

The Discovery Of Viral Hepatitis: A Military Perspective

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ABSTRACT

Viral hepatitis is one of the most common infectious diseases and over the years the jaundice associated with it has been known by many names. Several viruses are now known to cause hepatitis in humans, but sixty years ago, these viruses were unknown. In the years before and during the Second World War, there emerged a significant understanding of the clinical and epidemiological nature of the disease due to the dedicated efforts of doctors and scientists around the world. By the end of the war years, the discrete entities of Hepatitis A and B had been identified and preventative measures were proving to be effective. However, the bane of viral hepatitis was far from being resolved.

Key Words: *Hepatitis, Virus, Military History.*

Introduction

Hepatitis A virus (HAV) is highly infectious and most commonly affects children in conditions of overcrowding and poor sanitation. Hepatitis B virus (HBV) is one of the most common viruses in the modern world and ranked by the World Health Organisation as one of the top ten killers. It is responsible for approximately 1.5 million deaths worldwide each year, two thirds of which are attributable to primary hepatic carcinoma following HBV infection. More than 350 million people are chronically infected with HBV.

Early Observations Of Viral Hepatitis

Hippocrates documented the first cases of jaundice in the fifth century BC. He records an epidemic of jaundice on the island of Thassos, during which the people were first afflicted with fever and vomiting, then developed jaundice and stiffness over the next seven days. The disease was usually fatal in those who did not suffer a fever, but those who did usually survived. This description is almost certainly a viral hepatitis, although it is subtly different from modern forms and thought to be attributable to an extinct viral strain.

Although hepatitis and jaundice had been known for centuries, the identity of the infectious agent remained elusive. In 1840,

the German scientist Jacob Henle, Professor of Anatomy at Zurich published a landmark thesis based on deductive work and logical argument (1). His theory stated that microscopic organisms were the cause of contagion and infectious disease and that the manifestation of some diseases was attributable to live particles that behave like parasites in human beings. He laid down three postulates to identify these agents, firstly that the agent must be consistently present in the sick, secondly, that the agent can be isolated, and thirdly that the agent can reproduce the disease when administered to a healthy individual. His theory was slow to be accepted because scientists had difficulty believing an infective agent could pass through the incredibly fine filters that were in use at the time. These 'filterable agents' were only later identified as viruses (Latin: 'slimy liquid' or 'poison').

In 1883, doctors in a shipyard in Bremen issued 1,289 workers with the smallpox vaccine. In the six months after vaccination, the German researcher Lurman observed the first cases of hepatitis attributable to inoculation, as fifteen percent of the workers developed jaundice (2). This association of inoculation with jaundice was known as 'German shipyard disease' but still the infectious agent itself remained elusive.

Soldiers have always been prone to venereal and tropical diseases. Arsphenamine was introduced for the treatment of syphilis in 1909, and almost immediately jaundice became a recognised complication, although this was often reported to be a manifestation of the toxic action of the drug. The malaria parasite was also being inoculated for the treatment of neurosyphilis and jaundice was again a recognised complication. This association of unexplained hepatitis and jaundice following inoculation, particularly measles and yellow fever, was well known to the medical profession in the early part of the twentieth century. Yellow fever was responsible for an extremely high death rate among British soldiers in Africa and South America and although a vaccination was available, it was itself associated with a high incidence of fatal jaundice. In 1937, Dr MacCallum, a British liver specialist, was appointed to investigate the infectious agent and produce a vaccine without these complications. The first conclusion from the research team was that the yellow fever virus

in the vaccine was not responsible for the post-inoculation jaundice (3).

In 1938, Findlay and MacCallum summarised their findings and noted that in every case the inoculum had contained 'homologous substances' or pooled adult serum or blood products, either in the form of 'homologous serum' or 'homologous tissue suspensions' (4). Various explanations were provided, including hypersensitivity and anaphylactic reactions to components of human serum, or hepatic antibodies in the human serum. They also hypothesised that a virus may have been present in apparently normal human serum and therefore in healthy donors. The following year, the same team concluded that the yellow fever virus in the vaccine was not responsible for the post-inoculation jaundice and that the agent that caused infective hepatitis must have been present in the apparently normal human serum used to prepare the vaccines (5). Over the next few years, there were innumerable reports of delayed jaundice following the inoculation of pooled adult serum or plasma, whole blood, or certain batches of vaccine containing apparently normal human serum. The jaundice associated with inoculation, which was epidemiologically different from infective jaundice, was termed serum hepatitis.

A Military Perspective

Epidemics of jaundice have long been associated with armies in the field. Hepatitis was known to be contagious because epidemics often occurred in overcrowded and unsanitary conditions, and was a significant problem during the First World War. Even so, the mode of transmission was still uncertain. Epidemic hepatitis occurred again in the Second World War, especially in the Mediterranean theatre where more than thirty thousand cases were reported in a two-year period. However, during the war years, it became increasingly obvious that there were two distinct types of hepatitis. Infective (or epidemic) hepatitis was associated with overcrowding and poor sanitation whereas the other form of hepatitis, known by many names including post-arsphenamine jaundice and homologous serum jaundice, was associated with the direct inoculation of infected blood, serum or plasma.

The Military Hospital, Hollywood, had been built in 1898 as part of a new barracks. It provided healthcare not only to the resident battalions at Hollywood and Kinnegar, but also to the local residents. At the outbreak of the Second World War it was under the command of Lt Col E Lambkin RAMC and consisted of 79 permanent beds and 66 beds in a hutted extension. By July 1941, the number of beds had been increased to 180, and the hutted extension had been taken over by Major A J Johnson RAMC, Command Specialist in Dermato-

logy specifically for the treatment of the increasing number of venereal diseases.

The Quarterly Reports from July to September 1941 reveal that a full-time medical officer was required solely for the routine administration of the hutted extension, as in addition to daily duties and outpatient clinics, 'on occasion, more than sixty intramuscular and sixty intravenous injections have been given in a single day, exclusive of venepuncture for blood tests and other routine work' (6).

Jaundice was known to occur at any stage of untreated syphilis, but the jaundice that occurred shortly after arsenotherapy was far more significant. For one thing, arsenotherapy could be used safely in early untreated syphilis with rapid clearing of any jaundice, whereas in 'post-arsphenamine jaundice' there was no such rapid response and in some cases an exacerbation of liver damage and poorer outcome.

The British Army Method for the treatment of early syphilis involved the use of neoarsphenamine and consisted of weekly injections for ten weeks, followed by an interval of four weeks, when a second similar course was given. Third and fourth courses were given if required after a four week rest period.

Before the war and up to 1941, the incidence of jaundice in treated syphilitics was about two per hundred new cases. Despite there being no change in the treatment protocols, the War Office began to notice an increase in the incidence of jaundice associated with anti-syphilitic treatment such that by mid-1943, rates of almost 1 in 2 treated cases were being reported (7).

The first epidemic of jaundice was noted at the Military Hospital, Hollywood, between January and March 1942 in soldiers undergoing arsenotherapy. Almost all the cases were in soldiers attending Hollywood for weekly treatments, and it was assumed that overcrowding of the outpatient department on the day syphilitics were treated might have contributed to the spread of an infective form of hepatitis. The staff undertook the necessary steps to prevent overcrowding at subsequent clinics and this simple step initially appeared to control the epidemic. However, one soldier died during this period as a result of the infection.

In March 1942, the Military Hospital, Londonderry, was handed over to the American Expeditionary Force and the venereal disease department transferred to the Military Hospital, Hollywood, which was designated as one of the main venereal disease 'Continuation Treatment Facilities' in Northern Ireland. There was a corresponding increase in the number of outpatient attendances at Hollywood with over four hundred and sixty admissions for venereal diseases recorded during this three-

month period. March 1942 also ended with an extensive outbreak of hepatitis amongst United States Army personnel. A questionnaire survey led epidemiologists to conclude that the epidemic appeared to be attributable to contaminated yellow fever vaccination containing human serum that had been administered just prior to embarkation. By 14 April 1942, the United States Surgeon General had ordered the implicated vaccine lots to be withdrawn and replaced with vaccine that did not contain human serum. The epidemic reached a peak in June 1942, after which the number of reported cases returned to the previous baseline level. Approximately fifty thousand personnel were hospitalised with symptomatic jaundice and it is estimated that more than three hundred thousand were inadvertently infected (8). This is the largest point source outbreak of HBV ever recorded (9).

Following this outbreak, all cases of jaundice amongst British troops in Northern Ireland, of whatever type, were to be segregated to prevent further compromise of healthy personnel. The Military Hospital, Holywood, was designated to receive all soldiers who developed jaundice from August 1942. In the first six weeks, however, only 29 British cases were admitted. Sixteen were attributed to post-arsphenamine jaundice, two to infective jaundice and the rest to other diseases. One soldier later died. The most interesting case of the series was that of Cpl Cash RAMC, Assistant in the District Laboratory at Holywood. He had handled blood serum from many of the United States Army personnel affected and took ill on 7 August 1942 with a condition closely resembling the American cases. Intensive investigations were carried out, including passage experiments in the hope of isolating a specific virus. None was identified. He recovered fully within six weeks (10).

All cases of jaundice were originally kept in hospital until no longer icteric and then transferred to Convalescent Depots. However, due to the large number of inpatients and prolonged admission times, soldiers were subsequently only kept in hospital during the acute stages, and when clinically free from malaise, anorexia, hepatomegaly and choluria, ambulant and on full diet, they were transferred to a Convalescent Depot while still slightly jaundiced. Earlier discharge from hospital was introduced to reduce the total duration of absence from duty as hostilities continued, and soldiers were on average admitted for three weeks followed by two weeks rehabilitation in the Depots.

The incidence of jaundice at the beginning of 1943 did not show a corresponding increase in civilian practice in Northern Ireland and one of the more interesting hypotheses was that glycogen exhaustion

caused by intensive military training might be a cause! It was also proposed that procedures particular to Army venereal disease clinics before 1943 had selectively built up a population isolate with an inordinately high proportion of infected donors and/or a stock of instruments more or less permanently contaminated with the causative agent. An alternative proposal was that circumstances peculiar to the treatment of syphilis or to the syphilitic process itself resulted in susceptibility to the blood-borne causative agents and jaundice in appropriate circumstances (11).

Several important observations were also made around this time. Firstly, the incidence of communicable diseases at the peak onset of jaundice was trivial and suggested that the causative agent either remained longer in the blood or was vastly more resistant to sterilisation procedures than the agent of any common communicable disease (11). The disease was not spread by contact as in infective hepatitis and occurred despite standard clinical controls. The incubation period of infective hepatitis was known to be approximately 20-40 days, whereas that for serum hepatitis was much longer with most cases occurring 80 days or more after exposure. If the same causative agent were responsible, the incubation period of infective hepatitis would be assumed to be longer when compared to direct blood-blood transmission. Secondly, there was evidence that an episode of infective hepatitis conferred immunity to subsequent attacks but there was insufficient evidence to conclude the same for serum hepatitis, although the evidence was suggestive. The most important observation was that neither seemed to confer immunity to the other. In other words, the evidence suggested that the causative agent in post-arsphenamine jaundice was probably identical to that of homologous serum jaundice, but was distinct from that of infective hepatitis (7). The identification of two distinct forms of viral hepatitis was a significant development.

By mid 1943 evidence suggesting that this was largely the result of infection from contaminated syringes employed for intravenous injections led to the issue of instructions to promote more careful sterilisation (12). By then, individual treatment centres had already begun to change their clinical practice but shortage of instruments and erratic supply chains delayed full implementation of the prescribed procedure for some months. It was hypothesised that post-arsphenamine jaundice was caused by inoculation of infected material from an imperfectly sterilised syringe. MacCallum suggested that if patients were given a syringe at the beginning of their treatment, and that only this syringe was used throughout their treatment, then transmission of the disease

should be prevented (7). A small study seemed to prove this theory, with only one soldier developing jaundice during treatment. This soldier had received inoculations at another hospital due to postings, and if the proposed incubation time was extrapolated backwards, the point of infection was traced to the second hospital.

In 1943, medical officers of the Ministry of Health prepared a memorandum (13) to collect all known incidents of jaundice following the inoculation of blood products. An important study was subsequently undertaken by the British Army on those soldiers who received transfusions in Forward Treatment Units during the Normandy campaign from June to November 1944 (11). The amount and type of transfusion (whole or pooled blood) was collated on more than 1500 soldiers who received transfusions during that time. Pooled plasma was found to be more icterogenic than whole blood. The explanation offered for this was that one bottle of whole blood was made from blood from a single donor, whereas plasma comes from large pools of blood from many donors, and an icterogenic agent in the blood of a single contributor could contaminate up to five hundred bottles.

By the end of the war, aided by the collation of data obtained during the austere environment of the Normandy landings, there was enough evidence to conclude that there were two distinct types of hepatitis. The first and most common problem was a highly contagious hepatitis with a shorter incubation period that occurred in epidemic form in areas of poor hygiene and sanitation and appeared to be transmissible by the faecal-oral route. The second type was less common with a longer incubation period and was spread by inoculation of infected blood, serum or plasma. Both types were thought to be viral in origin. However, the nomenclature for these two distinct diseases continued to cause confusion within the medical profession. In 1947, MacCallum suggested that the viruses responsible for the two forms of hepatitis should be called hepatitis A and B (14). At this stage, however, it remained uncertain whether these were two distinct organisms or just two different strains of the same organism. It took another twenty-five years before the World Health Organisation Committee on Viral Hepatitis finally adopted the terminology (15).

Conclusion

By the early 1960s, research into viral hepatitis had reached a deadlock. However, in 1963, Baruch Samuel Blumberg

discovered a previously unknown protein in the blood of an Australian aborigine (16). This protein was known as the Australia antigen and it soon became apparent that this protein was related to HBV as it was only found in the serum of HBV-infected patients. The protein was subsequently identified as the viral surface antigen when HBV itself was discovered (17). Research and vaccine development in the following years have vastly increased our understanding of the diseases but the complexity of the viral hepatitis story continues to widen. However, the value of epidemiological observation and simple preventative medicine techniques during the war years cannot be underestimated.

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