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EXPERT COMMITTEE ON HEPATITIS

First Report

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EXPERT COMMITTEE ON HEPATITIS

First Session

Liège, 21-26 July 1952

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EXPERT COMMITTEE ON HEPATITIS

First Report[1]

The problem of hepatitis was considered by the Third World Health Assembly and the following resolution was adopted:

"The Third World Health Assembly,

Considering the high incidence and wide distribution of epidemic hepatitis and the serious practical problem involved by the possible conveyance of serum hepatitis by blood transfusions and parenteral application of human blood derivatives,

REQUESTS the Executive Board and the Director-General to make arrangements for convening, in 1952, an expert committee to consider the problems of epidemic and serum hepatitis and to make relevant recommendations."[2]

The Expert Committee on Hepatitis held its first session in Liège from 21 to 26 July 1952. Professor J. R. Paul was elected Chairman, Professor G. C. O. Olin, Vice-Chairman, and Dr. F. O. MacCallum, Rapporteur.

1. Introduction

In this report the attempt has been made to assemble briefly the available information on the epidemiological and public-health aspects of those forms of virus hepatitis which are now designated as "infectious hepatitis" and "serum hepatitis". These two, probably related, diseases are almost identical clinically, but their methods of control deserve separate consideration. While these diseases are not new, they have been recognized with increasing frequency; and the growing use of parenteral forms of therapy has probably been responsible for a great increase in actual numbers of artificially transmitted cases of hepatitis. Furthermore, several

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[1] The Executive Board, at its eleventh session, adopted the following resolution:
The Executive Board

1. NOTES the first report of the Expert Committee on Hepatitis;
2. THANKS the members of the committee for their work; and
3. AUTHORIZES publication of the report.

(Resolution EB11.R14, *Off. Rec. World Hlth Org.* **46**, 5)

[2] Resolution WHA3.30, *Off. Rec. World Hlth Org.* **28**, 25

new concepts regarding these forms of virus hepatitis have come into being within the past ten years ; perhaps the most important of these is that the condition previously designated as " catarrhal jaundice " is now recognized as a sporadic form of infectious (or serum) hepatitis.[3]

Both infectious and serum hepatitis appear to be common diseases, worldwide in distribution. In some epidemics there has been a relatively high mortality, and the diseases have become of social and economic importance. The classical cases are characterized by two stages of illness —a pre-icteric and an icteric stage—but it is also clear that many cases occur without clinically recognizable jaundice (non-icteric hepatitis). As a rule, the classical symptoms and signs include : anorexia, nausea, vomiting, abdominal distress, liver enlargement, and jaundice which may last for variable periods of from 1 to 8 or 10 weeks ; in a very small fraction of the cases, hepatic disease may be prolonged for a number of years.

No attempt will be made in this report to present a description of the clinical features of these diseases or to outline currently accepted methods of treatment, since these can readily be found elsewhere. Mention should be made, however, that antibiotics have no place in the treatment of the ordinary forms of these diseases. And it can be stated that there is no single diagnostic test as yet available which will allow one to recognize either infectious or serum hepatitis with certainty and that the numerous liver-function tests currently employed merely indicate the degree of liver damage which may occur in the course of the illness.

The committee has attempted to review briefly the existing knowledge regarding the etiological agents, their methods of spread, and the general circumstances under which these diseases are apt to occur. This is done in order to guide physicians, surgeons, and health officers in methods of control or prevention, and to indicate the present trends of research.

Experimental work on these diseases has been severely handicapped because of the lack of an experimental animal or of other means for propagating the virus to allow a study of the properties of the etiological agents and for the possibility of developing immunological tests.

One of the special features of the problem which these diseases present is that the agents causing them are more heat-resistant than are the usual (non-spore-forming) bacteria or viruses which cause disease in man.

The ease with which infectious and serum hepatitis have inadvertently been transmitted from one person to another has received special attention in the report because, as a result of the increasing use of parenteral forms

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[3] Under the heading of " infectious (or serum) hepatitis " one can now group the diseases previously known as " epidemic jaundice ", " catarrhal jaundice ", and some cases of acute yellow atrophy of the liver.

of therapy, the control of hepatitis transmitted in this way has become a problem of public-health significance.

2. Terminology

In view of the large number of terms which have been used to describe these diseases in the past, some of which are inappropriate, the committee considers it necessary to indicate a terminology which gives a more correct description of each disease.

The following terms have been widely used to describe one form of hepatitis: " infectious hepatitis ", " infective hepatitis ", " epidemic hepatitis ", " viral hepatitis (IH) " and " catarrhal jaundice ".

The committee strongly condemns the continued use of the term " catarrhal jaundice ". This term, which has been in common usage since 1855, is based on a misconception of the pathological processes involved, and has delayed recognition of the essentially infectious nature of the disease.

The first four names are based on the recognition of the pathology of the disease. However, the qualifying term " epidemic " does not reflect all aspects of the epidemiology since in many areas the disease is not epidemic, but endemic or sporadic. No such objection applies to the term " infectious hepatitis " which has the additional merit of emphasizing the infectious nature of the disease, which the term " infective hepatitis " fails to do.

The committee recognizes that there is merit in a term which stresses the virus etiology of the disease, but points out that the term " viral hepatitis (IH) " is incorrectly derived etymologically and that the qualifying expression " (IH) " stands for " infectious hepatitis ". Therefore, the committee recommends that this form of naturally occurring hepatitis should be known as " infectious hepatitis ", and will use this term in the present report. However, the committee sees no objection to the continued use of the term " epidemic hepatitis " in those countries in which the disease is predominantly epidemic.

In view of the present lack of knowledge concerning serum hepatitis, the committee is unable to recommend the adoption of a single term for this condition. The committee recognizes the widespread use of the following terms: " serum hepatitis ", " homologous serum hepatitis ", " inoculation hepatitis ", and " transfusion hepatitis ". The term " viral hepatitis (SH) " has also been used but is objected to for reasons already given in connexion with the term " viral hepatitis (IH) ".

For purposes of this report, the committee will use the term " serum hepatitis ", but this is not to be considered as condemning the other terms.

It is chosen solely for convenience, and the committee wishes to stress that it is to some extent misleading since the virus is found in whole blood and certain of its derivatives and not merely in the serum.

3. Differentiation Between Infectious and Serum Hepatitis

Recognizing the importance of being able to differentiate between infectious and serum hepatitis, the committee reviewed the clinical, pathological, and biochemical findings with the purpose of indicating distinguishing features. The committee concludes that there are no differences sufficiently characteristic to enable a differential diagnosis to be made in any given case. However, clinical studies which have been made on large groups in which the true diagnosis was reasonably certain on epidemiological grounds (i.e., typical epidemics of infectious hepatitis, or outbreaks associated with the large-scale use of icterogenic blood-products) have revealed small differences which, in conjunction with epidemiological evidence, may be regarded as suggestive. These, together with certain epidemiological differences, are summarized in table I.

TABLE I. COMPARISON OF CERTAIN FEATURES OF INFECTIOUS HEPATITIS AND SERUM HEPATITIS

Clinical and epidemiological feature	Infectious hepatitis	Serum hepatitis
Incubation period	15-40 days	60-160 days
Type of onset	Acute	Insidious
Fever—over 38°C (100.4°F)	Common	Uncommon
Seasonal incidence *	Autumn-winter	Year round
Age preference	Children and young adults	Any age

* Temperate climates.

On clinical grounds the difference in mode of onset is the only significant observation. In serum hepatitis the onset is usually insidious with little or no fever, the temperature rarely exceeding 38°C (100.4°F); and the preicteric stage with gastric symptoms is generally inconspicuous. Infectious hepatitis may have an insidious onset without fever, but it is more frequently acute, often with a temperature of over 38°C (100.4°F); the preicteric phase is often well marked with prominent gastro-intestinal symptoms. Later in the disease, no clinical differences can be detected.

No reliance can be placed on liver-function tests [4] in differentiating between the two forms of hepatitis. It is of interest, however, that, though

[4] A list of some liver-function tests will be found in Annex 1, page 25.

flocculation tests may be negative in as many as 20% of all cases, when positive they tend to be more strongly positive in the early stage of infectious hepatitis than in serum hepatitis.

Liver biopsy by needle puncture will not enable the two conditions to be distinguished.

The most useful epidemiological observation which will help in differentiating the two diseases is the incubation period. In infectious hepatitis due to virus A,[5] the incubation period is most usually 20-35 days, with extremes of 15 and 40 days. In serum hepatitis due to virus B,[5] the incubation period is generally between 60 and 160 days. However, it must be pointed out that hepatitis may follow inoculation of blood containing virus A, in which case the incubation period is usually 15-40 days.

In temperate zones, infectious hepatitis is most frequent in the autumn and winter, but summer epidemics also occur. In tropical regions, the seasonal incidence is less marked, and the disease may occur at any time of the year. The incidence of serum hepatitis is less influenced by season. These differences may be the result of different modes of spread.

Infectious hepatitis is predominantly a disease of children and young adults, although old people may be affected and some severe outbreaks have been recorded among middle-aged women. Serum hepatitis occurs in all age-groups. It has been suggested that it tends to be less severe in young children, but it is certainly not always so, since serious outbreaks among infants, with a high mortality, have been recorded.

4. Hepatitis Viruses A and B

It was agreed by the committee that, for the purposes of discussion, two viruses—A and B—would be considered, although the possibility that these may be only two variants of a single virus, or that there may be more than two viruses, could not be excluded.

By the term "virus A" the committee is referring to strains of virus which are associated with outbreaks of naturally-occurring infectious hepatitis. Virus B represents the agent which may be present in human blood which when inoculated parenterally produces hepatitis usually after a period of 60 to 160 days. The exact origin of virus B is at present unknown. A comparison of available information on these viruses is made in table II.

No satisfactory experimental animal has yet been found, and our knowledge of the viruses is based entirely on observations of naturally occurring and experimental infection in man. As it has not been

[5] See section 4.

TABLE II. COMPARISON OF HEPATITIS VIRUSES A AND B

	Virus A	Virus B
Filtrability:		
Seitz EK filter	Passed	Passed
Gradocol membrane with pore size 52 mμ	Not done	Passed
Susceptible host	Man	Man
Virus in faeces	Acute phase	Not demonstrated
Virus in duodenal contents	Acute phase	Not done
Virus in blood	3 days before onset and in acute phase	Incubation period and acute phase
Route of infection (experimental)	Oral and parenteral	Parenteral
Duration of carrier state:		
blood	Unknown	As long as 5 years (one adult) *
faeces	As long as 16 months (one child) *	Not demonstrated
Immunity:		
homologous	Present	Suggested *
heterologous	None apparent	None apparent
Prophylactic value of gamma-globulin	Good	Equivocal or absent

* This information is derived from very limited experiments.

possible to measure the state of existing immunity either in volunteers or in naturally acquired infections, and also since the experimental studies have been carried out only in small groups of individuals, negative results are not of statistical significance.

The size of neither virus has been completely determined. Virus A is known to pass a Seitz filter which holds back the smallest bacteria, but information concerning filtration through gradocol membranes of known pore-size is not available. Certain workers have reported on measurements made of objects present in electron micrographs of presumed human egg-passage material, but these await adequate confirmation. Virus B has passed through a membrane with pore size 52 mμ which means it has a probable diameter, at least in one direction, of not more than 26 mμ.

The most distinct difference between these two viruses is that virus A has been found in the faeces in the acute phase of the disease but virus B has not. In a single experiment virus A was not found in stools midway in the incubation period. The possibility that virus B may be present at some early stage of the disease, e.g., the period between inoculation and onset of symptoms or jaundice when the virus has been shown to be present in the blood, has not been investigated.

Both viruses have been found in the blood during the acute phase of the disease. Virus A was also found in the blood of one patient three days before the onset of symptoms. On the other hand, one of the most prominent characteristics of virus B is that it has been found circulating in the blood early, midway, and late in the incubation period, the longest known period before jaundice being 87 days.

There have been several experiments in which nasopharyngeal washings suspected to contain viruses A or B have been tested, but none of these has been sufficiently satisfactory for technical or other reasons for definite conclusions to be drawn from the results. Experiments with urine have also been indefinite, but it seems possible that if some other accompanying infection, e.g., bilharziasis, produces blood in the urine, either virus might be present in the urine at certain times.

A second distinguishing feature has been that both stools and blood known to contain virus A have, when given by either oral or parenteral routes, produced hepatitis with jaundice after incubation periods of 15 to 40 days. By contrast, virus B has been infectious only when given by parenteral routes.

Various epidemiological observations have suggested the possibility that some persons who had been infected with virus A were symptomless carriers at intervals of some months after clinical recovery. A very small number of experiments with stools and blood from adult patients who had persistent symptoms suggestive of chronic hepatitis have given negative results in tests for virus. Recently, however, the virus has been found in the stools of two young children with persistent symptoms as long as 5 and 16 months, respectively, after the onset of their acute illness. It is impossible to comment further on this point until additional data on similar observations are available. Virus A has not so far been demonstrated in the blood after the acute stage of the disease, but virus B has been shown to be present in blood for at least five years after its first detection in an individual with hepatic cirrhosis. There have been several other proved examples of its persistence for at least two years. It is obvious that the question whether an individual's blood can contain virus B in an infective form for periods of five to ten years or more can only be settled by future observations.

Both epidemiological and experimental studies indicate that in the vast majority of individuals one attack of virus A produces immunity to reinfection with that virus but does not produce immunity to virus B. Further confirmation of this state of immunity has been provided by the satisfactory prophylactic effect of administration of human gamma-globulin against infection with virus A. On the other hand, the information with regard to virus B is less satisfactory. A relatively small number of direct-inoculation experimental studies suggested that one attack of virus B produced homologous immunity but not heterologous immunity to A, but unfortunately there has been little satisfactory evidence of the presence of antibodies to virus B even in gamma-globulin fractions of the blood of convalescents from virus B infection.

No mention has been made in table II of the growth of the viruses in the developing chick embryo or in cultures of various human and animal

tissues. Although several workers appear to have demonstrated the growth of A and B viruses in such media, no pathognomonic lesions or identifying tests are available other than inoculation into man. Also, the results of these experiments have not always been consistent, and some workers have failed to achieve any success. However, in one laboratory the culture viruses appear to have retained certain of the characteristic features, e.g., oral infection with A and a long incubation period after parenteral inoculation of B.

Amniotic fluid containing presumably-inactivated hepatitis virus A has been used for making skin tests. Unfortunately the technical problems involved have made it difficult to obtain reproducible results, although one group of workers has found a high percentage of positive tests in children recovered from infectious hepatitis. In addition, an apparent reduction of the incidence of hepatitis was found during an epidemic in children who had had skin tests. It is impossible to say yet whether or not this suggests any immunizing effect.

5. Resistance to Physical and Chemical Agents

It is of particular importance to emphasize that there is no evidence to indicate that any of the commonly employed antiseptics such as alcohol, ether, or Zephiran (alkyldimethylbenzylammonium chlorides) inactivate hepatitis virus A or B. In table III are recorded certain data concerning the resistance of both viruses to various chemical and physical agents. Virus A (in serum and faeces) survives heating to 56°C for 30 minutes and remains active in materials (serum or faeces) frozen 1-1½ years at –10° to –20°C. It may withstand chlorination in water (1 part chlorine residual per million) for 30 minutes, although this amount of chlorine was effective in an experiment when organic material in the water had undergone previous coagulation and settling.

Virus B (in serum) survives heating to 60°C for 1 hour. It remains active at a temperature of –10° to –20°C for 4½ years, in a desiccated state at room temperature for at least a year, in serum containing merthiolate in a concentration of 1/2,000, in a mixture of equal parts of phenol and ether in 0.5% concentration, in a 0.2% concentration of tricresol, and in blood containing nitrogen mustard. It is inactivated in human albumin by heating at 60°C for 10 hours. Recent clinical studies of recipients of plasma which had been stored in the fluid state at room temperature for three to six months have indicated that the incidence of serum hepatitis was so low as to suggest that inactivation of virus might have occurred. Further work is required before any conclusions may be drawn from these observations.

TABLE III. COMPARISON OF RESISTANCE OF HEPATITIS VIRUSES A AND B TO PHYSICAL AND CHEMICAL AGENTS

	Virus A	Virus B
Temperature resistance		
56°C, 30 minutes	Survived	Survived
60°C, 1 hour	*	Survived
60°C, 10 hours (albumin)	*	Inactivated
—10 to —20°C, 1½ years	Survived	Survived
—10 to —20°C, 4½ years	*	Survived
Ultra-violet irradiation	*	Equivocal
Chlorine 1 p.p.m. residual, 30 minutes	Survived, or inactivated †	*
Tricresol 0.2%	*	Survived
Phenol-ether (equal parts) 0.5%	*	Survived
Ether 10%, 24 hours at 4°C	Survived	*
Triple ether extraction of serum	*	Survived
Merthiolate 1/2,000	*	Survived
Nitrogen mustard (500 mg/litre)	*	Survived

* Not done.
† Inactivation followed adequate coagulation and settling of water.

Earlier experimental studies suggested that virus B was destroyed in plasma by ultra-violet irradiation, but subsequent investigations have indicated that experimentally this is not always true and multiple cases of hepatitis have been reported to follow the injection of a single pool of irradiated plasma. It is not determined whether such occurrences represent intermittent breakdowns in the irradiation apparatus or alterations in strain or amount of virus in the plasma. It may be said at the present time that the intensity and conditions of ultra-violet irradiation necessary to sterilize plasma of hepatitis virus are not known, although extensive investigations are under way to define these conditions, as well as to determine other possible methods of inactivation. For example, preliminary observations of the effects of certain chemicals on plasma containing hepatitis virus B indicate that sulfur mustard (0.005 M final concentration) and β-propriolactone (4 g/litre) inactivate this virus.

6. Viruses Causing Hepatitis in Animals

In spite of repeated attempts by many investigators to infect animals with hepatitis viruses A and B, the great majority of such experiments yielded negative or inconsistent results. A number of isolated claims have appeared within the past ten years indicating that human hepatitis viruses A and B have been propagated in embryonated eggs and in tissue cultures, but such studies also deserve confirmation at this time.

Of special importance, therefore, are the efforts which have been made to isolate and study the properties of these animal " hepatitis " viruses which seem to occur naturally and to produce hepatic disease as their main lesion in certain species of lower animals. Included among agents of this type are the following:

(1) *Mouse hepatitis virus (MHV) of Gledhill and Andrewes.* The agent (or agents) discovered in England [6] can be found in more than 50% of mice of a certain strain (P strain), and the inoculation causing infection in susceptible mice may be resolved into two filtrable components. Inoculation of susceptible mice with both components produces a fatal hepatitis; one component (L) is thermolabile and susceptible to terramycin; the other component (S) is relatively thermostable and insusceptible to terramycin.

(2) *Virus of Rubarth's hepatitis contagiosa canis.* This agent, discovered in Sweden,[7] produces liver lesions in dogs in which nuclear inclusions are found. The disease apparently is very widespread in the canine family, since immunity is widespread and gained early. Apparently the disease does not go on to cirrhosis. It is transmissible to eggs.

(3) *Rift Valley fever virus.* Rift Valley fever has long been recognized in Africa as a virus disease of both man and sheep, causing hepatitis in the latter. Its natural form of transmission is believed to be through insects.

(4) *Virus of hepatitis in horses.* In South Africa, in England, in the USA, and in Norway, cases have been described of hepatitis in the horse following injection of homologous (horse) serum. It has been presumed that these have been due to a virus existing as an asymptomatic viraemia in horses.

The committee believes that further work on these and similar agents is desirable and that knowledge of these animal hepatitis viruses and their

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[6] Gledhill, A. W. & Andrewes, C. H. (1951) *Brit. J. exp. Path.* **32**, 559

[7] Rubarth, S. (1945) *Skand. VetTidskr.* **35**, 356

usual modes of transmission might lead to a better understanding of the pathogenicity of human hepatitis viruses A and B.

7. Natural and Artificial Methods of Spread of Virus

Complete knowledge of the natural mode of spread of infectious hepatitis is not available because of the lack of an experimental host other than man. However, numerous observations and reports have been made on this subject over a period of many years, in civilian and military communities in different parts of the world, which give very valuable information on this point. Those observations and investigations which have been made since 1940 particularly in warm climates or under battle conditions have suggested that the faecal-oral route has been the important method of spread of virus A. Contact infection appears to be the commonest way of transmission. However, a number of examples of apparent food-borne and water-borne outbreaks in temperate climates have also been described. The frequent demonstration of the presence of virus A in the stools of patients in the acute stage of infectious hepatitis together with observations on the widespread distribution of other faecal organisms in the normal environment clearly indicate how easily fingers, food, and fomites can be contaminated with virus A and infection by brief direct contact can take place. As virus is excreted in the stools it is easily conceivable that in those countries with poor sanitation, when excreta and sewage are exposed, filth flies may act as mechanical vectors of the virus from the stool to exposed food which then infects man by the oral route.

In some countries, particularly those with poor sanitation, the incidence of hepatitis is regarded as being very low. However, many observations suggest that in reality the disease in these countries is endemic with widespread infection in early childhood. The morbidity resulting from these early infections cannot yet be assessed though it is known that hepatic cirrhosis can result. The possibility that certain forms of hepatic cirrhosis described in a number of tropical countries may be related to infection with hepatitis viruses is worthy of further consideration.

In some countries, particularly in temperate climates, observers have had the belief that infectious hepatitis has been spread by droplet infection from nasopharynx to nasopharynx. It is true that in some outbreaks about 20% of patients have had catarrhal symptoms of the upper respiratory tract, but attempts to demonstrate virus A in nasopharyngeal secretions collected during the acute state of infectious hepatitis have been unsuccessful. However, many epidemiological observations have suggested that patients with infectious hepatitis have been infectious a few days before

the onset of their symptoms. Tests for the presence of virus have not been carried out on nasopharyngeal washings collected at this time.

Since virus A is present in the blood stream during the acute stage of the disease, it may also be spread by inoculation of blood during prophylactic or therapeutic procedures such as vaccine injections, transfusions, venepunctures, etc. (see section 4, page 8).

Virus B, as already stated in table II, has not been found in the stools or conclusively demonstrated in the nasopharyngeal secretions, although some observations have been made which suggest that contact infection can occur. The only method of spread of which there is unequivocal proof is by parenteral penetration. Infection with this virus has occurred in individuals who have received blood for prophylactic or therapeutic procedures, in individuals undergoing multiple injections of various prophylactic and therapeutic substances such as vaccines, insulin, gold, and antibiotics, where the syringes and needles used for injections are presumed to be contaminated with infected blood, and also in individuals who have only had blood removed for examination. In the latter instance blood-contaminated syringes, needles, lancets and other instruments used for collecting the blood appear to be the means of transfer.

In addition to this there are certain occupational procedures such as the processing of blood in blood banks (transfusion centres) and the collection and examination of blood in hospital laboratories during which infection with this virus can occur. The exact site of penetration is not usually determined in these cases but is presumably through skin abrasions or accidental needle pricks.

There is evidence that virus B can pass through the placenta from mother to child and, as already stated, the virus has been shown to be present in the blood of a single individual for at least five years. A review of the situation in England and Wales in 1949 indicates that as many as 0.5% of donors might be carrying this virus in their blood. This suggests that it would be possible for virus B to maintain itself in man without recourse to any other mode of spread than injection of blood or blood-products.

There is no satisfactory information on the transmission of either virus A or B by blood-sucking insects.

8. Epidemiological Information

It is not possible to plan satisfactory control measures against a disease without adequate data on its prevalence. The logical method of acquiring this information is by means of compulsory notification (reporting) at the national level complemented by collection and publication of the data by

the epidemiological services of the WHO. Such a measure, however, needs to be justified by its probable value in the control of the disease.

The committee believes that the following reasons justify the addition of hepatitis to the list of notifiable (reportable) diseases.

(1) Hepatitis is an acute disease with average mortality of the order of 1-2 per 1,000. Recovery from an acute attack normally takes about six weeks in young adults, and may be followed by prolonged disability. In certain countries epidemics with a high mortality have been described involving especially older adults. It is therefore a potentially serious disease which should be prevented if possible.

(2) The occurrence of an epidemic of infectious hepatitis, or an outbreak of serum hepatitis due to the large-scale use of an infected blood-product, may not be detected in the early stages, except in institutional epidemics, unless notification (reporting) is compulsory. During this delay many more cases of infectious hepatitis would have occurred, and more patients may have been inoculated with the infected blood-product.

In epidemics of infectious hepatitis certain preventive measures are possible (see section 9, page 16), and in outbreaks of serum hepatitis the infected blood-product may be identified and withdrawn.

(3) Some epidemics of infectious hepatitis are water-borne or food-borne, and their control is clearly a public-health problem. These would be likely to escape notice in the absence of compulsory notification.

(4) A marked increase of notification in an area might lead to the suspicion that faulty medical techniques were responsible for cases of serum hepatitis. This could be investigated and rectified.

(5) In countries which have a national transfusion service, the information available from notifications would be of great value not only in assisting the service to check the safety of its products, but also by enabling the service to avoid bleeding donors in an area affected by an epidemic of infectious hepatitis.

(6) In areas where there is an active epidemiological service, compulsory notification would make it possible to carry out badly needed field observations, particularly on sporadic cases, which might be expected to yield valuable information on the epidemiology of these diseases and their methods of spread.

Incomplete reporting of cases of hepatitis is inevitable since non-icteric cases are common in many countries, especially among children, and, being difficult to diagnose, would not generally be reported. Nevertheless, the reporting of icteric cases would serve as an index of the prevalence of the disease in an area.

Since there is at present no way of differentiating with certainty between infectious and serum hepatitis in a given case, it is impossible to notify the two diseases separately. Nevertheless, the committee considers that the notification should include an expression of the opinion of the practitioner as to the most probable diagnosis (e.g., infectious hepatitis, history of contact, cases in the neighbourhood, in the family, or in the school, etc.; or serum hepatitis, no history of contact, history of transfusion, parenteral injections, blood tests, etc.).

The committee recognizes that compulsory notification of hepatitis might result in technical and other difficulties in many countries, but considering its value as an essential part of control measures, the committee recommends that both infectious and serum hepatitis should be made compulsorily notifiable in all countries as soon as circumstances permit.

9. Control Measures of Infectious Hepatitis

9.1 *General measures*

The committee is of the opinion that direct contact is the commonest form of transmission and that the faecal-oral route is the important mode of spread of the disease; attention should therefore be directed towards its interruption. In general the precautions to be taken both by public-health authorities and hospitals are those which are usually applied in respect to the enteric fevers, e.g., personal cleanliness, safe disposal of excreta, prevention of contamination of food, water, and milk supplies directly or by the hands of infected persons, fly abatement and screening of kitchens and latrines. The stools are considered to be infectious for three weeks from the onset of illness. If epidemiological investigations suggest that a water supply is the source of infection, it is emphasized that the usual chlorination procedures will be certainly ineffective unless preceded by filtration and settling of the water, but even then in the light of present knowledge it cannot be assumed that chlorination will always be effective.

Provided that suitable precautions can be taken in the home, the patient need not be removed to hospital unless his clinical condition warrants it.

Quarantine is not recommended for contacts. However, a careful watch should be kept for suggestive symptoms such as fever, anorexia, and dark urine.

As pointed out in section 11 (page 21), special care should be taken in the sterilization of all instruments which have been used for the collection of blood or injection of these patients.

9.2 *Specific prophylaxis*

Gamma-globulin. Normal human gamma-globulin, in the amount of 0.01 ml per pound (0.022 ml per kilogram) of body-weight administered intramuscularly, has been shown to prevent infectious hepatitis when given after exposure and as late as 6 days before the onset of symptoms. The duration and mechanism of such protection is not clearly defined. Observations of groups of children inoculated with gamma-globulin and subsequently heavily exposed to hepatitis virus A under epidemic conditions over a period of several months suggest that the protection may be of a more permanent nature than is usually associated with passive immunization alone. The reason for this is not yet understood. The administration of gamma-globulin is recommended in certain family outbreaks, particularly for adults in whom the disease tends to be more serious, and for the control of epidemics in institutions and certain other closed groups.

10. Prevention of Spread of Hepatitis Viruses A and B by Human Blood and its Products

The committee is of the opinion that the dangers of serum hepatitis are not appreciated by many sections of the medical profession, largely owing to the long incubation period which conceals the relationship between a transfusion and subsequent hepatitis. It also appears to the committee that many non-essential transfusions of blood and plasma are given. Therefore, the committee recommends that national health authorities should call the attention of the medical profession in their countries to the dangers of transmitting hepatitis by transfusion of plasma and whole blood, and also by the use of certain blood derivatives, and should advise that plasma, particularly large-pool plasma, should not be used unless the advantages likely to be gained by its transfusion outweigh the risk of transmitting the disease.

10.1 *Blood products which may contain hepatitis virus*

It has already been pointed out that the term " serum hepatitis " is misleading since the virus can be transmitted in other blood products as well as serum. The committee therefore lists in table IV those blood products which have been proved to be potentially infectious, those which are probably potentially infectious, and those which are almost or completely free from danger. Although two cases of hepatitis which might have been serum hepatitis have been reported, following the use of gamma-globulin, the committee regards the risk as negligible.

TABLE IV. INFECTIVITY OF BLOOD PRODUCTS

Material	Potentially infectious		Non-infectious	Infectivity unknown
	Proven	Probable		
Whole blood	+			
Packed red cells		+		
Serum	+			
Plasma	+			
Fibrinogen	+			
Fibrin foam [a]			+	
Thrombin [b]	+			
Antihaemophilic globulin fraction				+
Gamma-globulin [c]			+	
Albumin heated at 60°C for 10 hours [d]			+	

[a] Sterilized by dry heat at 160°C for 1 hour.

[b] Thromboplastin (placental extract) used as an activator might conceivably have been the vehicle for the virus in some cases.

[c] Two cases of hepatitis following the use of gamma-globulin have been recorded; serum hepatitis could not be excluded.

[d] Albumin as produced commercially in the USA.

10.2 *Preventive measures*

10.2.1 *Blood-donors*

The committee recognizes that there is no generally applicable method of ensuring that a prospective donor is not harbouring hepatitis virus. At present it is only possible to detect carriers by injecting their blood into susceptible volunteers. It is stressed that a carrier may have no history suggestive of hepatitis (jaundice) [8] and that liver-function and other clinico-pathological tests may be normal.

Although exact knowledge is lacking, the committee is of the opinion that a history of hepatitis (jaundice) may indicate an increased probability that the donor may be a carrier of virus, and the findings of an enlarged liver and/or abnormal liver-function tests further increase the probability. In the light of present knowledge the committee is unable to fix the period following an attack of hepatitis after which it could be safely assumed that the virus is no longer present. In one case the carrier state is known to have persisted for five years, the maximum duration of observation (see section 4, page 9), and it is possible that it may persist much longer. Therefore, the committee advises that, when circumstances permit, no person should be accepted as a blood-donor if there is a history of hepatitis (jaundice) at any time.

[8] Hepatitis often occurs without jaundice and such cases may become carriers. However, the committee feels that the diagnosis of non-icteric hepatitis is so difficult that it would be impractical when questioning blood-donors to ask for a history of non-icteric hepatitis. It is also pointed out that few laymen will understand what is meant by hepatitis and therefore the donor should be asked if he has had jaundice.

However, circumstances will arise in which it may be necessary to accept as a blood-donor a person with a history of hepatitis (jaundice). Under these circumstances, the committee recommends that

(1) no donor should be accepted, except in case of life-saving emergency for a single transfusion, if he has a history of hepatitis (jaundice) within one year;

(2) if the donor has a history of hepatitis (jaundice) more than one year before, liver-function tests should be performed;[9]

(3) the blood from a donor with a history of hepatitis (jaundice) should not be used in the preparation of large plasma pools until methods of sterilization are available.

It is clear that the rejection of all donors with a history of hepatitis would appreciably reduce the number of donors available. The reduction will vary from country to country according to the incidence of hepatitis. Precise information on this point is not available. However, one recent survey suggests that the reduction may be of the order of 5%-10%. The committee is of the opinion that if non-essential transfusions of blood and plasma were not performed, the fact that the number of available donors is reduced would be of less importance.

10.2.2 *Preparation of blood and its derivatives*

Size of plasma pools. It has been shown that incidence of serum hepatitis is much higher (about 10%) following the transfusion of plasma (mainly dried) from large pools containing 250 to 300 or more separate donations of blood than it is from small pools containing only 10 separate donations. The incidence following the use of small pools is not significantly higher than that following single transfusions of whole blood (about 1%). Therefore, the committee recommends that, if pooling is necessary, whenever possible dried plasma should be prepared from small pools of about 10 and not more than 20 donations.[10]

Sterilization of blood-plasma. The use of ultra-violet irradiation and certain chemicals for the inactivation of hepatitis virus in plasma pools has been considered in section 5 (page 11).

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[9] It has been found that changes in the serum-protein as measured by flocculation tests, including thymol turbidity (see Annex 1, page 25), may be useful in suggesting that a donor may be a carrier of virus.

[10] The committee recognizes that machines in use in certain areas for drying plasma in large pools are expensive and difficult to replace. The need for their continued use can only be decided with a full knowledge of the local circumstances. If they must be used the committee stresses the need for special care in selecting donors and the introduction of effective inactivating techniques immediately they become available.

10.2.3 *Maintenance of records*

Subsidiary but important means of control are afforded by the maintenance of accurate records of the origin, distribution, and administration of blood and blood-products. Such records should include :

(1) Record of the names, etc., of donors contributing to each product ;

(2) Recording of batch numbers of products issued to hospitals and systematic distribution of products to hospitals ;

(3) Accurate recording in the patient's case-papers of the batch number of the product used, with the date of administration, and of the patient's name in the hospital record of products received and issued. In view of the importance the committee attributes to this matter, it is recommended that one individual in each hospital should be made responsible for ensuring the proper completion of these records.

10.2.4 *Reporting*

The question of notification of cases of hepatitis is discussed in section 8 (page 14). However, the committee feels that useful additional information might be obtained by a simple follow-up system to detect cases of serum hepatitis following administration of blood and blood-products. The institution of such a system in conjunction with the above records would make it possible to withdraw an icterogenic blood-product at the earliest possible moment.

The committee suggests that each patient receiving a potentially icterogenic blood-product should be given a card explaining that jaundice sometimes occurs as a late complication of the treatment, and that if it should occur at any time up to 160 days after the treatment he should visit his own doctor or the hospital. The card should carry the address of the local health authority, hospital, or blood-transfusion centre as the case may be. It should be enclosed in an envelope and posted by the private doctor when the patient reports with hepatitis. A design for a suitable card will be found in Annex 2 (page 26).

Such a simple follow-up system will not detect all cases of serum hepatitis, but it is believed that in certain areas the system will detect an appreciable number of cases which would otherwise be missed. It is suggested that it should be tried on an experimental basis in selected areas in the first place, and only adopted on a large scale if the results justify it. However, under special circumstances and where conditions permit, the value of the follow-up system would be greatly increased by arranging for a visit to each patient after 160 days. Such a scheme would require additional staff and would need to be carefully planned if it is to be valuable. It is therefore recommended only as a special study in selected areas.

The committee is aware that in many countries serum hepatitis is regarded as being extremely rare. This is an impression only, since in these countries the disease is not notified and no careful follow-up has been carried out of recipients of transfusions. The committee, therefore, recommends that such surveys should be carried out in countries in which the disease is believed to be uncommon with a view to estimating its true incidence.

11. Measures to Ensure the Safety of Medical Procedures Involving Parenteral Penetration

It is now well known that serum hepatitis is transmitted not only by transfusions and the injection of infected blood-products, but also by the accidental inoculation of traces of infected blood remaining in a hypodermic needle and syringe from the previous occasion on which it was used. It is not so generally appreciated that the disease may be transmitted by any procedure in which the skin or mucous membrane is broken by an inadequately sterilized instrument which has previously been used on another human. This risk is present in innumerable medical, surgical, clinical-laboratory, and dental procedures, and even in such things as tattooing. That the risk is indeed a real one is shown by the fact that it has been estimated in some countries during the past few years that about 1 in 200 blood-donors carry hepatitis virus B in their blood. During outbreaks of hepatitis the risk may be considerably increased. It is further confirmed by the greatly diminished incidence of the disease in certain areas following the introduction of the measures described below.

Since the amount of blood needed to cause infection is extremely small and since, as already pointed out, the virus is relatively resistant to heat and other physical and chemical agents, many measures, at present in common use for the sterilization of syringes, needles, and other instruments, are ineffective and will not prevent the accidental transmission of the disease.

A special problem is presented by mass immunization-campaigns in which many thousands of injections are given in a short time. It is a practical impossibility in most countries to provide a separate sterilized syringe and needle for each injection, and it has been shown that changing the needle alone does not prevent the transmission of traces of blood from one patient to the next, since the nozzle of the syringe itself becomes contaminated. This risk has to be accepted on many occasions because the importance of the immunization campaign outweighs the risks of hepatitis. Recently, attempts to overcome this difficulty have been made by the construction of simple valve-like devices which are changed with the needle

between each injection and which prevent contamination of the nozzle of the syringe.[11]

Recommendations to ensure the safety of medical procedures involving parenteral penetration

(1) Every parenteral penetration must be performed with syringes, needles, or other instruments sterilized as outlined below. Such penetrations include all kinds of injections or aspirations, the taking of specimens of capillary and venous blood, tests and vaccinations performed by scarification, as well as many other surgical and dental procedures.

(2) Syringes, needles or other instruments must be thoroughly washed in water immediately after use to prevent organic material coagulating or drying on the surfaces of the instruments and interfering with the effect of subsequent sterilization.

(3) The following methods of sterilization are acceptable: boiling in water for at least 10 minutes, steam under raised pressure (autoclave), and dry-heat sterilization (hot-air oven). If the temperature can be properly controlled in all parts of the hot-air oven, treatment at 170°C for half an hour is adequate, otherwise treatment at 180°C for one hour is recommended. Lancets and other instruments used for capillary-blood sampling and scarification may be sterilized in an open flame after washing in cold water.

(4) No chemical disinfectants are accepted for the sterilization of instruments.

(5) When shortage of equipment and staff makes it impossible to resterilize syringes between each injection, for example in mass immunization-campaigns, the needle must be changed and sterilized between each injection, the syringe being resterilized before it is refilled. Although this procedure may reduce the risk of serum hepatitis, it does not eliminate it.

(6) The above recommendations should be followed by all medical and allied personnel.

The committee recommends that national health administrations should endeavour by propaganda, by education, and by regulations, to secure strict observance of these recommendations on the part of all medical and allied personnel.

Serum hepatitis is known to be relatively common among patients undergoing treatment in venereal-disease, diabetic, and other clinics in which many injections are given, and blood samples taken. The incidence

[11] A promising device of this nature which is worthy of an extensive trial has been set up by Professor R. Gispen (see: Gispen, R. (1952) *Lancet*, **2**, 171).

of the disease should be materially reduced if the recommendations given above are carefully followed. Nevertheless, the committee believes that the institution of a system of follow-up cards, on the lines outlined in section 10 (page 20), would serve as a valuable check on the efficacy of the techniques adopted.

12. Fields in which Research Work on Hepatitis is Especially Indicated

It will be evident from this report that there are many unanswered questions with regard to both infectious and serum hepatitis. Nevertheless, there is a reasonable chance that some of them might be solved in the near future by research work, either in the microbiological laboratory, or by epidemiological or clinical investigation of patients.

Of the many problems in which research work is desirable, only a few which appear to the committee to be most urgent have been listed :

12.1 *Virus laboratory research*

(1) At present, only man is known to be susceptible to infection by either hepatitis virus (A or B). Consequently studies on the viruses have been greatly hampered by the absence of a suitable animal host. In spite of the previous failures which have accompanied attempts to adapt the viruses to laboratory animals, these attempts should be continued.

(2) One hopeful lead in the investigation of these viruses has been the reports of their adaptation to the embryonated egg and tissue culture. The advantages of the possible development of this work are obvious. Material from infected eggs and tissue culture might serve not only as a skin-test antigen but possibly as a source of antigen for complement-fixation or other immunological tests which are so badly needed in the diagnosis and study of these diseases.

(3) The duration of the carrier state in various stages of the clinical disease in both infectious and serum hepatitis should be further investigated, and the materials tested should also include throat washings and urine.

(4) As a corollary to the study of the human disease, further studies on native viruses which produce hepatitis in different species of animals, such as the murine virus of Gledhill and Andrewes, or the virus of Rubarth's hepatitis contagiosa canis are desirable. The " serum hepatitis " of horses would also seem to deserve some attention.

(5) Further determinations of the degree of the thermo-stability of hepatitis viruses A and B and their degree of resistance to chemicals and other physical agents are badly needed.

12.2 *Epidemiological observations*

Much more data are urgently needed on the prevalence and frequency of infectious and serum hepatitis as they occur among different age-groups within different countries, and in populations living under different social and environmental conditions within the same country.

The high incidence of cirrhosis of the liver in young children living in certain tropical countries and its possible relation to virus hepatitis deserves investigation.

12.3 *Clinical investigation*

More data on the frequency with which cirrhosis of the liver occurs as a sequela of acute viral hepatitis should be accumulated in different countries.

Studies on the symptomatology of the pre-icteric stage of infectious and serum hepatitis are desirable.

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Annex 1

EXAMPLES OF TESTS OF HEPATIC FUNCTION WHICH MAY BE USEFUL IN DIAGNOSIS AND PROGNOSIS OF INFECTIOUS AND SERUM HEPATITIS

Pre-icteric or non-icteric phase	Icteric phase	Post-icteric phase
(1) Urine bilirubin	(1) Total serum bilirubin	(1) Bromsulfalein dye retention
(2) Urine urobilinogen	(2) One minute direct serum bilirubin	(2) Total serum bilirubin
(3) Bromsulfalein dye retention	(3) Cephalin flocculation	(3) One minute direct serum bilirubin
(4) Cephalin flocculation	(4) Thymol turbidity	(4) Thymol turbidity
(5) Thymol turbidity	(5) Serum alkaline phosphatase	
(6) One minute direct serum bilirubin		

The committee acknowledges that this list is small ; however, its purpose is to provide examples and it is hoped that the lack of completeness will not be regarded as prejudicial to many other tests of hepatic function which are commonly in use in various parts of the world. Although biopsy of the liver has not been discussed, it is appropriate to mention here that this procedure may be of great value in making a differential diagnosis and in detecting persistent or progressive hepatic disease in a small percentage of patients.

Annex 2

MODEL OF FOLLOW-UP CARD FOR THE STUDY OF SERUM HEPATITIS

FOLLOW-UP CARD Ref. No. .....

Patient's name .....

Address .....

Hospital number of patient ..... Hospital .....

Treatment given ..... on (date) .....

Signature of issuing officer .....

Onset of jaundice (date) ..... (To be filled in by doctor before posting)

Name and address of private doctor .....

.....

The treatment you have been given is sometimes complicated by the late appearance of jaundice. If this should occur between now and .....* (160 days after treatment), you should visit your doctor and ask him to enclose this card in an envelope and post it to the following address : .....

.....*

* To be filled in by issuing officer.

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