Serum Hepatitis and the Seroprophylaxis of Measles

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Dedicated to Prof. Werner Schäfer on the occasion of his 60th birthday

The events leading to the recognition of serum hepatitis ("homologous serum jaundice") as a disease entity are described and reasons given why seroprophylaxis against measles played an important role in this discovery. The injection of human serum as a prophylactic was practised on an increasing scale from about 1920 to about 1950, by which time it had largely been superseded by immunoglobulin (gamma globulin). Apart from the transfusion of blood and blood products the other major human to human transfer of material was vaccination against yellow fever in the years 1937—1940. The consequences of this large scale interchange between human subjects included the dissemination of serum hepatitis virus, and the possibility of transfer of other viruses is discussed.

Serum hepatitis has recently become amenable to laboratory study, in spite of the fact that the virus which causes it has not yet been isolated. Much of the interest in the disease has centred around the patients and staff of renal dialysis units and those involved in renal transplantation, but the treatment of chronic renal failure is only one of a number of situations involving operative treatment of the patient and the transfusion of large volumes of blood, either as repeated small transfusions or as a large quantity given at once. Transplant surgery and major cardiac surgery are, like renal dialysis, procedures which twenty years ago were performed on relatively few patients, but have now become routine measures practised widely on relatively large numbers of patients, and they too have contributed to the increase in the quantities of blood and plasma transfused. There has also been an increasing range of blood products, such as anti-haemophilic globulin, cryoprecipitate, concentrated platelets and radioiodine-labelled fibrinogen, some of which are available as preparations pooled from several donors. In addition, some of these situations involve either artificial suppression of the immune response, as after transplants, or a natural diminution in this response, as in the uraemic patients on long-term renal dialysis.

There has also been a steady increase in the number of surgical operations, and in elaborate diagnostic procedures such as cardiac catheterization and various radiological investigations, all entailing at least some spillage of the patient’s blood and its contact with doctors and perhaps other patients. The application of these techniques has of course entailed an enormous increase in laboratory investigations involving the handling of samples of blood and serum. This increase in the scale of laboratory investigation extends also to non-surgical patients, for example to those undergoing intensive therapy for leukaemia or chorion-carcinoma, such therapy involving the combination of blood transfusion and immuno-suppression.

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It is now known with certainty, from experiments with human volunteers, that serum hepatitis (SH) is caused by a filterable agent, which is presumed to be a virus, and that it is different serologically and biologically from the agent of epidemic infectious hepatitis (IH) which is also thought to be a virus. Biologically, the principal difference is the dependence of SH virus upon artificial procedures for its transmission, although it is now clear that it can, even if less readily, be passed, too, by the oral route, as IH can, and probably by air-borne spread also. The practical development which has made SH more accessible to study is the discovery of the Australia antigen, a substance found in the blood of patients at some stage of the disease, and of symptomless carriers. The exact constitution of Australia antigen varies from patient to patient, particularly in the proportion of the characteristic large particles first described by Dane, Cameron and Briggs, particles which are at present believed to represent the virus itself. The Australia antigen, and also antibody to it, can be detected by various serological techniques. Besides the confirmation of its association with the disease itself, the techniques now to hand have enabled the mapping of its geographical distribution and hence, by extrapolation, the virus, throughout much of the world. Its distribution is high in the countries and islands of the Pacific, in the accessible parts of South-east Asia generally, in tropical Africa and in central and southern America. It is much lower in northern America and North west Europe. A high incidence of the antigen in an area is usually associated with a high carrier rate, but not necessarily with a high incidence of the disease, at least in a clinically obvious form.

It is generally supposed that there has been an increased incidence of SH in recent years in various developed countries, especially Japan and the U.S.A. For example, in New York City there was a rise of approximately 50% in the number of reported cases of SH in the first five months of 1969, compared with the same period in 1968. The question arises as to why there has been this recent increase in its incidence in areas such as the U.S.A., an increase which has been particularly marked in hospital practice. Various suggestions have been made. The virus may have been present in a relatively small number of symptomless carriers, but has recently found it possible to emerge more and more into the open because of the increase in the number, variety and complexity of medical manipulations. If so, and if it is passed principally by physical contact, if may well be asked how it managed to maintain its existence before this time? In fact this would be not such a difficult matter as may be supposed. Medical (and dental) procedures may have had less variety, and the population been lower, but both people and procedures were dirtier, and the cutting, cupping, bleeding and leaching (not to mention activities such as acupuncture and tattooing) which went on before the age of asepsis were that much more likely to transmit anything from syphilis to SH. The rise in addiction to narcotics (involving intravenous injections with unsterilised and frequently shared syringes) may be an additional factor, but this may be counterbalanced to some extent by the almost total replacement of the glass syringe by its disposable counterpart in many countries, thus eliminating, for example, the transfer of SH virus by syringes in venereology clinics and indeed in medical practice in general. Probably the increase is attributable to several factors working together, including the increased number, variety and complexity of medical procedures, and the increased use of blood and blood products involved in present day medical practice.

The recognition of serum hepatitis as an entity

It is now nearly 100 years since the first clearly identifiable outbreak of SH in an area of low Australia antigen incidence was reported, and some of the principal recorded and well documented outbreaks between then and the time when the entity of "homologous serum jaundice" was recognised are given in Table 1. The first recorded outbreak in North west Europe was among the employees of a large firm in the seaport of Bremen in 1883. Many of these had been vaccinated against smallpox, and the source of the hepatitis virus is likely to have been the human serum used in the vaccine, because the incidence varied from batch to batch among the several batches of vaccine used. About the same time, an outbreak which, judging by the long incubation period involved, is also likely to have been SH rather than IH, occurred in an institution for mental defectives at Merzig in the Saar, in 1885, again following large scale smallpox inoculation. Here
the source could have been a hepatitis carrier among the patients, and was not necessarily a constituent of the vaccine. These two outbreaks are briefly reviewed by Gardner. The cases of "acute yellow atrophy" of the liver recorded by McDonald in 1908 and 1918 in syphilitic patients receiving arsenotherapy were probably examples of SH, although the danger of transmission of SH virus by syringes was not generally realized for many years. An outbreak among diabetic patients, in whom of course both blood-taking and injections are common, was reported in 1938 by Graham.

The matter of transmission of SH by medical procedures came to a head almost simultaneously over measles prophylaxis using human serum, on the one hand, and over yellow fever vaccination using Théier's 17D vaccine containing human serum on the other. By this time, i.e. the middle of World War II, human serum used for prophylaxis of other infections, e.g. mumps, had also become involved, as well as other procedures, summarised in Table 1. During World War II the term "homologous serum jaundice" was coined, and the unity of the syndrome, and hence probably the uniformity of the causative agent, recognised.

Table 1. Some reported outbreaks of serum hepatitis, arranged chronologically.

<table>
<thead>
<tr>
<th>Date</th>
<th>Authors</th>
<th>Procedure</th>
<th>Recipients</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1883</td>
<td>Lürman</td>
<td>Smallpox vaccination</td>
<td>+</td>
<td>Virus vaccination</td>
</tr>
<tr>
<td>1908</td>
<td>MacDonald</td>
<td>Arsenical injections</td>
<td>+</td>
<td>Syringe transmission</td>
</tr>
<tr>
<td>1918</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1936</td>
<td>Findlay and McCullum</td>
<td>Yellow fever vaccination</td>
<td>+</td>
<td>Virus vaccination</td>
</tr>
<tr>
<td>1937</td>
<td>MacNalty</td>
<td>Measles prophylaxis</td>
<td>-</td>
<td>Seroprophylaxis</td>
</tr>
<tr>
<td>1938</td>
<td>Properties</td>
<td>Yellow fever vaccination</td>
<td>+</td>
<td>Virus vaccination</td>
</tr>
<tr>
<td>1938</td>
<td>Soper and Smith</td>
<td>Hospital diabetic patients</td>
<td>+</td>
<td>Syringe transmission</td>
</tr>
<tr>
<td>1938</td>
<td>Graham</td>
<td>Yellow fever vaccination</td>
<td>+</td>
<td>Virus vaccination</td>
</tr>
<tr>
<td>1942</td>
<td>Morgan and Williamson</td>
<td>Transfusion of plasma or serum</td>
<td>+</td>
<td>Blood transfusion</td>
</tr>
<tr>
<td>1944</td>
<td>Beeson et al.</td>
<td>Mumps prophylaxis</td>
<td>+</td>
<td>Seroprophylaxis</td>
</tr>
<tr>
<td>1944</td>
<td>McFarlan and Chesney</td>
<td>Arsenical injections</td>
<td>+</td>
<td>Syringe transmission</td>
</tr>
</tbody>
</table>

1. Vaccination against virus diseases with vaccines containing human serum.
2. The use of non-disposable syringes and other instruments for medical procedures.
3. The transfusion of blood and the administration of blood products.

These four procedures differ in the date of their introduction and widespread adoption, in the quantity of material transferred from one patient to another, and in the ages both of the donors and the recipients. These differences will be considered in each case, and with particular regard to the likelihood of the procedure causing either the disease SH, or disseminating the virus in such a way as to produce the carrier state in the recipient.

1. Vaccination against virus diseases — This has not ceased to be practised since the time of Jenner. It seems to have been a common practice to add human serum, usually of rather uncertain provenance, to vaccines. From the data given by Lürman, the outbreak in Bremen in 1883 was attributable to the human serum in particular batches of vaccine, but the hygiene of medical practice in the 1880's had scarcely emerged from pre-Listerian days, and Jehn's outbreak in the institution at Merzig may well have originated, as suggested above, with one of the mental defective inmates rather than with the smallpox vaccine itself. The cases arising from yellow fever vaccination 60 years later are undoubtedly attributed to the human serum in the vaccine. The quantity of serum was relatively small, because of dilution in the vaccine, it came
from adults, and the recipients were principally adults. However, it is significant that in the mass vaccination against yellow fever performed about the same time in Brazil, the incidence of overt jaundice in children was less than that in adults receiving the same batch of vaccine. The significance of this difference will be discussed later.

2. Transmission by syringes and other instruments — This came to light next, and may have arisen from the introduction of organic arsenical compounds for the therapy of syphilis in the 1900’s. The mechanism of transmission here probably differed from that causing SH among diabetics, in whom it is more likely to have been caused by finger pricks for blood sugars than by the use of communal syringes. The quantity of material transferred would be comparatively small, and both donors and recipients would be largely, though by no means exclusively, adolescents or adults.

3. The transfusion of blood and blood products — Blood transfusion, although adopted before 1914, and although receiving some impetus from the 1914–18 war, was not practised, even in countries with advanced and sophisticated medical practice, on any large scale until the mid-1930’s. It received a great impetus from the need for organised services for civilian and service casualties in the 1939–1945 war, and the use of pooled plasma was introduced about 1940–41. The work of Cohn and his colleagues on blood proteins in the 1930’s paved the way for the adoption of gamma-globulin about 1944–45, but this was not widespread until the 1950’s. Leaving aside gamma-globulin and specific blood products, it may be said that blood transfusion involves what is by microbiological standards a very high dose of material passing from donor to recipient, and that, while donors were virtually exclusively adult, recipients were principally, but by no means exclusively, adults, since even babies received blood transfusions, in spite, of the technical difficulties, quite early after blood transfusion became a generally available measure.

4. The serophrophylaxis of bacterial and viral infections with human serum — The infections concerned in this fourth category, are principally pertussis, mumps, and measles, although human serum was also tried for the prophylaxis of varicella. In the sheer quantity of prophylaxis performed, and the seriousness of the disease, measles overshadows all the others. There seems to be no outbreak of SH attributable to serophrophylaxis for pertussis, although from the report of Smith in 1936 it is clear that human serum was being used quite extensively for the purpose at that time. The use of convalescent serum for the prophylaxis of mumps seems to have been on a lesser scale than for either pertussis or measles, but SH did follow its use in British and United States troops in World War II. This leaves measles, a disease against which serophrophylaxis was practised, in the years between 1916 (its earliest known large scale use) and about 1950 (by which time it was falling into disrepute) on a scale much greater than may be generally realized.

Compared with the three previous categories of procedure (viz. inoculation of vaccines containing human serum, syringe transmission and the transfusion of blood), there are interesting differences in the circumstances of measles prophylaxis. The donors were at first all convalescent children who could yield only small volumes of blood, and the rare convalescent teenager or adult must have been a much sought-after individual. Later it was appreciated that, because almost every adult had in childhood suffered from measles, non-specific adult serum was also effective although it needed to be used in larger doses. The volumes used, compared with the size and age of the recipient, were often relatively large for a small child, e.g. up to 40 ml, either of whole blood or of serum.

The procedure was highly effective, and in view of the then prevailing mortality of measles in certain groups of children, can well be justified. More and more serum from adults was used, and pooling became the accepted procedure, although in fact the use of pooled serum had been reported early by Richardson and Connor in 1919. Indeed it was the use of a pool of 880 ml of sera from no less than 26 donors which caused the severe outbreak in England in 1937 reported by MacNalty involving 41 cases with 8 deaths. This first brought the danger to light, and yet, surprisingly, did not bring the procedure into disrepute, for the use of measles convalescent serum seems to have continued well into the 1950’s, in spite of the introduction, effectiveness and safety of gamma-globulin. While it may be argued that it was the use of larger and larger pools of adult serum which increased the chance of a disaster eventually occurring, another
explanation is possible. It may be that from about 1920 onwards a generation had been temporarily protected, passively, against measles, but seeded, some of them permanently, i.e. as carriers, with the SH virus, and when they, as adolescents or young adults, contracted measles, the next generation of children, recipients of their serum, developed hepatitis in sufficient numbers to draw attention to the phenomenon.

Considerations in the use of human serum in the prophylaxis of measles

Justification for the procedure: Because of the low mortality of measles in the developed countries today it may be forgotten how high the mortality has been in the past, let alone the trail of complications and sequelae. So far as mortality is concerned, for example, this was 5.8% in children over 5 (and much higher at ages below this) in Glasgow in 1908. In comparison with other diseases at this time, measles killed more children in Vienna in 1912 than scarlet fever, pertussis and diphtheria put together. In the years 1891-1900 the mortality was 10.99% in the poorest quarters of the city and only 0.55% in the richest. In 1913 in the U.S.A. there was 8,108 deaths from measles as compared with 4,588 from scarlet fever, pertussis and diphtheria put together. In the years 1900 to 1911 in the U.S.A. it is estimated that 100,000 children died from measles and, in New York City as late as 1922 there were 977 deaths from measles.

These figures, selected somewhat at random, show that the problem at that time was a serious one, and that the burden fell on the poorest children. In particular it fell upon institutionalised children, and in infants’ homes a mortality as high as 26% has been recorded in an outbreak in Central Europe. There was therefore a real urgency and a genuine justification for attempting to prevent the disease if possible, and to contain an outbreak when one occurred.

The scale of seroprophylaxis against measles: It is not surprising that the rise of serotherapy and the great success of diphtheria antitoxin, as well as the then reasonably justified view that human sera were sterile fluids (provided syphilis and tuberculosis had been excluded), should lead to the suggestion of the use of human sera as a source of antibodies against measles. Once it had been tried and found to be effective there was justification for further extension and its use on as large a scale as possible. Admittedly the protection given was only passive, but it could stave off the disease until the child was older and it could prevent or contain an institutional outbreak. In 1923 DEBRE and REVINA showed that it could, if given at the right time, help to confer a permanent active immunity, and this provided even further justification for the procedure. There is evidence that the technique was in widespread use on a large scale throughout the 1920’s and 1930’s. For example DECKWITZ in Munich in 1921 had a highly organised service and was issuing at least 1500 doses of anti-measles serum a year. Some idea of the extent of the practice can be gleaned from Table 2. For example, in 1930 children were being immunised at the rate of some 3000 a year in New York, a city whose population at that time was about 6,000,000. It was not until 1937 that the occurrence of jaundice was first reported by MACNalty in England, the outbreak concerned being that previously mentioned, with 41 cases and 8 deaths. In the same year, PROPERT reported seven cases in an institution for mental defectives, and later others were found.

The inculmination of this procedure in the spread of serum hepatitis: It may be asked why a period of about 20 years elapsed between the first use of measles prophylaxis with human serum and the realization that serum hepatitis could be transmitted in this way. The reasons are various, complex and in some respects interconnected with each other:

a) Lack of recognition of the connection with the inoculation — The incubation period of SH is so long that the connection with the prophylactic inoculation was not easily recognised, or the case of jaundice could have merged into the background of infective hepatitis prevailing at the time. There was apparently little organised follow-up once the danger of measles was over, or only a brief one, although HAAS and BLUM mention a period of 16 months in their study.

b) Lack of risk from the donor — At first small quantities were used and sera were not usually pooled. Then, to even out the effect of the poor antibody producers, and also for convenience, sera were pooled. Then large doses were given when it was realized that protection was dose-dependent, and when an adolescent (or even more rarely an adult) convalescent case was available. The next
<table>
<thead>
<tr>
<th>Date</th>
<th>Numbers inoculated</th>
<th>Authors</th>
<th>Place</th>
<th>Source of serum, blood or plasma</th>
<th>Pooling (If stated, with number of donors in pool)</th>
<th>Period of follow-up (If mentioned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1916*</td>
<td>48</td>
<td>PARK and ZINGHER</td>
<td>New York</td>
<td>Convalescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1916**</td>
<td>1</td>
<td>NICOLLE and CONSEIL</td>
<td>Tunisia</td>
<td>Convalescent (brother)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1919</td>
<td>14</td>
<td>RICHARDSON and CONNOR</td>
<td>Providence, U.S.A.</td>
<td>Convalescents</td>
<td>+ (2—8)</td>
<td></td>
</tr>
<tr>
<td>1920</td>
<td>172</td>
<td>DEGKWITZ</td>
<td>Munich</td>
<td>Convalescents, Adults***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1921</td>
<td>145</td>
<td>KUTTER</td>
<td>Berlin</td>
<td>Convalescents, Adults***</td>
<td>+ (3)</td>
<td></td>
</tr>
<tr>
<td>1921</td>
<td>261</td>
<td>von TORDAY</td>
<td>Budapest</td>
<td>Convalescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1922</td>
<td>16</td>
<td>MCEAL</td>
<td>Rochester (Minn.)</td>
<td>Convalescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1922</td>
<td>„At least 1500 per annum“</td>
<td>DEGKWITZ</td>
<td>Munich</td>
<td>Convalescents, Adults***</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>1922</td>
<td>„6—8 per week“</td>
<td>DEBRÉ and RAVINA</td>
<td>Paris</td>
<td>Convalescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1924</td>
<td>102</td>
<td>ZINGHER</td>
<td>New York</td>
<td>Convalescents, Adults***</td>
<td>+ (3)</td>
<td></td>
</tr>
<tr>
<td>1924</td>
<td>48</td>
<td>WEAVER and CROOKS</td>
<td>Chicago</td>
<td>Convalescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1926</td>
<td>„More than 1500 in a period of 6 months“</td>
<td>PARK and FREEMAN</td>
<td>New York</td>
<td>Adult convalescents</td>
<td>3 weeks</td>
<td></td>
</tr>
<tr>
<td>1926</td>
<td>95</td>
<td>HAAS and BLUM</td>
<td>New York</td>
<td>Adult and child convalescents</td>
<td></td>
<td>16 months</td>
</tr>
<tr>
<td>1926</td>
<td>395</td>
<td>KINGSBURY</td>
<td>Kuala Lumpur</td>
<td>Convalescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1927—28</td>
<td>206</td>
<td>GUNN</td>
<td>London</td>
<td>Convalescents</td>
<td>+ (3 or more)</td>
<td></td>
</tr>
<tr>
<td>1929—30</td>
<td>513</td>
<td>MORALES and MANDRY</td>
<td>Porto Rico</td>
<td>120 convalescents, 393 adults***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1930</td>
<td>116</td>
<td>BARENBERG et al</td>
<td>New York</td>
<td>60 convalescents, 56 adults***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1931</td>
<td>628</td>
<td>NABARRO and SINGY</td>
<td>London</td>
<td>Adult convalescents only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1937</td>
<td>109</td>
<td>England (various)</td>
<td>Convalescents</td>
<td>+ (26)</td>
<td>41 cases</td>
<td>(8/41 died)</td>
</tr>
<tr>
<td>1936—38</td>
<td>158</td>
<td>Ministry of Health</td>
<td>Convalescents</td>
<td>+</td>
<td>22 cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>memorandum (Lancet 1943)</td>
<td>Adults</td>
<td>+</td>
<td>6 cases</td>
<td>(1/6 died)</td>
</tr>
<tr>
<td>1932—42</td>
<td>36,000</td>
<td>Ministry of Health</td>
<td>Convalescents, Adults</td>
<td>+</td>
<td>2 month follow-up</td>
<td></td>
</tr>
</tbody>
</table>

* Reported 1924  ** Reported 1918  *** Adults = non-specific (i.e. non-convalescent) adults.

Table 2. Measles prophylaxis with human serum.

A step was that non-convalescent adult serum, i.e. serum, or sometimes blood, from anyone who had had measles (and this meant virtually all adults) was used. When the effectiveness even of this material was also realized, these sera began to be pooled also, and it is almost certainly significant that the outbreak mentioned above which brought the matter to light was caused by a pool from no less than 26 donors.  

C. The immune situation in the recipient — There are two particular considerations here, viz., the age of the recipient and the intrinsic nature of measles infection itself. In the first place, the great majority of recipients of anti-measles serum were children under the age of 8 and the majority under the age of 5. It appears that at such an age children who are infected with SH virus are more likely to develop a subclinical infec-
tion without overt jaundice than to present with a \textit{frank} clinical hepatitis. This is clear from the work with yellow fever vaccine administered to children in Brazil in 1942\textsuperscript{18}. They may also at this age have a higher resistance to infection at all, or, a third probability, they may have a higher capacity of acquiring some measure of tolerance to the SH virus and become carriers, perhaps for life. Haemophiliacs are also interesting in this connection, since they are prone to receive multiple administrations of blood products from an early age, with a consequent risk of exposure to SH virus, but rarely develop overt hepatitis.

So far as measles infection, considered as a biological process, is concerned it is interesting and perhaps unique among the acute childhood infections in that it produces a state of dysimmunity in the patients. This has been described in detail by Kempe and Fulgniti\textsuperscript{58}. For example, children with measles have an abnormal tuberculin reaction\textsuperscript{39, 49}. Those who are asthmatic suffer less from asthma and those with nephrotic syndrome or eczema improve, at least temporarily. It would not therefore be surprising if a child developing or incubating measles, and injected with SH virus, reacted abnormally to the virus. Using vaccine strains of measles it has been shown that interferon production does not occur for about a week after infection. This would allow time for immunological misfortune, perhaps for acquisition of a degree of genuine immunological tolerance to SH virus, to occur in a child whom measles and SH virus were unwittingly enabled to infect at approximately the same time.

\textbf{Consequences and implications}

It is interesting to note from Table 1 that, of all the procedures mentioned, the seroprophylaxis of measles was the one case where most of the recipients, or potential recipients, of SH virus were children rather than adults. These are not only those most likely to become carriers, for the reasons stated above, but are those who have the longest expectancy of life. In fact when the actual years involved are scrutinised it is clear that the procedure was at its height between 1916 and 1946, i.e. that it involved principally the generations born from about 1910 to 1940. These recipients will have lived on into the age of large scale surgery and of frequent blood donation and blood transfusion mentioned earlier, in fact into the age of what have been called the super-techniques, into a day of rising addiction to hard drugs taken by intravenous injection. It is also true that in this period there was still by our present standards comparatively poor hygiene, since syringes were communal and not always heat-sterilized, and were rarely disposable. It seems therefore that a significant number of the present adult population of North America and of some countries of Europe (aged $30-70$) may have been seeded with SH virus by one means or another. This does not of course answer the question of the original genesis of the virus, but studies of the distribution of Australia antigen, and by implication the virus, suggest that it is at least possible that it was originally an insect-born virus which has reached other countries at a medically opportune era and become established partly with the help of the medical profession, although this is of course speculation.

This hypothesis would suggest that we are dealing with a virus transmitted predominantly by mechanical means, either by arthropods, or by human activities, or by both. It would have been prevalent in certain areas of the world, e.g. Central Africa and the Pacific littoral, and became introduced into the Northern hemisphere in the 19th century. A parallel is provided by yellow fever, which, with the general expansion of travel in the 19th century, caused an outbreak, with some 6000 deaths, in Lisbon in 1857, and an outbreak in Wales with 13 deaths, at about the same time. It is just possible that the latter was in fact SH rather than yellow fever. Even assuming that it was yellow fever, this does not exclude the possibility that it was spread to the North Atlantic countries at the same time. If it had been smouldering in Europe all the time, we might expect a high background incidence of Australia antigen in Europe today. These were the years when the steamship, together with the building of the Suez Canal, brought south east Asia within easy reach of Europe within the incubation period of SH.

It is also interesting to speculate whether the present generation of adult haemophiliacs, as well as many adult diabetics, contain within them, as a kind of "epidemiological fossil", the SH virus which many of them received early in life. Such a suggestion would be borne out by the finding of
CHERUBIN et al. from the Harlem Hospital, New York, that in spite of the high incidence of Australia antigen-positive blood transfused, the occurrence of clinical hepatitis in recipients is surprisingly low.

The present situation with regard to serum hepatitis is one largely of our own creation, but it is a situation which is not beyond our control. It can be contained by good techniques, and the SH virus should be treated with respect rather than panic. It will always remain a hazard until every individual is, in as full a sense as possible, a medical problem. Nevertheless, it is likely that acute serum hepatitis and chronic non-malignant liver disease are likely to increase in incidence, and indeed there is reason to suspect that the first of these two is doing so.

There is another and more speculative consideration. It is by no means unlikely that other agents, at present undetected and undetected, perhaps with extremely long latent periods running into years (rather than months as in the case of SH) have been seeded artificially in the population concerned. Where there has been an apparently inexplicable rise in incidence of a particular disease in one of the relevant age groups, a virus with a long incubation period should be considered as a possibility. Certainly there was in the years 1920–50 a very large scale transfer of material from man to man, quite apart from the transfusion of blood. For example, the number receiving yellow fever vaccine containing human serum ran into the millions 18, 43. The transfer of a virus which persisted for years and later caused disease could, for example, explain the otherwise unaccountable element in the increase in acute leukaemia in recent decades 42, while some recently described viruses of man, e.g. some papovaviruses, and the reoviruses, at present scarcely associated firmly with any one disease, could also have been unwittingly spread, with long-term consequences yet to be disclosed. The population concerned should be regarded in the light which these considerations of the particular case of serum hepatitis may throw on artificially transmitted human disease of long incubation period in general.

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Neuraminidase antibodies are known to inhibit hemagglutination by X-15 and X-15(HK) recombinant viruses. However, the level of inhibition observed varies when different batches of chicken erythrocytes are employed, and the test generally detects neuraminidase antibodies with less sensitivity than an enzyme inhibition test. By titrating neuraminidase antibodies in the presence of anti-IgG globulins, with appropriate specificity, the hemagglutination-inhibition activity of neuraminidase antibodies is enhanced and the effect of cell variation is minimized. Consequently results obtained with this modified method for titrating neuraminidase antibodies become comparable to those obtained by measuring enzyme-inhibition. The improved hemagglutination-inhibition procedure possesses the important advantages of greater convenience and economy. Similar enhancing effects may also be obtained with egg white and guinea pig serum.

Materials and Methods

Human sera

For use in most experiments, pools were prepared employing equal aliquots from 24 or more serum pairs. These serum specimens were obtained from army recruits bled before and after vaccination in 1968 with 300 CCA units of A2/Aichi/2/68 virus. In one experiment paired specimens from this vaccine group and from another group receiving 250 CCA units of A2/Japan/305/57 vaccine in 1957 were employed. The bleeding interval was two weeks in each case. Sera were used untreated in the neuraminidase enzyme inhibition (NI) test, and were treated with trypsin-periodate 10 for the hemagglutination inhibition (HI) test. All specimens were devoid of antibodies to the hemagglutinin of A/Equine/1/Prague/56 virus.

Viruses

Seeds of recombinant viruses X-15 and X-15(HK) were kindly supplied by Dr. E. D. Kilbourne. Both viruses contain hemagglutinin antigen derived from A/Equine/1/Prague/56 virus. However X-15 contains neuraminidase antigen derived from A2/RI/5*57 virus 11, whereas X-15(HK) contains neuraminidase