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INFECTIVE HEPATITIS: A PROBLEM OF WORLD HEALTH *

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I have chosen infective hepatitis as the subject of my Harveian Lecture for several reasons. First of all, I have been interested throughout practically the whole of my professional life in the problems of hepatic disease and of jaundice, and have taken some small part in their investigation in Britain during the past 30 years. Next, the main disease which I propose to discuss—under a different name from that which I was first taught to employ—has not only an interesting ancient history but a quite astonishing modern one; and has proved itself to be, from numbers alone, the most important of all the diseases of the liver associated with jaundice. Lastly, although scarcely on the same scale as malaria and influenza, this disease has shown itself capable in favourable circumstances of spreading widely in pandemic form, and might easily do so again.

I later refer to two other forms of infective hepatitis, either very closely allied to or, according to one view, identical with acute infective hepatitis of the common kind—namely, homologous serum jaundice and syringe-transmitted hepatitis. Neither of these was known to exist until comparatively recent times.

This disease-group, if I may call it so at present, has been clearly proved to result from virus infection, and our difficulties in its investigation simply emphasize that we are still at an early stage in our knowledge of all virus diseases and their propagation.

The History of Catarrhal Jaundice

Catarrhal jaundice was the name used by clinicians for many years to describe the disease now more accurately classified as acute infective or viral hepatitis. It was well known first only in its *sporadic form*, but even then was recognized as by far the commonest type of jaundice seen in clinical practice in Britain, Europe, and America. Its occurrence in epidemic form, both in peace and in war, is described later. Sporadic catarrhal jaundice was always recognized as benign, and the rare progression to acute yellow atrophy (acute necrosis) of the liver was taken to be the result of a different disease. Its onset was always associated with gastro-intestinal upset, and when Virchow (1864) described the pathology in a single case as a catarrhal obstruction of the common bile duct, the mechanism of the disease appeared to be reasonably explained and its first name justified. It was assumed that a microbic infection, not necessarily specific, spread upwards from the disturbed intestine to block the bile duct by catarrhal inflammation or cholangitis. This fitted the accredited view in the early years of this century that, as Eppinger (1908) taught, all varieties of jaundice were essentially obstructive, whether the obstruction occurred in the larger extrahepatic ducts (as in catarrhal jaundice) or in the finest bile capillaries within the liver (as in cirrhosis).

This conception of the pathology of catarrhal jaundice, although doubted by a few, continued until after the end of the first world war, when certain new discoveries about hepatic diseases and about the mechanics of jaundice were made, and could not be denied. The old conception, however, died hard; and I recall with some amusement the many friendly arguments I had with the late Sir Arthur Hurst until he finally recanted about the disease we are now discussing.

I should like to add here, in fairness, that I have never denied the possibility of an ascending cholangitis spreading up from the intestine to produce a true catarrhal and obstructive jaundice. I have notes of cases of this kind which exhibit a striking and unusual clinical history, and some day I hope to write a full account of them.

The new developments in the early years after the first world war cannot easily be placed in chronological order, so I shall place them in order of importance. The first, in my own view, was the discovery by Hijmans van den Bergh, of Utrecht (actually in 1913, but known in Britain only in 1918), of his method of estimating small amounts of bile pigment in small amounts of blood serum. This method, now so well known as the van den Bergh reaction, brought about a revolution in our whole knowledge of the production of jaundice. It gave us the modern definition of jaundice as essentially "bilirubinaemia," and when exploited as a clinical and experimental means of investigation it made possible a new and rational classification of jaundice (McNee, 1922–3) into three varieties—obstructive, toxic and infective (hepatitic), and haemolytic—which is still in common use to-day.

The other new development was the gradual realization of the conception of "hepatitis"—the idea that by far the majority of diseases or disorders of the liver are essentially due to damage, sometimes temporary but often permanent, leading to death of the glandular cells of the organ. This conception grew so slowly that its origins cannot accurately be traced, but the van den Bergh technique added greatly to its acceptance and proof.

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My own first experience of a genuine hepatitis came during the first world war when Weil's disease (spirochaetosis icterohaemorrhagica) broke out in Flanders (McNee, 1920). The spirochaetal cause had just been discovered, fatal human cases were examined *post mortem*, and, best of all, the whole evolution of the damage to the liver cells and the processes of repair could be studied in guinea-pigs inoculated with the disease.

With this and other experiences in mind, some dating from before the war and concerned with epidemics, the probability that the old catarrhal jaundice was pathologically a hepatitis—generally benign but sometimes going on to acute necrosis (yellow atrophy)—was strongly suggested. Final proof, in Britain at least, was long in coming, for patients do not die in the earliest stages of the disease. Opportunities came, however, first to Gaskell (1933) in Cambridge, and later to Barber and Osborn (1939) in Derby, of examining the tissues of two patients who died after an operation and as the result of an accident, and in both cases a typical hepatitis was found. In Rolleston and McNee's textbook (1929) the disease was described as common infective hepatic jaundice, but this has gradually been superseded by acute infective hepatitis.

Epidemics of Jaundice in War and Peace

Simply for convenience, epidemics of jaundice, clearly due as we now know to different causes, may be divided into those occurring in wars and those occurring in countries or communities in peace. War epidemics have always been the greater, and are considered first; but in modern "total war" civilians may suffer almost as much as the fighting forces.

The growth of bacteriology has enabled us to separate clearly some of the clinical varieties of jaundice, but even then several recognizable causes may be present at the same time and lead to diagnostic difficulties. What we now know as Weil's disease, a rat-borne infection due to a spirochaete, was evidently quite common in many campaigns, especially when, as in the good old days, the belligerents and their horses retired to winter quarters. Malaria, bacillary dysentery, and the enteric group of fevers, all potential causes of jaundice in a proportion of sufferers, have often occurred together in war and led to confusion.

The real question before us is whether what was often loosely termed "campaign jaundice" included many cases of acute infective hepatitis. The largest outbreak of all, referred to both by Willcox (1916) and by Von Bormann *et al.* (1943), seems to have been during the American Civil War, when 22,509 cases were reported, with 161 deaths. This was before the advent of bacteriology, but the benign nature of the disease must leave us with a strong suspicion of infective hepatitis. In the South African War 5,648 cases of jaundice are recorded with a small mortality and little bacteriology.

In the first world war, to my own personal knowledge, epidemics of jaundice, except for the small one soon identified as spirochaetosis icterohaemorrhagica, were never noted among the millions of British and Allied troops deployed in the trenches of Flanders. In the Eastern Campaign, particularly in the Dardanelles and in Mesopotamia, the circumstances were quite different, and have been fully described by Willcox. No actual figures for the Dardanelles campaign are available, but careful examination on the spot by bacteriologists of repute, such as C. J. Martin and Ledingham, failed in by far the majority of cases to reveal a bacterial cause such as typhoid, paratyphoid, or dysentery. Virus investigation was then scarcely in its infancy, but it now seems reasonable to conclude that most of the many jaundiced men suffered from acute infective hepatitis. In Mesopotamia in 1917–18, among a much smaller number of troops, it is known (Willcox) that 2,403 cases of jaundice occurred in British soldiers with 18 deaths, and 3,897 in Indian soldiers with 28 deaths.

In countries and communities at peace the history of epidemics of jaundice is a long one, but as none of the outbreaks until recent times was large they failed to attract more than local attention. The best historical account I have read is by Von Bormann *et al.* (1943), stimulated by their interesting and careful investigation of a number of small epidemics in German villages in 1937–8. By this time they were firmly able to give as the title of their monograph, "Hepatitis Epidemica in Deutschland." Their historical researches take them back as far as 1629, and they refer to an outbreak in the English Army in Flanders in 1743. They also state that the first definite description of a civilian epidemic labelled "icterus epidemicus" was given by Herlitz in Göttingen in 1791.

For reasons already described, however, and with the great advances in our knowledge in the early nineteen-twenties, it is only then that civilian outbreaks of jaundice began strongly to attract attention and rigid investigation of their cause. In Britain credit for attracting attention to outbreaks in children and the obvious infective character of the disease is due to Cockayne (1912). Between the wars many small epidemics were reported, chiefly affecting schoolchildren, and particular attention must be drawn to the work of Pickles (1939) in a country practice, and to the paper by Cullinan (1939). I took part in several investigations myself, in association with my colleague Okell at University College Hospital, but our results were negative, and we knew nothing then about virus infections. All we recognized was the obvious infectivity—over 60% of the pupils in one preparatory school—and that the probable incubation period was round about 30 days. It became clear from the many small outbreaks in different parts of Britain that by 1939 the infecting agent was widely spread throughout both country districts and the towns.

At the same time small epidemics were occurring in many European countries—in Germany, and particularly in Scandinavia, where severe and fatal infections took place in adults as well as children.

Relations of Homologous Serum Jaundice and Syringe-transmitted Jaundice to Acute Infective Hepatitis

It is true that the term "homologous serum jaundice" came into use in Britain only after publication of the memorandum prepared by medical officers of the Ministry of Health (1943). I have always understood that Dr. W. H. Bradley had a large share in the preparation of this invaluable document. It seems almost certain that syringe-transmitted hepatitis is the same disease, and I wish to recall that syringe-transmitted jaundice has an older history, not mentioned in the above memorandum, and tending to be forgotten. Omitting subcutaneous injection of morphine and a few other drugs, large syringes and long needles came into common use only with the advent of "salvarsan" about 1909. I can remember learning the technique with poor syringes until I obtained a German Luer type, and I can also remember the services of a surgeon being required for the "dangerous" operation of lumbar puncture. Not long after the extended use of salvarsan compounds intravenously, concern began to be expressed over sudden outbreaks of jaundice in V.D. clinics. The drug was naturally suspect, as a potential hepatic poison; and this led to the setting up of a Salvarsan Committee of the Medical Research Council, which published two reports, in 1919 and after the first world war in 1922. I shall make reference only to the second report, since I was then a member of the committee and knew the facts now to be described at first hand.

In 1917 an outbreak of jaundice, with nine deaths, occurred at a barracks in Dublin where V.D. patients were being treated. The injection technique would now be

described as defective, and to make the story short it was proved that the deaths all resulted from the transmission of malignant malaria by injection. This outbreak thus does not directly concern jaundice, but may be one of the first accounts of a fatal disease accidentally transmitted by intravenous injection. In the same year a serious outbreak of jaundice, with 15 deaths, occurred at the V.D. department of Cherryhinton Military Hospital, Cambridge. The Salvarsan Committee could come to no decision on this outbreak, but excluded specially toxic batches of the drug. We can see this outbreak now as one of syringe-transmitted jaundice, and it is of some interest that the committee drew attention to the fact that at the same time there was a small epidemic of jaundice among children in an elementary school near by, affecting 15 children and one adult.

The next outbreaks of what we now term homologous serum jaundice, and the first to attract widespread attention, are well described in the Ministry of Health memorandum, and need only brief reference here. They are concerned with 41 cases of jaundice and eight deaths following injection subcutaneously of measles convalescent serum into children in the South of England in 1937. Two years later a similar incident from a single batch of pooled convalescent serum occurred in Leeds, fortunately without any deaths.

Here indeed was a clinical puzzle which at the time none of us who were consulted could resolve. Moreover, it was noted with astonishment, just as in the "late jaundice" referred to in the M.R.C. report of 1922, that the jaundice did not begin until on an average about three months after the injection. This was an added puzzle, which remains with us to-day, and is discussed later.

The jaundice which may occur at an interval of about three months after blood transfusion may also be left for subsequent discussion, since blood transfusions were comparatively infrequent and this hazard was not recognized until the period of the second world war.

I began to carry out blood transfusions in France as early as 1915, in association with my surgeon friend Hamilton Drummond, of Newcastle-upon-Tyne, using the primitive Kimpton tube, a large bomb-like container of glass tapering to a glass cannula at one end. Some of our patients were jaundiced when they died, but they were all severely wounded men, mostly with gas-gangrene, and this disease may have accounted for the icterus, although the possibility of incompatibility of the donor's blood cannot be excluded. It seems extraordinary to admit that until Roger Lee, of the Harvard Unit from Boston, first presented us with Type II and Type III sera and taught us to use them to establish the four Moss groups (a classification now superseded) not one of us in France knew anything whatever about blood groups and blood incompatibilities. (A similar gap in knowledge between America and Britain occurred later about coronary thrombosis and its clinical syndrome, and is still quite incomprehensible.)

Once blood grouping was known, and technical improvements were made in methods, I often carried out in the later stages of the war as many as 20 blood transfusions in a single day after a battle, but never heard of jaundice as a result. It would seem that the infective agent which causes homologous serum jaundice was not widely dispersed among the soldier-donors at that time, and it may be added that few of them could possibly have suffered from acute infective hepatitis during their sojourn in France, where no outbreak ever occurred.

Acute Infective Hepatitis and Homologous Serum Jaundice in the Second World War

All that I have said so far leads up to the climax of the second world war, and no one imagined in advance that these two infections, if indeed there are two, would be of such enormous importance as war diseases, not only in the combatant forces of all nations involved but in the war workers at home. It is common knowledge that modern wars are always a powerful stimulus to medical research, and there began at once intensive investigation into the problems of infective hepatitis.

I do not intend to deal with the clinical aspects of the pandemic, which was at its height between 1942 and 1944, and then gradually declined. Everyone, however, is agreed that the acute stages of infective hepatitis and homologous serum jaundice are clinically identical, and that the only real difference is the length of the incubation period.

I may perhaps mention here an important after-effect of the acute hepatitis, fortunately affecting only a small minority of patients. I refer, of course, to the progression to chronic hepatitis or cirrhosis (Lucké and Mallory, 1946; Rennie, 1951), a sequel which may trouble physicians for years to come, and also pension boards.

I prefer in the space available to consider critically the epidemiology, our newly acquired knowledge of aetiology and transmission, and the problem of whether there is only one, or more than one, disease.

There are many gaps in our understanding of why epidemics and pandemics suddenly break out, and about their periodicity. This applies to some virus diseases, such as influenza, which has been most closely studied, but not of course to smallpox. All I have said earlier goes to prove that the infective agent of acute hepatitis was widely spread throughout the world in the years prior to 1939, and, as was noted for the influenza pandemic of 1918–19, that small outbreaks were common for some time before the great explosion.

It is difficult to trace where the main epidemic really started, and I doubt if the war history, when published, can be very informative. My first information came, not from the Navy, but from the account sent by Cameron, of Edinburgh, from Palestine in October, 1942, but not published until the following July (Cameron, 1943). He notes that the epidemic began in troops in Palestine (342 cases) in 1940, and thereafter rapidly increased. It may well be that the explosion took place in different places almost simultaneously, for soon infective hepatitis was widespread over Europe and North Africa. I have seen figures indicating the extent of the pandemic in British and American soldiers, but none concerning our enemies. It must suffice to say that the numbers were so large as to influence war strategy, and both combatant sides were almost certainly equally afflicted.

Homologous serum jaundice first came into prominence as a war disease among our American allies, and followed extensive preventive inoculation with a yellow fever vaccine, containing human serum, prior to their departure from America on foreign service. It has been shown since then by Havens (1946) that as little as 0.01 ml. of infective serum is enough to cause the disease. During the first six months of 1942, just as the pandemic of infective hepatitis was rapidly reaching its zenith, 28,505 Americans inoculated against yellow fever developed jaundice, and 62 died. Since the incubation period was about three months, a number of these men—especially air crews in training—had reached Northern Ireland and East Scotland before they fell ill. I was thus personally able to observe some of them closely. I saw no clinical difference whatever between what I still describe here as the two diseases, except that after homologous serum jaundice recovery seemed slower, and convalescence was often not complete for three months.

British soldiers and airmen, who were not inoculated in this way, naturally escaped this large outbreak, and the first British foretaste of the problem came from the developments of blood transfusion.

Blood transfusion, and especially the preparation and use in battle areas of pooled and stored human blood products of various kinds, developed enormously during the war, and the impetus has of course carried on into peace with the permanent establishment of our blood transfusion services and blood banks.

There has never been any suggestion, so far as I am aware, that much, if any, of the pool blood products had been derived from donors who had recently suffered from infective hepatitis, but there is still a loophole here. One thought instead of the already known puzzle of syringe-transmitted jaundice and the outbreaks of measles convalescent serum jaundice between the wars; and the memorandum of the Ministry of Health, when published, drew at once the strongest attention to this new problem and the necessity to attempt its solution.

The Infecting Agent, or Agents, of Infective Hepatitis and Homologous Serum Jaundice, and their Mode of Transmission

It was shown by Cameron (1943) in Palestine and by Voegt (1942) in Germany that infective hepatitis could be transmitted from man to man by subcutaneous injection of blood in the early stage of the disease. All ordinary bacteriological investigations had always been negative, and no experimental animal had proved susceptible to the disease. The inference seemed obvious that a virus was concerned, and that nothing short of experiments on human volunteers would suffice to give the required knowledge about the disease and its transmission. Such experiments were carried out, actually during the war years, both in Britain and in America, but in modest numbers, for it had to be remembered that the disease carries a small but quite definite mortality rate. This was quite different from the human transmissions of trench fever with which I was actively concerned in the first world war, for there was no fear of fatalities or permanent sequelae. Transmission experiments in the field were forbidden by the British military authorities, and were therefore undertaken at home under the auspices of a committee set up by the Medical Research Council.

An excellent and concise account of the experiments, including both British and American work, is given in the M.R.C. Report (1951). The difficulties were enhanced by the need to find volunteers in different centres, and a very few experiments were carried out in my own department (Rennie and Fraser, 1946). The work was mainly concerned with the transmission of acute infective hepatitis and to a less extent with homologous serum jaundice. This was inevitable because the main and immediate war problem concerned the first condition, but in a way unfortunate because the second remains with us in civilian life as a continuing trouble.

The easiest way of approach, in discussing the human experiments, is that taken in the M.R.C. Report by MacCallum, Stewart, and Bradley, and to consider the possibility of infective hepatitis being due to virus A, and homologous serum jaundice as due to a different virus, B.

It seems to be proved up to the hilt that virus A, derived from patients with acute infective hepatitis, can be transmitted readily to human volunteers by the faeces taken in the early stages of the disease. These experimental observations, moreover, have had striking clinical proof from the observations of Neefe and Stokes (1945) in America on an epidemic of jaundice in a summer camp in which the water supply became contaminated from the latrines. Virus B, from cases of homologous serum jaundice, has seldom been transmitted except by direct injection of blood or serum.

The sum total of all the experiments, both in Britain and in America, does not in my opinion provide adequate proof of the existence of two separate viruses, even when the small number dealing with the question of cross-immunity (Havens, 1945; Neefe, Stokes, and Gellis, 1945) is taken into account. I need not emphasize, however, the extreme difficulty of all such experimental transmissions in a limited number of volunteers in different places, quite apart from the technical problems of the preparation of suitable inocula in the laboratory.

Space alone prevents me from a careful consideration of the individual experiments, but for those who are interested the results are all available in the M.R.C. Report.

Discussion

Acute infective hepatitis, the old catarrhal jaundice, has a long history, and we can read of its sporadic incidence and of occasional epidemics over a period of many years.

Homologous serum jaundice has only a short history, for even if the outbreaks of syringe-transmitted hepatitis in V.D. clinics are included, that takes us no further back than about 1910 at the earliest. Moreover, since the infective agent, so far as is known, is transmitted only by parenteral injection—therapeutic or accidental—of blood or blood products, the possibility of this being a new or hitherto unrecognized disease would, in my view, require the most convincing proof. Such a disease would, on the face of it, seem to stand a poor chance of long survival without a natural means of spread.

It is worth while to compare and contrast the two conditions in the light of our present incomplete knowledge, and note their similarities and differences. There is complete agreement that their clinical features and pathology (Dible, McMichael, and Sherlock, 1943) are identical, but that their period of incubation is different. The means of transmission of homologous serum jaundice seems to be clear-cut and entirely artificial, unless we have been completely led astray. Acute infective hepatitis, on the other hand, can obviously spread rapidly by natural means, but there is not yet full agreement about the portal of entry. Field observations among our combatant forces during the war pandemic strongly suggested the agency of flies and faeces—that is to say, entry by the mouth into the alimentary tract. In civilian outbreaks, especially among children, the majority verdict has always been in favour of droplet-infection through the nasopharynx. These two views do not seem to be completely incompatible, for by both methods the virus would at some time be in the mouth, and it is not necessary to assume that a primary nasopharyngeal infection must always pass on to the trachea and lungs. On the whole, the most likely portal of entry would seem to be the mouth, since we are dealing with a disease which obviously involves the gastro-intestinal system quite early—the stomach first, soon followed by hepatic enlargement and jaundice. The possibility of faecal infection of the fingers in school-children cannot be ignored, especially when one thinks of the notorious frequency of typhoid fever among the nursing attendants of this disease even in well-known hospitals.

The transmission experiments to human volunteers, already briefly described, present real difficulties, and it is true that the relatively small number so far carried out, both in Britain and in America, have strongly suggested to the investigators that there are two diseases—one due to virus A and the other to virus B.

It may seem bold to doubt this conclusion, but, as I have stated, I hold that the experiments so far reported are still quite inadequate for proof. If the careful account of them in the M.R.C. Report is read, the inherent difficulties will be fully realized, and it will be noted how many of the attempted transmissions were negative in comparison with the positives. The only result which seems certain—and it is of the greatest epidemiological and practical importance—is that the virus of acute infective hepatitis is present in the faeces in the acute stages of the disease.

If I suggest, as I now intend to suggest, that we are dealing with only one disease, and not two, what evidence can I marshal in favour of my hypothesis?

I must assume that the single virus, already well spread through the community, especially in children, for a number of years, can survive in the body of a previous sufferer from the disease for a long but indefinite time. To account for homologous serum jaundice my argument would necessitate the presence, from time to time at least, of the virus free in the blood stream. To account for acute infective hepatitis a long-term carrier state with the virus in the faeces is all that need be considered.

Let us now examine these two possibilities. I admit frankly my difficulties in trying to explain the presence of

the virus, even from time to time, in the blood serum of a healthy blood donor with no previous history of jaundice. It is well known that acute infective hepatitis may occur without any obvious trace of jaundice at all, and in civil practice may very easily be missed. I saw many cases of this kind during the war pandemic, but, being on the alert, had no doubts about the diagnosis. I cannot, however, explain the continued presence of the virus in the blood, because I know so little of how viruses live and how long they survive under differing conditions. I can only think of one analogy, from my own clinical experience, which may or may not be significant. I have seen cases of herpes, particularly herpes labialis, in which the virus seems to live quietly for many years but makes its presence known only when some other infective process occurs in the body.

In connexion with a resting reservoir of the virus of infective hepatitis in the faeces of a previous sufferer—recognized or unrecognized—from the acute disease, I have something to say based on my past experience of the carrier state in a bacterial disease.

In the Ypres salient, in the early part of the first world war, I had the remarkable experience, partly shared with the late Adrian Stokes, of hunting out successfully hundreds of typhoid carriers among Belgian refugees who were infecting our troops in their billets behind the lines. These unfortunate carriers were shown to be carriers only when diarrhoea was deliberately induced, and without the field help of the Friends Ambulance Unit and a convenient drug swallowed on the spot (calomel) the labour would have been in vain. I have long concluded, with good clinical evidence to support me (chronic typhoid cholecystitis and gallstones, outbreaks traced to an unrecognized carrier 40 years after the acute fever), that most patients who have had typhoid fever continue to harbour the specific bacilli in their upper intestine for life. When they are well they are safe, for the bacilli are rapidly outgrown in their slow passage through the colon; but when diarrhoea is present they may be active and dangerous carriers of the disease.

I cannot say if this analogy will hold between a bacillus and a virus, but I suggest that this point may be worth bearing in mind when considering the possibility of chronic faecal carriers of infective hepatitis in outbreaks of the disease. This hypothesis could be tested now only by further transmission experiments to human volunteers, and these are unlikely in Britain. Otherwise we must wait until the virus can be cultivated and identified in a laboratory, or some animal is found to be susceptible to the disease.

I must not avoid the problem of the two incubation periods—about 30 days and about 90 days—and it is true that most of the other virus diseases of which I have clinical experience (smallpox, measles, influenza) have a remarkably constant incubation period, or at least one not varying within wide limits. I can only suggest, for clearly I do not know, that there may be some difference, worth investigating in virus laboratories, between a virus when free in the faeces and when contained or constrained in some way in the blood. Lichtman (1949) puts forward a similar point of view, and suggests that the virus may become attenuated in the blood serum.

Prevention and Control

Acute infective hepatitis in its epidemic form is not at present subject to any possible control, and we must await the cultivation of the virus in the laboratory before any question of active immunization could arise. We are really in the same position about acute poliomyelitis, another virus disease in which the faeces may be a reservoir.

Syringe-transmitted hepatitis and homologous serum jaundice obviously could be controlled if we knew a certain way of destroying the virus in the serum. Considerable steps have already been taken in this direction by means of exposure to ultra-violet light, but the results are still insecure.

All pooled quantities of human sera appear to contain antibodies of some kind to the virus of hepatitis in the globulin fraction, and "immune globulin," in doses of 10 ml., has already been used with some success as a preventive after blood transfusion.

This, however, concerns only individuals, and not the great problem of a major epidemic.

Summary

In this Harveian Lecture I have tried to put before you some of my thoughts on acute infective hepatitis and on the conditions known as homologous serum jaundice and syringe-transmitted hepatitis.

I remain so far unconvinced, for reasons I have given, that we are dealing with more than one disease, due to a single virus and not to two.

There are still many things to explain, which only future advances in our knowledge of viruses can make clear.

The virus of acute infective hepatitis is now widely spread throughout the world. The disease occurs sporadically and in small outbreaks at frequent intervals, and has already once exploded in real pandemic form. In these respects it resembles influenza.

Having once rapidly spread as a pandemic, this course of events might be repeated at any future time. In this sense the disease has thus become a problem of world health.

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C. E. Vulliamy, in his book of essays *Rocking Horse Journey* (1952, p. 94), writes: "Miss Cobbe [Frances Power Cobbe, 1822–1904, philanthropist and religious writer] is probably the only person who has ever suggested that our highly respectable scientific publications, the *Lancet* and the *British Medical Journal*, were the corrupters of youth in public libraries. 'Who would have thought 30 years ago,' she wrote, 'of seeing young men in public reading-rooms snatching at the *Lancet* and the *British Medical Journal* from layers of what ought to be more attractive literature and poring over hideous diagrams and revolting details of disease and monstrosity?'"