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WHO EXPERT COMMITTEE ON HEPATITIS

Second Report

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WHO EXPERT COMMITTEE ON HEPATITIS

Geneva, 10-16 December 1963

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WHO EXPERT COMMITTEE ON HEPATITIS

Second Report

The WHO Expert Committee on Hepatitis met in Geneva from 10 to 16 December 1963. Professor Jan Kostrzewski was elected Chairman, Professor B. K. Aikat, Vice-Chairman, and Dr J. Mosley, Rapporteur.

INTRODUCTION

For this report the available information on viral hepatitis has been assembled and critically considered.¹ Hepatitis due to viruses such as yellow fever, Coxsackie and herpes simplex is not included. Where relevant, information which appeared in the first report of the WHO Expert Committee on Hepatitis² has been included since the English edition is now out of print. The term viral, or virus, hepatitis includes the diseases frequently described as infectious hepatitis (IH) and serum hepatitis (SH), two closely related conditions which are clinically similar but which differ in some important respects. Infectious hepatitis spreads usually by the faecal-oral route but sometimes also parenterally; most cases occur in children and young adults. The incubation period is between 15 and 50 days. In temperate climates infectious hepatitis is commoner in autumn and winter than at other seasons. Serum hepatitis is spread only parenterally and most cases occur in adults. The incubation period lies between 50 and 160 days and there are no seasonal variations in incidence.

Viral hepatitis is common in all parts of the world. During recent years the reported incidence has increased considerably in some countries, due mainly to better notification. In countries in which the incidence is known to be high viral hepatitis is recognized to be an important health and economic problem. In typical cases there is a pre-icteric and an icteric stage, but anicteric cases (cases without jaundice) are very common, especially in children. Symptomless (inapparent) infections are also very common.

¹ Some of the information on the clinical and pathological aspects and on recently isolated potential etiological agents was based on the answers to questionnaires sent out by WHO and completed by workers in Chile, Czechoslovakia, Eastern Germany, India, Italy, Nigeria, Poland, Romania, the United Kingdom, the USA and the USSR.

² *Wld Hlth Org. techn. Rep. Ser.*, 1953, 62.

The characteristic symptoms and signs include anorexia, nausea, vomiting, abdominal distress, liver enlargement and jaundice. Typically, the duration of illness is usually between two and eight weeks, but may be longer. Attacks are more severe in the old than in the young, in whom the disease may be very mild and brief. There is no specific treatment. Laboratory diagnosis depends on biochemical tests. These are not specific for viral hepatitis and they do not distinguish between the two types of the disease. Virological and serological studies have been severely hampered by the lack of a suitable experimental system for the isolation and propagation of the agents and by the present uncertainty of the role of the numerous different viruses recently isolated from sporadic and epidemic cases. The agents present in infected faeces or serum are more heat-resistant than the usual viruses causing disease in man. Gamma-globulin is effective in the prevention of infectious hepatitis, but its value in the prevention of serum hepatitis is less clearly defined. General measures for the control of infectious hepatitis are similar in many respects to those employed for other enteric infections. Control of serum hepatitis requires special consideration since this disease spreads in most instances as a result of medical procedures.

TERMINOLOGY AND CLASSIFICATION

In this report the term "viral hepatitis" is used to include both infectious hepatitis (IH) and serum hepatitis (SH).

The current International Classification of Diseases¹ distinguishes "infectious hepatitis", classified under infectious diseases (092), and "serum hepatitis", classified as a complication of medical procedures in the section on injuries, according to nature of injury (N-code) and according to external cause (E-code). Further differentiation is made depending on whether the medical procedure was prophylactic (N997, E943) or therapeutic (N998.5, E951). If therapeutic, preference is given in single-cause classification to the underlying disease.

The Committee considered the provisions of the International Classification of Diseases in the light of recent knowledge, new principles of classification, terminology, the need for identification of sequelae (early and late) and the desirability of obtaining in tabulations the full count of the conditions recorded.

It was aware, on the one hand, of the advantages of having under infectious diseases one category for "viral hepatitis", with three subdivisions for "infectious hepatitis", "serum hepatitis", and "viral hepatitis, unspecified". On the other hand, it recognized the convenience of

¹ World Health Organization (1957) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death... Seventh revision, Geneva.*

classifying "serum hepatitis" with other infections and complications of medical procedures in a separate section, as in the present International Classification of Diseases. It concluded that "serum hepatitis" need not be transferred under infectious diseases, provided that it is distinctly identified under complications of medical procedures and that it is shown in morbidity and mortality tabulations whenever stated on medical records.

A separate category should be available for sequelae (early and late) to include hepatic necrosis due to viral hepatitis and post-hepatitis cirrhosis. It was suggested that the terms "acute and subacute yellow atrophy of the liver" should be replaced by "acute and subacute necrosis of the liver" and that "post-hepatitis cirrhosis" be used to designate cirrhosis of the liver when this is believed to be a sequel of viral hepatitis.

The Committee, noting that the Eighth Revision of the International Classification of Diseases is to take place in 1965, recommends that the above views be taken into account in so far as they are compatible with the envisaged over-all arrangement of the Classification and the provisions for other situations of a similar nature.

MORBIDITY AND MORTALITY OF VIRAL HEPATITIS

Clustering of epidemics of jaundice reported in the literature suggests that several waves of increased prevalence of viral hepatitis have occurred at intervals during the past century. The apparent recent increase in the amount of the disease should be viewed in this long-term perspective.

Viral hepatitis was made reportable in Denmark in 1928. Most countries which now have compulsory notification adopted the practice around 1950, but reporting is still far from universal. The period and countries for which morbidity data are available, therefore, are relatively limited.

Since there is at present no way of differentiating with certainty between infectious and serum hepatitis in a given case the two types are generally reported together. Though the true proportions of infectious hepatitis and serum hepatitis may vary from country to country and time to time, it is generally agreed that infectious hepatitis is by far the more common. Examples of reported hepatitis rates for a number of selected countries from 1950 to 1962 are presented in the accompanying table. In some countries cyclic variations are evident with five- to ten-year intervals between epidemic peaks, and in others there has been a progressive increase throughout the period for which data are available, probably due to continuing improvement in reporting practices. Data from Scandinavian countries, particularly Denmark, show cyclic variations with a progressive over-all decrease in incidence.

In comparing reported rates of viral hepatitis from various areas, it is evident that considerable variations exist. Reported morbidity data do not

HEPATITIS

MORBIDITY OF INFECTIOUS HEPATITIS (CASES PER 100 000 POPULATION) IN SELECTED COUNTRIES,
LISTED ACCORDING TO MORBIDITY TRENDS

Country	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962
Italy	0.7	0.6	1.1	1.2	2	3	3	4	5	6	10	14	11
Yugoslavia	—	—	—	—	—	—	46	67	85	80	81	137	125
Eastern Germany	—	5	19	35	47	97	163	211	197	246	281	292	163
Czechoslovakia	159	282	281	277	392	375	301	184	190	252	286	272	207
Poland	—	—	3	7	35	72	90	93	151	260	258	192	155
Hungary	—	—	76	134	133	159	200	195	197	185	163	176	152
United States of America	—	—	12	22	31	20	12	9	10	13	23	41	29
Canada	—	—	17	22	30	25	18	18	27	27	34	66	64
Switzerland	15	17	33	56	78	67	29	20	18	22	20	20	18
Netherlands	—	26	46	53	57	35	21	20	24	84	147	51	12
Belgium	0.3	1	8	7	7	5	3	5	4	8	10	9	5
Israel (Jewish population)	103	111	69	72	96	76	76	57	87	77	149	65	115
Finland	101	73	90	95	157	163	168	141	76	50	40	37	29
Norway	24	20	25	57	69	88	82	43	32	35	29	17	14
Sweden	36	17	17	15	15	14	28	10	12	16	12	13	9
Denmark	158	129	119	90	103	118	121	75	56	39	32	27	24

— = not reported.

represent more than a proportion of the cases and this proportion varies from country to country and from time to time. This limits but does not nullify the usefulness of reporting, which is merely the first step in a series in so far as the study of infectious disease is concerned. It is possible to check the reliability of morbidity figures by surveys in which appropriate sampling techniques are used.

The Committee recommends that countries which have not already done so should make notification compulsory and stresses the need for the evaluation of the information obtained.

There are many justifications for compulsory reporting. Individual case reports by the physician or hospital provide data for analysis of the fluctuation of total incidence, and for evaluation of geographical factors, age and sex, within a country. This is the basis for determining the extent of the problem in any community. It is also a necessary first step in instituting control measures, since the many possible modes of transmission of infectious and serum hepatitis result in a multiplicity of patterns, each of which must be evaluated separately. The notification form should include the name of the patient, place of work or school, age, sex, home address, diagnosis, date of onset of illness, name of reporting physician and date of the notification. A relatively simple technique for studying the behaviour of infection in a community is the use by local health departments of a brief follow-up form. In addition to the information on the notification form the follow-up form should give information on the following points :

(a) history of personal contact with a patient during the past two months ;

(b) history of transfusion of blood (or blood products) during the past six months ;

(c) history of injections (e.g., drugs, vaccination, blood tests, skin tests) or dental intervention in the past six months ;

(d) whether women patients of child-bearing age are or are not pregnant ;

(e) whether jaundice occurred and if so the date on which it was first noted.

Such morbidity data, not an end in themselves, provide the means for the early detection of deviations from the expected disease pattern. By appropriate analysis valuable new epidemiological information may be obtained. For example, shifts in age- and sex-specific attack rates are often of considerable value in alerting the public health officer to the occurrence of unusual epidemiological situations. The fact that in Sweden and the United States of America raw shellfish are more commonly eaten by adults than by children and more often by males than by females resulted

in a marked shift in the usual age and sex distribution of cases in these countries when outbreaks associated with this vehicle for infection recently occurred. Predominance of cases among adults has also been observed when serum hepatitis constitutes a significant proportion of total cases in the community. In such situations preventive measures are available and can be applied if the mode of transmission is identified.

Though it might reasonably be expected that mortality data would be more accurate than morbidity data, this is not true with present reporting practices. Deaths from viral hepatitis may be included under a variety of other classifications, and jaundice due to other etiologies may be inaccurately coded as due to viral hepatitis. It is usually not possible to evaluate the accuracy of coding those deaths ascribed to acute and sub-acute necrosis of the liver and to other possible sequelae of viral hepatitis. A comparison of morbidity/mortality ratios, in various countries, however, may be useful as a guide to under- and over-reporting of both types of data.

EPIDEMIOLOGY OF VIRAL HEPATITIS

Information on the period of infectivity of patients with serum hepatitis and infectious hepatitis has been obtained from epidemiological studies and volunteer experiments.

Infectivity of infectious hepatitis

Faecal filtrates from infectious hepatitis patients have been shown to transmit the disease when administered to volunteers by the oral route. Serum is infective by both the oral and parenteral routes. Transmission, therefore, can occur from person to person by the faecal-oral route, and also as a result of transfer of blood by any procedure which breaks the skin or mucous membranes. Blood and serum are infective during approximately the same period as faeces, and virus is excreted in the faeces of individuals infected by the parenteral route. In studies of experimentally infected subjects viraemia and faecal excretion of the agent have been demonstrated during the pre-icteric stage and have ceased by about three weeks after onset of jaundice. Studies of urine and nasopharyngeal washings are limited and inconclusive.

In one series of experimental transmission studies with a virus having an average incubation period of 40 days, the agent was demonstrated to be in the faeces of icteric patients from about 16 days before until between one and eight days after the onset of jaundice. Individuals with anicteric infections are believed to excrete the virus for a comparable period of time. Virus excretion between eight and 18 days after onset of jaundice was not studied.

Attempts to transmit the disease with faecal pools collected during convalescence, 19 to 33 days after onset of jaundice, were unsuccessful. In another study of two children with chronic anicteric hepatitis, infective faeces were obtained five and 15 months respectively after the diagnosis was made, but it is not known whether they were infective throughout the whole of these periods.

Infectivity of serum hepatitis

Experimental transmission of serum hepatitis has been produced by blood taken as long as 89 days before the onset of symptoms and four to eight days after jaundice has occurred. It is known from follow-up studies of blood transfusions that the blood of some donors may be continuously or intermittently infective for many years. Blood and blood fractions containing serum hepatitis virus have produced disease experimentally only when given parenterally. Faeces, urine and nasopharyngeal washings administered orally have not been shown to be infective.

Environmental factors

Available data indicate that most cases of infectious hepatitis are due to person-to-person transmission, the effectiveness of which appears to be related to the closeness of contact. Persons living in the same household as a patient are at the greatest risk. Spread between families and in communities usually occurs as a result of activities which provide for close contact between preschool and school-age children. In most studies the lower socio-economic groups have a higher prevalence of infectious hepatitis in childhood, presumably as a result of greater crowding, poorer sanitation and less adequate personal hygiene.

The recognition of water- and food-borne epidemics of hepatitis has resulted in an increased awareness of the potential importance of this mode of spread. In Delhi, India, an estimated 29 000 cases occurred in 1955-56, as a result of contamination of the municipal water supply. Elsewhere, four epidemics spread by milk have been reported; in two of these, contaminated water used to wash dairy equipment was responsible. Ingestion of raw shellfish from polluted waters is known to have caused three epidemics. The incriminated clams and oysters were widely distributed and cases occurred in different parts of the country, thus making it difficult to recognize the common vehicle of infection. Contamination during preparation has resulted in transmission by other foods, including custard, sandwiches, orange juice, salads and cooked meat.

Mechanical transfer of the virus from faeces to food or eating-utensils by flies and cockroaches has been suggested, but there is no evidence that this mode of transmission has any significance.

The parenteral transmission of serum hepatitis or infectious hepatitis usually occurs in one of three ways : (1) through therapeutic administration of blood and unsterilized blood products or, rarely, by transplantation of human tissue ; (2) by use of a contaminated instrument which has broken the skin of two persons, the first of whom was viraemic ; and (3) through accidental cuts or scratches.

The risk of transmitting viral hepatitis by the use of blood and untreated blood products may be summarized as follows :

Whole blood. The frequency of viral hepatitis from the transfusion of whole blood ranges between 0.09% and 4.1% (usually less than 1%). The larger the number of units administered, the greater the risk of transmitting the disease. In some areas it has been observed that blood from donors receiving payment has been responsible for a higher frequency of hepatitis than that obtained from voluntary donors.

Plasma. Untreated pooled human plasma carries a higher risk than whole blood and the risk increases with the size of the pool. The attack rates in several studies ranged from 0.12% to 12.2%.

Fibrinogen. Fibrinogen cannot be sterilized without loss of its biological properties. The assessment of the risk it involves is difficult because it is generally given with whole blood. The attack rate, which in one instance was 17%, appears to be related to the size of the pool from which the fibrinogen is prepared.

Antihaemophilic globulin. The risk with antihaemophilic globulin is probably similar to that from fibrinogen.

Thrombin. Thrombin prepared by the ethanol or by the ether method may transmit serum hepatitis.

There have been no cases of hepatitis attributable to gamma-globulin prepared by the cold ethanol method of Cohn, and only one doubtful case attributable to gamma-globulin prepared by the cold ether method. Available evidence indicates that ammonium sulfate precipitation and ethacridine (Rivanol) precipitation are also safe methods of preparation, but specific follow-up studies have not been reported. Other products prepared from pooled plasma can be sterilized by heat. Stable plasma protein solution, albumen, fibrin foam and plasminogen appropriately treated are safe.

Viral hepatitis has been transmitted parenterally by needles, tubing, bottles and syringes used for intravenous, intramuscular, subcutaneous, and intradermal injections ; needles and syringes used for venepuncture, lancets used for scarification and capillary puncture ; dental equipment ; tattooing needles ; and improvised equipment used by narcotic addicts.

Accidental inoculation of medical, nursing and laboratory personnel dealing with patients or handling human blood is well recognized. In

Sweden a curious form of accidental infection has been recently described in cross-country runners with scratches on their limbs.

Transplacental transmission of serum hepatitis has been suggested on the basis of very limited observations which require confirmation.

No evidence for transmission of either infectious or serum hepatitis by haemophagous arthropods has been produced.

Host factors

Infection may or may not result from exposure. When infection takes place it may be apparent or inapparent. Estimates of the ratio of apparent to inapparent cases vary widely depending on the laboratory tests used and the population surveyed. Natural resistance may play some role in determining whether infection will occur but there are no methods for evaluating it. Acquired immunity plays a demonstrable role in protection against the homologous agent. The duration of protection is unknown, but from epidemiological observations it is presumed to be life-long in most instances.

Second attacks of icteric disease, both presumably due to infectious hepatitis virus, have been observed in up to 5% of patients. The interval between such episodes varies from several months to many years. It has also been found recently that inapparent infections may occur in persons who some months later develop icteric disease. A number of hypotheses can be brought forward to explain second attacks (for example, infection with antigenically distinct strains, or the recrudescence of a chronic process), but more information on the etiology and immunology of the infection is required before the mechanism of second attacks can be clearly understood.

Epidemics of both infectious and serum hepatitis which were associated with common vehicles of infection and in which large populations were apparently exposed to the same degree of infection have brought to light some factors other than acquired immunity which influence the attack rates. During water-borne epidemics of infectious hepatitis in Sweden, India and the United States of America attack rates increased with age up to 25 years. In Delhi the incidence in pregnant women was significantly higher than in non-pregnant women of the same age-group.

In the late 1930s and early 1940s many people were inoculated with yellow fever vaccine containing human serum contaminated with serum hepatitis virus. It was found that the attack rates of viral hepatitis varied with age and with ethnic group, the older age-groups and white races having the higher attack rates.

CLINICAL-PATHOLOGICAL CLASSIFICATION OF ACUTE HEPATITIS AND ITS SEQUELAE

Though viral hepatitis in its typical acute form is readily recognizable, there are many variations in the clinical picture and many inapparent infections occur. Diagnosis of the sporadic case may be difficult, especially in the older patient.

Available data suggest that there are no significant clinical differences between infectious hepatitis and serum hepatitis in either the early or the late manifestations. Observations in some epidemics suggest, however, that there is a higher proportion of severe cases in serum hepatitis than in infectious hepatitis. The usual clinical manifestations are discussed below.

Acute anicteric hepatitis

Acute anicteric hepatitis is characterized by malaise, anorexia and gastrointestinal disturbances and sometimes fever. In children these manifestations may be very mild and recognized with difficulty. It is diagnosed on the basis of such symptoms occurring during an epidemic of hepatitis or following exposure to a patient or other known source of infection. The diagnosis is supported by the palpation of a tender enlarged liver, bilirubinuria, and an elevation of the serum transaminase values. Jaundice is not recognized clinically but an increase in the conjugated serum bilirubin often occurs and is of diagnostic value. Though not recommended as a routine procedure, needle biopsy of the liver will usually confirm the diagnosis. The extent of the histological changes is variable and not always in accordance with the mildness of the clinical picture.

Acute icteric hepatitis

The prodromata are malaise, anorexia, moderate fever and discomfort in the right upper abdominal quadrant. These last usually for a few days but may extend to two weeks. The faeces lighten in colour, the urine darkens and jaundice appears. Headache, arthralgia, myalgia and skin rash are less common symptoms. These manifestations subside as the jaundice develops. The jaundice usually deepens during the first week of the condition and persists for seven to 14 days. Then the faeces darken again and the jaundice gradually vanishes. In children the prodromata, particularly the fever, may be mild or absent and jaundice may last only a few days.

A rise in the level of the serum transaminases and positive flocculation tests support the diagnosis. The white blood cell count is usually normal

or slightly decreased with relative lymphocytosis. Liver biopsy confirms the diagnosis, but is seldom necessary.

At varying intervals after the acute attack it is not uncommon for the serum transaminase level or conjugated serum bilirubin to increase again. Less commonly these biochemical changes may be more gross and accompanied by repetition of the symptoms and signs of the original attack and by overt jaundice. Recovery from such relapses is usually complete.

Cholestatic hepatitis

Viral hepatitis may take a more prolonged course with jaundice of the cholestatic (obstructive) type. The illness starts usually with jaundice that deepens rapidly; pruritus is conspicuous. Hepatomegaly may or may not be present.

The jaundice and pruritus persist for two to six months but recovery is complete. Liver biopsy shows the morphological features of hepatitis and marked bile stasis.

Fulminant hepatitis

This rare form of the disease usually results in death within 10 days. With an apparently typical acute onset, deep jaundice, persistent vomiting, fetor hepaticus, confusion and drowsiness appear, and delirium and coma supervene. The jaundice deepens and the liver shrinks in size. Widespread haemorrhages (bruising, petechiae and gastrointestinal bleeding) may occur. Leucocytosis may be present. This form of the disease may develop so rapidly that jaundice is inconspicuous and the disease may then be confused with acute psychosis or meningoencephalitis.

Persistent (chronic) hepatitis

In persistent hepatitis remissions and recrudescences occur at intervals for about a year.

In some patients the original attack is typical of the acute icteric type; in others this is not so. The recrudescences usually resemble mild attacks of the acute disease with gastrointestinal discomfort, vague upper abdominal pain and malaise. Biochemical changes include a mild hyperbilirubinaemia and increased serum transaminase values.

Liver biopsy shows portal-zone cellularity and scarring with intralobular foci of inflammation. Variable degrees of hepatocellular necrosis are present, though the normal architecture is preserved.

The prognosis is usually good.

Progressive (subacute) hepatitis

In this condition, instead of the usual recovery observed in acute hepatitis, fluctuating jaundice, mild pyrexia and bouts of vomiting persist. The liver remains enlarged and splenomegaly develops. Signs of hepatocellular failure appear, including ascites, hypotension and, terminally, coma. Blood biochemical tests reflect gross hepatocellular failure, particularly low serum albumin and high gamma-globulin levels with positive flocculation tests. Death from liver failure usually supervenes within one to three months. Some patients may die from intercurrent infections or gastrointestinal haemorrhage. The disease is not invariably fatal and unexpected clinical recoveries are sometimes noted, though biochemical alterations usually persist. Morphological evidence of hepatic cirrhosis is always present.

Post-hepatitis cirrhosis

If acute viral hepatitis can progress to disruption of the lobular architecture, then cirrhosis is inevitable. Despite some negative evidence from follow-up studies, it is generally thought that this sequence of events can occur, though rarely.

Post-hepatitis syndrome

Some patients have persistent symptoms such as fatigue, anxiety, failure to regain lost weight, fat intolerance, and abdominal pain, without biochemical or histopathological abnormalities. The basis of this syndrome is obscure; some of the symptoms may have a psychogenic origin. It rarely persists for more than a year.

Post-hepatitis hyperbilirubinaemia

The persistence of an elevated serum bilirubin level after apparent complete recovery from the disease has been reported by some authors. Liver biopsy findings are normal. The differentiation of this syndrome from one of the hereditary disorders of bilirubin metabolism or from a well-compensated haemolytic state is extremely difficult.

Other possible sequelae

The relationship of viral hepatitis to the active cirrhosis usually affecting young people (sometimes called active juvenile cirrhosis, plasma cell hepatitis or lupoid hepatitis) is uncertain, but there is some evidence that it may be a precursor. Primary liver cell cancer is more frequent in livers

with a coarse nodular cirrhosis than in those with the fine septal type. A relationship has been suggested, particularly in Africa, between viral hepatitis, coarse nodular cirrhosis and primary liver cell cancer. This possible association deserves further study.

PATHOLOGY OF VIRAL HEPATITIS

Knowledge of the pathological picture of viral hepatitis was considerably extended by the introduction of the technique of liver biopsy. However, only a limited amount of information is available on the morphology in the incubation period, in mild cases (where biopsy is not usually necessary) and in severe cases (in which it is contra-indicated by the disturbance of the blood coagulation). Biopsy is not required in the typical case, but can be very helpful when diagnostic uncertainties exist, especially early in the disease. It is not possible on histological grounds to differentiate between the lesions of serum and infectious hepatitis. There seems to be little correlation between the clinical and pathological picture, but this may be due in part to the sampling errors inherent in needle biopsy, where only small specimens are obtained. No single histological feature is diagnostic of virus hepatitis. The general picture is of disruption of liver cell plates, changes in the liver cells, a mesenchymal reaction and usually preservation of the reticulin framework of the liver. Liver cells show necrotic changes, usually multifocal, often marked in paracentral areas, and occasionally massive. Individual cells may show ballooning or contain acidophil bodies. Nuclei show pyknosis and karyolysis and vary in size. Fatty change is usually minimal and the presence of excess fat in the liver cells is against the diagnosis of viral hepatitis. Fatty changes may be noted during convalescence or after corticosteroid treatment.

The characteristic mesenchymal change is mononuclear (lymphocytic, monocytic and plasma cell) and is seen in the portal zones, dispersed through the sinusoids and in compact intralobular foci related to liver cell necrosis and associated with condensation of the reticulin. A polymorphonuclear reaction is found in very early cases or where cholestasis is marked.

Kupffer cells and endothelial cells are proliferated and swollen and often contain excess of lipofuscin pigment.

The bile ductular reaction is variable. Ductular proliferation in the portal zones is frequent.

Evidence of hepatocellular regeneration is shown by cellular atypism, polyploidy, frequent mitosis, numerous binucleated cells and cytoplasmic basophilia. Such regenerative changes may or may not be associated with the destruction of the hepatic architecture characteristic of cirrhosis.

Recent observations by renal and intestinal biopsy on sufferers from acute viral hepatitis contracted in Korea have shown lesions in the duodenum, jejunum and kidney. Further observations are needed on the nature and location of such extrahepatic lesions.

POSSIBLE LONG-TERM SEQUELAE OF VIRAL HEPATITIS

Cirrhosis is defined as a diffuse and chronic hepatic lesion in which fibrous tissue bands join central veins to portal tracts and so disorganize the normal hepatic architecture. Nodular regeneration is constant.

There are conflicting opinions on the frequency of cirrhosis following hepatitis. According to some observers it has no place in the natural history of viral hepatitis; according to others a chronic progressive hepatitis and cirrhosis may occur after a disease that is clinically indistinguishable from viral hepatitis. This concept is particularly important when the possibility that subclinical or anicteric infection may lead to chronic hepatic disease is considered. The Committee believes that cirrhosis can follow hepatitis and that it is usually of a coarse nodular type.

Follow-up studies of epidemics of viral hepatitis have so far failed to show a high frequency of recognizable long-term hepatic sequelae. The Committee is cognizant of the problems inherent at the present time in designing and carrying out such studies, particularly in obtaining suitable control groups known with certainty not to have had hepatitis. Needle biopsy would be the best method of demonstrating morphological changes in such studies but cannot be justified in symptom-free individuals who have no signs of disease. The long-term follow-up and eventual post-mortem examination of persons with and without a reliable past history of hepatitis would be useful. The routine collection of reliable data on the incidence of viral hepatitis, on possible sequelae and on related liver diseases in children and adults in different parts of the world would be of some help, as would the collection and storage of serial specimens of serum from acute and convalescent patients and serial or single specimens from patients with chronic hepatic disease for examination when the etiology of viral hepatitis has been clearly determined.

DRUG-ASSOCIATED HEPATITIS

Some drugs are known to cause forms of hepatitis which may be difficult to distinguish from viral hepatitis. These can be classified in three broad groups:

(1) Drugs which produce a hepatitis closely simulating viral hepatitis, clinically, biochemically and morphologically. These include pyrazinamide,

iproniazid and its derivatives, zoxazolamine, cinchophen and possibly halothane. It has been suggested that these drugs either activate a latent infection or render the subject more susceptible to hepatitis virus infection ; there is no evidence to support or refute these hypotheses.

(2) Drugs which produce a clinical picture similar to the cholestatic form of viral hepatitis. These include the phenothiazine group, e.g., chlorpromazine.

(3) Certain steroid derivatives, such as methyl testosterone, which also produce a cholestatic jaundice, though this is seldom associated with clinical manifestations.

In view of the importance of recognizing drug-induced hepatitis, it is essential to elicit a very careful history about the intake of drugs, particularly because in the established stage of the disease it may be impossible to distinguish between viral and drug-associated hepatitis.

LABORATORY TESTS IN VIRAL HEPATITIS

None of the present laboratory tests is specific for viral hepatitis.

Serum transaminase assays

When viral hepatitis is suspected on clinical or epidemiological grounds, estimation of the level of the serum L-aspartate : 2-oxoglutarate aminotransferase (serum glutamic oxalacetic transaminase, SGOT) and serum L-alanine : 2-oxoglutarate aminotransferase (serum glutamic pyruvic transaminase, SGPT) can be regarded as valuable indices of liver cell injury.

Both these tests can be used with advantage in early cases before the appearance of jaundice, in anicteric illnesses, in the differential diagnosis of jaundice, and for detection of inapparent cases in epidemiological surveys. Serial estimations showing a distinct increase and subsequent decline of enzyme activities are preferable to single determinations. The peak level is usually observed one or two days before or after the onset of jaundice.

The pattern of alterations observed with the two enzymes differs to some extent in time of appearance and development and in children compared with adults. The SGPT may be preferred because it is more specific for hepatocellular injury, and remains elevated for a longer period in the course of the disease. Where a single transaminase estimation is made, as in surveys, the SGPT is likely to be the more useful test. Where

difficulties in clinical diagnosis exist, estimation of both transaminase levels may give more information.

To facilitate comparison of data from different laboratories, the Committee endorses the use of the unit recommended by the Commission on Enzymes of the International Union of Biochemistry¹ and described as follows :

“ One *unit* (U) of any enzyme should be defined as that amount which will catalyse the transformation of 1 micromole of substrate per minute, or, where more than one bond of each substrate molecule is attacked, 1 micro-equivalent of the group concerned per minute, under defined conditions. Where two identical molecules react together, the unit will be the amount which catalyses the transformation of 2 micromoles per minute. The temperature should be stated, and where practicable should be 25°C. The other conditions, including pH and substrate concentration, should be optimal. In order to avoid inconvenient numbers, terms such as milli-unit (mU), kilo-unit (kU), etc., may be used. ”

Serum alkaline phosphatase assay

In differentiating between jaundice due to cholestasis and hepatocellular damage, estimation of serum alkaline phosphatase activity may be of considerable help, especially in combination with serum transaminase assay.

Serum flocculation tests

In laboratories where facilities for transaminase assays are not available, flocculation tests may be useful. However, the limitations of these tests must be recognized, particularly in geographical areas where abnormal findings may be related to causes other than hepatitis. The thymol turbidity test is considered the most reliable.

Serum bilirubin

This test is of very limited value in the diagnosis of viral hepatitis. Estimation of total bilirubin and, if possible, of the conjugated bilirubin in the first sample with serial estimations of the total bilirubin subsequently can be of considerable help in evaluating the course of the disease.

Urinary bilirubin

This procedure may be of diagnostic value in the anicteric case and the early pre-icteric stages of the disease. It is not sufficiently sensitive to be useful in epidemiological surveys.

¹ International Union of Biochemistry (1961) *Report of the Commission on Enzymes*, London & New York, Pergamon Press, p. 45.

Leucocyte count

A total and differential count of leucocytes should be a routine procedure. It is particularly useful in the differential diagnosis of jaundice due to infectious mononucleosis.

Serological tests

There are at present no known specific serological tests for virus hepatitis. Rhesus erythrocyte and one-day-old chick erythrocyte agglutination tests have been reported but are not considered to be sufficiently specific to be of value.

Tests in general population and contacts

Surveys of the general population cannot usefully be made with the laboratory tests at present available. When it is desirable to follow known close contacts of hepatitis patients or groups of people otherwise exposed to infection the serum transaminase assays are useful for the detection of anicteric and pre-icteric cases. Their value is directly proportional to the frequency of sampling of the same individual since the increase in levels may be transient. Flocculation tests remain positive longer but when used in surveys are less likely to be specific for current hepatitis virus infection than when used for the diagnosis of cases. Tests for bilirubin in the urine are of little value even if performed daily.

ETIOLOGY

Several viruses are known to cause hepatitis in animals (e.g., in dogs, sheep, cattle, horses, swine, mice, ducks and canaries) but there is no evidence to indicate that any of these are etiologically related to infectious or serum hepatitis of man. Recently there have been reports from the United States of America of over 90 cases of hepatitis in handlers of freshly imported non-human primates (mainly chimpanzees, but also gorillas, woolly monkeys and Celebes apes). The epidemiological association is clear but the animals in question did not exhibit evidence of hepatitis and the source of their infection remains obscure. Attempts to induce infection in chimpanzees with human hepatitis materials (both infective hepatitis and serum hepatitis) have met with failure. Although "chimpanzee-associated" human hepatitis is of relatively small importance as a public health problem its virological and epidemiological implications are of sufficient interest to warrant the encouragement of intensive studies

of potentially infected animals and the continued surveillance of people associated with the capture, shipping and handling of such animals.

Several human viruses ordinarily associated with specific clinical manifestations not related to the liver are occasionally observed to produce clinical and pathological evidence of hepatic involvement. These include the herpes viruses, some of the ECHO and Coxsackie viruses, cytomegalic inclusion virus as well as others. However, there is no evidence to suggest that any one of these agents is etiologically related to the commonly occurring, sporadic, epidemic or endemic forms of infectious hepatitis or to serum hepatitis.

Between 1950 and 1958 several initially encouraging reports of human hepatitis virus isolations were published, but efforts to repeat or extend the original observation failed. During the past five years published and unpublished reports of tissue culture methods for the isolation of hepatitis viruses have appeared with increasing frequency from laboratories in several countries. To date these reports have not been confirmed. On the basis of currently available information concerning some 18 viruses or groups of related viruses reported to be related to human hepatitis, the Committee observed that :

(1) The agents are not uniform in cultural, biological and other characteristics. The majority fall into the range of the smallest known human viruses and they survive temperatures of 56°-60°C for periods of 30 minutes or longer. A few of the agents have been precisely identified as new types or subtypes of recognized virus groups (e.g., adenovirus, REO virus) while others seem to be antigenically unrelated to known virus groups.

(2) The general relationship of any given agent to naturally occurring sporadic cases of viral hepatitis has not been firmly established. A few have been found to induce clinical symptoms and/or biochemical changes related to hepatitis in volunteer subjects.

The Committee in reviewing the extensive current researches into the etiology of viral hepatitis recognized the complexity of the problem. It considered that some of the difficulties would be lessened if there were a free exchange of information and materials between investigators and to this end made the following suggestions :

(1) An investigator who has isolated a virus he considers important in the etiology of viral hepatitis should, after carrying out extensive preliminary investigations in his own laboratory, attempt to prepare adequate amounts of stable antigen and specific antiserum for use in further definitive investigations. These further investigations should include attempts to isolate virus, and also studies of serial specimens of serum, from well-documented sporadic and epidemic cases of hepatitis in general communities and institutions in different localities.

(2) For confirmatory studies he should then make available to other competent laboratories in different geographical areas the virus strain, the antigen and the antiserum, and also such other special materials as may be necessary for the repetition of techniques.

The Committee also suggested that new tissue culture systems and similar advances in laboratory techniques should be intensively studied to determine their suitability for isolation or recognition of the agents of viral hepatitis. Material thought from previous experiments in volunteers or from epidemiological observations to be infective should be used in these studies.

CONTROL OF VIRAL HEPATITIS

Infectious hepatitis

The virus of infectious hepatitis is excreted in the faeces for as long as two weeks before the appearance of jaundice in the icteric patient. It is also probable that the anicteric patient may excrete the virus for a similar period. Virus may therefore be widely disseminated in a community before the diagnosis is made. For this reason isolation and quarantine of patients and contacts cannot be expected to influence significantly the spread of hepatitis. Patients need not be removed to hospital unless their clinical condition warrants it.

The general measures to be taken to limit the spread of infection from recognized patients and contacts are those usually applied when other enteric infections occur: personal cleanliness and the safe disposal of faeces and urine of patients and contacts. The agent of infectious hepatitis is more resistant to heat and chemicals than most human viral and bacterial pathogens. Linen and other items of clothing soiled by patients should be autoclaved or boiled if this will not damage the fabric. Contamination of food, water and milk directly or indirectly by contacts or patients or by sewage should be prevented. Contacts need not be quarantined, but those who are food-handlers should be given specific advice and recommendations on personal hygiene. They need not be excluded from work unless facilities for personal hygiene are considered inadequate, but should be isolated as soon as symptoms begin to develop. If the water supply is thought to be contaminated, chlorination cannot be considered effective unless the water has first been allowed to settle and has been filtered. Even then, some degree of risk may remain.

The accidental transmission of infectious hepatitis by syringes, needles and other medical and dental equipment can best be controlled by the use of disposable items or by employing sterilization techniques as recommended in the section on serum hepatitis below.

Gamma-globulin in the prevention of infectious hepatitis

The efficacy of gamma-globulin in the prevention of clinical infectious hepatitis has been established by studies in many parts of the world. The priorities for the administration of gamma-globulin will vary from country to country. The aim of any programme should be, within the limits of the amounts available, to protect as many of those at high risk as possible and also those, such as pregnant women, in whom the illness may be more serious than usual.

Gamma-globulin in a dose of 0.02 ml to 0.04 ml of a 16% concentration per kilogram of body-weight will effectively prevent hepatitis with jaundice in the usual short-term type of contact exposure—for example, in a household. Gamma-globulin is of value if given at any stage of the incubation period, but the earlier the better. It is of no value in treatment. A dose of 0.06-0.12 ml per kg will give a longer period of protection, perhaps up to five or six months. Consequently, where supplies allow, the larger dosage may be indicated for potentially susceptible persons travelling to areas where the incidence is thought to be high. In these circumstances it is probable that not more than two doses are required at an interval of five to six months, since under conditions of high exposure inapparent infection during passive protection should give active immunity.

Serum hepatitis

Serum hepatitis may be controlled to a significant degree by measures aimed at reducing the risk associated with the use of blood and blood products, by the use of sterile disposable equipment when possible for medical, dental and public health procedures, by proper cleansing and sterilization of non-disposable equipment before use for any individual procedure, and by the prompt reporting of cases. The same measures will provide for reduction in the risk of parenteral transmission of infectious hepatitis.

Discrimination in the use of blood and blood products which may transmit serum hepatitis

Whole blood. Many unnecessary transfusions of blood are given. There are few indications for the transfusion of a single bottle of blood and, in view of the risk of transmitting hepatitis, the indication should be carefully assessed. Blood should not be administered if the potential advantages do not outweigh the risk of acquiring hepatitis.

Choice of donors. The common practice of rejecting persons with a past history of jaundice at any time is based on the knowledge that some of them may be carriers. However, many proved carriers have had no previous

known episode of jaundice and most adults have probably recovered from an inapparent infection with infectious hepatitis virus. So far there is no known laboratory test which can detect with certainty any significant proportion of carriers of hepatitis virus. For routine screening of donors such tests are not worth while. In the present circumstances the rejection of potential donors with a previous history of viral hepatitis should be continued.

It is recommended that blood donors should also be rejected :

- (a) if they have received a transfusion in the previous six months ;
- (b) if they have been in contact with hepatitis in the previous six months ;
- (c) if their blood is suspected of having been responsible for a case of post-transfusion hepatitis.

All donors should be carefully screened to exclude narcotic addicts and others who might be potentially unsatisfactory.

Plasma. Plasma should not be used if stable plasma protein solution or albumen are satisfactory substitutes. Irradiation of liquid plasma with ultraviolet light is not an effective method of inactivating the virus of serum hepatitis. Since the risk of contamination with serum hepatitis increases with the number of donors contributing to each pool, the risk may be reduced by limiting the size of the pool to 10 or 20 donors. Also storage of liquid plasma at a mean temperature of 27°C-31.6°C for six months may substantially reduce the risk of transmitting serum hepatitis. None of the chemical methods of sterilization of plasma can be regarded as entirely satisfactory. The results from using β -propiolactone in conjunction with ultraviolet light are encouraging. Investigation of ethylene oxide is still at an early stage.

Other blood products. Fibrinogen, antihæmophilic globulin and thrombin, prepared by present methods, carry a risk of transmission of serum hepatitis.

Records of blood and blood products. 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 :

- (a) records of the identifying data for donors contributing to each product ;
- (b) records of batch numbers of products issued to hospitals and of all data relating to batches ;
- (c) accurate records in patients' 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.

Recommendations on medical procedures involving parenteral penetration

In medical procedures involving parenteral penetration, sterile disposable equipment (if available) should be used once only and discarded. Items at present available include syringes, needles, transfusion sets, evacuated specimen tubes, lancets for scarification etc., and blood-diluting pipettes.

In the absence of disposable equipment it is recommended that a separate syringe and needle should be used for each injection and sterilized before being used again. Syringes, needles or other instruments should be thoroughly washed in water immediately after use to prevent organic material from adhering to the surface and interfering with subsequent sterilization.

For sterilization instruments should be boiled in water for at least 10 minutes or subjected to steam under pressure or to dry heat. Lancets and similar instruments used for scarification or capillary blood sampling may be sterilized in an open flame after being well washed in cold water.

In mass immunization campaigns when shortage of equipment or staff may make it impossible to sterilize syringes between each injection, the needle should be changed and sterilized after each injection and the syringe (if it contains multiple doses) should be sterilized each time it is emptied.

These measures will reduce, but not eliminate, the risk.

On the evidence at present available no chemical disinfectants are considered safe for the sterilization of instruments.

Serum hepatitis has occurred relatively often in patients attending venereal disease, diabetes and other clinics at which many injections are given and blood samples taken. In them, special attention should be paid to the safety of the procedures employed.

Gamma-globulin in the prevention of serum hepatitis

The results of studies on the effect of gamma-globulin in preventing post-transfusion serum hepatitis have been conflicting. In a recent trial, gamma-globulin was administered in a dose of 10 ml within one week after transfusion and 10 ml one month later. A comparable group of patients served as controls. The attack rates of icteric hepatitis were approximately 1% in the gamma-globulin group and 4% in the control group. The attack rates of anicteric hepatitis were essentially the same (about 7%) in both groups. These data require further confirmation. At the present time it would be neither realistic nor justifiable to recommend the use of gamma-globulin with every transfusion. More information must be acquired before a potentially efficacious dose and dosage schedule can be recommended. Also, from a practical point of view, restraint must be urged because the available supply of gamma-globulin would be completely inadequate if it were used for all patients who receive blood transfusions.

RECOMMENDATIONS

It is recommended that the views expressed under "Terminology and Classification" (page 4) be taken into account in the Eighth Revision of the International Classification of Diseases in 1965 in so far as they are compatible with the envisaged over-all arrangement of the Classification and the provisions for other situations of a similar nature.

Countries which have not already done so should make notification compulsory and the information obtained should be evaluated. A supplementary follow-up form should be used by local health departments for studying the behaviour of infection in a community (see page 7).

The relationship between viral hepatitis and cirrhosis and other possible long-term sequelae deserves further study, despite the difficulties in obtaining sound data on these questions.

The use of the unit recommended by the Commission on Enzymes of the International Union of Biochemistry (see page 18) for estimating the level of SGOT and SGPT is endorsed.

In studies of the etiology of viral hepatitis a free exchange of information and materials between investigators is recommended. New tissue culture systems and similar advances in laboratory techniques should be intensively studied to determine their suitability for the isolation and recognition of the agents of viral hepatitis.

In medical procedures involving parenteral penetration, sterile disposable equipment should, as far as possible, be employed. It should be used once only and discarded. In the absence of disposable equipment a separate syringe and needle should be used for each injection and sterilized before being used again. More detailed recommendations on such medical procedures are given on page 24.

The priorities for the administration of gamma-globulin will vary from country to country. Recommendations on use and dosage are given on pages 22 and 24.

Recommendations for the control of serum hepatitis are given on pages 22 and 23.

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