VOL. LXXIX. NOVEMBER, 1942. No. 5.

Journal
of the
Royal Army Medical Corps.

Original Communications.

SOME EXPERIMENTAL WORK ON INFECTIVE HEPATITIS IN THE M.E.F.

BY MAJOR C. E. VAN ROOYEN,
Royal Army Medical Corps,
Pathologist,
AND
MAJOR IAN GORDON, *O.B.E.,*
Royal Army Medical Corps,
Medical Specialist.
(*From a Military Hospital, Middle East Force.*)

INFECTIVE hepatitis or epidemic catarrhal jaundice, also alluded to in military medicine as the jaundice of campaigns, is a disease of world-wide distribution. Since the discovery of *L. icterohæmorrhagiæ* in 1914 by Inada *et al.* (1916), infective hepatitis or so-called catarrhal jaundice has been recognized as a clinical and pathological entity separate from spirochætal jaundice. Both diseases were encountered during the Great War, 1914-18, and were extensively studied by many observers. Spirochætal jaundice was prevalent in the French, German and British Armies of the Western Front and a lesser number of cases were reported from Gallipoli. Epidemic catarrhal jaundice, on the other hand, presented a different distribution. In France and Flanders, cases occurred singly or in groups, whereas in the Eastern theatres of war, notably in Alexandria (July, 1915), Gallipoli, Mudros, Salonika and Mesopotamia, it appeared in epidemic form. According to the History of the War. Medical Services. Diseases of the War. Vol. I,

676 cases of jaundice were evacuated from Suvla Bay and 456 of these affected the 53rd Division. Other interesting facts on record were that, on evacuation of the Peninsula in December, 1915, jaundice from Suvla Bay was brought back to Egypt by the 53rd Division but rapidly died out by the end of January, 1916. The 10th Division carried it from Suvla Bay to Salonika when a third of the total sick admitted to hospital suffered from the malady. Subsequently for some inexplicable reason it vanished spontaneously in December, 1915, and did not return. The 13th Division bore the disease with them from Suvla Bay to Egypt and thence to Mesopotamia where epidemic jaundice recurred and 555 cases were notified in June, 1916. In concluding his remarks, Hunter makes the interesting comment that "The usual history in any battalion affected commenced with one or two isolated cases; then there was an interval of about three to four weeks, then a large number of cases for three weeks, finally an occasional case for a few more weeks."

During 1915-16, specimens of blood, urine and liver biopsy tissue were examined bacteriologically by Captain (now Professor) T. J. Mackie, R.A.M.C., but no specific organisms could be isolated and the ætiology of epidemic jaundice remained obscure.

Today another epidemic of jaundice has appeared in the Middle East theatre of war and we have again tried to elucidate its nature by the employment of all available methods. The number of cases at our disposal has been sufficient to provide us with a constant supply of blood, stomach washings and bile from early and late stages of the illness. Such material has been subjected to intensive bacteriological, cytological and animal inoculation tests. Our laboratory findings have been in the main negative but the extent of ground covered is reported below. The description of technical work is followed by a discussion on the ætiology of the disease.

Observations on Bile.

Technique of Obtaining Specimens.—The method of duodenal intubation as recommended by Lyon (1923) was adopted with the exception of the volume and concentration of the magnesium sulphate solution used as a cholagogue. Lyon advises the use of 75 c.c. of 33 per cent solution of magnesium sulphate but it has been shown by Fidler, Innes and Davidson (1941) that magnesium sulphate in such concentration is highly irritant to the duodenal mucosa with the resultant production of large numbers of epithelial cells.

Consequently we used as a cholagogue 5 to 10 c.c. of a 25 per cent solution of magnesium sulphate. The employment of this volume and concentration, which was sufficient to excite a satisfactory flow of bile, as much as 200 c.c. in one case, did not appear to cause desquamation of duodenal epithelium.

Clinical Data.—Samples of bile were aspirated by duodenal intubation from eleven patients in different stages of infective hepatitis. During the

first week of the illness the presence of anorexia, nausea and vomiting made the passage of the duodenal tube exceedingly difficult but, in seven instances, this was successfully accomplished. In the later stages of the disease the procedure was easier. In four subjects, notwithstanding the existence of jaundice accompanied by clay-coloured stools, a small quantity of bile was recovered by the duodenal tube. It thus seemed that there was no complete stoppage of the bile flow in the cases which we studied. In four patients we were able to withdraw bile within twenty-four to forty-eight hours of the reappearance of normal stools. This was performed to investigate the characteristics of the early flow of bile immediately after a period of suppression varying from five to fifteen days (*see* Table I).

Control material comprised bile obtained from six healthy male adults by precisely similar methods. It was subjected to the same treatment.

TABLE I

DUODENAL INTUBATION

Case no.	*Day of jaundice*	*Quantity of bile removed*	*Stool*	*Remarks*
1	2	10 c.c.	Clay	Average case.
2	5	40 c.c.	Clay	Moderately severe case.
3	5	200 c.c.	Clay	Mild case.
4	5	100 c.c.	Light brown	Clay stools on previous day.
5	6	80 c.c.	Light brown	Clay stools on previous day.
6	7	100 c.c.	?	Average case.
7	7	20 c.c.	Normal	Average case.
8	8	70 c.c.	?	Severe case.
9	10	20 c.c.	Clay	Average case.
10	14	90 c.c.	Normal	Jaundice clearing.
11	15	10 c.c.	Normal	Jaundice clearing.

BACTERIOLOGICAL EXAMINATIONS.

All the bile collected from each patient was pooled, 10 to 15 c.c. were centrifuged in an angle centrifuge at 5,000 r.p.m. for one hour, the supernatant fluid discarded and the deposit plated out on a variety of solid media. The following were employed: Serum agar; 4 per cent horse blood agar; coagulated sheep blood; Dorset's egg medium; Loffler's serum medium. A few fluid media were also utilized and consisted of glucose broth, brilliant green in peptone water and sodium tetrathionate media. The Dorset's egg and cooked meat were incubated at 37° C. for a month and the remainder for three to seven days prior to examination.

Conclusion.—No specific micro-organisms were isolated with constancy. Precisely the same bacterial flora was present in both normal and in pathological material and comprised staphylococci, hæmolytic and non-hæmolytic enterococci, pneumococci, coliform bacilli, large Gram-positive bacilli, yeasts and moulds. No spirochætes, parasites or ova were detected.

Microscopical Observations.—Films were prepared from each specimen of bile after centrifugation. These were examined by dark field illumination as well as after staining by each of the following procedures. Gram;

Fontana silver impregnation; Neisser; Ziehl-Nielsen; Paschen's stain for virus elementary bodies and lastly Giemsa's prolonged staining technique.

From a study of the foregoing methods of staining it will be appreciated that they are comprehensive enough to demonstrate a wide range of pathogenic micro-organisms as well as large cellular elements.

Conclusion.—About one hundred microscopic preparations were scrutinized closely but they failed to reveal any significant constant differences between the bacteriological constituents of bile obtained from cases of infective hepatitis on the one hand and normal (control) bile on the other.

A search was conducted for virus bodies but none were found. In the absence of a susceptible experimental animal, such a procedure becomes very difficult because suspicious particles of organized matter or other structures noticed cannot be associated with the disease.

Cytology of Bile.

Special attention was paid to the results of investigations on bile originating from patients whose stools were either clay-coloured or alternatively the colour of which had returned to normal for a day or two.

On each occasion the centrifugalized deposit contained relatively scanty lymphocytes, polymorphs and amorphous granular debris which predominated in the field. Indeed, there was no difference between the pathological and normal specimens. Consequently, there was nothing to suggest the existence of inflammation of the columnar epithelial lining of the large bile canaliculi.

Collectively, bile from eleven selected cases of infective hepatitis was examined but in no instance was there evidence of biliary catarrh. It may well be that owing to the necrotic action of bile a large number of cells are destroyed but this fails to account for the absence of inflammatory cells in the acute phase of the disease.

Examination of Gastric Contents.

The fasting gastric juice was examined in thirty-six cases. Samples were removed during the first few days of jaundice and later during convalescence when icterus had practically disappeared. Nine cases showed achlorhydria at the commencement of illness with the return of free acid during convalescence. On the other hand twenty-five cases showed variations in the amount of free acid of not more than 10 c.c. of N/10 HCl.

Likewise the amount of mucus at different stages of the disease lay within normal limits.

Proof of gastric catarrh was lacking but gastroscopy would be necessary to confirm this finding.

Conclusion.—We have found no evidence of biliary or gastric catarrh to support the contention that jaundice is caused by obstruction. Infective hepatitis as studied by us appears to be due to a toxic process affecting primarily the liver parenchymal cell, resulting in reduction of biliary secretion.

This loss of function of the bile-secreting mechanism may be adequate to explain the occurrence of jaundice.

Animal Inoculation Experiments.

Bile and *stomach washings* were secured from ten cases and animals were fed with large volumes of each specimen.

Mice, white rats, jerboas, rabbits, guinea-pigs, monkeys (*Lasiopyga grisevirdis* or *Cercopithecus æthiopis*), Abyssinian baboons (*Papio hamadryas*), a young *pig* and three *kittens* were employed.

Blood, containing 1 per cent sodium citrate, was withdrawn from twenty proved cases of infective hepatitis during the febrile, pre-icteric and early icteric phase of the illness. It was introduced in each of the above-mentioned animals by one or other of the following routes—subcutaneously, intravenously, intraperitoneally, intracerebrally, intratesticularly and intracorneally. The animals were maintained under observation for six to eight weeks and subsequently discarded. No definite results were forthcoming. There is one point worth mentioning, which may constitute a source of error, in connexion with animal inoculation tests with blood obtained from cases of infective hepatitis. On four separate occasions it was noticed that mice and rabbits, injected intracerebrally and intraperitoneally, died three to seven days later. Saline emulsions of liver, brain and spleen were promptly prepared from such animals, examined aerobically and anaerobically for bacteria, and passaged to fresh stock, but the latter remained unaffected. At first the effect was difficult to interpret but it now seems likely that death of the animals was attributable to traces of bile salts, pigments and toxic substances in patient's blood. It is well known that formed bile (whether normal or pathological) when injected into skin or other organs is an intensely necrotic substance. Its dermo-necrotic effect can be demonstrated in the rabbit by injecting 0·2 c.c. of normal bile intradermally. We also noticed that if 0·3 c.c. of serum from a deeply jaundiced patient was injected subcutaneously in a rabbit an area of localized erythema developed after twenty-four hours and rapidly disappeared without necrosis.

Consequently apparent initial positive animal inoculation results should be accepted with reserve and a second passage attempted before drawing any conclusions.

One young *pig* about 6 weeks old was injected intraperitoneally with 25 c.c. of blood from two early cases of infective hepatitis, forcibly fed with pooled stomach washings of twenty-three different cases, and inoculated intraperitoneally with 100 c.c. of a Seitz filtrate of stomach washings from three additional cases of infective hepatitis. The animal was kept under observation for three months but remained well and thrived.

Another interesting negative experiment was one in which large volumes of blood from two febrile cases of infective hepatitis were introduced in two large *Abyssinian baboons* but without ill-effect. Each creature received 20 c.c. in the peritoneum, 5 c.c. in the liver and 5 c.c. in the testicles. The

results were negative as far as could be judged. No temperature chart was kept owing to the difficulty in handling such obstreperous beasts.

One *Cercopithecus* monkey was injected in the liver and peritoneum with 10 c.c. of the citrated blood and seven days later a transient rise in temperature occurred which lasted for a week accompanied by slight diarrhœa. No explanation (e.g. monkey malaria) was found to account for the swinging pyrexia and it was assumed that the inoculum was responsible for it.

Similar species of monkeys injected with blood procured from non-infective hepatitis cases did not react in this manner.

Neutralizing tests are required before the specificity of the pyrexia can be claimed. Unfortunately these are beyond the scope of our meagre local facilities; moreover it is dubious if this angle of approach is likely to yield practical results because the monkeys used are either non-susceptible to infective hepatitis or else only feebly so and, as such, are of little use as experimental animals.

It is interesting to recall that Findlay (1940) likewise produced a transient febrile reaction in Rhesus monkeys eleven to fourteen days after feeding them with blood taken from patients during the first seven days of illness.

Animal Histology.—In order that the existence of inapparent infection might not have passed unrecognized a number of mice, jerboas, rats, rabbits and guineapigs were killed from two to six weeks after they had been inoculated with blood or fed with bile and stomach washings and their tissues examined histologically. No lesions were found.

Immunological Experiments.

Since pyrexia often occurs at the onset of infective hepatitis several convalescent sera were tested for the possible presence of agglutinins for *B. proteus* X19, OXK and OX2, *Brucella abortus, melitensis* and *B. paratyphosus* C. Findings were constantly negative.

Yellow Fever Mouse Protection Tests.—Sera from eight convalescent cases of infective hepatitis ranging in duration from two to twelve months were subjected to mouse protection tests by Doctor Mahaffey of the Rockefeller Yellow Fever Research Institute, Entebbe, Uganda. All tests were returned negative; thus virus neutralizing antibodies for yellow fever were absent in infective hepatitis as observed in Egypt. So far as the present epidemic and our studies are concerned the question of jaundice due to yellow fever vaccination does not arise (*see* Findlay *et al.*, 1939).

Histology of Human Liver in Infective Hepatitis.—Despite its high morbidity the mortality rate from infective hepatitis is negligible. Pathologists in the Middle East have kept a sharp lookout for fatal cases and the following is a description of the morbid histological changes found in the liver of a patient who presumably died from an unusually severe attack of the malady.

Major D. T. Stewart, N.Z. General Hospital, provided us with a histological section of liver derived from a fatal case of the disease. The lesions were recently described by himself at the Conference of Pathologists, G.H.Q., M.E., 19.3.42. In brief, the essential features were as follows: Liver parenchyma showed much cloudy swelling and eosinophilic staining with considerable peripheral lobular necrosis. Lymphocytic and plasma cell infiltration was present together with karyorrhexis and karyolysis of liver cell nuclei. The bile canaliculi were distended and contained inspissated bile but there was no sign of inflammation of these channels.

The sections forwarded to one of us were scrutinized for acidophilic intranuclear (Torres) inclusion bodies but none were noticed. Likewise a search for Councilman bodies proved in vain. Dark-field illumination of the section was also negative. The general impression gained was that the appearances of liver from the fatal case of infective hepatitis were unlike that found in yellow fever damage. In conclusion, the histological changes support the observations made in connexion with the cytology of bile in that the essential lesion in the organ is damage to liver-parenchyma cells and not inflammation of bile canaliculi.

Convalescent Serum Therapy.

Convalescent serum was administered to nine selected cases. Serum was derived from six different cases of infective hepatitis four to six weeks after recovery. Prior to use each batch was passed through a Seitz filter, Kahn tested and proved to be bacteriologically sterile.

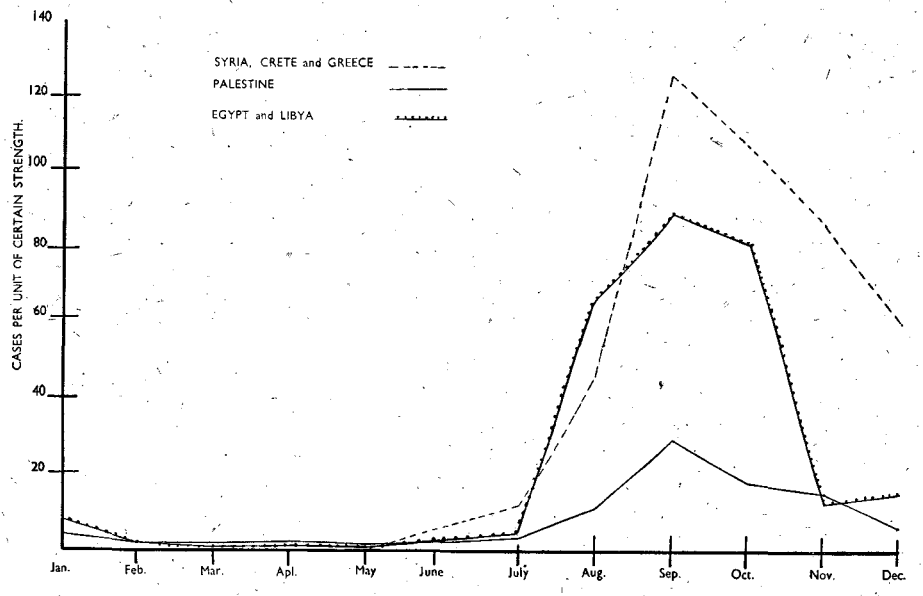
Owing to the difficulty of obtaining patients in the pre-icteric phase of the illness consecutive cases within twelve to twenty-four hours of the onset of jaundice were chosen. Six received 10 c.c. and three cases received 20 c.c. of serum intramuscularly. The icterus index was estimated before the administration of serum and thereafter daily to ascertain whether its exhibition ameliorated the clinical course of the malady.

The results showed that serum failed to control the degree and duration of jaundice. Likewise serum had no effect on the anorexia, nausea and flatulent dyspepsia which were complained of by some patients during the first few days of jaundice. From the above results it appeared to us that human convalescent serum in no way modified the course of the established disease.

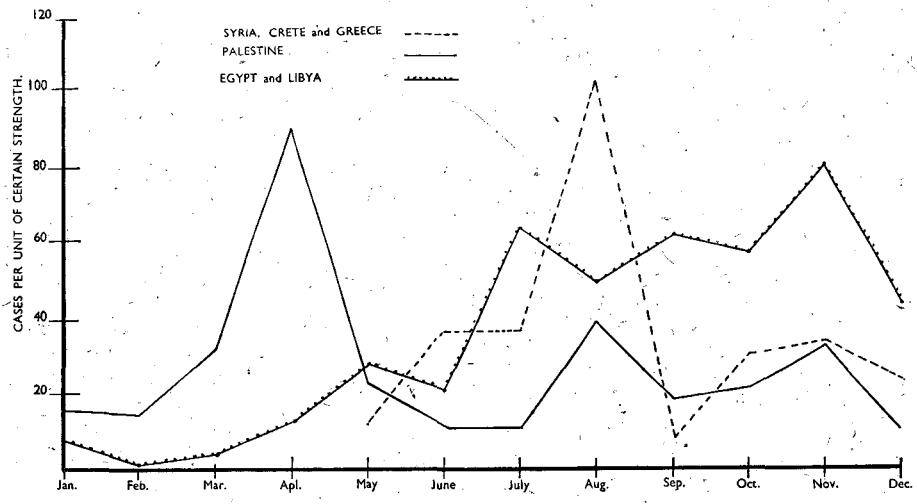
Epidemiology of Infective Hepatitis in a Large Unit of the M.E.F.—Through the courtesy of Colonel N. Hamilton Fairley, Graph I was provided by Lieutenant J. B. Fletcher, Officer Commanding Statistical Subsection Medical History and Information Section, and indicates the numbers of infective hepatitis patients admitted to hospital for a certain force in the Middle East during 1941. Graph II depicts the incidence of dysentery for the same period among the same group of soldiers.

Epidemic jaundice reached the maximum simultaneously in *Syria*, *Crete*, *Greece*, *Palestine*, *Egypt* and *Libya* during the month of September and, in

Syria, Crete and *Greece*, altogether 126 cases per " unit of certain strength," were notified (*see* Graph I). Lieutenant J. B. Fletcher, O.C. Statistical Sub-Section, in his interpretation of Graph II, states that during 1941 the



GRAPH I.



GRAPH II.

peak incidence of dysentery occurred in August for *Greece, Crete* and *Syria*, and in November for *Libya* and *Egypt*. The peak for *Palestine* recorded in April he commented " is I think largely spurious as there were large troop movements at that time and the relationship of the sickness figures for all

theatres does however show a slight peak in April—May." Finally he closed with the remark that "I cannot see any correlation between the incidence of jaundice in September—October and the incidence of any other disease." Neither did the frequency of respiratory infection (as exemplified by pneumonia) shed any light on the problem. The aggregate of pneumonia cases was so small as to make statistical deductions impossible.

Conclusion.—From the statistical data applicable to a large body of troops it was not possible to correlate or otherwise link the 1941 epidemic of infective hepatitis with any other disease or ascertainable obvious factor. There is a remote probability that the dysentery peak in August and jaundice peak a month later in September may be related on the grounds that the incubation period of infective hepatitis is four to five weeks. It is thus conceivable that both dysenteric infection and infective hepatitis were acquired simultaneously during August and disseminated *via* the same mechanism. Unfortunately, coincidence may equally well explain the above result.

Discussion.

Infective hepatitis ranks among the most refractory types of disease amenable to scientific investigations. The long incubation period and the absence of a susceptible laboratory animal together constitute a formidable obstacle to progress in any direction. From clinical evidence, a multiplicity of types of the disease is said to occur. Hurst and Simpson (1934) describe two varieties of catarrhal jaundice, namely epidemic catarrhal jaundice and infective hepatic jaundice, both arising in epidemic form. Lisney (1937) mentions a probable third type, namely simple catarrhal jaundice occurring sporadically. Findlay (1940) also contends that on pathological evidence there are two kinds of epidemic jaundice—true catarrhal or obstructive jaundice and infective hepatitis—but adds that clinically there are no symptoms by which they can be differentiated. The literature contains numerous excellent descriptions of liver lesions found at biopsy and autopsy in cases of infective hepatitis and, for these, the reader is referred to the publications of Morgan and Brown (1927), Findlay and Dunlop (1932), Gaskell (1933), Cullinan (1939), Roholm and Iversen (1939), Findlay *et al.* (1939) and Findlay (1940).

The general non-specific character of the histological picture in infective hepatitis is well epitomized by Cullinan (1939) in the following paragraph: "In true catarrhal jaundice the parenchymal necrosis is mainly in the central zone of the lobule and that obstruction of the bile ducts with cholangitis is a condition which constantly brings about such a central necrosis by pressure alone. With this I agree, but an initial central necrosis is also the outstanding characteristic of primary acute necrosis of the liver where there is no question of obstruction." Thus study of the hepatic morbid histological architecture does not reveal the cause of liver cell damage in infective hepatitis.

Diversity of opinion has also been expressed on the ætiology of infective hepatitis. Hurst (1940) contends that epidemic jaundice occurring in Gallipoli and Mesopotamia during the Great War was obstructive in character and was caused by gastro-duodenal catarrh. The official History of the War. Medical Services. Diseases of the War. Vol. I, contains the following passage:—"The cause of the jaundice in these cases seems to be obstruction in the biliary tract. The symptoms are not usually severe or lasting enough for there to be any involvement of the smaller ducts within the liver and are best explained by swelling of the papilla of Vater as part of a duodenal inflammation due to the localization of infection in the duodenum." In two autopsies Willcox (1922) reported that there was intense catarrh of the duodenum and larger bile ducts and Jones and Minot (1923), from a study of duodenal contents in twenty-six cases of catarrhal jaundice, concluded that jaundice was due to intestinal infection which spread up the biliary tract.

Views contrary to the above have been expressed by Cullinan (1939), Newman (1942) and others, all of whom assert that infective hepatitis or epidemic jaundice is a toxic hepatitis which may appear in sporadic or in epidemic form.

We, too, support the above hypothesis and are in complete agreement with the remark expressed by Lieutenant-Colonel Cullinan (in a personal communication) that infective hepatitis as it now occurs in the Middle East Forces is identical with so-called epidemic and sporadic catarrhal jaundice afflicting civilians in Great Britain.

At present a series of investigations is in course of progress to ascertain the degree of liver damage in cases of infective hepatitis by means of the hippuric acid test. Although the results are incomplete preliminary findings indicate that well-marked liver inefficiency is present. The wider application of this test and other liver efficiency tests should prove helpful in the recognition of liver damage in infective jaundice.

Every endeavour we have made to transmit the condition to laboratory animals has failed and we are reluctantly compelled to resort to speculative reasoning as to its ætiology and mode of propagation. No specific bacterium has been isolated and a search for a virus agent has been unrewarded. From the epidemiological point of view, the position cannot be correlated with any known insect or animal vector and, similarly, water, food and fomites do not seem to be implicated. It is interesting however to recall that the outbreak which occurred at Mount Allison in Canada was due to water borne infection (*see* Fraser, 1931).

Confronted with such a baffling situation there is no alternative but to surmise that the reservoir of infection is man, among whom the disease is disseminated by droplet infection, and that the rapidity with which it spreads throughout a district is more compatible with a virus infection than any other group of pathogenic agent.

The area in which we have worked has been one of active troop movements and, although 180 cases have been treated by one of us, it has been

impossible accurately to trace contacts and to calculate the incubation period. It has been estimated at four to five weeks.

Newman (1942) has suggested that the disease may be perpetuated in man by ambulatory unrecognized cases of infection. We not only concur with his opinion but would go further by stating that at the time of an epidemic in all probability a *very large number* of individuals are exposed to infection and the reaction of each varies according to his susceptibility. Thus a person may develop signs and symptoms ranging from those simulating a mild attack of "influenza," "gastritis" and the like to a typical attack of infective hepatitis. The ambulatory patient may thus harbour the disease and constitute the source of infection to others.

We suspect that numerous abortive cases develop during an epidemic but they are difficult to identify and in all probability never reach hospital. We have seen three such patients whom we diagnosed as cases of infective hepatitis without jaundice and details of them are as follows:

On November 2, 1941, Major G. A. G. M. took ill with retro-ocular headache, malaise, anorexia, marked nausea and vomited once. There was fever of 99° to 101° F., tenderness in the right hypochondrium but no hepatic enlargement; w.b.c. 3,800; polymorphs 63 per cent; lymphocytes 30 per cent; monocytes 5 per cent; eosinophils 1 per cent; basophils 1 per cent; icterus index 9 per cent; plasma cholesterol 110 mgm. per cent. The urine was examined daily and bile salts and pigment were found only once (November 6, 1941). Anorexia and flatulent dyspepsia persisted for fourteen days. The onset of jaundice was confidently anticipated but it did not develop.

In January, 1942, one of us (I. G.) developed malaise, complete anorexia, slight nausea at the sight and smell of food and a feeling of abdominal distension as soon as a few mouthfuls of food were swallowed. On two occasions a temperature of 99° F. was recorded. No biliuria or jaundice developed and recovery occurred in four to five days.

Signalman J. C. was admitted to the jaundice ward for dyspepsia and pes cavus. On the 26th day after admission he developed similar symptoms and slight fever of 99° to 100° F. There was tenderness over the liver but no biliuria or jaundice developed. The icterus index was 11 and the hippuric acid test showed the liver efficiency to be 75 per cent of normal. In five days he had completely recovered.

We have discussed this subject with a number of Regimental Medical Officers who think they too have seen similar types of cases although they have not had any reason to allocate them to this category. Dyspepsia is so common a symptom in the Army that the recognition of the abortive case of infective hepatitis on purely clinical grounds is difficult.

In addition to the symptomatology, which resembles that of the pre-icteric stage of the disease, three tests may be of help. (1) Examination of the urine for the presence of bile and urobilinogen; (2) the intradermal histamine test (*see* Cullinan 1939) and (3) the icterus index. We suggest that investigations on these lines would furnish valuable information concerning the occurrence and numbers of abortive cases, which are of great epidemiological importance.

First it would seem that at the time of an epidemic the exposure rate is very high and a large number of men become exposed to infection. Secondly the reaction of such individuals would depend on their state of immunity. Thus it is quite probable that many would suffer from the customary signs and symptoms experienced during the pre-icteric febrile period of the disease and then recover completely. More receptive persons, on the other hand, after experiencing the systemic phase of the illness may become jaundiced. It may well prove to be that at the peak of an epidemic the disease spreads with great rapidity throughout the military population and that cases showing jaundice represent a fraction of the total number infected. The ratio of immune to non-immune persons also seems to be high. We have watched a patient who was transfused with one pint of blood derived from a donor who developed symptoms of infective hepatitis a few hours after he had been bled. The recipient was kept under observation for two and a half months and he did not develop the disease. Moreover during the recent epidemic in the Middle East although many blood transfusions were given (at the time of the second Libyan campaign) we only know of two cases which may conceivably have contracted jaundice as the result of having received blood from donors in the incubation stage of the disease. Therefore our opinion is that the risk of the disease being transferred by transfusion is negligible—and is as small as the chance of transmitting any other infective condition by the same means.

Convalescent serum has not convinced us that it is of therapeutic value in dealing with the established disease and further work on this aspect of the problem may well be directed towards prophylactic measures.

With regard to other measures little else can be advocated. Much remains to be discovered and, pending such time as controlled human volunteer or positive animal transmission experiments are instituted, the outlook seems bleak.

Conclusions.

(1) So far, every effort to find a specific bacterium or virus entity in the blood, bile and stomach washings from cases of infective hepatitis has failed.

(2) Despite determined efforts to discover a susceptible experimental animal none has been found.

(3) Infective hepatitis as observed by us in the M.E.F. is essentially a benign illness which may or may not be followed by jaundice.

(4) In cases showing jaundice we have found no indications of obstruction or catarrh of the bile passages and therefore consider that the associated jaundice is toxic in character and primarily due to damage of the liver parenchymal cell.

Acknowledgments.

We take this opportunity of expressing our gratitude to Dr. R. P. Wilson and Dr. J. O. W. Bland of the Memorial Ophthalmic Laboratory, Giza, for their great hospitality and the facilities which they so cheerfully placed at

our disposal, and also to Colonel H. D. F. Brand for his permission to publish this paper and Brigadier W. D. Small and Colonel J. S. K. Boyd for their interest and helpful encouragement.

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