Netherlands
The Journal of Medicine

EDITORIAL

Hepatitis C: many small steps

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Surprisingly few researchers have managed to produce an electron micrograph of hepatitis C virus (HCV).[1,2] Of course, we do not doubt the existence of HCV. The discovery of HCV was a milestone for molecular biology and virology. For the first time, the application of molecular genetic techniques led to the discovery and description of a human pathogen. In the late 1980s Houghton and colleagues studied plasma of a chimpanzee, highly infectious for 'non-A, non-B hepatitis'. Applying blind expression cloning of a cDNA library, obtained from the chimpanzee plasma, the '5-1-1' protein was obtained, which was recognised by antibodies of a well-characterised chronic non-A, non-B hepatitis patient.[3,4] The recognition of non-A, non-B hepatitis in clinical practice predates the discovery of its cause by many years.[5] It has been estimated that in the 1960s, one in five patients receiving blood transfusions in the USA acquired non-A, non-B hepatitis.[6] The Nixon administration improved this situation markedly by promoting the collection of blood among unpaid volunteers, instead of using prisoners and paid donors as the source of blood. Following the identification of HCV, assays were developed for the detection of HCV antibodies and HCV RNA, enabling the diagnosis of hepatitis C in patients and the screening of blood donors. Nevertheless, the diagnosis of acute hepatitis C remains tricky because specific antibodies may still be absent in a recently infected patient. The diagnosis of acute recent hepatitis C must be based on detection of HCV RNA. Regarding the safety of blood transfusion in the Netherlands, the screening of each blood donation for both HCV antibodies and HCV RNA has decreased the risk of transmission of HCV to less than 1 per 10 million donations.[7]

What is the global burden of HCV? The World Health Organisation estimates 170 million persons to be chronically infected with HCV. For comparison: 450 million persons are thought to carry hepatitis B virus. Locally the HCV/HBV ratio may be different. In Amsterdam, random sampling of the population enabled Baaten and colleagues to calculate the number of Amsterdam citizens chronically infected with HCV or HBV to be 3709 and 2453 respectively.[8] You may grow old without knowing you are infected with HCV, but guidelines agree that treatment of HCV infection must be considered for each HCV-infected person.[9,10] In the long run a significant but poorly defined number of patients will develop significant liver disease: intermittent or chronic hepatitis; and cirrhosis in 5 to 25% of patients over a period of 25 to 30 years. Subsequently, HCV-induced cirrhosis introduces the risk for hepatic decompensation (in 30% over 10 years) and hepatocellular carcinoma (in 1 to 3% per year).[10] In this issue of *The Netherlands Journal of Medicine,* Vlaar and colleagues describe that HCV-associated malignancy is not limited to hepatocellular carcinoma: HCV may induce cholangiocellular carcinoma or B-cell lymphoma.[11] They warn to be aware of HCV-associated B-cell lymphoma, especially when patients have HCV-associated mixed cryoglobulinaemia and incomprehensibly high serum levels of lactate dehydrogenase.

Several studies demonstrate that hepatitis C is not a sexually transmitted disease (STD).[12,13] As an exception to this rule, HCV has recently become an STD among HIV-infected men having sex with other HIV-infected men. Transmission of HCV during birth or via breast feeding is rare. Arthropod-borne transmission of HCV and an animal reservoir have not been found. How then is it possible that HCV maintains its existence as a human pathogen? We must conclude that HCV solely depends on parenteral blood-borne transmission between humans. This is less odd than it seems. World-wide, native tribes perform body piercing and ritual or beautifying tattooing and scarification. This practice is old: over 50 tattoos were observed on Ötzi the iceman, whose mummified body was found 5300 years after his death, in a glacier on the border between Austria and Italy. In the 20th century the popularity of tattooing probably waned. Luckily for HCV, three very efficient parenteral ways of transmission took over: the wide spread use of blood transfusion and

blood products; intravenous drug abuse; and insufficient sterilisation of medical equipment. When donor screening for HCV was introduced in the Netherlands in 1991, over 200 regular donors were found to carry HCV. During many decades this cohort of donors must have infected thousands of patients, especially via pooled blood products such as clotting factor. It appeared that in 1991 all haemophilia patients had already been infected with HCV. The consequences of the historical and ongoing use of unsterile medical equipment cannot be underestimated. Attributed to this cause, currently 9.8% of Egyptians are chronically infected with HCV.[14]

Hepatitis C is not only an outlier regarding its discovery and transmission, it is the only major chronic virus infection that can be cured. Modern antiviral treatment, based on the daily oral administration of ribavirin and weekly subcutaneous injection of pegylated interferon, results in a cure rate of 50% in patients infected with HCV genotype 1 or 4, and 80% in patients infected with HCV genotype 2 or 3.[9] This success was obtained via small, incremental improvements in the antiviral regimen for HCV. In the early 1990s, HCV therapy consisted of the injection of interferon 3 MU, three times a week, for 48 weeks. This regimen caused sustained response in only 9% of genotype 1 infections and in 30% of genotype 2 or 3 infection. Ribavirin as monotherapy for HCV has no effect on HCV replication, but added to interferon (since 1998) it is synergistic, with clearance of HCV in 30 and 60% of cases, respectively. Since 2002 interferon has been replaced by a pegylated form of interferon which shows increased blood levels over a longer period of time, and thus can be injected once per week. Notwithstanding this success, we still do not know what we are doing: the mechanism of action of interferon and ribavirin in curing HCV remains unknown.[15] Interferon obviously 'modulates the immune response' while ribavirin may 'push HCV over the mutation threshold'.

In this issue of *The Netherlands Journal of Medicine*, Gevers and colleagues introduce an additional step in the gradual improvement of HCV therapy.[16] They report that HCV genotype 1 infected patients, with a slow response to peginterferon plus ribavirin treatment, benefit from a prolonged treatment of 72 instead of 48 weeks. This improved regimen may be short-lived. In the course of 2011 the registration of two HCV protease inhibitors (telaprevir and boceprevir) is foreseen. For HCV genotype 1 infection, triple therapy consisting of peginterferon plus ribavirin plus telaprevir or boceprevir is expected to boost the cure rate, while at the same time the duration of treatment may be decreased.

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