donated blood to supplement or replace other measures such as testing for elevated ALT levels or for anti-hepatitis B core antibody. The availability of a specific HCV test will make it possible to verify the different opinions about the significance of post-transfusion hepatitis for both donor and recipient.

On one hand there is much evidence that hepatitis after transfusion is usually mild or asymptomatic, and chronic liver disease has not been recognised as a major problem in poly-transfused patients in the past. However liver biopsy studies in patients with persistent slight serum alanine transferase elevation show disturbing features of cirrhosis. Even the prevalence of hepatitis in recipients of banked blood in different prospective studies has varied from as low as 2 to 40 per cent or even higher.

Reassessments in the light of anti-HCV testing have begun to appear. A study from the Netherlands transfusion service clearly shows the value of anti-HCV testing for identification of infectious donors but suggests that only high antibody levels reliably predict infectivity. As it stands, the test cannot provide the final answer to the problem since only about half the suspect clinical cases in the Dutch series were anti-HCV positive, and two of the nine hepatitis C cases had not received an antibody positive donation.

More recently an English group using a sensitive method for detecting the HCV genome using the polymerase chain reaction (PCR), found that only one in six of HCV antibody positive donors was positive on this indicator of viraemia. These results correlated well with the transmission of the disease to recipients.

Studies reporting the prevalence of anti-HCV in blood donors from around the world show remarkably consistent results ranging from about 0.25 to 2 per cent in different countries. This is in contrast to the much greater geographic variation known for hepatitis B and to the variation in the risk of post-transfusion hepatitis found in different areas.

Results of testing of groups with a high risk of blood-borne infections show hepatitis C infection rates of 65 to 80 per cent in intravenous drug users and haemophiliacs, 20 per cent in haemodialysis patients, and 8 per cent in homosexual men. These results suggest the epidemiological pattern of hepatitis C infection is different to that of hepatitis B and human immunodeficiency virus.

Investigation of patients identified as having "cryptogenic" chronic liver disease has revealed that a high proportion are anti-HCV positive, although many lack a history of blood transfusion. This hepatitis C group responds well to treatment with interferon, though the disease usually returns when treatment is stopped.

Until the natural routes of transmission are elucidated it will be difficult to advise either patients or blood donors with positive results in the first-generation tests about their risks of transmitting hepatitis to their contacts or about the likely consequences for their own health.

Nevertheless, the long impasse in understanding this disease has been overcome and rapid progress should follow.

Yvonne Cossart

Professor,

Department of Infectious Disease

University of Sydney

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EDITORIAL COMMENT

An expert committee with representatives from the Red Cross Blood Transfusion Service, gastroenterologists, infectious disease specialists, drug and alcohol workers and the NSW Health Department will report on the epidemiology of hepatitis C in NSW and develop a strategy to reduce transmission of the disease.