THE DIAGNOSIS OF INFECTIVE HEPATITIS AND ITS SEQUELAE

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The object of this presentation of a well-known and frequently documented subject is to emphasize the diagnostic difficulties of the clinical pictures presented by infective hepatitis. From the point of view of diagnosis, consideration must be given to the following stages of the disease, the differentiation into stages clearly not being absolute:—

A. Acute Infective Hepatitis

(i) The pre-icteric phase, with pyrexia and intestinal manifestations dominating the picture.

(ii) The icteric phase, with jaundice as the dominant manifestation. The type varies from the fulminating to the average type of case with jaundice lasting two to three weeks.

(iii) The post-hepatitis syndrome, the stage of symptoms without signs.

(iv) Infective hepatitis without icterus.*

(Homologous serum jaundice and post-arsphenamine jaundice are included for the purpose of discussion under the heading of acute infective hepatitis.)

B. Chronic (Post-Infective) Hepatitis

This includes the 'inactive hepatitis' of Barker³, the 'peri-acinar' or 'cholangitic' type of Eppinger¹⁵, and the 'cholangiolitic' type of Watson and Hoffbauer⁵⁴. The clinical pictures may be persistent hepatomegaly with or without symptoms, or recurrent jaundice of all grades of severity with or without symptoms, or a combination of these manifestations.

C. Post Infective Hepatitis Cirrhosis

Each of these phases will be considered as a diagnostic problem in itself in which the clinical picture, the biochemical tests of liver function, and liver biopsy will be considered in their relation to diagnosis. It is not the purpose of this paper to give a critical evaluation of all liver function tests, on which subject many reviews and standard books have been written. Recent reviews by Osgood⁴² and Stein⁵¹ offer a fair assessment.

The Pre-Icteric Phase

In the majority of cases infective hepatitis at this stage presents as a 'P.U.O.' with anorexia and

nausea as the prominent symptoms, to which may be added myalgic pains and the other usual accompaniments of any pyrexial illness. This pyrexial phase may last from a day or two to a week or two. Many cases in military practice were discharged from hospital with the diagnosis of 'short term P.U.O.' only to return a few days later with jaundice¹⁴. During the pre-icteric phase, a minority of cases may experience severe abdominal pain suggesting the diagnosis of cholecystitis or appendicitis, and laparotomy may appear to be indicated. The normal white cell count of infective hepatitis is a valuable aid in the diagnosis. The milder cases may in the pre-icteric phase be afebrile and complain only of anorexia and nausea with possibly some vomiting, and a complete absence of physical signs on examination. Such cases are apt to be labelled 'neurosis' or 'gastritis'—diagnoses frequently proved wrong by the later appearance of jaundice, the vanity of the doctor possibly suffering more from such error than the welfare of the patient.

Physical signs apart from the pyrexia in the pre-icteric phase are conspicuous by their absence although there may be some hepatic tenderness on palpation or 'fist' percussion. Special investigations of the blood at this stage are of some diagnostic value. The total leucocyte count is normal or reduced. There is a relative lymphocytosis, a feature common to many other virus affections such as influenza and sandfly fever. Atypical mononuclear cells such as are found in infective mononucleosis may be seen in an appreciable number of cases, reaching as high as 60 per cent. of the total white cell count². Hepatitis may complicate infective mononucleosis and the diagnostic difficulties in such an instance are obvious. Heterophil antibodies have not been reported in infective hepatitis. Their presence or absence is, however, neither diagnostic nor exclusive of infective mononucleosis. At this stage of infective hepatitis the blood sedimentation rate as a rule is normal³. The urine may or may not show excessive quantities of urobilinogen. Urobilinuria is not a reliable diagnostic aid⁵⁴ since it is frequently absent at this stage of infective hepatitis and present in many other conditions of

short term fever. Bilirubinuria at this stage may be detected by chemical analysis a day or so before its presence is clinically suspected, the methylene blue test¹⁹ being a simple and useful routine, particularly where the disease is epidemic and coincident with other epidemic pyrexial diseases such as influenza or sandfly fever.

Tests of hepatic function at this stage may be abnormal. According to Barker and others² the cephalin cholesterol and bromsulphthalein tests show a defect in 50 to 75 per cent. of cases. Other reports confirm the finding of abnormal liver function tests. Other infections may show defective hepatic function tests at this stage⁴¹, but in such cases the abnormality is in single tests rather than in batteries of tests. It would appear then, that tests of hepatic function in the diagnosis of infective hepatitis at the pre-icteric stage, have only a limited value. Examination of liver histology by biopsy at this stage has not been reported on extensively, but Mallory³² describes grades and quality of histological change in the pre-icteric stage indistinguishable from the changes which are seen during the icteric phase.

The Icteric Phase

Once hyper-bilirubinaemia becomes apparent, either by noticeable jaundice or by darkening of the colour of the urine, it is clearly necessary to decide whether the condition is one of intra-hepatic (hepatocellular, toxic, or infective) jaundice, extra-hepatic obstructive (surgical) jaundice, or haemolytic jaundice. Under the heading of hepatocellular jaundice, in which condition an obstructive element of greater or less degree is always present, must be considered diseases in which hepatitis is a usual accompaniment of the condition, e.g. infective hepatitis, homologous serum jaundice, post-arsphenamine jaundice, the acute infections of yellow fever and Weil's disease, chemical and vegetable hepatotoxins; and the diseases in which hepatitis is an occasional accompaniment e.g. the very important condition of malignant tertian malaria with hepatic involvement, and infectious mononucleosis or pneumonia. Under the heading of extra-hepatic obstructive jaundice must be considered in particular stone in the common duct with its eventual cholangitic hepatitis of Himsworth²⁵, and malignant obstructions. Haemolytic jaundice can be readily differentiated from the other two types of jaundice by its haematological characteristics. The haemolytic jaundice of malignant tertian malaria and of the sulphonamides are two conditions that must be considered in the diagnosis of any case of haemolytic jaundice. In the differential diagnosis of jaundice the value of an accurate clinical history and examination cannot be over-

emphasized. In very few cases will biochemical tests or study of liver cell structure by biopsy do more than confirm the clinical diagnosis. Nevertheless such tests are of value in assisting not only in diagnosis but also in prognosis, and, as in the case of plasma prothrombin estimations, in the assessment of fitness to undergo operations.

Hepatocellular jaundice and extra-hepatic obstructive jaundice. First must be considered the distinction between hepatocellular jaundice with its obstructive element, e.g. infective hepatitis, and extra-hepatic obstructive jaundice such as that due to gall stones or carcinoma. All important in the differential diagnosis is the clinical history and picture. In case of stone in the common duct, the history or observation of pyrexial attacks with discomfort or actual pain may be helpful, but these may be absent, and furthermore in surgically or post-mortem proved cases of hepatocellular jaundice, including occasional chronic forms of infective hepatitis, episodes of pyrexia occur with severe right upper abdominal pain. Watson and Hoffbauer⁵⁴ report one case in which an initial attack of infective hepatitis occurred in 1912, the patient eventually dying with cirrhosis of the liver in 1945, three laparotomies having been performed in the previous 13 years in the search for a stone in the common duct on account of painful pyrexial episodes and recurrent obstructive jaundice. Liver biopsy in a jaundiced period during 1932 showed normal liver cells and some slight periportal fibrosis. Neither at laparotomy nor eventually at *post-mortem* following a fatal haematemesis was any organic cause of chronic recurrent obstructive jaundice found.

Contrariwise, jaundice due to stone in the common duct may simulate hepatocellular jaundice. In one's own recent experience there is a case of a woman aged 57 admitted to hospital in November, 1946, with jaundice of obstructive type of some six weeks duration, pruritus, right upper abdominal discomfort, the patient showing at the time of admission to hospital defective hepatic function tests (cephalin cholesterol, thymol turbidity, hippuric acid). Biopsy at that time was not done. Within six weeks of the time of admission the condition improved and the patient was discharged from hospital free of jaundice and symptoms. A year later there was a recurrence of obstructive jaundice of mild and varying degree, pruritus, and slight upper abdominal discomfort with occasional pyrexia over a period of some weeks. Biochemical tests again showed deficient liver function. Laparotomy was performed and a stone was found obstructing the common duct; there was macroscopic and microscopic evidence of hepatic cirrhosis. The diagnosis of chronic hepatitis of cholangio-hepatic type was correct,

but the primary cause was the obstruction caused by the stone.

Hepatic function tests may be of some value in the differentiation of extra-hepatic obstructive jaundice and intra-hepatic hepatocellular jaundice if carried out early in the disease. There is great difference of opinion regarding the relative merits of these tests, *vide* Cantarow and Trumper⁸. All agree that more than one of the many available tests must be applied in each case. Sherlock^{46 47} correlates biopsy studies with hepatic function tests and concludes that a single specimen of venous blood examined for bilirubin, alkaline phosphatase, and serum albumin content gives information regarding diagnosis and extent of liver damage as adequately as more complicated batteries of tests. Serum bilirubin increases proportionately to the extent of liver cell damage in acute hepatitis; phosphatase is rarely above 30 King-Armstrong units in hepatocellular jaundice and often up to 90 units in obstructive jaundice; and serum albumin reduction is proportionate to liver cell defect in acute hepatitis and cirrhosis. Sherlock⁴⁸ points out the unreliability of the hippuric acid test unless the renal function has been shown to be normal. All authors agree that, apart from the serum bilirubin level, which merely reflects the degree of jaundice, tests of liver function carried out early are of some value in distinguishing the two conditions of hepatocellular and extra-hepatic obstructive jaundice, hepatocellular function being normal in early extra-hepatic obstructive jaundice. In the course of a few weeks, however, the function tests in obstructive jaundice become abnormal due to the associated cholangio-hepatitis^{31 25}. Himsworth, in emphasizing the parenchymal damage that supervenes sooner or later on obstruction, and after discussing liver function tests, concludes that there is yet no test which approaches in value a careful clinical assessment. Liver biopsy is of value if undertaken at an early stage of the jaundice. In infective hepatitis, homologous serum jaundice and post-arsphenamine jaundice, a characteristic picture is seen^{13 31 32 43 47} whereas in the early stages of extra-hepatic obstructive jaundice, the liver cells are normal. It is pointed out, however^{31 47 49}, that in as short a time as two to three weeks from the onset of extra-hepatic obstruction, liver cell necrosis and periportal fibrosis may appear and are indistinguishable from the post-infective hepatitis picture. It is essential, therefore, that liver biopsy as an aid in differentiation be carried out at an early stage of the jaundice.

With all modern aids, however, one can but agree with Lipp and his co-workers²⁷ who, after reviewing 412 cases of jaundice in their clinic, concluded that careful evaluation of the clinical history

and the findings on clinical examination gave a correct diagnosis in 90 per cent. of cases of jaundice, and in the majority of this group of cases the laboratory findings supported the diagnosis. In the remaining 10 per cent. of their cases, however, both the clinical and the laboratory evidence were inconclusive, and in all cases of obstructive jaundice of obscure aetiology laparotomy was regularly advised in order to avoid overlooking a possible extra-hepatic surgical lesion. In this connection Himsworth²⁵ in discussing cholangio-hepatitis (ascending cholangitis) with its eventual parenchymal failure and cirrhosis of the biliary (Hanot) type consequent upon obstruction, concludes that it is impossible to be certain that extra-hepatic obstruction is absent and advises that cases diagnosed as cholangio-hepatitis should be surgically explored. His emphasis on careful clinical assessment in the diagnosis has already been mentioned.

Having considered the differences between extra-hepatic obstructive jaundice and intra-hepatic hepatocellular jaundice, it is necessary to discuss the various types of hepatocellular jaundice. The first consideration is whether the three conditions of infective hepatitis, homologous serum jaundice and post-arsphenamine jaundice, are the same or different conditions, and if different whether they can be differentiated.

Homologous serum jaundice. This is generally regarded as being due to a virus infection but whether this is identical with the virus of infective hepatitis is in dispute. The disease has followed prophylactic inoculations in which the virus is a part of the inoculated material, as in the case of yellow fever vaccine, or in which the virus is conveyed from one individual to another by the multiple dose per syringe technique of giving prophylactic inoculations, as in the epidemic spread by tetanus toxoid inoculations described by Capps, Sborof and Scheiffly¹⁰. Therapeutic convalescent serum, transfusions of plasma or whole blood, and imperfectly sterilized syringes used in venereal and diabetic clinics have spread the infection. As little as 0.01 cc. of infected plasma or serum is sufficient to convey the virus^{28 32}.

The clinical picture of homologous serum jaundice is indistinguishable from infective hepatitis unless it be true as is claimed by McMichael³¹ and Ginsburg²⁰ that homologous serum jaundice tends to be more severe than infective hepatitis, a difference of little value when considering individual cases. Biochemical hepatic function tests in the various stages of the two conditions are identical. Thus, Neeffe and co-workers⁴¹ report defective liver function tests in the pre-icteric stage between the time of the experimental inoculation of volunteers with infected

plasma and the onset of the jaundice, as well as during the icteric phase. In their experience, serum bilirubin level, cephalin flocculation, bromsulphthalein excretion, plasma vitamin A and plasma prothrombin activity were found both in the pre-icteric and the later stages to detect hepatic disturbances more consistently and promptly than did estimates of urobilinuria, serum albumin and globulin, serum alkaline phosphatase, hippuric acid excretion and blood sedimentation rate. They noted that bilirubinuria was observed early and, furthermore, before any significant increase in serum bilirubin level. Serum bilirubin became increased above normal after the cephalin cholesterol and other hepatic function tests had shown dysfunction. In some of the cases, all tests except the serum and urinary bilirubin were abnormal, these being obviously cases of hepatitis without jaundice. The bromsulphthalein excretion they considered to be reliable as a guide to recovery as it was the last test to return to normal and was specially valuable in following cases without jaundice. Control series of tests on disorders such as influenza not usually associated with clinically detectable liver abnormality showed occasional single test deviations from the normal, but never was the whole battery of tests abnormal as in hepatitis.

According to Dible and others¹³, Mallory³² and other observers, liver biopsy does not assist in the differentiation of homologous serum jaundice from infective hepatitis and for that matter from post-arsphenamine jaundice.

The incubation period is said to differ, being 60 to 120 days in homologous serum jaundice and one-half to one-third of this time for infective hepatitis, this being used as evidence that the viruses are of a different type. Such argument is not necessarily correct as it is known that a combination of virus and immune body increases the incubation period of any virus, and in the case of homologous serum jaundice the virus, being contained in the serum, is of necessity injected along with immune body. In this connection it is interesting to note the incubation period of the jaundice induced by Gardner and others¹⁸ who inoculated over 300 volunteers suffering from rheumatoid arthritis with serum from cases of infective hepatitis. The incubation period from the time of inoculation to the appearance of the jaundice in the 10 per cent. of volunteers who developed jaundice was from 27 to 131 days. Cameron⁷ reported incubation periods of up to six months in volunteers inoculated with infective hepatitis serum but the subjects of his experiment were living in an area where infective hepatitis was endemic. It has also been suggested by Havens²⁴, Neefe⁴¹ and others, that the portal of entry of a

particular virus may determine differences in its incubation period. Neefe and others⁴¹ indicate that in their nine volunteers inoculated with yellow fever vaccine or with plasma, 12 to 35 days elapsed from the date of the inoculation to the first biochemical or clinical manifestations of hepatitis, 65 to 110 days elapsing before jaundice was added to the picture. They remark without comment that the period of 12 to 35 days is the accepted incubation period of infective hepatitis.

It has not been finally decided if a cross immunity between homologous serum jaundice and infective hepatitis exists. Neefe and co-workers³⁹ in a small but well-controlled series of human volunteer experiments found results which strongly suggested a lack of cross immunity. They noticed in their series furthermore, that infective hepatitis serum given parenterally to volunteers failed to cause jaundice, whereas orally administered infective hepatitis virus in the form of filtrates of faeces did cause jaundice; on the other hand serum from homologous serum jaundice cases administered parenterally was followed by jaundice. Havens²³ reported human volunteer experiments which suggest that no cross immunity exists. Gould²¹ studied the incidence of infective hepatitis and yellow fever homologous serum jaundice in the armed forces, and found that the incidence of infective hepatitis in subjects with previous homologous serum jaundice was rather higher than in those who had not had homologous serum jaundice. His findings, furthermore, suggested that clinical and subclinical infective hepatitis conferred immunity against a further attack of infective hepatitis.

Contact infection from homologous serum jaundice has not been confirmed, while it is, so far as is known, the common mode of spread in infective hepatitis. Findlay and Martin¹⁷ are among the few who have claimed to transmit homologous serum jaundice following yellow fever immunization by intra-nasal instillation of virus. Neefe and others^{38, 40} failed to cause jaundice in 19 volunteers within a two to four month period after ingestion of filtrates of faeces from cases of homologous serum jaundice whereas filtrates of faeces from infective hepatitis cases taken by mouth caused jaundice in 26 days in six out of 12 volunteers.

It remains uncertain whether the two viruses of homologous serum jaundice and of infective hepatitis are identical or separate entities. Havens²² reviews his own and other extensive studies and sums up with the statement: 'It is not yet determined whether the differences in route of inoculation, length of incubation period, distribution of virus, period of infectivity and lack of cross immunity are representative of the

activities of actually different viruses or of antigenic differences of various strains of one virus.' One must therefore conclude that there are no methods, clinical, chemical or histological, of distinguishing homologous serum jaundice from infective hepatitis, nor is there any definite evidence to decide whether one or two viruses are implicated.

Post-arsphenamine jaundice. In the human subject this should not be called arsenical hepatitis since there is little evidence that arsenic directly causes the hepatitis. The vast majority of such cases occur between the fifteenth and twentieth weeks of arsenical treatment³³, but cases may develop later in the course of treatment or after the completion of treatment. Delay in the appearance of jaundice after completion of arsenical treatment does not exclude all relationship between arsenic and jaundice since it is known that delayed hepatic damage, the 'massive hepatic necrosis' of Himsworth, may occur months after removal of the patient from contact with the so-called hepatotoxins, such as T.N.T. or cincophen²⁶. Cases occur after the first or second injection of arsenic, and such cases have been claimed, not necessarily justifiably, to be due to the arsenic, on the grounds that a virus conveyed by syringe could not have incubated in so short a time⁶. Although it is accepted that jaundice can occur as part of a Herxheimer reaction between the fifth and the twenty-fifth days of treatment⁴⁴ it is also possible that early jaundice is an example of biotropism with the arsenic sensitizing the liver to invasion by the virus of infective hepatitis which is lying latent in the body awaiting an opportunity to attack. That factors other than a hepatotoxin are necessary before such toxin can exert its action on the liver is a reasonable hypothesis. In animal experiments such factors, in the case of chemical toxins, are locality⁵², climatic factors of temperature and barometric pressure^{35 36 37}, and diet, which subject Himsworth²⁵ reviews very adequately. By analogy, if the virus of infective hepatitis is regarded as an hepatotoxin, it seems, for instance, possible that the high mortality of the malignant type of infective hepatitis described in Copenhagen by Bjorneboc and others⁴, in which 37 per cent. of a series of 303 cases were dead in a matter of months, could have been due to the association of a standard infective hepatitis virus acting in conjunction with some other factor, for example malnutrition. Attempts to induce jaundice by oral administration of faeces and nasopharyngeal washings from post-arsphenamine jaundice cases failed, whereas inoculation of serum (sero-negative) from such cases was followed by jaundice (MacCullum²⁹).

Dible and McMichael¹², in a liver biopsy study

of 35 cases of post-arsphenamine jaundice, offered the opinion that post-arsphenamine jaundice, infective hepatitis, and homologous serum jaundice were one and the same disease, and that post-arsphenamine jaundice was not due to the arsenic. They pointed out that in animals jaundice is produced by arsenic after doses 15 times the maximal equivalent dose administered to human cases of syphilis. The histological picture in the three conditions is described as an hepatic inflammation of varying intensity and distribution which is common to post-arsphenamine jaundice, infective hepatitis, and homologous serum jaundice^{12 13 32}.

The facts that massive mapharside treatment consisting of 1,200 mgm. of the drug given in five days can be carried out without any demonstrable defect of hepatic function⁵³, that jaundice is rare under massive arsenotherapy, and that many cases are reported of arsenical administration being continued during post-arsphenamine jaundice without adverse effect on the jaundice or the patient³⁴ hardly support the supposition that arsenic has a direct hepatotoxic action. Cormia and Blauner¹¹ reported six cases of jaundice amongst 500 syphilitics treated by massive arsenotherapy over a period of two years, and remarked that the six cases occurred in a short circumscribed period during which there was a general increase in infective hepatitis amongst the population. They suggested that infection was at least a factor in the production of post-arsphenamine jaundice. Nevertheless the majority of venereologists advise withholding arsenic for three months after the post-arsphenamine jaundice has disappeared. The clinical picture and course in the individual case of post-arsphenamine jaundice differ in no significant manner from infective hepatitis. Acutely fatal cases occur, mild average cases, and cases leading to chronicity. Such cases of post-arsphenamine jaundice are infrequently associated with other manifestations of arsenic toxicity such as dermatitis or peripheral neuritis³⁴. Collective studies, however, do show a different course and prognosis. In Borensztein's series⁵ of 226 post-arsphenamine jaundice cases there were 40 deaths, a percentage of deaths far exceeding the under 1 per cent. mortality of infective hepatitis. Of 36 deaths from acute liver necrosis in the Middle East^{14 12} were receiving arsenic prior to death, the incidence of post-arsphenamine jaundice to infective hepatitis at the time being 1 to 13.

Biochemical studies of hepatic function in post-arsphenamine jaundice differ in no way from those found in infective hepatitis. The incidence of post-arsphenamine jaundice varies from clinic to clinic, from 0.6 per cent. to 40 per cent. and

more of cases under treatment, this aspect of the subject being reviewed by Marshall³³ and others. There is little evidence to support syphilitic disease of the liver as the cause of jaundice. There is therefore no method of differentiating post-arsphenamine jaundice from infective hepatitis nor is there evidence that they are different diseases. The concensus of opinion is that post-arsphenamine jaundice is a virus jaundice of homologous serum type.

Specific types of infection. Specific types of infection with liver affection as a dominant concomitant must clearly be considered as a cause of acute hepatocellular jaundice. Weil's disease and yellow fever in particular require mention; the latter in view of present day air travel facilities no longer remains a disease to be considered only in endemic tropical areas. The clinical and biochemical picture in both these conditions is that of an acute hepatocellular jaundice with parenchymal hepatic failure of all grades, but the specific character of the disease is diagnosed only by the features of epidemiology, the general clinical characters, and specific immunological investigations. Malignant tertian malaria must be considered in all cases of acute pyrexial illness with jaundice. The jaundice can be hepatocellular or haemolytic or of both types. Any practitioner in malarious countries has had experience of cases diagnosed and treated as infective hepatitis that in reality were malignant tertian malaria, such errors arising through not carrying out the simple procedure of a blood examination. Patients contracting malarial infection in endemic areas can nowadays reach non-malarial parts of the world quite readily within the incubation period of the disease.

The Post-Hepatic Syndrome

This special heading connotes a not at all uncommon clinical problem. The syndrome consists of symptoms of lassitude, anorexia, dyspepsia, occasional diarrhoea, and a lack of interest in the everyday things of life. On clinical examination there are no abnormal physical findings, and by definition hepatocellular tests, if carried out, are normal; biopsy of the liver shows none of the described features of infective hepatitis. On this type of evidence it is tempting to label such a case psychoneurotic and indeed this may be correct. Sherlock and Walshe⁵⁰ describe 20 cases of this type in which the hepatic function tests favoured by Sherlock were applied and correlated with liver biopsy findings. In these patients hepatic function tests were normal, liver biopsy was normal, with the exception that in three of the cases there was residual portal scarring, and in 16 the liver was palpable. The authors suggested

that these patients had learned how to push their livers down by diaphragmatic action and they regarded them all as psychoneurotic. One hesitates to accept normal hepatic function tests and even normal liver histology by present day histological techniques as proving the absence of all hepatic disease. It is known that hepatic function tests (apart from a raised serum bilirubin) and biopsy may be normal in the face of persistent relapsing jaundice and eventual portal cirrhosis following infective hepatitis⁵⁴. We accept the diagnosis of infective hepatitis, acute and chronic, in the absence of jaundice and raised serum bilirubin, but with abnormalities in function tests other than estimation of serum bilirubin. It seems that a combination of normal histology, normal serum bilirubin, and normal hepatocellular function tests is not incompatible with a disturbed hepatic function that could serve as a basis of symptoms. Physical signs such as a tender liver, enlarged or not, or even a recurrence of jaundice, may be induced in such cases after strenuous exercise or by a long jolting ride in a vehicle over rough roads, indicating the organic basis to the symptoms^{3 14}.

The post-hepatitis syndrome may be due to other complicating diseases. In areas where amoebiasis is endemic, the differential diagnosis between amoebiasis and the post-infective hepatitis syndrome is important on account of the specific treatment required for amoebiasis, particularly the hepatic forms. The differential diagnosis of these two conditions will be discussed later. Duodenal ulcer and cholecystitis are amongst the conditions that must be excluded in this post-hepatitis syndrome.

Infective Hepatitis without Jaundice

Eppinger¹⁵ in 1937 drew attention to the *post-mortem* findings of severe liver damage compatible with the findings of infective hepatitis, where there had been no jaundice during life. Neefe⁴¹ and others have studied cases of homologous serum hepatitis induced in volunteers and in some of these cases serial biochemical liver function tests were abnormal without the development of jaundice at any stage. MacCallum and Bauer³⁰ reported the same experience. Mallory³² described appearances in liver cells indistinguishable from the appearance of infective hepatitis in cases with no jaundice, and Capps⁹ agreed with the existence of such an entity. Barker³ described cases of chronic hepatitis in which tender hepatomegaly with defective hepatic function but without jaundice persisted after infective hepatitis. Popper and Franklin⁴³ have reviewed the recent literature on this subject.

The symptoms in such cases are general fatigue

with or without pyrexia, dyspepsia, occasionally diarrhoea, and on examination there is hepatomegaly after if not before exercise, and liver tenderness. Clinical jaundice, bilirubinuria and hyperbilirubinaemia are absent. Hepatocellular function tests show abnormalities in the majority of cases. The white cell count is normal or low as in infective hepatitis with jaundice. The condition may be acute or chronic. Clearly such an entity as infective hepatitis without jaundice presents difficulties in diagnosis, particularly if the liver is not palpable at the time of the examination, and such cases are likely to be labelled psychoneurotic. Where the liver is palpable and tender, hepatic amoebiasis, either diffuse or with abscess formation, must be considered. One has personally seen cases of hepatic amoebiasis presenting with this very same clinical picture in which rest in bed alone without emetine has produced dramatic temporary improvement even where abscess formation was later proved, the temperature subsiding, the white cell count returning to normal, and the symptoms being relieved, this improvement lasting for a matter of weeks. Clearly infective hepatitis with rest in bed could follow the same course. In the case of amoebic hepatitis there is eventually a recurrence of symptoms, and the abscess if present will at some time become manifest. In amoebiasis the hepatic function tests are usually normal, and liver biopsy material, unless the needle happens to strike an abscess, is normal and fails to show the appearances of infective hepatitis.

Chronic Hepatitis

Chronic hepatitis following infective hepatitis may present itself as a persistent hepatomegaly with or without defective hepatic function tests, or as a chronic, recurring, mild or severe obstructive type of jaundice, with greater or less degrees of ill health in any of these types of case. We are indebted to Barker and others³ for emphasizing the chronic stage of infective hepatitis, which in some degree follows about 10 per cent. of cases of acute infective hepatitis. These authors described chronic cases as complaining of lassitude, dyspepsia with discomfort, particularly in the right hypochondrium, anorexia, bouts of diarrhoea, and showing, on examination, hepatomegaly and defective hepatic function tests, the latter being common though not invariable. The tests carried out by Barker and his co-workers included estimation of serum proteins, plasma prothrombin, bromsulphthalein excretion, serum cholesterol, serum alkaline phosphatase and serum bilirubin. Over a period of 12 months the authors noted improvement in many of these cases. The defective tests were not consistently related to the

presence or severity of the symptoms. The urine in these chronic cases sometimes showed excessive urobilinogen, the results being too variable to be of value. Barker considered the bromsulphthalein test to be of greater value than other tests in the follow up of such cases. The blood sedimentation rate was reported as frequently normal; this is in agreement with the findings of Stein⁵¹. The authors moreover drew attention in passing to cases presenting mild recurrent jaundice with or without defective hepatocellular function and often lasting years with more or less good health, the periods of poor health occurring during the periods of mild jaundice. Such cases are more fully described by Watson and Hoffbauer⁵⁴. 'Inactive hepatitis' is a term suggested by Barker and reserved for those cases of post-infective hepatic hepatomegaly without symptoms.

Watson and Hoffbauer⁵⁴ investigated cases presenting recurrent obstructive jaundice, corresponding to one clinical type referred to by Barker, and also corresponding to Eppinger's second type. Eppinger¹⁵ considered that there were two types of catarrhal jaundice clinically and anatomically distinct, the first being the hepatocellular type which is the average case of infective hepatitis lasting three or four weeks and clearing completely, and the periacinar or cholangitic type, with more severe jaundice of longer duration (two to four months), palpable liver and spleen, sometimes ascites, acholic stools, and urobilinogen absent in the urine, at least for long periods. Such cases may be laparotomized for surgical causes of obstruction with negative results. Watson and Hoffbauer's cases showed in general prolonged recurrent regurgitation jaundice following an attack of infective hepatitis with pruritis, hyperbilirubinaemia and bilirubinuria, increased serum alkaline phosphatase, normal or almost normal hepatocellular function tests, and liver usually enlarged but not necessarily tender. Urobilinuria was intermittently present. Biopsy revealed no mechanical causes of obstruction to the bile channels, there being some periportal fibrosis in a few of the cases, but the liver cells were normal apart from the presence of occasional multinucleated cells which were regarded as evidence of hepatic cell regeneration. Details of one of their cases have been outlined in an earlier paragraph. Because of the absence of mechanical obstruction, in this and other cases, the authors postulated a functional change in the permeability of the bile canaliculi (cholangioles), likening it to the functional change in the renal glomerular epithelium in orthostatic albuminuria, and gave the name 'cholangiolitic hepatitis' to the condition. The later cirrhotic stage they call 'cholangiolitic cirrhosis.' Whether the opinion is right or wrong,

the authors certainly did draw attention to the clinical syndrome of this type of case. Sherlock⁴⁶ stated that she has not seen the type of case described by Watson and Hoffbauer. One has, however, had personal experience of two cases of this type both with mild recurrent jaundice, usually subclinical, following infective hepatitis, the attacks being associated with mild ill health. Both cases had normal hepatocellular function tests and normal appearance of liver cells on biopsy at the last examination which was three years after the initial attack of infective hepatitis, and both cases are leading normal sedentary types of life.

In chronic hepatitis, the presence of fatty changes in the liver cells seen in biopsy sections is against the diagnosis of a stage of infective hepatitis. Popper and Franklin⁴³ found the changes described in infective hepatitis by Sherlock⁴⁷, McMichael³¹ and Mallory³², and pointed out that in what they call the toxic variety and in malnutrition, fatty changes were common. They described 21 cases of the toxic variety, the toxins being arsenic, cinchophen, that of pneumonia and thyrotoxicosis, and they stated that fatty changes were present in three of these cases. Unfortunately they did not specify which toxins were causative in these three cases. This should be considered in relation to the findings of Dible and his co-workers¹³ and Sherlock⁴⁷, that post-arsphenamine jaundice is indistinguishable from infective hepatitis under the microscope. In cases of chronic hepatitis, cholecystograms may be abnormal due to defective hepatic excretory function, and it is tempting to regard such cases as cholecystitis with stone formation and recurring obstructive jaundice, and to advise operation. As in the case of the icteric phase, laparotomy may be necessary in the full knowledge that no surgical obstruction may be found, but it must be reiterated that in certain cases there are no means of ascertaining without laparotomy whether surgical obstruction is present or not.

Post-Infective Hepatitis Cirrhosis

There seems little doubt that post-infective hepatitis portal cirrhosis occurs, indistinguishable clinically and pathologically from other types of portal cirrhosis such as alcoholic or malnutritional cirrhosis. Statistically, only a small percentage of cases of portal cirrhosis give a previous history of jaundice, the figures varying from 5 to 15 per cent. in different published series. Sherlock⁴⁶ after reviewing the literature adds nine cases of her own, showing on serial biopsy the gradual development of periportal fibrosis in which portal cirrhosis could reasonably be attributed to the preceding acute hepatitis. Of these cases, six were infective

hepatitis and three were post-arsphenamine jaundice. In one case death from haematemesis took place due to cirrhotic portal hypertension two and a half years after the attack of acute infective hepatitis, and in another a period of six years elapsed between the infective hepatitis and the manifestations of portal cirrhotic hypertension. It is of value to refer again to the case of Watson and Hoffbauer⁵⁴ which showed normal liver cells and some slight periportal fibrosis and cellular infiltration at the time of the first liver biopsy 13 years before death from haematemesis due to advanced portal cirrhosis, and 24 years after the attack of infective hepatitis. Sheldon and James⁴⁵ described two cases of cirrhosis three years after the actual attack of infective hepatitis, the picture being in these cases identical with the picture described as 'toxic or post-necrotic cirrhosis' or 'healed yellow atrophy' of Mallory. Sherlock noted that she has not seen nodular hyperplasia after infective hepatitis as described by Sheldon and James. King²⁸ reported a case of infective hepatitis aged 19, who, after partial clinical recovery, eventually died of acute hepatic failure ten months after the attack of infective hepatitis. During the partial recovery phase he suffered from general feelings of ill health, and hepatic function tests showed deficiencies. Biopsy at the second month showed greatly thickened portal tracts with liver cells showing only slight abnormalities, and repeat biopsy at the sixth month showed complete distortion of normal hepatic structure with very cellular fibrous tissue and islands of proliferating liver cells. At post-mortem examination, there was a dearth of liver cells and great increase in portal fibrous tissue. Fernando and others¹⁶ describing 102 cases of cirrhosis in Ceylon drew attention to a nodular cirrhosis that followed continuously upon or after an interval following an attack of jaundice, differing from the Laennec type of cirrhosis which in their series was not preceded by jaundice. They offered no explanation for the cause of the jaundice. Dible¹³ described residual scarring after infective hepatitis under two headings, firstly, fibrosis confined to the anatomical portal tracts, without functional hepatic disturbance, and which may disappear with the passage of years, and secondly, severer cases where the reticulum framework of the lobule is destroyed through loss of liver cells, fibrous tissue condensing in the spaces previously occupied by the liver cells, and in such cases followed by permanent cirrhosis. They considered that only in the latter type of case will portal hypertension develop. Cameron and Karunaratne⁶ poisoned rats with carbon tetrachloride and produced cirrhosis which resolved to normal with disappearance of the cirrhotic fibrous tissue on

stopping the administration of the carbon tetrachloride. This reversibility of fibrosis noted both experimentally and in human cases, is obviously important in considering prognosis and assessing symptoms in relation to anatomical defects.

It has been pointed out by McMichael³¹ and others that study of cirrhotic liver structure by biopsy may give false results, and this conforms to one's own experience, the biopsy needle failing to cut a true section of liver structure, travelling between fibrous bands and removing nothing more than a few liver cells. In one example in my own experience, a case of Banti's disease with normal liver function tests was reported as having histologically normal liver cells obtained by liver biopsy. Splenectomy was advised but abandoned after opening the abdomen, on account of gross macroscopic hepatic cirrhosis, confirmed histologically. Evidence is strong that portal cirrhosis can follow an attack of infective hepatitis. Histologically such cirrhosis in its end result is indistinguishable from cirrhosis due to many other causes. The mechanism whereby chronic progressive disease of an organ such as the liver can be initiated by an acute virus affection of that organ is unknown. King²⁶ suggested the possibility that primary damage to liver cells initiates an abnormal auto-antibody production which gives rise to secondary and progressive liver damage. Cases are recorded and have been quoted in which cirrhosis with portal hypertension has developed in as short a time as two and a half years after the acute attack, or as long as 33 years after the acute attack. In cases of portal cirrhosis, the causative action of infective hepatitis can but be hazarded on the past history of an attack of jaundice. In considering the prognosis of infective hepatitis the development of cirrhosis in a small percentage of cases must be remembered.

General Comments

Infective hepatitis in its various stages can simulate many diseases of the liver. The less common pictures such as chronic hepatitis with or without jaundice, acute hepatitis without jaundice, or the post-hepatic syndrome, must not, however, be used as scrap heaps on which to throw all obscure cases of hepatomegaly with a vague symptomatology. It is not proposed to list all the possible conditions which may simulate these less common forms of infective hepatitis. A pyrexial illness with hepatomegaly is always a challenge to the diagnostician. The following is a selection of cases in my own experience that have presented such difficulties and in which a final answer was obtained:—

1. A male, aged 45, complained of recurrent attacks of ill health with pyrexia over a period of

five years with occasional jaundice, and with periods of good health between the attacks. The only finding on examination was a moderate hepatomegaly. After prolonged medical treatment and many investigations, laparotomy revealed the case to be one of an hydatid cyst with a low grade infection in it.

2. A patient of 25 was pyrexial for four weeks with no focal sign other than a palpable liver. Biopsy revealed tuberculous foci. The case died later of miliary tuberculosis. All investigations, including X-ray of the chest up to the time of the biopsy, had been negative.

3. A patient of 52 with right upper abdominal pain for two months with intermittent pyrexia was operated on as a case of cholecystitis and no abnormality was noted. Fourteen days after the operation a pleural effusion developed at the right base, amoebiasis was obviously suspected, but a liver biopsy revealed actinomycosis.

4. A military officer, aged 28, had a temperature for four weeks with hepatomegaly and some glandular enlargement in the neck. All investigations as to cause were negative until sternal puncture revealed kala-azar.

5. A Bantu male subject of 32 had a pyrexial illness lasting some five weeks with tender hepatomegaly as the only focal sign on examination. Biopsy revealed primary carcinoma of the liver, the commonest form of carcinoma in the male Bantu.

6. A girl of 15 complained of upper abdominal discomfort as a rule after exercise, and on examination she was found to have a tender liver with three inches enlargement. There was no jaundice. All examinations were reported negative but it was noted that the venous pressure in the neck was increased and after investigation the case was found to be one of constrictive pericarditis.

Until specific immunological reactions and bacteriological procedures become available for use in the diagnosis of infective hepatitis in all its stages, the condition will continue to cause difficulty in diagnosis.

Summary

The subject of infective hepatitis has been reviewed with particular attention to the diagnostic difficulties that may arise in the different stages of the disease from the pre-icteric to the chronic, and including cases without jaundice and cases ending in portal cirrhosis.

The relative merits of the clinical picture, biochemical tests of hepatic function, and liver biopsy studies are discussed with regard to their value in diagnosis, and it is pointed out that careful clinical assessment remains the most important single diagnostic aid.

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