

Viral Hepatitis—The Silent Killer

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Unraveling the disease of hepatitis was like a Sherlock Holmes mystery as physicians throughout the last century searched for the identity of these silent killers involved in endemic and epidemic diseases afflicting millions of persons. Hepatitis, a silent and mysterious killer for many centuries, is derived from the Greek word, ‘hepa’ (liver) and ‘itis’ (inflammation).

Hippocrates (460 to 375 BC) had already described the clinical features of epidemic jaundice, which remains the same today. His description of fulminant hepatitis was both very dramatic and accurate... “The bile contained in the liver is full of phlegm and blood, and erupts (out of the liver). After such an eruption, the patient soon raves, becomes angry, talks nonsense and barks like a dog. Most patients die within the space of eleven days ...” He recommended a special diet of ‘melikraton’ which is honey and water, which is still an acceptable advice today. Interestingly, Hippocrates also suggested the concept of immunisation but he had little idea of the true cause then.

The Napoleonic Wars, American War of Independence, Dardanelles and Gallipoli campaign in 1915, and World War I and II, killed thousands of troops from infectious jaundice.¹

There are animal and human hepatitis viruses. Both produce the same pathogenic disease as the humans. The human hepatitis viruses are important human pathogens, and are a major public health problem in many parts of the world. They affect both the rich and the poor, killing many millions annually by their acute or the end stage of their chronic diseases. At least 2 of the hepatitis viruses are responsible for human liver cirrhosis and primary hepatocellular carcinoma (PHC), one of the leading cancers in the world and the third highest in the Asia Pacific region. They are Hepatitis B (HBV) and Hepatitis C viruses (HCV). Both incur high cost of health care and cause serious morbidity and even death. However, they are not identical. Molecular science has identified them as a DNA Virus (HBV) and RNA Virus (HCV)

Early pioneering studies in 1943 by Dible,² using needle biopsy, led to the histological diagnosis of acute hepatitis. Gutzeit, a German pathologist went further and showed the progression from acute hepatitis to liver cirrhosis. He estimated that about 10 million persons, both in the

German forces and in the rest of the population developed hepatitis in World War II. Human experiments conducted in the name of medical science were carried out by Nazi Germans on allied prisoners of World War II. Prisoners of war were injected with hepatitis infected blood. Other human guinea pigs were made to drink infected urine and duodenal juices. Major Havens in the Australian Medical Corp and 2 medical colleagues from Yale, Paul and van Rooyen³ reported in 1945 experimental transmission of hepatitis to humans, and cited the work of Voegt in 1942, Germany, who had fed 4 volunteers with the duodenal juices of 2 patients in the later stage of infectious jaundice and thus, caused jaundice in the recipients. Voegt’s work was incomplete, but Voegt also claimed to have induced jaundice by inoculating human infected serum, the drinking of urine and injection of haemolysed red blood cells. Outbreaks of hepatitis also occurred in British troops in Palestine.

The first evidence of parental transmission of hepatitis was in 1987 when Seef⁴ showed that in 1942, 50,000 servicemen in United States (US) were infected with what appeared to be HBV and had developed antibodies to it. This occurred in the troops receiving yellow fever vaccine. In Brazil, England and US, some individuals who had received convalescent mumps sera, yellow fever vaccine, or transfused blood also developed hepatitis.

Significant human experiments were done by Saul Krugman⁵ in 1967 in the outbreak of 2 types of hepatitis at a mentally retarded home at Willebrook Sate School in New York. The first was the typical infectious hepatitis with an incubation period of 30 to 38 days, and the second resembled serum hepatitis with a longer incubation period of 41 to 108 days. These studies cannot be repeated today.

The breakthrough in molecular science by Crick and Watson on the structure of DNA in Cambridge, England, won them the Nobel Prize for Medicine and Physiology. This opened up a Pandora’s box of the molecular science of hepatitis viruses, characterising them into molecular types and the functions of their genes. These discoveries subsequently led to the development of designer vaccines and antiviral drugs targeted at the functioning genes which amplified the viruses.

But it was Baruch Blumberg,⁶ a physician scientist at

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Fox Chase Cancer Center, Philadelphia, US, using the immune-electrophoretic test to detect alpha globulin, discovered the specific immunoreactive proteins against the sera of Australia aborigines, which he called the “Australia Antigen”. Keenly interested in anthropology, he travelled to many countries, and collected sera, from individuals in Cebu, Peru, Rogenlap Atoll, Southeast Asia, and the Mediterranean region, and they showed the presence of the Australia Antigen.

In 1976, Blumberg⁶ was awarded the Nobel Prize for Medicine and Physiology for his discovery of new mechanisms for the detection of dissemination of infectious diseases. He later went on to develop diagnostic tests and a vaccine for Hepatitis B, and Merck, Sharpe and Dohme was the manufacturer of these vaccines in the US.

In 1972, the World Health Organization (WHO) classified the Hepatitis viruses into Hepatitis A (HAV), and Hepatitis B (HBV). HAV was transmitted orally, and HBV was a parental transmission which was more serious as it was associated with liver cirrhosis and primary hepatocellular carcinoma (PHC). PHC was then the leading cancer cause of death in many Asian and Southeast Asian countries and one of the top 3 cancers in the Asia Pacific region and eighth⁶ in the world. WHO estimated in 1975 that of 300 million carriers of HBV, 180 million were in the Asia Pacific region.

The WHO Western Pacific Regional Office was a pioneer in taking steps to identify the extent of hepatitis B diseases in its region. On 29 September 1985, a meeting was held in Nagasaki to outline a strategy for prevention and control. WHO then assisted many countries to obtain quality hepatitis B reagents. More information was gathered on the magnitude of the problems of hepatitis, liver cirrhosis, and PHC. Huge studies by Palmer Beasley⁷ in Taiwan on 22,707 Chinese men, and also in countries in the Asia Pacific region, showed that PHC was caused by chronic HBV. Soon many other WHO offices throughout the world participated in similar studies indicating that HBV and PHC were endemic. The early vaccine studies by Pierre Maupas⁸ showed safety and efficacy, whilst in Singapore,⁹ the transmission of HBV into young babies and children by carriers in the family could be prevented by plasma-derived HB vaccines and these hepatitis B vaccines could be incorporated into the childhood immunisation programme without affecting their efficacies brought forth much hope.

The International Agency for Research in Cancer (IARC) of the WHO took an active interest in the vaccine, as it was the first time that an oncogenic human viral cancer might be prevented by a vaccine. Singapore was chosen, because of her strong logistic support from the Government. The National Cancer Registry was linked with IARC, and a national tracer system. The HB vaccination was introduced in Singapore on 1 October 1985, with approval from the

Cabinet.

Twenty-five years later, on 2 October 2010, the results were published,¹⁰ which showed that both the HBV carrier rates had fallen from 9.1% (1975) to below 2.7% (2010); and liver cancer rates from 27 per 100,000 (1978 to 1982) to 17.8 per 100,000 (2002 to 2007).

Thousands of lives were saved in Singapore and millions worldwide, when more vaccines were manufactured and became readily available for the poor countries of Africa and Asia through the Gates Foundation.

Molecular science soon identified Hepatitis C, D and E as one of the three pathogenic non-A and non-B human hepatitis viruses together with the numerous molecular types of HBV and HCV viruses. The structure and function of the genes soon became important, as designer antiviral drugs were made against them. For HBV, there are drugs that inhibited the DNA Polymerase genes (like Lamivudine and Adefovir), while others like Gancyclovir and Entecavir act on the priming gene.

Hepatitis A, B and E vaccines are now available for human prophylaxis, but HCV continues to elude the manufacture of vaccine and better antiviral drugs, despite the molecular structure being known.

As we celebrate World Hepatitis Day this year, let us continue to remember the contributions of the pioneers whose relentless researches and diligent work have saved the lives of millions worldwide.

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