1948

Infectious hepatitis and its epidemiology

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INFECTIOUS HEPATITIS
AND ITS
EPIDEMIOLOGY

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SENIOR THESIS
PRESENTED TO THE
UNIVERSITY OF NEBRASKA
COLLEGE OF MEDICINE
1948

Infectious hepatitis is an acute hepatic inflamation 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. Through the years it has been variously known as catarrhal jaundice, epidemic jaundice, infective hepatitis, and infectious hepatitis.

Jaundice epidemics are described in letters between Pope Zacharias and St. Boniface in the eighth century.

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 where the disease appears to be endemic.

On 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 persons affected in 1863, in which both children and adults were attacked.

One of the largest epidemics in this country occurred during the Civil War. 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.

An epidemic occurred during the Franco-Prussian War with 2344 cases in the Prussian army and 407 in the civilians and troops in Paris. Flindt in 1890 published an article in an obscure Danish journal in which he saw a connection between acute yellow atrophy and infectious hepatitis. He showed epidemiological evidence that the epidemic and sporadic forms were linked and could terminate in acute yellow atrophy.

Cockayne, 1912, summarized the findings to that time in England. The World War 1 epidemic began in British troops stationed in Egypt and spread to Galliopoli with 2194 cases from September to November and from there moved to the Middle East.

Wilcox, 1919, made a clear classification and seperated 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 Summers in New York 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. Cullinan gave a list of reported outbreaks from 1926-34 in England. Jones and Minot

in 1923 published a careful clinical estimate of the disease, pleading for more attention to its extent and potential dangers.

In the Scandanavian countries it has become especially widespread and virulent.

In the 1930's English literature contained scattered reports of outbreaks as did literature of other countries, with few American reports. One cannot be certain that all these outbreaks belong in a single group, since the etiologic agent had not been discovered, but there appears 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, and British and American armies, as well as civilians in Palestine have suffered serious morbidity from the disease; as have the navies.

INCIDENCE

The disease is most commonly reported in children although any age group may be attacked, especially in a group such as the army. Inasmuch as the childhood form of this disease is very mild and easily overlooked, it has been suggested that infectious hepatitis is far more prevalent than commonly realized. Most adults have

been exposed in early life and may even have had the disease in unrecognized form so that they have acquired a certain degree of immunity. In a series of one hundred and fifty cases, Hardy and Feemster showed those between 6-40 years the most often affected.

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 most instances 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 U. S. from 1931-41 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 hemishpere 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.

CLINICAL PICTURE

Although the main purpose of this paper is to discuss the epidemiology of infectious hepatitis, a brief clinical picture of this disease should be given so that it may be clearer what we are discussing. Infectious hepatitis is a transient, and usually mild, icteric condition with a mortality usually less than 0.4 per cent. Early symptoms point to a disturbance in the upper gastrointestinal tract; the evidence of liver damage occurring later. Clinically the disease may be divided into two stages, preicteric and icteric, each phase having characteristic symptoms and signs. Anorexia, nausea, fever and abdominal pain are the characteristic signs of the preicteric stage. It may last from five to ten days. The liver is seldom enlarged. The icteric stage follows, lasting from two to ten weeks. Abdominal discomfort, in the form of epigastric or right upper quadrant pain, continued nausea, enlargement and tenderness of the liver, and light or even clay colored stools are the usual symptoms in this stage. jaundice is usual, but clinical jaundice is not an essential part of the picture. A marked weight loss is seen also.

PROGNOSIS

Prognosis is very favorable in the vast majority of cases, especially so in children and young adults. Rarely after the disease has run a benign course for 3-4 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. Mortality figures reviewed by Lucke range from 0.24 to 0.44 per cent whereas Stowman reported 0.1 to 1.0 per cent.

Jersild has recently reported an interesting and serious epidemic of infectious hepatitis in Europe. Ninety nine per cent of the cases occurred in women, seventy nine per cent of the women being over fifty years of age. The mortality was high; sixty per cent. The possibility of a highly malignant virus is emphasized and the possibility that estrogens may exert some liver protecting influence is brought out.

TREATMENT

In treatment, dietary management has been 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, are not 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 diseased. Darmady in England treated 32 patients in 1945 with a high protein dient with added vitamin B complex and liver extract. Twenty-nine others were given a control diet. No difference in the clinical course was noted. Wilson and Higgins in 1945 were unable to note any difference as the result of orally administered Methionine. Barker, Capps, and Allen remark that the matter of low fat intake is not yet settled; except in the most benighn cases the gastrointestinal tract cannot easily handle fat because bile is being excreted with difficulty. Morphine and barbiturates should be used cautiously because of the presence of active liver disease.

Long in 1946 stated bed rest is necessary until jaundice has disappeared or the icteric index is under 18.

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 therapeutically, however Stokes and Neefe believed they used it successfully on a girl's camp epidemic in 1944. Recent reports by Gellis suggest that it confers passive immunity against infectious hepatitis for at least 6-8 weeks.

Treatment of plasma with ultra violet light seems to have promise in preventing the transmission in this way as suggested by Oliphant and Holloender.

PATHOLOGY

Virchow believed this disease was the result of an inflamatory swelling of the orifice of the common bile duct. This, he believed, was filled with mucous and desquamated cells resulting in an obstructive type of jaundice. Since that time this theory has been virtually disproven. It has gradually come to be regarded as an inflamatory disease of the liver parenchyma. Up until the past war information was scanty because of the few post mortems performed on this commonly benighn disease. Also the needle biopsy has added valuable information in the various stages of the disease process. Eppinger performed posts on three soldiers dying of other causes during the first World War. He found widespread disease

of the liver with no obstruction of the extrahepatic ducts. Since his time there have been isolated posts and occassional biopsies but until the work of Lucke and Mallory no new information was added. These men found in the fatal cases which came to autopsy a liver reduced in size weighing from 800 to 1200 grams. The surface smooth or finely wrinklea, color not distinctive. Cases dying somewhat later than most showed yellowish or greenish nodules projecting from the surface. The cut surface showed large red meat like areas where the landmarks were indistinct, or gone. In contrast were irregular bile stained patches which were lobulated.

The microscopic appearance of the red areas showed destruction of liver cells but the lobules were still outlined by proliferating bile ducts. This picture is characteristic of infectious hepatitis. The destructive change almost always begins in the center of the lobule. There was some evidence of inflamation with infiltration of leukocytes. The nodular areas showed atypical, regenerated, liver lobules. The small septal bile ducts showed marked proliferation and it was suggested that biliary epithelium may produce small amounts of hepatic cells which were atypical. Cholemic nephrosis, widespread peticheal hemorrhages, and meninoencephalitis were found in a number of cases.

The needle biopsy as developed by Roholm and Iversen has shown essentially the same pathology to a lesser degree in non fatal cases. No difference was found in the sporadic, epidemic, arsphenamine, or homologous serum types.

ETIOLOGY

To date the icterogenic agent has not been isolated in the sense that it has been seen, cultured or transmitted experimentally to laboratory animals. Since the studies of Mac Cullum and Findlay in 1937-38 it has become generally agreed that the etiologic agent has the characteristics of a filterable virus. The virus has not been seen with the electron microscope and has not been transmitted to an animal but man. They are not killed by 1:2000 solution of merthiolate, by .5 percent solution of phenol in ether, or by .2 per cent solution of tricresol. The ordinary method of chlorinating water does not affect them. Inactivation by autoclaving or by exposure to ultraviolet light is effective. It withstands heating to 56° C for at least one half hour. There is good reason to believe the agent is present in the blood stream in the pre-icteric phase and in the feces during the acute phase. In the following table are some of the apparent differ-

ences between infectious hepatitis and serum hepatitis:

	I.H.	S.H.
fever	present	absent
incubation period	20-45 days	60-150 days
transmission by feces	yes	no
transmission parenterally	yes	yes
homologous immunity	1 year	18 months
heterologous immunity	none	none
mortality	0.01-0.2 %	0.2-20 %

Recently many have taken the view that these are two diseases caused by two different viruses. However as Havens has pointed out many minor differences amy exist because of portals of entry and the possible presence of immune bodies in the serum.

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 the virus of infectious hepatitis have been called homologous serum jaundice and some cases due to agents similar to virus S H have been called infectious hepatitis. This is particularly apt to occur because both the virus of homologous serum 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 IH 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 preformed 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 blood product was obtainable. Likewise a person may have been considered to have homologous serum jaundice because of previous administration of 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 was the only disease which reached pandemic proportions during the recent was comparable almost to the flu of World War I. In spite

of extensive studies however its epidemiology is as yet incompletely 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 were not the cause of a series of epidemics he had studied. Kershaw at Boston in 1901 noticed that cases usually arose in the neighborhood of previous ones and that some districts remianed quite free; infection seemed able to linger in one place for some time.

In 1910 Vaisey showed where a rural epidemic had spread from one village to another three miles away, apparently carried by a child eight 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.

Meiner 1910, felt that it was particularly liable to pick out an individual already suffering from respiratory disease due to antecedent influenza.

Krasnebaeff, 1912, presented several cases which had spread within a family group, apparently due to close personal contact.

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

Glover and Wilson reported an epidemic in 1930 in a boys school where they believed the disease was spread wia 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 appearence 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 recieved, but after the break through at El Alamein in the autumn of 1942 and later in the spring of '43 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 bet-

ween 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 is possible that some at least brought the disease along with them. Such German medical literature as has been available indicated 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, Gordon, 1942, van Roonyen and Gordon, 1942, Cameron, 1945. Infectious hepatitis was the greatest cause of disabling illness among United States forces in the Mediterranean area. From Januaryl, 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 cent per month for the entire American army in N. Africa.

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

A few states in the U. S. 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.

Exact knowledge as to immunity is not yet available. It appears to be highly infectious in children but well tolerated by them. The age group attacked, 6-40, suggest that older persons may have acquired immunity by a 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 are not found to be immune to experimentally induced attacks of infectious hepatitis.

The 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 intervals of about a month. He thought it quite safe to return children to school after two weeks, and he did not hesitate to admit cases to the general wards of a hospital when jaundice was once established.

Bates, 1936, said the period of infectivity lasted four weeks after the onset of jaundice. Pickles, 1939, felt the period to be eight days before and up to two wiiks after the onset of jaundice.

The limits of the infective period, or when the etiologic agent appear in the blood or stool and how long it remains there, have been studies 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 reported in 1942 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 in 1945 found that stools obtained three weeks after the disappearance of jaundice in human volunteers convalescent from experimentally induced infectious hepatitis were not infectious when fed to other human volunteers.

Havens in 1946 attempted to determine the period of infectivity of patients with experimentally induced infectious hepatitis and the infectivity of urine and nasopharyngeal washing 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 four 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 four and five days after onset of the disease and one and two days before the appearance of jaundice contained enough virus to produce infectious hepatitis with jaundice in five out of nine 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 five out of six volunteers. Urine and nasopharyngeal washings, obtained on the same days as the stools and which were demonstrated to be infectious, appar-

ently did not contain virus in sufficient amount to produce clinical disease. Convalescent phase stools were again negative.

Havens and others in 1944, in another series of experiments, found the agent present in blood obtained 60 days prior to the onset of jaundice.

The problem of epidemiology has been studied by two means; the collecting and analysing 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 three months later, 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 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 location, 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 N. 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 tne disease. They also knew of a woman with infectious hepatitis who in previous months had recieved 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 pobably have been infected during the exposure period on board ship.

It has been reported from the Mediterranean are a 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 inf ctiou was enteric. It also infers fecal contamination of food and water or both with the causative agent. On saipan and Ti ian 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 co rcluded that transmission via the upper resiratory 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 Alemein 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.

In the spring of 1944 an outbreak of 24 cases of infectious hepatitis occurred among students at Western Reserve University school of Medicine. The study of this epidemic by Read and Bancroft revealed the fact that the causative agent of infectious hepatitis may also be transmitted by food. All the patients so infected ere members of a single fraternity. Four of the 24 infected patients lived in the fraternity house and ate all of their meals at the house. The remaining 20 victims did not live in the house but all ate part of their meals there. No cases occurred in members who did not eat or ate only occassional meals at the house or non-members in spite of close contacts in classrooms and laboratories. A careful study showed all

water came from the municipal supply. Evidence pointed strongly to spread through some articles of food served at the fraternity.

Sheehan made a study of the infectious hepatitis epidemics that occurred in our armies in the Mediterranean war zones. He came to the conclusion that such could well be transmitted by biting insect. The onset of the Mediterranean epidemics occurred about three months after the onset of the season of blood sucking insects and the end of the epidemics were about three months after the end of that season. Which insect remains a matter of speculation.

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 co tamination of 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 the infectious hepatitis introduced into the camp early in the season; their studies will be presented in more detail in the section on transmission

experiments.

Murphy and Petrie in 1946 report an outbreak in Georgia in which all of the cases seemed to be associated with a single milk supply. The families involved were interviewed. Almost all had not eaten outside the home and the food was obtained from various sources throughout the city. Water was obtained from a common source in all the homes of the city. Of eight households involoved seven were supplied with milk from one dairy. The remianing case frequently drank milk in an involved household. This dairy was investigated and found to be completely void of any convenien es for handling milk. A neighboring family had had two cases of infectious hepatitis previous to the outbreak of the epidemic. Less than one hundred feet from the well, from which water w s obtained to wash milking utensils, was an outdoor toilet used by both families. Conditions were such that spread through contaminated milk was most probable.

In a study of many military epidemics, one will always find some outbreaks where there is a question as to whether the spread was via the respiratory or gastrointestinal tracts. In 1943 studies were initiated by the office of the surgeon, Headquarters, North African

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 w s would there by 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 occassions.

For investigation into the mode of spread and the pattern of the appearance of cases, it was found that the company, was the unit of choice. This is the house keeping unit of the army and may be considered as the military counter part 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 the cases in time and place with no apparent chain of contace between them strongly suggest 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 1944 and January 9, 1945, 13 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 w s then investigated as a possible food borne outbreak.

While this outbreak involved only 13 cases, it was a relatively severe one, and 13 per cent of the total strength of the u it were attacked within a four 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 three 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 through the sleeping quarters in a random fashion, since all personel ate the same food cooked in the same ditchen 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 infect on 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 definately, in this case, to 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 infecti us hepatitis, and in many outbreaks, the hypothesis os 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 is 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 w ich are transmitted directly fro. person to person by way of the respiratory tract, highest rates are usually found among those who work indoors under donditions of close contacts. 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 gastro-intestinal spread could never be entire-

ly eliminated.

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

Hepatitis was noted in horses after immunization with horse serum preparations against horse sickness, Theiler, 1919, equine encephalomyelitis, Marsh, 1937, and grass sickness, Gordon, 1938. Andersen, 1937, and Andersen and Tulinuim, 1938, reported the successful transmission of epidemic hepatitis in pigs, from man to pig and 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 was not convincing to many investigators and has not been repeated.

Findlay, 1940, and Findlay, Mac Callum and Margatroyd, 1938, following the occurrance of hepatitis in men who had been immunized against yellow fever, attempted to transmit the hepatic disease to monkeys, hedgehegs, cats, dogs, ferrets, rabbits, guinea pigs, rats,

field moles, fowls, mice and pigeons. Pathological material was introduced by subcutaneous, intraperitoneal and intravenous infections, intranasal instillations and feeding. All experiments were negative as were also injections into 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 one out of four volunteers by feeding duodenal fluid obtained from two 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 duodenol fluid infection was 28 days.

In 1944 Mac Cullum and Bradley fed a preparation of infected feces by capsules or sprayed it into the nasal and pharyngeal passages and infected three out of twenty sex 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 four months.

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

At one institution, eight men were observed 125 days. Five were inoculated intracutaneously with serum known to contain icterogenic agent; of these, three contracted infectious hepatitis. The remaining three 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 three each, the remaining two being kept as controls. One subgroup

was fed and given intranasally sera suspected to contain the interogenic agent; of these, two contracted infectious hepatitis in 30 days and the third in 84 days. Another subgroup was fed urine and stool extracts alone; all remained well. The two 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 three different groups of human volunteers. When one lot of icterogenic serum in gelatin capsules was fed the three men, two contracted hepatitis in 30 days and the third in 84 days. When fecal material in capsules plus urine and stool extracts which had been filtered and dried were fed to three volunteers, two accuired jaundice at intervals of 20 days to 22 days. A third 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 five days of experimental disease, preicteric phase, the disease having been induced in two 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 two months. The heated filtrate of serum M K was administered in amounts of 1 cc to each of four men orally and intranasally. These men were observed 125 days, three of the four contracting moderately severe jaundice with marked constitutional reaction and jaundice after 23,24, and 34 days.

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 cc of urine to 17 men, with five 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 to 33 days.

Neefe and Stokes in 1945 preformed experiments with nasopharyngeal washings and urine pool specimans from 26 and 38 infected persons respectively. Specimens 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 was not present in the specimens. Oral administration, however, of combined serum from the patients showed that the agent was present, infecting two out of three volunteers in 26 to 33 days. Studies on parenteral inoculation were again begun by Voegt in 1942 by subcutaneous inoculation of duodenal fluid from two known

patients, he infected a patient in 19 days time. Cameron in 1943 injected blood serum from an infected patient intramuscularly into 6 vulunteers and gave all 6 the disease in 30 days time.

Oliphant, Gilliam and Larson in 1943 and Mac Callum and Bauer in 1944 inoculated icterogenic serum and tissue cultures subcutaneously and intranasally with positive result.

Havens, in 1945 in co njunction with the previously mentioned experiment on oral transmission and using the same serum labeled, M K inoculated four men with 1 cc subcutaneously and intracutaneously; one 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; six contracted the disease with an incubation period ranging from 20 to 31 days. Some of this latter group had recovered some months before from homologous serum jaundice, but this did not protect them against an attack of infectious hepatitis.

More recently, 1946, Rennie and Fraser subcutaneously inoculated a group of four volunteers with serum from a patient with subicteric acute infectious hepatitis resulting in two takes on the 56 and 60 days respectively.

Scattered cases have appeared in civilians following the war. Kunkel and Hoagland, 1947, reported an epidemic in a family living in a crowded apartment. Contact was thought to be the probable mode of spread in this outbreak.

SUMMARY AND CONCLUSIONS

A review of the report d epidemics of infectious hepatitis and the recent transmission experiments on humans brings out no complete answer to its epidemiology. However significant advances have been made and the following points are presented:

1. The etiologic agent is almost certainly a virus unusually resistant to heat, cold, drying, and the ordinary chlorination of drinking water.

2. The means of transmission may be varied. The virus has been shown to be present in blood, feces, nasal washings, and duodenal contents during the acute stages of the disease.

3. Substantial evidence is presented showing tran-

smission by droplet infection through upper respiratory tract, contaminated food and water, and incompletely sterilized syringes.

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