

# Nobel Prize for the Discovery of Hepatitis B and C: A Brief History in Time

Mamun Al-Mahtab<sup>1</sup>, Partho P Roy<sup>2</sup>, Md Sakirul I Khan<sup>3</sup>, Sheikh MF Akbar<sup>4,5</sup>

## ABSTRACT

In 2020, the Noble Prize for Medicine jointly went to three scientists for hepatitis C virus-related discoveries. Earlier in 1976, an American scientist won this award for the discovery of hepatitis B virus. The Noble Prize, constituted as per the will of Alfred Noble, is awarded every year for achievements that benefit human beings in the best possible way. Although humans have known hepatitis as a deadly disease for hundreds of years, it was the discovery of hepatitis B and C viruses that changed the way we knew the hepatitis viruses forever and paved the way for saving millions of lives all over the world, the reason why the Noble Committee has on two different occasions picked up the great minds behind the discovery of these two hepatitis viruses and recognized them by conferring them with the highest recognition that one dreams of.

**Keywords:** Hepatitis B virus, Hepatitis C virus, Nobel prize.

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## THE NOBLE PRIZE

Alfred Nobel was born to a Swedish family of engineers on 21 October 1833. He developed a career as a chemist, engineer, and inventor. He gathered a fortune from the patent of the 355 inventions he had to his credit, the one that made him most famous being dynamite. He lost his brother Ludvig in 1888. Mistaking his brother as him, a French newspaper made a headline, which read, "The merchant of death is dead". On reading this newspaper report, Alfred Nobel rewrote his will and donated his fortune to create a number of prizes, which would confer "greatest benefit on mankind". Noble donated US\$ 186 million, which was 94% of his assets.

## A BRIEF HISTORY IN TIME

The history is not at all brief. There is mention of viral hepatitis in the Old Testament and in clay tablets founding Babylon. Our current knowledge of viral hepatitis is the culmination of research by many over the last 150 years. The first scientist to discuss hepatitis is perhaps Hippocrates who discussed and defined causes as well as treatment of what he called *ikteros*.<sup>1</sup> In 1865, based on his autopsy findings in a patient with obstructive jaundice, the pathologist Rudolf Virchow described inflammation of duodenal mucosa as the cause of jaundice.<sup>2</sup> However, it was much later in 1944 that Sir William Osler endorsed Virchow's concept and the term *catarrhal jaundice*, initially proposed by Rudolf Virchow, made its way into medicine.<sup>3</sup> There was significant advancement in the modern understanding of jaundice during World War I, when autopsies carried on soldiers who had fallen from catarrhal jaundice revealed that not the duodenal mucosal inflammation, but inflammation of the liver was the underlying cause of jaundice. However, this concept was not well established until the groundbreaking study by a group of Danish researchers who biopsied 38 patients of catarrhal jaundice and conclusively demonstrated that diffuse hepatitis and injury to the hepatic parenchyma was to be blamed.<sup>4</sup>

Our quest for viral etiology of jaundice possibly dates back to the 1930s when it was discovered that certain viruses could be transmitted vertically and later to the findings of research in the

<sup>1</sup>Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

<sup>2</sup>Shaheed Suhrawardi Medical College, Dhaka, Bangladesh

<sup>3</sup>Department of Anatomy and Embryology, Ehime University Graduate School of Medicine, Ehime, Japan

<sup>4</sup>Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan

<sup>5</sup>Miyakawa Memorial Research Foundation, Tokyo, Japan

**Corresponding Author:** Mamun Al-Mahtab, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, Phone: +880 171 156 7275, e-mail: shwapnil@agni.com

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1950s when we learnt that viral transmission was also possible through the feco-oral route.<sup>5</sup>

Vaccination was used against small pox in the 1790s, but it was first brought to the notice of scientists when mass vaccination of the workers at a shipyard in Bremen, Germany, almost a 100 years later, resulted in outbreak of jaundice.<sup>6</sup> The Germans experienced a similar outbreak of jaundice the same year at a mental asylum in Merzig.<sup>7</sup> There are reports of other incidences where outbreak of jaundice occurred following administration of injectable medications in the early 20th century: For example the Mayo Clinic experience of jaundice following treatment of syphilis<sup>8</sup> and in Sweden when there was an outbreak of jaundice in a diabetes clinic following repeated use of lancets for collecting blood samples.<sup>9</sup> In 1944 Beattie and Marshal proposed the use of individual syringe for every syphilis patient, as to their observation the cause of jaundice in them was not the drug but the syringes contaminated with infected sera.<sup>10</sup> In the 1930s there were at least two outbreaks of hepatitis in children following vaccination against mumps and

measles that reminded the scientific community of the German experience of 1885 and strengthened the belief that it was the syringe and not the drug or the vaccine that was to be blamed.<sup>11,12</sup> And when during World War II, when more than 100 British soldiers developed jaundice after administration of convalescent serum of mumps that was almost conclusive.<sup>13</sup> There are numerous reports of such outbreaks of jaundice ever since following vaccination in the world literature dating back to the 1940s and 1950s.

## THE DISCOVERY OF HEPATITIS B VIRUS

With this background, Blumberg and colleagues discovered hepatitis B virus (HBV) in the USA almost half a century ago. However, this landmark discovery of outcome is of unrelated research. In their pursuit to unearth the cause of transfusion-associated jaundice, they came across a protein in the stored serum of an Australian aborigine, which they subsequently identified as the HBV surface antigen (HBsAg).

Blumberg was a unique character. He started his academic carrier in mathematics, but eventually switched to medicine. The reason for this change in carrier was simple—medicine offered more travelling opportunities! He got interested in infectious diseases from his experience in Surinam, where he spent a summer as a third-year medical student. His first published paper was on the diversity of the clinical course of filariasis among different populations.<sup>14</sup> Later he concentrated on starch gel electrophoresis of serum samples collected from different population groups and animal species to demonstrate the differences in mobility and concentration of different serum proteins. In the course of this research, in 1964 he discovered in the serum of that Australian aborigine suffering from leukemia that stained red with azocarmine, instead of taking up Sudan black indicating high protein content.<sup>15</sup> Blumberg and colleagues failed to identify this particular antigen in 700 healthy US blood donors, but did pick it up in 8 out of 70 leukemia patients.<sup>16</sup> At that time, it was believed that leukemia was a viral disease and following the above observation, it was believed for some time that this antigen may belong to the leukemia virus.

However, the concept of leukemia virus was challenged when this antigen was found in 30% of Down's syndrome patients with leukemia staying in larger institutions compared to only 3% of them staying in smaller facilities.<sup>17</sup> This association between the presence of antigen in serum and social setting led to the suggestion that overcrowding and poor sanitation may be the reason and therefore that the antigen may be infectious in origin. In the subsequent years, studies from different parts of the world revealed that patients of a wide variety of illnesses ranging from leukemia, hemolytic anemia, hemophilia, chronic renal failure, etc. requiring multiple blood transfusions more frequently have the antigen in their serum.<sup>5</sup>

The antigen was studied under an electron microscope which suggested that it was likely to be a virus capsid,<sup>18,19</sup> which was later confirmed by Dane and colleagues.<sup>20</sup>

Blumberg's discovery was important for two reasons: firstly it gave a conclusive answer to the decade-old quest of so many researchers to identify a viral cause of hepatitis. More importantly it demonstrated that there are millions asymptotically, but chronically, infected across the globe who are potential candidates for developing liver cirrhosis and even liver cancer. Blumberg was amply rewarded for his groundbreaking discovery when he was decorated with the Nobel Prize in Medicine in 1976.

## THE DISCOVERY OF HEPATITIS C VIRUS

The discovery of hepatitis C virus (HCV) is a more recent development. Screening tests for HAV and HBV made it possible in the mid-1970s to examine cases of transfusion-associated hepatitis (TAH) and to demonstrate that only approximately 25% resulted from HBV and that none were related to HAV. Consequently, approximately 75% of TAH became classified as non-A, non-B hepatitis (NANBH). Subsequently, chimpanzee studies demonstrated that NANBH was a result of a transmissible agent. Alter and colleagues at the National Institute of Health in the USA had, by then, identified that a new form of hepatitis existed, which was caused neither by HAV nor by HBV and termed it non-A, non-B (NANB) hepatitis. However, it was Houghton and colleagues from Chiron Corporation who identified this NANB hepatitis virus and termed the new agent as hepatitis C virus (HCV).<sup>21</sup> Subsequently the HCV genome sequence was mapped and seven genotypes of the virus were identified. The discovery of HCV not only allowed the development of HCV detection assays but also facilitated identification of potential targets of HCV antivirals. In the absence of a vaccine against HCV, it would have been impossible for mankind to tackle this deadly virus without the advent of the directly acting antivirals (DAAs).<sup>22,23</sup>

This year the Nobel Prize in Medicine was jointly awarded to three scientists from two ends of the Atlantic, two from the USA and one from the United Kingdom for their collective efforts in cracking HCV. They are Harvey J. Alter, Michael Houghton, and Charles M. Rice. Earlier the discovery of HBV only led to the reduction of TAH, but not its elimination. The pioneering work of these three Noble Laureates not only led to the discovery of a new TAH virus, but also allowed the development of screening methods that have significantly curtailed the risk of acquiring hepatitis from contaminated blood as well as the development of antiviral drugs, ultimately saving the lives of millions across the globe.

## CONCLUSION

One organ, *the liver*, one disease, *chronic liver disease*, two viruses, *HBV and HCV*, and "*the recognition*", the Noble Prize is unique and possibly there is no second example of this. Superficially it may seem bit unusual for the Noble Committee to recognize the discovery of two different viruses with similar implication in modern technological age. However, as we dig deep and take a brief journey in time, it becomes evident that not only have these discoveries a long-lasting impact on our civilization, such discoveries were also not made overnight. It took us centuries to identify these two invisible enemies and no doubt that these discoveries will go a long way in ensuring sustainable development for our next generations. Although Nobel prizes have been awarded for HBV (1976) and HCV (2020), the Nobel Committee has mentioned that the prize in 1976 was awarded for "for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases" and that paved the way for Nobel Prize in 2020 by elaborative studies about mechanisms underlying disease pathogenesis and drug development.

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