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# Etiology and epidemiology of infectious hepatitis

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# THE ETIOLOGY AND EPIDEMIOLOGY OF INFECTIOUS HEPATITIS

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# INTRODUCTION & NOMENCLATURE

It is largely due to the military importance of infectious hepatitis that renewed interest has been stimulated in this disease. The illness attained pandemic proportions during the past war, large outbreaks occurring in many parts of the world and in the armies of a number of nations. Control of infectious hepatitis has been seriously handicapped by the lack of any conclusive evidence concerning its etiology and epidemiology; though to date a specific virus has not actually been isolated and cultured, all evidence points toward a virus as the most likely etiologic agent, and recent experiments on transmission of the disease have been performed under the assumption that the etiologic agent was unquestionably a specific, filterable virus. This paper will present a short overall study of infectious hepatitis and then delve into the specific problems of etiology and epidemiology.

Before beginning a discussion of the disease process in general, a word on nomenclature will prove of value, for with additional details concerning the disease process appearing in the more recent literature, new terminology has arisen which constantly perplexes the reader.

In the past, the term, "catarrhal jaundice", was applied to the disease; this was at the time when investigators theorized the condition as essentially a gastritis passing on to the duodenum, whence inflammation spread up the bile duct leading to obstructive

jaundice. The epidemics have varied greatly in severity in different localities and in the same locality at different times in the past, and it is almost certain that two diseases or groups of diseases, different in etiology, have been described under the title, "epidemic" or "infectious catarrhal jaundice". The first of these, and the rarer, was described by Weil in Germany in 1886, and his name is usually applied to it, (Weil's Disease). But details of epidemics of the same kind had been published in France by Lancereaux in 1882 as, "Ectère grave essential", by Landouzy in 1883 as, "Fièvre bilieuse" or "Typhus hépatique bénin", and by Mathieu in 1886 as, "Ictère fébrile à rechutes". In Germany it has been called, "Biliöse Typhoid", "Icterus typhosus", and "Typhus biliosus nostras".

Much was written under the title, "Epidemic Catarrhal Jaundice", since Cockayne (1912) distinguished definitely the milder type of epidemic jaundice from that due to the spirochaete, (Weil's Disease); it was then that the term, "non-spirochetal infectious jaundice", was brought out as analagous to, "epidemic catarrhal jaundice". In recent years, although the name, "catarrhal", has been retained, the trend of opinion and much of the evidence has been toward a mild "toxic" jaundice as the explanation for these cases; when in 1937 it was first realized that the infection was localized in the liver rather than the duodenum and larger bile ducts, the term, "infectious hepatitic jaundice" (American) or "infective hepatic jaundice" (British), became the name of choice.

Hurst and Simpson (1934) published convincing evidence that "catarrhal jaundice" and "infective hepatic jaundice" are two distinct diseases which have been confused; according to these two men, "catarrhal jaundice" is much rarer.

If a disease is to be diagnosed as "catarrhal jaundice", early symptoms of gastritis should be well pronounced, and if this be the initial lesion, we should expect that a number of cases of gastritis without jaundice would be met with. On theoretical grounds, the van den Bergh reaction should help in differentiation by means of the direct positive result in catarrhal jaundice, which gives rise to obstruction, and by the biphasic reaction in toxic hepatitis. Readings, however, aren't sufficiently convincing and are probably of less value than the presence or absence of bile in the stools. The incubation period in infectious hepatitis is 3-4 weeks; it is less in the catarrhal form.

At present, the terms, "infectious" or "infective hepatitis", designate sporadic cases of the disease, and, "infectious" or "infective epidemic hepatitis", groups of cases during outbreaks of epidemic nature.

Occasional authors have referred to the condition as, "hepatocellular catarrhal icterus", a term of doubtful value.

"Homologous serum jaundice " refers to a hepatitis articially acquired from any cause. The clinical picture produced by this condition is similar to that observed in infectious epidemic hepatitis, but the incubation period appears to differ in the two diseases.

## HISTORICAL REVIEW

Infectious hepatitis is an acute hepatic inflammation characterized by gastric upset and jaundice. It was well known to Greek and Roman writers and is mentioned in the "De internis affectionibus", often attributed to Hippocrates, as the fourth kind of jaundice.

Letters between Pope Zacharias and St. Boniface in the eighth century, A.D. described jaundice epidemics.

The first undoubted reference to infectious hepatitis in epidemic form is that of Claghorn, who writes of its prevalence in Minorca in 1745. Epidemics were noted along the Ligurian coast of England from January to March, 1793 and elsewhere in Great Britain during 1794 and from 1807 to 1808.

In the British Isles there was an epidemic in 1852 almost confined to children during the autumn months. In addition, there was an extensive epidemic with 300 people affected, in 1863, in which both children and adults were attacked.

The disease was very common among Federal troops during the Civil War, and there were 22,569 cases with 161 deaths among a total of 2,218,559 men. This was a highly disabling, contagious type of jaundice. Pomeroy (1898) in Michigan and Leslie (1909) in Maine discussed serious outbreaks such as this one.

In the autumn of 1870, during the Franco-Prussian War, the disease was common among the civilians and troops in Paris.

Cockayne (1912) summarized the findings to that time in England.

Much was written after the British had had huge numbers of men sick with jaundice at Gallipoli and the Dardanelles in 1915-1916.

Willcox (1919) made a clear classification and separated epidemic catarrhal jaundice from other forms of contagious and non-contagious jaundice. Williams reported 700 cases in the 1921 New York outbreak. The Americans Williams, Wadsworth and Symmers in New York state and Hiscock and Rogers in Connecticut described it in college students in 1922. Blumer gave an extensive study of what he called infectious jaundice in the United States in 1923. Also in 1923 Jones and Minot published a careful clinical estimate of the disease, pleading for more attention to its extent and potential dangers.

In the 1930's, English literature contained scattered reports of outbreaks as did literature of other countries, with few American reports up to that time. One can't be certain that all these outbreaks belonged in a single group, since the etiologic agent had not been discovered, but there does appear to be a basic pattern in the histories of such episodes.

Following the outbreak of hostilities in the Mediterranean theater in 1940, German, Italian, French, British and American armies, as well as refugees in Palestine have suffered serious morbidity from the disease; the navies have by no means escaped.

## INCIDENCE

The disease attacks persons of any age, the reports will lead you to believe. In the United States and many other areas, Palestine especially, the disease is commonly seen in the civilian population as a disease of childhood, any epidemics usually lasting over a period of 1-2 months. Inasmuch as the childhood form of this disease is very mild and easily overlooked, it has been suggested that infectious hepatitis is far more common than usually realized and that most adults have been exposed in early life and have even had the disease in unrecognized form so that they have acquired a certain degree of immunity. Observations in Massachusetts in 1945 suggest that different age groups are preponderantly affected in different communities within a single outbreak period. Community A in Massachusetts, for instance, showed a higher rate among young adults, although the population was not preponderantly of any particular age group, whereas community C showed far greater incidence among children of early school age (6-10) in spite of the fact that adolescents and young adults were heavily exposed at school and in the home; either chance or the operation of unknown laws of susceptibility must account for this. One hundred and fifty-one cases collected in Massachusetts in 1946 by Hardy and Feemster showed those between 6 and 40 years the most often affected. The distribution was given as below:

| | |
|---|---|
| under 5 | 8.6% |
| 5-9 | 17.2% |
| 10-14 | 17.9% |
| 15-19 | 11.9% |
| 20-24 | 6.7% |
| 25-29 | 9.3% |
| 30-34 | 11.2% |
| 35-39 | 9.3% |
| over 40 | 8.0% |

In European reports, young adults, especially butchers, soldiers and sewermen were usually attacked in the outbreaks.

Both sexes seem to be about equally affected.

In England the epidemics have a striking localization to families. Relatives or close friends accustomed to visit the house may carry the infection away to their own homes and start a group of cases there. Persons sleeping together are more often affected, (Pickles, 1939; Newman, 1942; Propert, 1942; Nicol, 1942).

Reports of the 19th century outbreaks cover a wide area, and it's probable that infectious hepatitis occurs throughout the entire world; but in the absence of specific diagnostic tests, its exact distribution is unknown. In 1923, Blumer assembled information showing that epidemics have occurred in almost every section of the United States. Outbreaks have also been reported from Iceland, England, Europe, Scandinavia, Poland, Rumania, India and Africa.

In England, an interesting note is the fact that epidemics are most commonly reported from country districts.

In certain parts of the world, there is a distinct and rather sharp seasonal trend with an increase in prevalence coming on in the fall of the year and often building up to epidemic proportions during late fall and early winter. A study of the incidence of infectious hepatitis among troops in the United States from 1931 to 1941 reveals that admissions increase during late summer, reach a peak in November and December and then fall off sharply. It has been noted that in those regions of the southern hemisphere where seasons are reciprocal to ours, the peak incidence of infectious hepatitis in troops occurs during months corresponding to our autumn. In comparison, Hardy and Feemster's 1946 civilian epidemic in Massachusetts showed onsets in every month, the lowest number being in August and December and the highest in April.

## MORBID ANATOMY

The pathology is an inflammatory process leading to edema in the large bile ducts and the duodenum, thus accounting for jaundice and other evidence of obstruction to the normal excretion of bile pigment. Cockayne (1912) pointed accurately to the relation between the disease and acute yellow atrophy; he suggested then that a weakened liver made it simpler for the virus to attack.

With the advent of the needle biopsy, knowledge of the pathological process has been more certain. Dible (1943) has reported that most cases are pathologically benign, and following recovery, no changes in liver cells are visible. A small group of his patients showed mild but definite residual zonal fibrosis. Other groups showed classic cirrhosis as the end result, fatal cases showing acute and subacute hepatic necrosis of all grades of severity. The present view postulates that the virus causes damage in the hepatic cells themselves and that the clinical picture of obstruction depends on the inability of the cells to handle the bile pigment.

Lucke's autopsy findings (1946) in 125 fatal cases of probably infectious hepatitis among men in the armed forces suggest that the disease may cause widespread damage in the body. There were hyperplastic spleen changes in 75% of the cases, some of the kidneys showed cholemic necrosis, and there was edema of the brain and a meningoencephalitis in a moderate number of cases.

Lesions in the gastric mucosa of patients moderately ill with infectious hepatitis have been seen with the gastroscope, (Knight and Cogswell, 1945).

## CLINICAL COURSE

The course of infectious hepatitis can be divided into four stages, (Long, 1946). They are:

1. prodromal period - no jaundice
2. interval period - no jaundice
3. acute period - jaundice suddenly
4. chronic period - jaundice

There has been a great deal of controversy over the length of incubation period; because the virus is hardy and may survive in the environment as well as in the body of the patient or carrier, it is often difficult to trace the source of infection and thereby determine the day of exposure. Cockayne and Glover placed the incubation period, or the "period between cases", as 4 days. Pickles put it at 35 days. Rogers states that the period of incubation for his cases was 3-19 days, the average being 7. Cameron estimated it at 1-6 months. Stokes' work with chemical alteration of the virus leads one to speculate that the incubation period may be lengthened by unknown factors affecting the virulence of the causative organism. The incubation period at the present time is estimated as between 14 and 31 days, according to U. S. Public Health Reports. The prodromal period, when the phase of the course can be definitely singled out, varies from less than a day to about a week; associated with it are the symptoms of headache, abdominal pain, malaise, anorexia, nausea and vomiting. A fever is usually present though it may be so slight as to be missed. Jaundice usually occurs at the end of this stage, or not infrequent-

ly, the symptoms decrease after 24 to 48 hours for an interval period to be followed on the third or fourth day by the appearance of jaundice. The first sign of the approach of jaundice is the appearance of bile in the urine. Next a yellow scleral tint becomes apparent. The process may not cease at this point, especially in children. If the process is of sufficient severity, jaundice of the skin becomes evident and may last from 2 days to several weeks, averaging about 2 weeks. When the jaundice disappears, it goes in the reverse order, bile appearing in the urine intransiently in the convalescent period.

The onset of the acute period presents varying pictures in length and character; some have a grippe-like onset, there are those which begin either gradually or abruptly with chiefly gastrointestinal symptoms such as abdominal pain, frequently localizing specifically in the right lower quadrant; a few complain initially of a severe headache, whereas some have a backache at the onset. Mothers speak of apathy, listlessness and drowiness on the part of their children. The striking feature is the fact that onsets vary from community to community. Length of onset varies from a few days to 2 weeks and even 4 weeks and over in a few cases. Handy in New Hampshire in 1945 reported caring for patients who felt ill and had vague gastrointestinal complaints for 2 months, suggesting the possibility of peptic ulcer. Eventually such patients developed the usual picture of infectious hepatitis.

Allied symptoms and signs, in the order of frequency, are: anorexia, vomiting, fever, nausea without vomiting, symptoms of central nervous system involvement, abdominal pain, diarrhea, headache, backache, pruritis, sore breasts, menstrual irregularities, difficulty in reading, cough, urticaria, ankle edema, "rash", herpes labialis, herpes zoster, periorbital edema.

In general, the subjective complaints begin to disappear with the appearance of jaundice, but this won't hold true in severer cases. It should be emphasized that many patients were encountered in several epidemic groups who had virtually no symptoms except mild jaundice.

In civilian epidemics, one is struck with the increase in severity with age, but this is not without exception either; Hardy and Feemster (1946), in studying a 151 case civilian epidemic in Massachusetts, told of 3 men kept at their jobs with no apparent immediate ill effect during 10 days of jaundice, whereas 2 children were ill for 5 weeks and complained of nausea and epigastric pain long after clinical jaundice subsided.

Pregnant women become especially ill; when one bears in mind the relation between infectious hepatitis and acute yellow atrophy and considers the fetus an extra load for the liver, this observation is understandable.

Physical signs, besides jaundice, include enlargement and tenderness of the liver edge, bradycardia sometimes but not always and splenomegaly in 5-40% of non-fatal cases, (Hardy and Feemster,

1946); Lucke, in comparison, noted enlargement of the spleen in 75% of his non-fatal cases. Barker (1945) reported lymph node enlargement, and Long (1946) considered a palpable lymph node on the posterior border of the sternocleidomastoid muscle a definite diagnostic sign. If the disease progresses to definite jaundice in a given case, stools become clay-colored, as in obstructive jaundice from any cause.

Laboratory findings show most investigators employing the foam test to demonstrate biliuria. Albuminuria occurs occasionally, perhaps simply as part of an acute febrile illness. Hospital cases followed show a rise in bile pigment in the blood as the disease progresses; the level of bilirubinemia is the best index of severity of a given case of infectious hepatitis. An increase in prothrombin time, especially with a poor response to vitamin K therapy, is indicative of excessive liver damage, the van de Bergh is positive, cephalin flocculation 2 plus, alkaline phosphatase is increased. The bromsulphthalein test is no good when there's an associated jaundice. A white cell count is of some value in diagnosis at the onset when it may rise to 10 or 12,000; as the disease progresses, the count falls to normal. There's an associated relative lymphocytosis throughout the illness.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

During the onset a diagnosis is difficult since a specific test is lacking. These diseases come to mind: acute disease of the upper respiratory tract, grippe, influenza, an atypical pneumonia, enteric infections such as dysentery and acute appendicitis, and infectious mononucleosis. In the presence of an epidemic series, however, the problem is relatively simple. The white cell count during onset is helpful, especially in ruling out acute appendicitis; in Weil's disease, the count is elevated to around 20,000, the clinical picture appears more serious from the start, and the specific organism, "Leptospira ictero-haemorrhagiae", can be found in the blood. Infectious mononucleosis may produce jaundice; if done at the right time, a heterophile agglutination test with sheep's red blood cells will decide the question. In the tropics, Malaria and Sandfly fever have to be differentiated; Cameron (1943) stated that Sandfly fever was the initial diagnosis in the majority of early patients in an epidemic in the British Army in Palestine, 1943; apparently the headache is less in infectious hepatitis, and it lacks the characteristic pain in, behind, and on movement of the eyes found chiefly in Sandfly fever.

Of academic interest only, since 1942, is the differential diagnosis of "homologous serum jaundice"; this condition has otherwise been called "serum jaundice", "serum hepatitis", "inoculation jaundice", "postinoculation jaundice", and "postvaccinal hepatitis".

Homologous serum jaundice will be more fully discussed in the section on etiology.

## CONVALESCENCE AND PROGNOSIS

The convalescent period of infectious hepatitis varies with the severity of a given case together with the age and temperament of the patient. In young adults, uniform histories of weakness, fatigueability, and loss of energy characterize the convalescence; this period ranges from 2 weeks to 4 months, the average being about one month. The return of appetite is slow, and in the absence of laboratory aids, this symptom is a distinct help in estimating the return of liver function to normal; when the appetite does return, it's almost impossible to give the patient enough to eat. The weight loss is striking; in studies by Hardy and Feemster (1946), 50% of their cases lost between 5 and 30 pounds.

Prognosis is very favorable in the vast majority of cases. Rarely after the disease has run a benign course for 3 or 4 weeks, a turn for the worst suddenly takes place; the patient becomes confused and drowsy, the temperature is elevated, there is nausea and vomiting, deepening of jaundice, then coma and death. When the liver can't be palpated, one immediately suspects acute yellow atrophy of the liver. Mortality figures reviewed by Lucke range from 0.24 to 0.44%, whereas Stowman reported 0.1 to 1.0%. Autopsy always shows complete hepatic necrosis.

## TREATMENT

In treatment, dietary management is the chief weapon. Jones (1943) considers a high sugar intake extremely important as protection for the hepatic cells; a daily intake of 300-400 grams of carbohydrate is a reasonable goal, best given by mouth. Barker, Capps and Allen (1945) think a high protein intake important; thus recent literature suggests the use of specific amino acids, notably Methionine and Cystine plus Choline. British workers, however, aren't satisfied that increased protein feeding alters the course of the disease. They feel that since the handling of proteins is one of the liver's foremost and most complicated tasks, it may not be best to give the liver large doses of protein to handle while disabled. Barker, Capps and Allen remark that the matter of low fat intake is not yet settled; except in the most benign cases, the gastrointestinal tract can't easily handle fat because bile is being excreted with difficulty. Vitamin K is needed only in the event of an infectious hepatitis attack severe enough to change the prothrombin level. Jones stresses the use of adequate doses of vitamin B complex during the acute and early convalescent phases, for the liver is temporarily unable to act in the synthesis of this vitamin. The use of sulfonamide drugs is contraindicated. Morphine and barbiturates should be used cautiously because of the presence of active liver disease.

Absolute bed rest is necessary until jaundice has disappeared

or the icteric index is under 18, (Long, 1946).

A new chapter in the prophylaxis of infectious hepatitis is opening with the use of gamma globulin, the antibody fraction of plasma employed in the attenuation of measles; the fraction is of no proven value therapeuticaly, however Stokes and Neefe believed they used it successfully on a girl's camp epidemic in 1944. Recent reports by Gellis (1945) suggest that it confers passive immunity against infectious hepatitis for at least 6-8 weeks.

Plasma was used successfully in controlling the military epidemics in the Mediterranean Theater of Operations, 1943-45.

## COMPLICATIONS

Very few second attacks have been reported in the same patient, however 2 cases were presented by Nelson (1946) who each had 5 distinct episodes of jaundice. In speculating as to the reason for repeated attacks, Nelson suggested the theory of resistance versus the amount of infection. In an individual with reduced immunity to the virus which causes infectious hepatitis, the epidemiological factors incident to military life might tend to provoke a particular attack which otherwise would be avoided. One other factor should be mentioned as possibly contributing to the recurrence, that is, congenital narrowing of the bile passages.

Certain variations from the normal course of the disease have been reported recently. Barker, Capps and Allen (1945) discussed acute hepatitis without jaundice in the Mediterranean theater. The clinical picture was exactly the same with the exception that clinical jaundice failed to develop. This is actually a milder form of the acute disease, and with proper management, these cases run a shorter and milder course than those with jaundice. Such a condition is important because inadequate treatment may result in the development of chronic hepatitis and epidemiologic complications.

During the course of studies on acute infectious hepatitis in the Mediterranean theater, it became apparent that certain symptoms and findings indicated a persistent hepatic disease for

prolonged periods of time with a tendency towards exacerbations and remissions. These cases presented a sufficiently distinctive and uniform clinical picture to justify their consideration as a separate group or syndrome which has been called, "chronic hepatitis", (Barker, Capps and Allen, 1945). It appeared that the frequency of the disease with this syndrome was due in part to the poor nutritional condition of many soldiers at the time of onset resulting from prolonged combat and inadequate treatment of the acute disease. The clinical picture was the same as that of acute hepatitis except for severity, duration and prognosis. One of the most characteristic features of this syndrome was the prolonged treatment necessary to effect recovery; thus, even with adequate therapy, 40% of the patients still had the active disease after 3 months. Immediate prognosis was good except in the presence of a severe relapse. Factors associated with the chronicity and relapse appeared to be inadequate rest, a poor diet during the primary acute attack, various intercurrent infections such as malaria, pneumonia and dysentery, traumatic wounds and surgical operations and excessive use of alcohol where the active hepatitis was present. Neefe and his associates (1945) have shown that in certain cases hepatitis may tend to run a cyclic course with several spontaneous exacerbations.

Barker, Capps and Allen reserved the term, "inactive hepatitis", for patients who have objective evidence of liver dysfunction and a past history of acute hepatitis but have a large non-tender liver,

bromsulphthalein retention satisfactory, and a normal tolerance to exercise. The symptoms aren't disabling, so no treatment is necessary.

Just recently an acute form of epidemic hepatitis of intense severity terminating fatally in less than 10 days has become prevalent; this has been termed the "fulminant form". Two such cases were reported in England, (Morgan and Brown, 1927; Findlay and Dunlop, 1932). In Sweden in 1930, Bergstrand reported a large number of similar instances. Propert reported 2 such fatal cases during 1939, death occurring within 2 and 5 days onset, jaundice being evident for only a few hours before death. In a series of 196 fatal cases occurring between August, 1943 and April, 1945, which were studied by Lucke, Baldwin and Mallory at the Army Institute of Pathology, over half the cases fell into this category. In contrast, only 1 such case was reported in the great Swedish epidemic of 1927; the usual duration of the fatal disease was then 4-6 weeks. In other words the course of the fatal hepatitis was then subacute. These divergences in duration reflect striking differences in the pertinent pathologic pictures. In the more fulminant form, the parenchyma of the liver was destroyed completely. In the more subacute form, making up approximately one-fourth of the 1943-45 series, destruction of the liver was incomplete.

It isn't known in how many patients the causal agent of hepatitis was introduced by therapeutic procedures, especially since

large epidemics of hepatitis were prevalent in several theaters of war. It is therefore an assumption, in this case, to regard all wounded cases as examples of, "homologous serum jaundice", and non-wounded cases, comprising approximately one-half of the series, as both "epidemic" and "endemic" variants of the naturally-occurring hepatitis.

Factors that could be clearly correlated with the duration of the disease were previous trauma and subsequent blood transfusions. In nearly all cases, trauma (combat wounds or burns), was of a serious degree and was sustained within 4 months of the onset of the hepatitis. Most of the wounded received transfusions of blood or its derivatives within a few days of injury; hence these cases probably may be regarded as examples of homologous serum jaundice. It is a significant fact that the mortality of patients with a history of trauma was 5 times as great during the first 4 days after onset.

Except for the tendency to a more rapid course in homologous serum jaundice, no difference was discernible between the naturally occurring fulminant hepatitis, in either endemic or epidemic variants, and the disease artifically induced by parenteral injection of blood or its derivatives.

There were two combinations of initial symptoms; an "infectious" type in which the disease was ushered in suddenly by symptoms common to many acute infections and a "gastro-intestinal" type in which the initial symptoms were similar to those encount-

ered in the subacute variety of the disease, (e.g., Lucke, Baldwin and Mallory, 1946). Portis, on the other hand, reported his cases in 1939 to be ushered in by cerebral symptoms so that a meningitis was at first suspected. In the final stage, there's usually an abrupt change for the worst initiated by cerebral symptoms, jaundice deepening rapidly, vomiting severe and sometimes projectile, gastro-intestinal hemorrhage up to a considerable magnitude and shock even developing in a number of cases.

## ETIOLOGY

It was earlier thought that some epidemic cases and a few other sporadic ones with similar symptoms were due to the, "bacillus proteus fluorescens". Jaeger (1912) found this organism in the water in which his patients had bathed and in the urine of internal organs and less commonly in the blood of such of his patients as died; it was also present in ducks dying of jaundice on the same water. The negative results obtained by Sandwich in Smyrna and Valassapoulo in Alexandria, the two places where the disease was most common in 1912 and where careful bacteriology examinations were made, suggest that the bacillus proteus had been only the cause of isolated outbreaks, even if it were capable of producing infectious hepatitis at all.

German authors in 1938 claimed to have been able to make the causative organism grow in chick allantoic membranes, but this work wasn't too convincing to American and British investigators and hasn't been repeated.

Seide and Luz in 1943 claimed to have cultivated from the duodenal fluid of patients with infectious hepatitis a specific agent whose behavior suggested it to be a filterable virus. So far as is known, this work has not been confirmed by others although several French investigators later in the same year concluded that the disease was caused by a virus present during the pre-icteric phase in the saliva, the upper respiratory passages and the blood.

As yet, the etiologic agent, (or "icterogenic agent"), hasn't been actually "isolated" in the sense that it has been seen, cultured and transmitted experimentally to laboratory animals, however it has been filtered through bacteria-tight filters and for this reason has been classified a virus. Almost all the properties of this virus have been determined by using man as the experimental animal.

In describing the virus of infectious hepatitis, it is necessary to also discuss the causative agent of homologous serum jaundice, for whether we're dealing with the same or two different virus strains is yet unknown. Havens (1945) showed the virus to be extremely resistant to heat (56°C for 30 minutes) and capable of passing through the finest bacterial filters, (Chamberlain no. 2 filter). Stokes et al (1945) suggested that chlorination of water contaminated with the virus of infectious hepatitis attenuated but didn't kill the organism; the virus was thus proved resistant to chemicals in strengths in which they're ordinarily used for the purification of water. In contrast to these similarities between the causative agents of the two conditions are certain differences which involve route of inoculation, duration of incubation period and period of infectiousness including the period when the virus of each disease is demonstrable in the blood stream. There is no evidence that heterogenous immunity exists, although homologous immunity is demonstrable in infectious hepatitis.

During the past war, many doctors, both in civilian life and in the services, were faced with the problem of giving dozens of intravenous injections in a day, using only a small number of syringes and with the prospect of great difficulty in replacing broken syringes. They not infrequently modified the full aseptic technique, the syringe and needle being thoroughly washed with tap water or sterile water but not boiled or otherwise sterilized between injections. The danger in this method is that to prove that the needle is in the vein, some blood is usually drawn into the syringe before the injection, and thus the inside of the syringe and needle become contaminated with blood. If the blood of one patient happens to be infected with a pathogenic agent, the syringe is thus capable of transmitting the infection to the next patient if it hasn't been sterilized between injections. The significance of this point was clearly shown in a paper by Bigger in 1943 when he suggested that this was probably the method of transfer of hepatitis following treatment with the arsphenamines.

Hepatitis due to inoculation with homologous serum has received considerable prominence in medical literature recently, (1942-43) owing to its widespread incidence following inoculation of troops with normal human serum, employed as a vehicle for the yellow fever virus. Similar sequealae followed administration of pooled human plasma, reconstituted dried human serum or whole blood transfusions in both civilian and army hospital work, following the injection of mumps convalescent plasma, (e.g., Beeson, Chesney

and McFarlan, 1944), after immunization against pappataci fever, in diabetic clinics where the spread was probably due to the syringes being used for collecting blood, (e.g., Graham, 1938; Droller, 1945) and even associated with neoarsphenamine administration as suggested by Bigger, (1943).

Sheehan in 1944 studied 6 groups of 35 to 100 patients each in clinics where neoarsphenamine was being given. In group one, 100 cases of jaundice developed in the course of syphilis treatment. These patients had had numerous intravenous injections before they developed jaundice; the practice in the clinic was that syringes were washed out but not sterilized between injections of different patients.

In group two, 80 women patients with syphilis were given neoarsphenamine injections, the syringes being sterilized in strong antiseptic each time; only 2 developed jaundice, and they had had some of their injections in another clinic.

With the third group, a treatment center was chosen where three-fourths of the patients developed jaundice after intravenous neoarsphenamine injections. Five male patients were then given every one of their injections with carefully sterilized syringes and meticulous precautions with any blood. These 5 men were under treatment from 5 to 27 weeks time, and none developed jaundice.

The fourth group of 34 men with Lues was picked up in an army camp. Divided into 2 subgroups for the purpose of treatment, one group was given injections on Wednesday, the other on Friday.

Syringes were washed out but not sterilized between injections on each treatment day, but they were thoroughly sterilized before each day's work. Thus ample opportunity for transmitting a blood-borne infection was afforded the members of one subgroup but not the members of the other subgroup. It so happened that one man in the Wednesday group had been treated for syphilis elsewhere and was incubating hepatitis before he came to this camp. In due time, he developed jaundice, and during the following 8 weeks, other men in the Wednesday subgroup came down with jaundice. The Friday subgroup, which started with no infected member, had no jaundice cases.

Further evidence was found in the fact that three orderlies who helped in the actual injections and frequently had their hands contaminated with blood from the patients developed hepatitis, and 3 laboratory assistants, who had the duty of separating serum from the blood of the patients for Kahn tests, also developed an identical hepatitis. None of these 6 patients had received a neoarsphenamine injection, nor had they received any injections from unsterile syringes. The infection may possibly have passed through small accidental scratches on the skin of their hands.

85 cases of homologous serum jaundice occurred in a sanitorium during the 5 years up to 1944. The common factor was that every patient had had blood taken from an arm vein for sedimentation rate estimations on admission and at monthly intervals corresponding to the monthly intervals between collection of blood samples and exposure to infection.

In all of these artificially-produced types of hepatitis there thus appears to be a blood-borne virus which is transmitted by injection into the body and produces jaundice about three months later. The real question of interest is whether the ordinary infectious hepatitis may not be due to the same or a similar virus, carried in the blood, transferred by a similar kind of method, and with an incubation period of about the same length.

In 1939, Cullinan stated that there seemed little doubt that both yellow fever and measles post-inoculation jaundice were identical with "common infectious jaundice". It seems possible that a hepatotoxic agent, perhaps a virus or substance in the serum of donors who have or have had common infectious hepatitis, was introduced by inoculation, and that this agent did not itself cause but predisposed to a subsequent infection of the disease, often in a more severe form.

Clinically all these homologous serum jaundice conditions are almost indistinguishable from infectious hepatitis; they too vary considerably from very mild to extremely severe cases, but as a rule, they may be said to possess a symptomatology milder than that of infectious hepatitis. Jaundice usually develops more slowly in homologous serum jaundice, and there appears to be a striking incidence of hepatomegaly without associated tenderness, the degree of tenderness varying inversely with the extent of enlargement. The incidence of splenomegaly is considerably less than in infectious hepatitis. Of course a previous history of immunization,

transfusion with either whole blood, blood or plasma products, or injection or blood withdrawal by means of an intravenous syringe strongly suggests the diagnosis.

One differential point may be the fact that many weeks or months may elapse between the initial inoculation and the onset of symptoms; in fact the incubation period of homologous serum jaundice nearly always is prolonged considerably over that of infectious hepatitis, varying from 69 to 111 days in most instances. Even this apparent discrepancy between the incubation periods of infectious hepatitis and homologous serum jaundice disappears when the incubation period of infectious hepatitis following subcutaneous injection and the incubation period of homologous serum jaundice following intranasal injection are considered, according to experimental investigations by Findlay, Martin and Mitchell in 1944.

Out of 689 people studied in whom jaundice appeared after yellow fever inoculation, only 4 gave a history of a previous attack of infectious hepatitis, (e.g., Findley, Martin and Mitchell, 1944). This suggests that those who suffered from homologous serum jaundice were selected because they didn't possess an immunity due to a previous attack of infectious hepatitis. An antigen made from the livers of patients dying with infectious hepatitis fixes complement with the sera of patients who have recovered from infectious hepatitis and from homologous serum jaundice; homologous serum jaundice, these workers suggest, would thus be due to

the use of serum, plasma or whole blood from a patient with a virus of the infectious hepatitis group in his blood; the virus might be present because the patient was incubating or was suffering from infectious hepatitis.

Perhaps the virus of infectious hepatitis appears occasionally in the blood of an immune person. In many virus infections, immunity is dependent on the continued presence of virus in the tissues; small amounts of virus are, it's supposed, liberated from time to time and stimulate formation of fresh amounts of antibody. This theory is now being tested experimentally in the case of infectious hepatitis and would explain the fact that donors of icterogenic serum are suffering from infectious hepatitis. By the withdrawal immediately of vaccine lots found to be the agents responsible for these homologous serum jaundice outbreaks and emphasizing the fact in clinics that all syringes should be thoroughly boiled for each individual patient, the incidence of such outbreaks has dropped almost 100% since 1944.

Because recent transmission experiments, to be later reviewed, have shown the causative agent of infectious hepatitis present in the feces of persons with the active disease, Neefe, Stokes and Reinhold, in 1945, attempted to determine if the causative agent of homologous serum jaundice were present in the feces of persons with the disease. The pools used in the experiments contained specimans from 6 different patients in various stages of the active disease; thus if the causative agent were commonly excreted

in the feces, it is probable that it would have been present in at least one of the stools. The systemic application of a group of liver function tests at least twice weekly made it improbable that a brief attack of hepatitis was overlooked. Consequently the failure of any of these men to show evidence of hepatitis suggests that the causative agent either was not present in the feces of these patients with homologous serum jaundice or wasn't active when administered by the gastro-intestinal route. This observation offers a possible explanation for one of the puzzling differences between homologous serum jaundice and infectious hepatitis, namely the apparent failure of epidemics of infectious hepatitis to originate from patients with homologous serum jaundice.

It was in 1946 that a number of investigations appeared in an attempt to disprove a connection between the two conditions. At the time of initiation of their studies in 1943, Neefe, Gellis and Stokes were inclined to share the opinion of many that the etiological agents responsible for infectious hepatitis and homologous serum jaundice probably were the same and that the differences noted in respect to incubation period, type of onset and frequency of secondary cases possibly were due to a difference in the route of entry. The results of studies reported by these men have indicated certain differences which appear to be incompatible with the concept of the existence of only one strain of hepatitis virus. Differences in the two viruses studied here show a lack of cross immunity indicating an antigenic difference; the two

viruses employed were:

Virus I.H., Pa. - the virus responsible for an epidemic of infectious hepatitis that occurred during the summer of 1944 at a civilian summer camp in Pennsylvania. This was transmitted by contaminated drinking water.

Virus SH - the virus present in a pool of mumps convalescent plasma; probably the same virus that as a result of its presence in certain lots of yellow fever vaccine was responsible for a large outbreak of hepatitis in the U. S. Army in 1942.

| | Observation | Virus I.H., Pa. | Virus SH |
|---|---|---|---|
| 1. | type onset of hepatitis | abrupt & usually with fever exceeding 100°F orally | comparatively insidious & usually afebrile or with fever not exceeding 100°F |
| 2. | interval from inoculation to onset of acute hepatitis | 17-34 days | 2 to 4½ months |
| 3. | incidence of hepatitis in normal volunteers following oral inoculation | high | 0 |
| 4. | incidence of hepatitis in normal volunteers following parenteral inoculation | low | high |
| 5. | presence of agent in feces | + | - |
| 6. | resistance to infection after previous infection with virus I.H., Pa. | + | - |
| 7. | resistance to infection after previous infection with virus SH | - | + |

Conclusions showed that:

1. Virus SH induced hepatitis after 2 to 4½ months in 72% of the normal volunteers inoculated parenterally but failed to induce the disease in any of ten normal volunteers inoculated orally.

a. feces from volunteers with virus SH hepatitis also failed when given by nasopharynx and oral routes or parenterally.
b. virus SH remained active after $3\frac{1}{2}$ years residence in frozen plasma.
c. there was no consistent effect on the interval from inoculation with virus SH to onset of hepatitis noted with different quantities injected parenterally.
d. following hepatitis due to virus SH, all volunteers tested were found to be resistant to reinfection with virus SH but susceptible to infection with virus I.H., Pa.

2. Virus I.H., Pa. induced active hepatitis in 73% of normal volunteers in 17-34 days inoculated orally and in only 11% inoculated parenterally.
   a. in volunteers who had recovered from SH hepatitis, however, parenteral injection of I.H., Pa. in contrast to results in normal people, induced hepatitis in 75%.

Similarly, Haven's (1946) recent work suggests that different strains of virus may exist. An effort was made to determine with one strain if the size of dose or route of inoculation had any effect on the length of incubation period of infectious hepatitis caused by this particular strain of virus. In one experiment, equal amounts of the same icterogenic agent were fed and inoculated parenterally into human volunteers. In another experiment, the same icterogenic agent was inoculated in graded amounts of the order of 1-, 10-, and 50- fold increasing doses, (o.ol ml. to o.5 ml. of infectious serum). The results revealed no appreciable difference in incubation period dependent on the route of inoculation or size of dose in the range of dosage used.

Havens (1946) also pointed out that failure to find the "virus" in a patient during the mid-incubation period of infectious hepatitis, as he did, if confirmed by further instances will constitute a

difference between this condition and homologous serum jaundice in which the vehicles, such as droplets, may play a part at these times.

There is a general tendency to diagnose all cases of hepatitis who have not had injections of blood, plasma, serum or biologicals containing blood products, as infectious hepatitis. Undoubtedly some cases of hepatitis due to agents similar to Virus I.H., Pa. have been called homologous serum jaundice, and some cases due to agents similar to Virus SH have been called infectious hepatitis. This is particularly apt to occur because both the virus of homologous serum jaundice and that of infectious hepatitis can be transmitted by parenteral introduction of blood or blood products. The two types described in connection with parenteral injection of virus I.H., Pa. and virus SH must be recognized. Furthermore, it has been suggested that these viruses may be transmitted by improperly sterilized syringes and needles used only for withdrawal of blood or for parenteral injections of materials of any type. Such procedures, often performed on large groups of persons for prophylactic or diagnostic purposes, may be overlooked as sources of infection with the homologous serum jaundice virus, and subsequent hepatitis developing in such persons is thus regarded as a naturally-acquired infectious hepatitis since no history of injection of a blood product was obtainable. Likewise a person may have been considered to have homologous serum jaundice because of previous administration of a blood product which, however, may have

contained the virus of infectious hepatitis rather than that of homologous serum jaundice. These and other factors may account for some of the apparent inconsistencies in the behavior of various hepatitis viruses of supposedly similar or different origin.

## EPIDEMIOLOGY

Infectious hepatitis stood out as one of the most important medical problems of the recent war, and in spite of extensive studies, its epidemiology is not yet fully understood.

Epidemics occur when natural conditions favor virus growth and when artificial conditions of crowding and poor conditions of all sorts exist.

In England, it was noted that two or more villages may be affected, and in such cases, each probably had its own local water supply. Peck in 1901 showed that food and water weren't the cause of a series of epidemics he had studied. Kershaw at Bolton in 1901 noticed that cases usually arose in the neighborhood of previous ones and that some districts remained quite free; infection seemed able to linger in one place for some time.

Vaisey (1910) in a rural epidemic showed that it spread from one village to another three miles away, carried by a child 8 years old who had mixed with affected children in the first village and who contracted the disease.

The steady spread of the disease in the larger epidemics reported in the past seems to indicate that personal contact is partially responsible for its propagation.

Krasnobaeff (1912) records that 3 brothers were attacked at intervals of 3-4 weeks; it was found that a child with jaundice had lived in the room in which they had stayed for 2 days.

Meiner (1910) noticed that it was particularly liable to pick out individuals already suffering from respiratory disease due to antecedent influenza.

Pickles (1930) reported 250 cases of jaundice in a population of 5,700 people; the majority infected were elementary school children, close contact in school being a definite source of infection.

Glover and Wilson (1930), in a boy's school of 400 boarders, reported 95 cases of jaundice; they thought the infection was spread via the nasopharynx.

Stowman referred to infectious hepatitis in 1944 as the "New Disease" of World War II. According to officers of the Italian Medical Corps, jaundice occurred only sporadically among Italian army personnel prior to 1940. Its first appearance in Axis troops was in 1940, when a mild epidemic occurred among German troops in North Africa. No reports of the incidence in 1941 were received, but after the break-through at El Alamein in the autumn of 1942 and later in the spring of 1943 in Tunis, many German and Italian prisoners developed jaundice after their capture. It has been reported that much infectious hepatitis also occurred among German troops in Russia and the Caucasus. A report of 600 cases seen in a German Military hospital on the eastern front between December, 1941 and November, 1942 was given by Jacobi, Kreyenberg and Dorschel in 1942; in a discussion of various predisposing factors such as cold and fatigue, it was noted that in the 1942 dysentery

season the authors saw only 21 cases of epidemic hepatitis among 1,700 dysentery patients. Many of these soldiers later came to Italy, and it's possible that some at least brought the disease along with them. Such German medical literature as has been available indicates that their experience has been identical with that of the United Nation forces with respect to the epidemiology of the disease. In the British armies fighting in the Mediterranean zone there were various severe outbreaks, (e.g., Gordon, 1942; Van Rooyen and Gordon, 1942; Cameron, 1943). Infectious hepatitis was the greatest cause of disabling illness among United States forces in the Mediterranean area, (North African theater of Operations). From January 1, 1943 to March 31, 1945 there were 35,000 cases reported from American units in the theater. At the peak of the epidemic period in the winter of 1944-45, weekly attack rates as high as 670 per 1,000 were recorded by certain divisions of the Fifth Army and this, if maintained, would be equivalent to an attack rate of 5% per month for the entire American Army in North Africa.

The American Navy in the South Pacific reported infectious hepatitis as have the German, Italian and French Navies.

The Scandinavian countries, Finland, and Switzerland, reported 65,000 cases in 1943.

A few states in the United States have reported it. California had 118 cases in 1943 and 335 in 1944. Handy reported well over 100 cases in a small New Hampshire town of 2500 between October, 1944 and April, 1945.

Sometimes unexplained gaps appeared in an epidemic where the disease appeared in one part of England, died out shortly, reappeared soon after in another locality, again died out and then became well-established and still was continuing a year later in a different part of the country. It may be that there were carriers. One doctor told Cullinan (1939) that he had observed two separate cases arising where there could have been no possible contact with other patients. However, both had been in contact with people who themselves might well have been in contact with the disease. The question of carriers is still unanswered.

Exact knowledge as to immunity is not yet available. It appears to be highly infectious in children but well resisted by them. The age group attacked (6-40 years) suggests that older persons may have acquired immunity by previous attack, but those who become infected have a liver less capable of regeneration than the child. It has been noted that troops newly introduced into an endemic or epidemic area are more susceptible to infectious hepatitis than is the local population; this observation was made in Egypt. Only speculation is possible at the present until it can be determined whether the subject is having or has had the disease. The fact that the gamma globulin of blood pools apparently contains antibodies against infectious hepatitis is suggestive of permanent immunity. Second attacks do infrequently occur, and there is no evidence that immunity to infectious hepatitis is induced by an attack of homologous serum jaundice.

Patients who had recovered from homologous serum jaundice six months before aren't found to be immune to experimentally-induced attacks of infectious hepatitis either.

The agent, or "virus", of infectious hepatitis is in the blood during the active stages of the disease and also during the interval between inoculation and development of the disease.

Cullinan (1939) felt the actual period of infectiousness must be short, as shown by the extraordinary periodicity in families and small villages where there is little isolation; his cases, often single, occurred in series at an interval of about a month. He thought it quite safe to return children to school after 2 weeks, and he didn't hesitate to admit cases to the general wards of a hospital when jaundice was once established.

Bates (1936) said the period of infectivity lasted 4 weeks after the onset of jaundice. Pickles (1939) felt the period to be 8 days before and up to 2 weeks after the onset of jaundice.

The limits of the infective period, or namely when the etiologic agent appears in the blood or stool and how long it remains there, have been studied in connection with recent human transmission experiments. Merely the findings in relation to period of infectivity will be related here. Most of these experiments in the transmission of infectious hepatitis to human volunteers have employed infectious material obtained from patients in the acute phase of the disease; other phases are not included in the results.

Voegt (1942) reported that the duodenal contents of patients, obtained on the 24th and 30th days of the naturally-occurring disease (before jaundice) were infectious. Neefe and Stokes (1945) found that stools obtained 3 weeks after the disappearance of jaundice in human volunteers convalescent from experimentally-induced infectious hepatitis weren't infectious when fed to other human volunteers.

Havens in 1946 attempted to determine (1) the period of infectivity of patients with experimentally-induced infectious hepatitis and (2) the infectivity of urine and nasopharyngeal washings of patients in the pre-icteric phase of experimentally-induced infectious hepatitis. The strain of virus used was originally obtained from the stool of a U. S. Army soldier who contracted epidemic infectious hepatitis in Sicily in September, 1943. It had been through 4 passages in human volunteers when the experiments began. The agent had produced the disease in 27 out of 40 human volunteers. Eighteen volunteers were fed or inoculated with serum or stools to be tested; serum and stools obtained 4 and 5 days after onset of the disease and 1 and 2 days before the appearance of jaundice contained enough virus to produce infectious hepatitis with jaundice in 5 out of 9 human volunteers. Serum and stools obtained in the convalescent phase, 25 to 31 days after onset of disease, were not infectious in the amount administered, however it appeared desirable to test pooled specimans of feces from several patients during the convalescent period in an attempt to

detect the appearance of a possible convalescent carrier state. At the same time, it also seemed desirable to test the infectivity of urine and nasopharyngeal washings of patients in the acute phase of infectious hepatitis when virus could be demonstrated to be present in the blood and feces. Sixteen volunteers were fed the stool filtrates, serum, urine and nasopharyngeal washings to be tested. Both acute phase serum and stool were infectious, as might be expected, producing hepatitis in 5 out of 6 volunteers. Urine and nasopharyngeal washings, obtained on the same days as the stools and sera which were demonstrated to be infectious, apparently didn't contain virus in sufficient amount to produce clinical disease. Convalescent phase stools were again negative.

Havens et al (1944), in another series of experiments, found the agent present in blood obtained 60 days prior to the onset of jaundice.

During the past war (1939-1945) there appeared to be several points of difference between the epidemiological pattern of the disease causing jaundice among troops in the Middle East and that found in epidemics of infectious hepatitis in England. An opportunity to collect information about these points occurred late in 1943 when some units of the British Army returned to Great Britain from the Mediterranean area with an epidemic of jaundice in progress among them. The epidemiological pattern of the outbreaks was very similar to that of civilian epidemics. Numerous instances of 20-40 day intervals between the onset in contacts were found in

the units just as they are in families during civilian epidemics. Lower incidence in some units might have been due in part to an immunity conferred by previous exposure to an epidemic. In these and other epidemics, the attack rate in officers was higher than in other ranks, and the attack rate in troops in the Mediterranean area was higher than in troops in Great Britain. The presence of endemic foci of infectious hepatitis in Mediterranean countries may be partially responsible for the high incidence in troops there.

The problem of epidemiology has been studied by two means: the collecting and analyzing of data on numerous epidemics and the conduction of actual transmission experiments on human beings. Four possibilities as to the mode of spread have been foremost in the investigator's minds; respiratory, gastro-intestinal, insect and fomite transfer.

A series of studies on past epidemics gives little evidence in favor of insect or fomite spread; instead respiratory and gastro-intestinal transfer appear the more likely. The apparent restriction of the disease in North Africa to certain insect-ridden areas plus the tendency of incidence curves toward a relationship with those of malaria and sandfly fever, but occurring 3 months later (3 months after the onset of the season of blood-sucking insects), has led observers to postulate that infectious hepatitis is transmitted by blood-sucking insects and that the prolonged incubation period observed in homologous serum jaundice also occurs in the naturally-occurring disease. The theory of

insect transmission seems very plausible to them. The fact that jaundice can be transmitted by inoculation of small amounts of serum, that the virus apparently remains in the blood of infected persons for long periods of time, that the disease seems to occur more frequently in certain locations, that there is a definite seasonal incidence and that secondary cases are hard to prove are all in keeping with this theory. However, in reviewing conditions in North Africa a month before one of these jaundice outbreaks, other investigators were led to trace its origin to conditions associated with high rates of diarrheal disease and dysentery. This observation may have been entirely valid, for it now seems likely that the spread of infectious hepatitis is related to unsanitary conditions. Its spread, therefore, might be expected under the same conditions which favor that of bacillary dysentery, and because of its rather long incubation period, would occur a month or more after a dysentery outbreak.

There is no data available to either prove or disprove the importance of contaminated articles. Since the virus is resistant to heat and chemicals, it may be transmitted by fomites. Suggestive circumstances were found by Hardy and Feemster (1946); two of the patients with infectious hepatitis in their series were postmen handling letters coming from a theater of war known to be heavily infected with the disease. They also knew of a woman with infectious hepatitis who in previous months had received daily letters from her son, sick in Italy with the disease.

Getty in 1946 studied 150 cases from a total of 241 admissions for epidemic hepatitis in a Marine division which entered combat in the Marianas, on Saipan and later on Tinian Island. The respiratory route seemed to offer the most satisfactory explanation for transmission in this epidemic. It would be difficult to explain how 25 men, out of an organization of 100, apparently infected on board ship enroute to base camp could have been infected in any other manner. If, for example, the enteric route were responsible, it would infer that the food or water had in some manner been contaminated, in which case since the food and water were standard, more than 25 men would probably have been infected during the exposure period on board ship.

It has been reported from the Mediterranean area and the South Pacific that certain military units with a high incidence of bacillary dysentery had, in the next month or two, a number of cases of hepatitis. This might suggest that bacillary dysentery caused a greater susceptibility to hepatitis or that the route for infection was enteric. It also infers fecal contamination of food and water or both with the causative agent. On Saipan and Tinian the only water authorized for drinking purposes was obtained from previously-filled and approved containers or from other recognized sources such as ships and shore distillation points. These sources were common to the entire division. Food was in the form of standard rations and was issued to all personnel. Two insects were common on Saipan and Tinian, the mosquitoes and flies. If

the latter were vectors, transmission would be mechanical, involving the contamination of food or water; there was little opportunity for such a thing to occur.

Getty concluded that transmission via the upper respiratory route seemed to offer the most satisfactory explanation for the spread of this epidemic.

Then there are epidemics which are just as much suggestive of an enteric means of spread. At one period during field observations made at the El Alamein battles, New Zealand and Australian troops occupied ground that had been recently recaptured from the enemy and was heavily contaminated with feces. Hepatitis assumed epidemic proportions in the occupying troops. In other parts of the Alamein line, British and Indian forces were on ground not previously occupied by the enemy and not heavily contaminated; in these troops, hepatitis was uncommon. Among the New Zealanders, the morbidity was greatest in the forward lines and least in the areas most remote from the enemy; in other words, infection was more common where men lived in the open and less common when they lived in tents. This observation casts some doubt on the view that airborne droplet infection is the important means of spread. It was thus assumed that feces contained the infective agent.

Hayward (1946) studied an outbreak in a Pennsylvania industrial city during the winter of 1944-45; this was a seaport and river city, with a population of 60,000 and considerable influx of wartime workers. In a series of 52 cases, the most striking

feature of the epidemic was the concentration of cases in a zone running across the center of the city while very few cases occurred throughout other districts. Investigation demonstrated that this zone followed closely the course of the municipal water main. In the vicinity of the pumping station and principal water main the flow is chiefly from the river and theoretically, the concentration of infective agent surviving a water purification procedure would be highest at this point. The fact that the epidemic didn't assume explosive form, characteristic of typical epidemics due to water or food-borne agents, isn't against the possibility, in view of variations in epidemic pattern, which can occur from intermittent contamination of water with the infective agent, effects of water treatment procedure on the concentration and activity of the agent, and the influence of concentration and activity of the agent on the incidence and incubation period of the disease.

Read, Bancroft et al reported a group of 24 cases at the Western Reserve University School of Medicine in 1946, all patients being members of a single fraternity. The facts indicated that regular eating at the fraternity dining room was an important factor in determining the risk of attack. An analysis of the number of meals eaten at the house revealed both more regular and more frequent eating by the patients than by the non-patients. Investigation showed that the kitchen and dining room were clean, left-over food was stored in the refrigerator, pasteurized milk was obtained daily, and all water came from the regular municipal

supply. A study of habits of the patients and a sample of non-patients revealed no essential difference. There had been no symptoms of unusual illness on the part of any employees handling food. Nevertheless, evidence pointed strongly to an epidemic spread through some article or articles of food served in the fraternity dining room.

Three reports deal with water as a vehicle for the spread of the virus via the gastro-intestinal tract. Frazier, (1945) a Canadian, believed his epidemiological observations, together with proved fecal contamination of the water supply, showed an epidemic to be water-borne. Hallgren (1945) had a similar theory when an explosive outbreak appeared in an institution and nearby village, both using water from some contaminated reservoir. Neefe and Stokes (1945) claimed an outbreak in a girl's camp due to contamination of a well by feces of a patient with infectious hepatitis introduced into the camp early in the season; their studies will be presented in more detail in the section on transmission experiments.

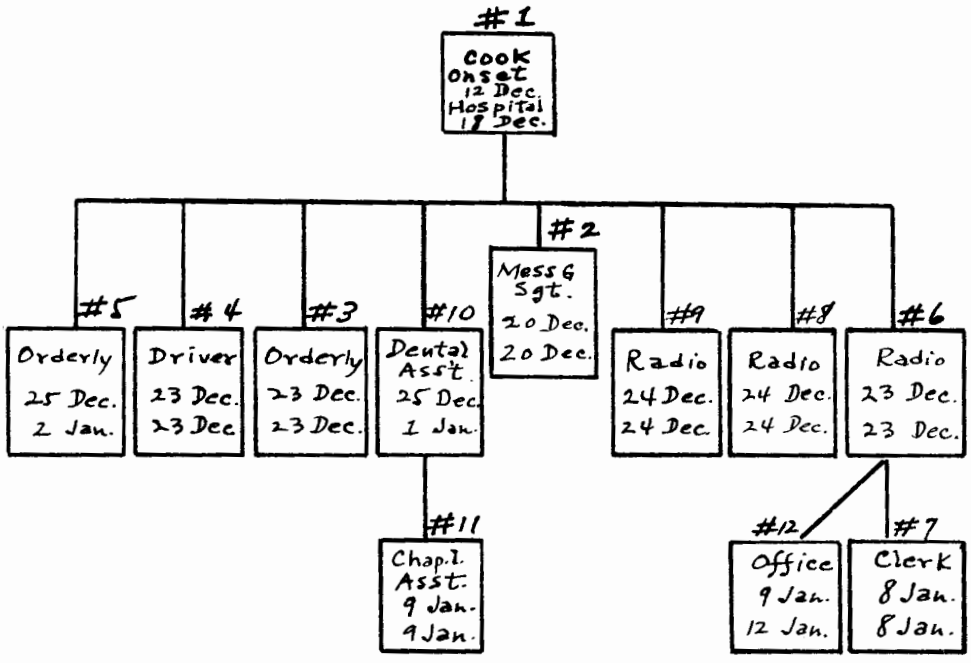
In a study of many military epidemics, one will always find some outbreaks where there's a question as to whether the spread was via the respiratory or gastro-intestinal tracts. In 1943, studies were initiated by the Office of the Surgeon, Headquarters NATOUSA, (North Africian Theater of Operations of the United States Army), which early recognized the importance of infectious hepatitis in the theater and that, in all probability, nowhere

else during the past war would there be an equal opportunity for the study of both clinical aspects and the epidemiology of the disease. Investigations were made between October, 1943 and June, 1945, during which period the incidence of infectious hepatitis reached epidemic proportions on two occasions.

For investigation into the mode of spread and the pattern of the appearance of cases, it was found that the company, (battery, squadron, etc.) was the unit of choice. This is the "housekeeping unit" of the army and may be considered as the military counterpart of the civilian family or household unit.

Although the general pattern of the distribution of infectious hepatitis in a military population is a reasonably definite one, it is difficult to be certain of the interpretation of the picture. The wide scatter of cases in time and place with no apparent chain of contact between them strongly suggests the presence of unrecognized or subclinical infections and the probability that these play an important role in the spread of the disease.

As an example, between December 12, 1944 and January 9, 1945, 12 cases occurred in the Headquarters company, 2nd Armored Group. The attack rate was quite high, one of the first patients being a cook; thus this was then investigated as a possible food-borne outbreak, as is shown in the accompanying diagrammatic representation of the relation of the cases and the most probable chain of infection:




Case 1. This was the first man to become ill. He was a "buddy" of patient no. 3.

Case 2. This mess sergeant roomed with patient no. 1.

Case 3. He was a roommate of patients no. 4 and no. 5 and a buddy of the cook (case 1).

Case 4. This man was a roommate of patients no. 3 and 5.

Case 5. This patient roomed with patients no. 3 and 4.

Case 6. He was a roommate of patient no. 7 and worked in the same office as no. 12.

Case 7. A clerk who worked in the same office and roomed with patient no. 6.

Case 8. He was a roommate of patient no. 9.

Case 9. This man reported ill the same day as his roommate, no. 8.

Case 10. He was a roommate of patient no. 4.

Case 11. This patient was a roommate of patient no. 10.

Case 12. He worked in the same office as patients no. 6 and 7.

While this outbreak involved only 12 cases, it was a relatively severe one, and 13% of the total strength of the unit were attacked within a 4-week period. The first case was followed in 11 to 14 days by a wave of 7 cases, all with onsets in a period of a few days. A third wave involving 3 more cases followed the second wave by 15 to 17 days.

One of the outstanding features of this outbreak was the relation of the cases to sleeping quarters. If the hypothesis were to be advanced that the outbreak was the result of an infection transmitted through common food or drink served in the mess, it would be expected that the cases would be scattered throughout the sleeping quarters in a random fashion, since all personnel ate the same food cooked in the same kitchen and served in the same mess. Circumstances surrounding this outbreak make person to person spread by way of the respiratory tract a distinct possibility.

Sufficient evidence was found to incriminate a well as the source of infection to an entire batallion. The incidence of disease was directly related to the amount of exposure to the water contained in this well, however, no evidence was available as to the means of pollution.

The upper respiratory passages were not proven definitely, in this case, to be a portal of entry because the possibility that ingestion took place could never be eliminated. However, there was some evidence that the virus was present in the nasal secretions during the initial prodromal stages of the disease and spread from such a source must be classed as respiratory regardless of the portal of entry. Respiratory spread is consistent with the epidemic pattern of infectious hepatitis, and in many outbreaks, the hypothesis of respiratory spread is much more in keeping with the facts than spread by way of the gastro-intestinal tract. It is consistent, moreover, with the seasonal incidence of infectious hepatitis.

The highest incidence among divisional troops was in the Headquarters companies. During that season, all troops were exposed to their first epidemic of infectious hepatitis, and hence it's reasonable to assume all equally susceptible to the disease. The higher rates among headquarters troops were, therefore, in all probability due to some environmental factor related to the mode of transmission of the disease.

If the disease were "filth-borne", (gastro-intestinal), it would be expected that the troops living under the most unsanitary conditions would have the highest incidence, and all conditions being equal, this would be in those companies having the poorest sanitary discipline. Headquarters troops, because of their more stabilized life, should have better sanitation in their living quarters than would be found in the billets of combat companies.

Moreover, headquarters troops are less likely to be affected by unsanitary conditions among native population or left by a retreating enemy.

On the other hand, in diseases which are transmitted directly from person to person by way of the respiratory tract, highest rates are usually found among those who work indoors under conditions of close contact. If this be the mode of transfer, we would expect the highest rates in headquarters troops since their duties keep them indoors most of the time, and this expectation was in keeping with the findings of this investigation, although gastrointestinal spread could never be entirely eliminated.

In the study of how infectious hepatitis spreads, two main difficulties have confronted the unravellers of the problem; the uncertain relationship between infectious hepatitis and homologous serum jaundice and the absence of a susceptible experimental animal for transmission experiments.

Hepatitis was noted in horses after immunization with horse serum preparations against horse sickness, (e.g., Thieler, 1919), equine encephalomyelitis, (e.g., Marsh, 1937), and grass sickness, (e.g., Gordon, 1938). Andersen, (1937,1938), and Andersen and Tulinius (1938) reported the successful transmission of epidemic hepatitis in pigs, from man to pig and from rat to pig. They considered that for successful transmission, a lowered vitality of the recipient was necessary. These Swedish investigator's findings have not yet been confirmed. German workers claimed the organism could be passed to birds, but their work wasn't convincing to many investigators and hasn't been repeated.

Findlay (1940) and Findlay, MacCallum and Murgatroyd (1938), following the occurrence of hepatitis in men who had been immunized against yellow fever, attempted to transmit the hepatic disease to monkeys, hedgehogs, cats, dogs, ferrets, rabbits, guinea pigs, rats, field moles, fowls, mice and pigeons. Pathological material was introduced by subcutaneous, intraperitoneal and intravenous injections, intranasal instillations and feeding. All experiments

were negative as were also injectionsinto developing chick embryos. Hoyle (1940) in England tried every possible route in mice, guinea pigs, and chick embryos; all were unsuccessful. Paul (1945) and his group tried all the animals named plus monkeys with no success.

With absolutely no success at animal transmission, attempts to transmit the disease by insect vectors were made. Cameron (1943) had entirely negative results with such experiments.

Actual experiments in human transmission, in comparison, have met with a high degree of success. From experiments done to date, it now appears that infectious hepatitis can be transmitted to man by a number of routes.

Early claims at success in transmission were made by Voegt (1942) in Germany. He described having infected 1 out of 4 volunteers by feeding duodenal fluid obtained from 2 patients late in the clinical course of the disease; he also claims to have produced hepatitis experimentally by ingestion of urine and of hemolyzed red blood cells from a patient. The incubation period for the duodenal fluid infection was 28 days.

In 1944, MacCullum and Bradley fed a preparation of infected feces by capsules or sprayed it into the nasal and pharyngeal passages and infected 3 out of 26 patients in 27-31 days. Havens et al, (1944) in recent experiments of the Neurotropic Virus commission of the U. S. Army, employed material from cases of infectious hepatitis, (and homologous serum jaundice), collected

in 1943 from American and British troops in Africa and Sicily. Sample sera and fresh stools were kept at dry ice box temperature for eight months, a dehydrated Seitz filtrate of urine and stool extracts at room or ice box temperature for 4 months.

The experiment consisted in administering these materials by different routes to 2 groups of human volunteers located in two different institutions.

At one institution, 8 men were observed 125 days. 5 were inoculated intracutaneously with serum known to contain icterogenic agent; of these, 3 contracted infectious hepatitis. The remaining 3 of the group were fed the serum and they remained well.

At the 2nd institution, 11 men were observed 110 days; they were divided into 3 subgroups of 3 each, the remaining 2 being kept as controls. One subgroup was fed and given intranasally sera suspected to contain the icterogenic agent; of these, 2 contracted infectious hepatitis in 30 days and the 3rd in 84 days. Another subgroup was fed urine and stool extracts plus fresh stool; 2 contracted hepatitis in 20 and 22 days respectively. The 3rd subgroup was fed urine and stool extracts alone; all remained well. The 2 controls, living in close proximity to the others, also remained well.

Havens in 1945, again employing material collected from troops in the Middle East, administered it by various oral routes to 3 different groups of human volunteers. When 1 lot of icterogenic serum in gelatin capsules was fed to 3 men, 2 contracted hepatitis

in 30 days and the 3rd in 84 days. When fecal material in capsules plus urine and stool extracts which had been filtered and dried were fed to 3 volunteers, 2 acquired jaundice at intervals of 20 to 22 days. A 3rd group received the urine and stool extracts alone, and not a case of jaundice resulted.

Havens, still later in 1945, employed serum obtained during the first 5 days of experimental disease, (pre-icteric phase), the disease having been induced in 2 human volunteers by feeding fecal material obtained from naturally-occurring cases. As such, this constituted first human passage material. The serum, designated by the author as, "M.K.", was stored at dry ice box temperature for 2 months. The heated filtrate of serum M.K. was administered in amounts of 1 c.c. to each of 4 men orally and intranasally. These men were observed 125 days, 3 of the 4 contracting moderately severe hepatitis with marked constitutional reaction and jaundice after 23, 24 and 34 days respectively.

In a similar manner Findlay and Willcox, in 1945, fed feces to 18 men, 7 exhibiting jaundice in 17-28 days and fed 30 to 50 c.c. of urine to 17 men, with 5 contracting the disease. Neefe et al, in 1945, worked with a large series of cases; 72 volunteers were fed infected feces, and 31 became jaundiced in 19-33 days.

Neefe and Stokes in 1945 performed experiments with nasopharyngeal washings and urine pool specimans from 26 and 38 infected persons respectively. Specimans were obtained both before and after the onset of hepatitis, so if the causative factor were

commonly present in the nasopharynx or urine, it should have been present in these pools. Evidence showed that the causative agent probably wasn't present in the specimans. Oral administration, however, of combined serum from the patients showed that the agent was present, infecting 2 out of 3 volunteers in 26-33 days.

Studies on parenteral inoculation were again begun by Voegt in 1942; by subcutaneous inoculation of duodenal fluid from 2 known patients, he infected a patient in 19 days time. Cameron, in 1943, injected blood serum from an infected patient intramuscularly into 6 volunteers and gave all 6 the disease in 30 days time.

Oliphant, Gilliam and Larson (1943) and MacCallum and Bauer (1944) inoculated icterogenic serum and tissue cultures subcutaneously and intranasally with positive results.

Oliphant in 1944 gave 21 subjects subcutaneous inoculations of infected serum; 4 contracted the hepatitis in 55 to 106 days. MacCallum and Bradley (1944) inoculated icterogenic serum and tissue cultures subcutaneously, infecting 3 out of 6 patients in 64-92 days.

Havens, in 1945, in conjunction with the previously mentioned experiment on oral transmission and using the same serum labeled, "M.K.", inoculated 4 men with 1 c.c. subcutaneously and intracutaneously; 1 of these inoculated with the heated serum filtrate contracted moderately severe hepatitis with marked constitutional reaction after 31 days. Again in connection with the Neurotropic

Virus Commission of the U. S. Army, Havens and his associates, using frozen infective serum from American and British soldiers, made subcutaneous and intracutaneous inoculations in 11 volunteers; 6 contracted the disease with an incubation period ranging from 20-31 days. Some of this latter group had recovered some months before from homologous serum jaundice, but this didn't protect them against an attack of infectious hepatitis.

Just recently, (1946), Rennie and Fraser subcutaneously inoculated a group of 4 volunteers with serum from a patient with "subicteric acute infectious hepatitis" resulting in 2 "takes" on the 56th and 60th days respectively.

A peculiar sidelight in all of these transmission experiments has been the effect of the disease upon Rheumatoid Arthritis. In England, G. F. Still in 1897 and Wishart in 1903 remarked upon the relief of pain in patients with rheumatoid arthritis who developed, "spontaneous jaundice". Hench in America (1910) made the same observation; he attempted to reproduce the effect by inducing artificial hyperbilirubinemia by intravenous injections of bile salts and bilirubin, but only transitory relief was obtained. MacCallum and Bauer (1944) included some volunteers suffering from rheumatoid arthritis in their parenteral transmission experiment series; there was a noticeable beneficial effect. Rennie and Fraser in 1946 noted a remission of rheumatoid arthritis in both of their patients given hepatitis by parenteral inoculation, but a relapse occurred within 6 months.

## SUMMARY AND CONCLUSIONS

From experiments done to date, it appears that the etiologic agent of infectious hepatitis, probably a virus, is in the blood stream before the onset of and during jaundice, that it's present in feces during acute stages of the disease, in the serum and possibly also in nasal washings and urine, and that the disease can be produced in man by feeding infected fecal preparations in capsules or by spraying them into the nasal and pharyngeal passages and by feeding and inoculating serum from cases of infectious hepatitis.

From these experiments, one main feature becomes apparent; there is justification for suspecting that the intestinal-oral circuit is part at least of the natural route of spreading infectious hepatitis in most epidemics. That respiratory transfer may also be a part of the picture can't be denied. Just what insect and fomite spread have to do with the epidemiological picture must await further investigation.

Though the question of similarity or dissimilarity between the etiologic agents of infectious hepatitis and homologous serum jaundice is still not settled, the majority of facts point to two separate disease entities, both virus in origin. Many reasons given by earlier investigators in an effort to explain the variations in disease pattern have been exploded by recent experimental findings, and studies of recent epidemics, fortified by the newly-acquired knowledge, through transmission experimentation, concerning

the mode of spread, justify the hypothesis that either two strains of virus or variations of the same virus are operating in these diseases. But then it is not of the utmost importance that these two disease entities be differentiated. It is more necessary at the present time, that further studies reveal the exact mode of transfer and more definite prophylactic and therapeutic measures with which to combat the disease.

BIBLIOGRAPHY

AMERICAN PUBLIC HEALTH ASSOCIATION: The Control of Communicable Diseases: An Official Report. Am. Public Health Ass'n. 6th ed., 149, 1945.

ANDERSEN, T. T.: Etiology of Hepatitis Epidemica, Acta med. Scandinav. 93: 209-227, 1937.

Etiology of Epidemic Hepatitis, Ugesk. f. laeger 100: 777-786, July 14, 1938.

ANDERSEN, T. T. & TULINIUS, S.: Etiology of Hepatitis Epidemica, Acta med. Scandinav. 95: 497-509, 1938.

BARBER, H.: Infective Hepatic Jaundice, Brit. M. J. 1:67, 1937.

BARKER, M. H.: (quoted by Hardy & Feemster) Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med., 235: 1-49, Aug. k, 1946.

BARKER, M. H., CAPPS, R. B., & ALLEN, F. W.: Acute Hepatitis without Jaundice in Mediterranean Theatre J. A. M. A. 128: 997-1003, August 4, 1945.

Chronic Hepatitis in the Mediterranean Theatre; A New Clinical Syndrome, J. A. M. A. 129: 653-659, 1945.

BATES, R.: Non-Spirochaetal Infectious Jaundice, Brit. M. J. 1: 521-524, 1936.

BERGSTRAND: (quoted by Cullinan, E. R.) Epidemiology of Jaundice, Proc. Roy. Soc. Med. 32: 933-950, 1939.

BLUMER, G.: Infectious Jaundice in the U. S. J. A. M. A. 81: 353-58, 1923.

CAMERON, J. D. S.: Infective Hepatitis, Quart. J. Med. 12: 139-155, 1943.

CLEGHORN: Epidemic Diseases of Minorca, 1744; quoted by Cockayne, E. A.: Catarrhal Jaundice, Sporadic and Epidemic, and its relation to Acute Yellow Atrophy of the Liver, Quart. J. Med. 6: 1-29, 1912.

COCKAYNE, E. A.: Catharrhal Jaundice, Spradic and Epidemic, and its relation to Acute Yellow Atrophy of the Liver, Quart. J. Med. 6: 1-29, 1912.

CULLINAN, E. R.: Epidemiology of Jaundice, Proc. Roy. Soc. Med. 32: 933-950, 1939.

DIBLE: (quoted by Hardy & Feemster; Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med., 235: 1-49, Aug. 1, 1946.)

DROLLER, H.: Outbreak of Hepatitis in Diabetic Clinic, Brit. M. J. 1: 623-625, 1945.

FINDLAY, G. M.: Infective Hepatitis and Catarrhal Jaundice, J. Roy. Army M. Corps 74: 72-79, Feb. 1940.

FINDLAY, G. M., DUNLOP, J. & BROWN, H.: Observations of Epidemic Catarrhal Jaundice, Trans. Roy. Soc. Trop. Med. and Hyg. 25: 7, 1931 & Brit. M. J. 1;652, 1932.

FINDLAY, G. M. & MACCALLUM, F. O.: Hepatitis and Jaundice associated with Immunization against certain Virus Diseases. Proc. Roy. Soc. Med. 31: 799-806, May, 1938.

FINDLAY, G. M. & MARTIN, N. H. : Jaundice following Yellow Fever Immunization; Transmission by Intranasal Instillation, Lancet 1: 678-680, May 29, 1943.

FINDLAY, G. M., MARTIN, N. H. & MITCHELL, J. B.: Hepatitis after Yellow Fever Inoculation; relation to Infective Hepatitis, Lancet 2: 301, 1944.

FRAZIER: (quoted by Hardy & Feemster: Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med., 245: 1-49, Aug. 1, 1946.)

GAULD, R. L.: Epidemiological Field Studies of Infectious Hepatitis in the Mediterranean Theater of Operations; clinical syndrome, morbidity, mortality, seasonal incidence, Am. J. Hyg. 43: 248-54, 255-72, 273-82, 282-88, 289-94, 295-98, 299-307, 310-313, May, 1946.

GELLIS, H.: Use of Immune Serum Globulin (gamma globulin) in Infectious (epidemic) Hepatitis in Mediterranean Theater of Operations; Studies on Treatment, J. A. M. A. 128: 1158-1159, Aug. 18, 1945.

GETTY, R. W.: Epidemiologic Study of Infectious Hepatitis, U. S. Nav. M. Bull. 46: 541-53, April, 1946.

GLOVER & WILSON: (quoted by Barker, H.: Infective Hepatic Jaundice, Brit. M. J. 1: 67, 1937.)

GORDON: (quoted by Cameron, J. D. S.: Infective Hepatitis, Quart. J. Med. 12, 139-155, 1943.)

(quoted by Sheehan, H. L.: Epidemiology of Infectious Hepatitis, Lancet 2: 8-11, 1944.)

HALLGREN: (quoted by Hardy & Feemster: Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med. 235: 1-49, Aug. 1, 1946.)

HANDY: (quoted by Hardy & Feemster: Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med. 235: 1-49, Aug. 1, 1946.)

HARDY, H. L. & FEEMSTER, R.: Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med. 235; 147-57, Aug. 1, 1946.

HAVENS, W. P., JR.: Properties of Etiologic Agent of Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. 58:203, 1945.

Epidemiological Studies on Infectious Hepatitis, Am. J. Pub. Health, 36: 37-44, 1946.

Viruses of Infectious Hepatitis & Serum Jaundice, Fed. Proc. Balt. 5:248, 1946.

Period of Infectivity of Patients with Experimentally-induced Infectious Hepatitis, J. Exp. M. 83:251-8, Mar., 1946.

HAVENS, W. P., JR., PAUL, J. R., VAN ROOYEN, C. E., WARD, R., & DRILL, V. A.: Human Transmission of Infectious Hepatitis by the Oral Route, Lancet 1:202, 1945.

HAVENS, W. P., JR., WARD, R., DRILL, V., PAUL, J. R.: Experimental production of Hepatitis by feeding Icterogenic Materials, Proc. Soc. Exp. Biol. & Med., 57:206, 1944.

HAYWARD, M. L.: Epidemiological Study of An Outbreak of Infectious Hepatitis, Gastroenterology 6: 504-10, 1946.

HELD, I. W., & GOLDBLOOM, A. A.: Hepatocellular Catarrhal Icterus and Hepatitis following the use of Yellow Fever Vaccine; Clinicopathologic Comparisons, New York State J. Med. 44: 270-279, 1944.

HENCH: (quoted by MacCullum, F. O., & Bradley, R., Lancet 2:228, 1944. Transmission of Infective Hepatitis to Human Volunteers.)

HISCOCK, I. V. & ROGERS, O. F.: Outbreaks of Epidemic Jaundice among College Students, J. A. M. A. 78:488-490, Feb. 18, 1922.

HURST, A. F. & SIMPSON, C. K.: Catarrhal Jaundice & Mild Hepatic Necrosis; their Pathology and Diagnosis, Guy's Hosp. Rep. 84: 173-185, April, 1934.

JACOBI, J., KREYENBERG, G., & DORSCHEL, W.: Erfahrungen bei ueber 600 Kranken mit Hepatitis epidemica, (Experiences with over 600 cases of Epidemic Hepatitis), Deut. Militararzt. v.8, 8:479-86, Aug., 1943.

JAEGER: (quoted by Cockayne, E. A.: Catarrhal Jaundice, Sporadic and Epidemic, and its relation to Acute Yellow Atrophy of the Liver, 6:1-29, 1912.)

JONES, C. M.: (quoted by Hardy, H. L. & Feemster, R.: Infectious Hepatitis in Massachusetts, New Eng. Jour. of Med., 235: 147-57, Aug. 1, 1946.)

JONES, C. M. & MINOT, G. R.: Infectious Catarrhal Jaundice; attempt to establish clinical entity; observations on excretion and retention of bile pigments and on Blood, Boston M. & S. J. 189:531-51, Oct. 18, 1923.

KERSHAW: (quoted by Cockayne, E. A.: Catarrhal Jaundice, Sporadic and Epidemic, and its relation to Acute Yellow Atrophy of the Liver, Quart. J. Med. 6:1-29, 1912.)

KNIGHT & COGSWELL: Preliminary observations of the gastric mucosa in patients with Infectious Hepatitis. J. A. M. A., 128: 803, July 14, 1945.

KRASNABAEFF: (quoted by Cockayne, E. A., Catarrhal Jaundice, Sporadic and Epidemic, and its relation to Acute Yellow Atrophy of the Liver, Quart. J. Med. 6:1-29, 1912.)

LANCEREAUX, O.: Cirrhose alcoolique a forme atrophique, Praticien, Par., IV, 604-606, 1881.

LANDOUZY, L.: (quoted by Cockayne, E. A.: Catarrhal Jaundice, Sporadic and Epidemic, and its relation to Acute Yellow Atrophy of the Liver, 6: 1-29, 1912.)

LESLIE, F. E.: Epidemic of catarrhal jaundice. Boston M. & S. J. 161:622, 1909.

LONG, P.: Infectious Hepatitis. Personal communication, Omaha Mid-West Clinic Society, Oct., 1944.

LUCKÉ, B.: Pathology of fatal epidemic hepatitis. Am. J. Path. 20:471-593, 1944.

LUCKE, B., BALDWIN & MALLORY, T.: The Fulminant form of Epidemic Hepatitis. Am. J. Path. 22:868, Sept., 1946.

MACCALLUM, F. & BAUER, D.: Homologous Serum Jaundice; transmission experiments with human volunteers. Lancet 1:622, May, 1944.

MACCALLUM, F. O. & BRADLEY, R.: Transmission of infective hepatitis to human volunteers. Lancet 2:228, 1944.

MARSH: (quoted by Cameron, J. D. S.: Infective Hepatitis. Quart. J. Med. 12:139-155, 1943.)

MATHIEU, A.: Typhus hepatique benin; rechute; guerison. Rev. de Med., Par., VI, 633-39, 1886.

MCFARLAN, A. M.: Epidemiology of infectious hepatitis in some units of the British Army in Sicily and G. Britain. Quart. J. Med. 14:125-146, July, 1945.

MEINERT: (quoted by Cockayne, E. A.: Catarrhal Jaundice, sporadic and epidemic, and its relation to Acute Yellow Atrophy of the Liver. Quart. J. Med. 6:1-29, 1912.)

MORGAN, M. T. & BROWN, H. C.: Epidemic catarrhal jaundice; some notes on epidemiology of disease and account of epidemic in midlands. Rep. Pub. Health & M. Subj. 42:1-27, 1927.

NEEFE, JR R., STOKES, J., JR. & REINHOLD, J. G.: Oral administration to volunteers of feces from patients with homologous serum hepatitis and infectious (epidemic) hepatitis. Am. J. M. Sc. 210:29-32, 1945.

Disinfection of water containing causative agent of infectious hepatitis. J. A. M. A. 128:1076-80, 1945.

NEEFE, J. R. & STOKES, J., JR.: Epidemic of infectious hepatitis apparently due to water-borne agent; epidemiologic observations and transmission experiments. J. A. M. A. 128:1063-75, 1945.

NEEFE, J. R., GELLIS, S. S. & STOKES, J., JR.: Homologous serum hepatitis and infectious (epidemic) hepatitis; studies in volunteers bearing on immunological and other characteristics of the etiological agents. Am. J. Med. 1:3-22, July, 1946.

NELSON, J. D.: Recurrent infectious hepatitis. Mil. Surgeon. 98:134-37, Feb., 1946.

NEWMAN, J. L.: Infective hepatitis; history of outbreak in Lavant Valley. Brit. J. J. 1:61-65, Jan. 17, 1942.

NICOL: (quoted by Sheehan, H. L.: Epidemiology of infectious hepatitis. Lancet 2:8-11, 1944.

OLIPHANT, J. W.: Jaundice following administration of human serum. Bull. New York Acad. Med. 20:429-445, 1944.

OLIPHANT, J. W. GILLIAM, H. G. & LARSON, C. L.: Jaundice following administration of human serum. Pub. Health Rep. 58:1233, 1943.

PAUL, J. R., HAVENS, W. P., JR., SABIN, A. B. & PHILIP, C. B.: Transmission experiments in serum jaundice and infectious hepatitis, J. A. M. A. 128:911-915, 1945.

PECK: (quoted by Cockayne, E. A.: Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the Liver. Quart. J. Med. 6:1-29, 1912.)

PICKLES, W. N.: Control of common fevers; epidemic catarrhal jaundice, Lancet 1:893-95, April 15, 1939.

Epidemic catarrhal jaundice, outbreak in Yorkshire. Brit. M. J. 1:944-946, May 24, 1930.

POMEROY, E. H.: Epidemic jaundice. Boston M. & S. J. 139:107-109, 1898.

PORTIS, S. A.: Symposium on analysis and interpretation of symptoms; jaundice. Clinics 2:1568-1585, 1944.

PROPERT, S. A.: Infective hepatitis. Brit. J. J. 1:197, 1942.

RAPPAPORT, E. M.: Hepatitis following blood or plasma transfusions: observations in 33 cases. J.A.M.A. 128:932-39, 1945.

READ, M. R., BANCROFT, H. (et al): Infectious hepatitis, presumably food-borne outbreak. Am. J. Pub. Health 36:367-70, April, 1946.

RENNIE, J. B., & FRASER, T. N.: Transmission of acute infective hepatitis; therapeutic effect on rheumatoid arthritis. Glasgow M. J. 27:157-66, June, 1946.

ROGERS, O. F.: Epidemic hepatitis. J. A. M. A. 123:1066, 1943.

SANDWICH: (quoted by Cockayne, E. A.: Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the liver. Quart. J. Med. 6:1-29, 1912.)

SEIDE & LUZ: (quoted by Getty, R. W.: Epidemiologic study of infectious hepatitis. U. S. Nav. M. Bull. 46:541-53, April, 1946.)

SHEEHAN, H. L.: Epidemiology of infectious hepatitis. Lancet 2:8-11, 1944.

STILL: (quoted by MacCallum, F. O. & Bradley, R.: Transmission of infectious hepatitis to human volunteers. Lancet 2:228, 1944.)

STOKES, J. JR.: (quoted by Hardy, H. L. & Feemster, R.: Infectious hepatitis in Massachusetts, 235:147-57, Aug. 1, 1946.)

STOKES, J., JR. & NEEDE, J. R.: Prevention and attenuation of infectious hepatitis by gamma globulin; preliminary note. J. A. M. A. 127:144, 1945.

STOWMAN, K.: Epidemic outlook in Europe. J.A.M.A. 128:185-188, 1945.

SURGEON GENERAL'S OFFICE, Washington, D. C.: Medical & Surgical History of the War of the Rebellion. iii:874, 1888.

SYMMERS, D.: Epidemic jaundice. J. A. M. A. 123:1066, 1943.

THIELER: (quoted by Cameron, J. D. S.: Quart. J. Med. 12:139-155, 1943.)

U. S. ARMY MED. DEPT. BULL.: Faeces, flied & Hepatitis. Bull. War Med. 5:696-697, July, 1945.

VAISEY: (quoted by Cameron, J. D. S.: Quart. J. Med. 12:139-155, 1943.)

VALASSAPOULO: (quoted by Cameron, J. D. S.: Quart. J. Med. 12: 139-155, 1943.)

VAN ROOYEN, C. E. & GORDON, I.: Some experimental work on infectious hepatitis in M. E. F. J. Roy. Army Med. Corps 79:213-225, 1942.

WADSWORTH, A., LANDWORTH, H. V., STEWART, F. C., MOORE, A. C., & COLEMAN, M. B.: Infectious jaundice occurring in New York State: preliminary report of investigation, with report of case of accidental infection of human subject with Leptospira icterohaemorrhagiae from rat. J.A.M.A. 78:1120, 1922.

WALKER, D. W.: Epidemiological aspects of infectious hepatitis in the U. S. Army. Am. J. Trop. Med. 25:75-82, 1945.

WEIL: (quoted by Cockayne, E. A.: Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the Liver. Quart. J. Med. 6:1-29, 1912.)

WILLCOX, W. H.: Epidemic jaundice of campaigns. Brit. J. J. i:297, Feb., 1916.

On jaundice with special reference to types occurring during the War. Brit. J. J. 1:565, May, 1919.

WILLIAMS, H.: Epidemic jaundice in New York State. J. A. M. A. 80:532-534, 1923.

WISHART: (quoted by MacCallum, F. O. & Bradley, R.: Transmission of infective hepatitis to human volunteers. Lancet 2:228, 1944.)