AN EPIDEMIC OF SERUM HEPATITIS STUDIED UNDER CONTROLLED CONDITIONS

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Nearly fourteen years have passed since the epidemic of hepatitis described in this report. It seems unlikely that the circumstances of this epidemic, with the unique opportunities for studying many patients who developed serum hepatitis under controlled conditions, will be reproduced. Therefore, despite the lapse of years, this report may seem timely.

In the late fall of 1945 there was an epidemic of influenza in Cleveland, Ohio. In December of that year, a study of the efficacy of influenza vaccine, given during the epidemic, was organized at a U.S. Naval Installation, the Field Branch, Bureau of Supplies and Accounts, in that city.

The average military population at the Field Branch at that time was 2742, but approximately 30% of the personnel were on evening or night duty or on liberty or leave at the time of vaccination. Therefore, a total of 1951 officers and enlisted personnel was included in the influenza study. On December 3, 1017 subjects, selected at random, were each given 1.0 ml. of influenza vaccine. An additional 934 randomly selected control subjects each received 1.0 ml. of control material by the subcutaneous route. One hundred eighty-four of them each received 1 ml. of distilled water as such. The remaining 750 unidentified members of the control group each received 1.0 ml. of distilled water containing 0.03 ml. of human plasma. That is, approximately 80% of the influenza control group received the human plasma subcutaneously. The lyophilized plasma had been prepared commercially, and was obtained from the stores of the Crile General Hospital. No record of the producer or the lot number was available. All the injections were given in six different lines. The same syringes were used repeatedly but a freshly autoclaved needle was used for each injection. All individuals in both the vaccinated and control groups were carefully followed for respiratory infection throughout the following 38 days and this study was reported to the Chief of the Bureau of Medicine and Surgery in February, 1946.

The Epidemic of Hepatitis

The present report concerns an epidemic of hepatitis which commenced amongst personnel of the Field Branch on January 15, 1946, 43 days after the influenza vaccine and the plasma-containing control material were

inoculated. During the 82 day course of the epidemic, a total of 543 patients were examined at sick call. Three hundred twenty-eight were in the influenza control group. Presumably, 80% or 262 of these had been inoculated with plasma. Hepatitis was actually diagnosed in 272. One hundred sixty-seven patients who had not received the influenza control injection were also examined. Ninety-four had received influenza vaccine and 73 were uninoculated. The diagnosis of hepatitis was established in 30 or 18% of this group.

The time of the onset of symptoms in the 302 cases of hepatitis is shown in Figure 1. The incubation period following plasma inoculation varied from 43 to 125 days and averaged 79 days. In addition, during the 23 days from March 7 through March 29, the liver function of 128 individuals who had not presented at sick call, but who were known to have received the influenza control injection was tested, at the time of their separation from the unit. Forty of these or 31.3% were found to have abnormal liver function; the serum bilirubin was elevated to 1.4 mgm. % or more in 10, and the thymol turbidity was above 7 Shank-Hoagland units in 37 instances. Six of these subjects were frankly jaundiced at the time of screening, with serum bilirubin from 2.0–7.2 mg. %. Twelve admitted to symptoms typical of hepatitis. None of these 40 cases were hospitalized or included in this study.

As shown in Figure 2, personnel were being detached from the unit throughout the entire epidemic period. At the time the first case of hepatitis developed, 43 days after vaccination, only 583 (77%) of the plasma-inocu-

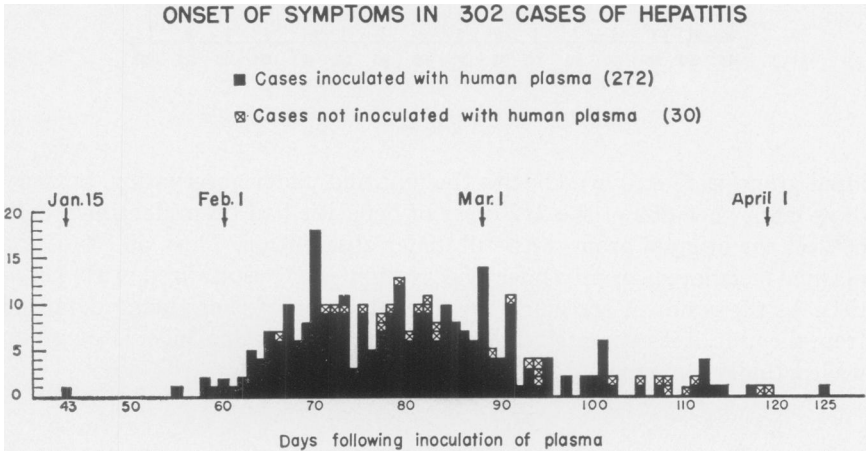

FIG. 1

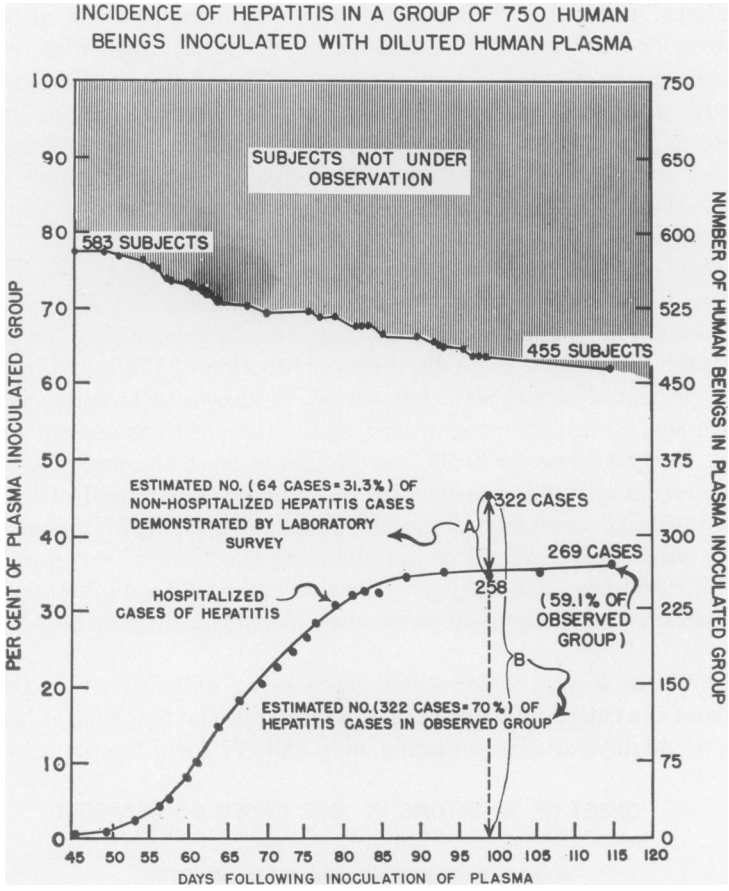

FIG. 2

lated group were still attached to the unit and under observation. Seventy days later when 269 of the 272 cases of hepatitis had been identified, only 60% of the original group was still under observation. Thus, 59.1% of the plasma-inoculated group under observation was hospitalized with hepatitis. As the result of screening the liver function of those being detached from the unit, it is estimated that 70% of the total plasma-inoculated group was actually infected.

Method of Study

The authors first arrived at the Bureau of Supplies and Accounts on February 13, 1946, and remained until the end of the hepatitis epidemic. At the time of arrival, 19 patients had been hospitalized with hepatitis. A

standard procedure was adopted for the diagnosis and study of each patient. Every person reporting to sick-call during the entire epidemic period was examined, and for uniformity, a check list of data concerning epidemiological facts, symptoms and physical signs was followed. The level of serium bilirubin[1] and thymol turbidity[2] was determined in each instance. In some cases where the diagnosis was uncertain bromsulphthalein retention[3] was also measured.

A large sick bay was prepared in a nearby hotel and all patients in whom the diagnosis of hepatitis was strongly suspected or established were admitted to this sick bay for treatment, or to the Crile General Hospital. Many of the patients were subsequently transferred to the Great Lakes Naval Hospital, Chicago, Illinois. Each patient was examined at frequent intervals throughout his illness, and liver function tests were repeated at approximately weekly intervals. Hospitalization was continued until the patient was symptomatically well and until liver function, as estimated by the selected tests, had returned to normal. The patient was then granted two weeks sick leave, re-examined and the liver function reevaluated before he returned to active duty. Hepatitis was diagnosed in all patients who reported to sick call with definite symptoms and signs of the disease and who had abnormal liver function. All the patients recovered from the acute attack of hepatitis and were ultimately returned to active duty or detached from the service with liver function apparently normal.

The Epidemic Population

On January 15, 1946, when the epidemic of hepatitis commenced, the military population of the Field Branch was 2389. One hundred sixteen were officers and 2273 were enlisted personnel; 1482 were men and 907 were women. In addition, there were 1454 civilians, 136 being men and 1318 women. None of the civilians participated in the influenza study or were checked for hepatitis.

The male officers and enlisted personnel and the civilians lived throughout the city in private homes, hotels and rooming houses and ate at home or in a large number of restaurants. All of the enlisted women and many of the female officers lived and obtained most of their meals in a large hotel near the Field Branch. There was intimate contact at work and play between the naval personnel who were inoculated with the plasma-containing control material and those who had received influenza vaccine or were uninoculated.

Value of Liver Function Tests for Early Diagnosis of Hepatitis

In Table I the ten most common presenting symptoms of the 302 patients with hepatitis are compared with their ultimate symptomatology

TABLE I

Ten Commonest Symptoms of 302 Patients with Hepatitis and 241 Patients without Hepatitis

Hepatitis (302)				Non-Hepatitis (241) Presenting	
Presenting		Final			
Symptoms	%	Symptoms	%	Symptoms	%
Anorexia	44.5	Dark urine	81.0	Nausea	61.8
Fatigue	26.2	Jaundice	79.4	Anorexia	58.5
Nausea	26.1	Nausea	77.8	Fatigue	50.0
Dark urine	21.7	Anorexia	75.4	Headache	43.6
Hives	15.1	Fatigue	66.5	Abd. pain	38.2
Vomiting	10.3	Abd. pain	48.3	Vomiting	32.8
Arthralgia	8.1	Headache	48.3	Chills/fever	29.5
Headache	7.7	Vomiting	40.2	Diarrhea	24.9
Pruritis	7.3	Back ache	33.7	Coryza	24.1
Rash	4.1	Pruritis	31.7	Back ache	20.0

and with the symptoms of the 241 additional patients who presented at sick call during the epidemic but did not have hepatitis. It is noteworthy that jaundice and abdominal pain were not common early symptoms of hepatitis and the presenting symptoms were usually not specific or diagnostic. Certain symptoms of an allergic nature, namely hives, arthralgia, and rash were common early symptoms in this epidemic. Chills, fever, diarrhea and coryza were common symptoms only in the non-hepatitis group. Probably the most striking clinical difference between the two groups of patients was that the symptoms in the non-hepatitis group, excluding a few individuals with some chronic illness, were of short duration, only a few days, while in the hepatitis group the disease was protracted for a number of weeks.

The value of liver function tests in establishing an early diagnosis in these patients is illustrated in Figure 3. The first serum specimen was obtained before the 7th day of disease in 63.5% of the patients and before the 14th day in an additional 23.7%. The serum bilirubin was over 1.5 mg. per cent in 72.8% of these early specimens and the thymol turbidity was more than 6 Shank-Hoagland units in 91.3%. Both tests were positive in 63.8% and both were negative in only 1.9%.

Non-icteric Hepatitis

That some patients with hepatitis may never develop jaundice is well recognized.[4, 5, 6] Almost all cases in children in some epidemics are non-icteric and it has been estimated that 50% of adult cases do not develop

jaundice. In the present epidemic, hepatitis without jaundice was diagnosed in 43 cases or 21.2% of the total 203 cases.

It can be seen in Table II that the disease was essentially the same in these two groups except for the presence or absence of jaundice. The allergic symptoms were a little more prominent in the non-icteric group. It is interesting that pruritis was nearly equal in the two groups and that bradycardia (pulse below 60) was also often observed in the absence of icterus.

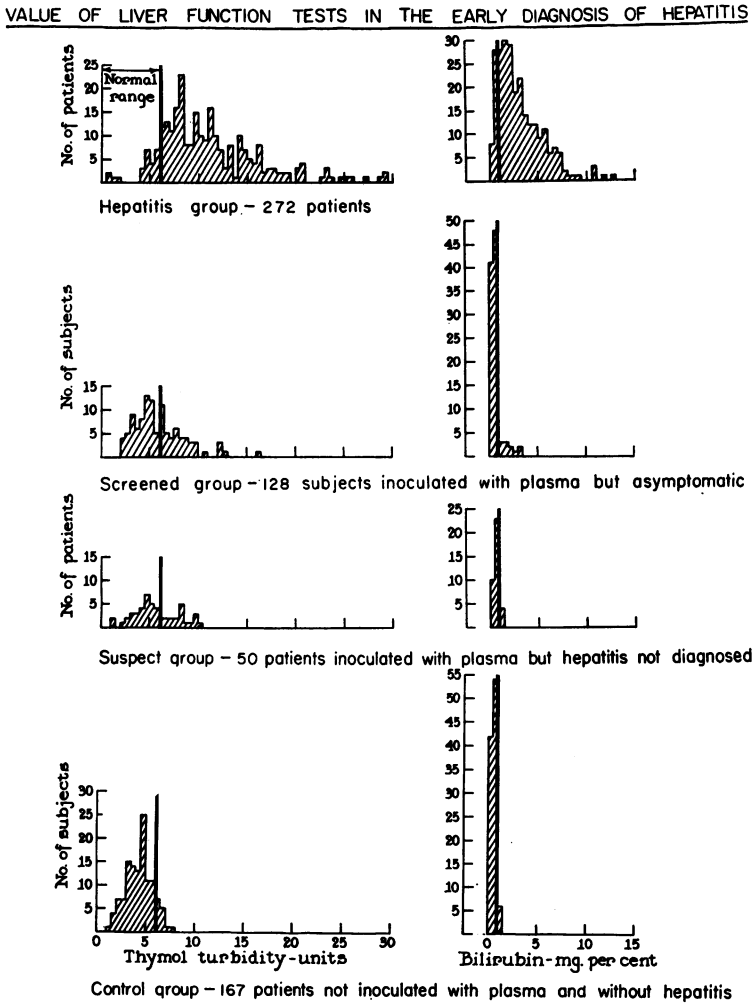

FIG. 3

TABLE II

Comparison of the 10 Commonest Symptoms of 43 Non-Icteric and 259 Icteric Patients with Hepatitis

Non-Icteric		Icteric	
	%		%
Symptoms		Symptoms	
Nausea	81.4	Jaundice	100.0
Fatigue	69.8	Dark urine	90.7
Anorexia	65.1	Nausea	77.2
Dark urine	55.8	Anorexia	77.2
Headache	46.5	Fatigue	66.0
Abdominal pain	44.2	Abdominal pain	49.0
Vomiting	39.5	Headache	42.9
Pruritis	39.5	Vomiting	40.5
Arthralgia	37.9	Back ache	34.7
Hives	32.5	Pruritis	34.4
Sign		Sign	
Icterus	0.0	Icterus	100.0
Hepatomegaly	69.8	Hepatomegaly	79.1
Hepatic tenderness	62.8	Hepatic tenderness	59.0
Bradycardia	18.6	Bradycardia	31.6
Splenomegaly	2.3	Splenomegaly	12.8
Petechiae	2.3	Petechiae	12.8
Spider angiomata	9.3	Spider angiomata	7.7

Figure 4 illustrates the serial liver function tests in 20 of these non-icteric patients. It is seen that in some instances the illness was protracted. However, as shown in Figure 5, the non-icteric disease was, on the whole, of shorter duration than when icterus was present. It is interesting that more women had non-icteric hepatitis than men. There were 29 females in this group and 14 males, or a ratio of 2.1 to 1. In the icteric group, there were 101 females and 158 males, or a ratio of 0.57 to 1. In the influenza control group, 80% of whom received the plasma inoculation, there were 421 females and 513 males, or a ratio of .82 to 1. These differences are highly significant; $p = <0.001$.

"Contact" Cases

As mentioned above, 30 cases of hepatitis were diagnosed in the personnel of the Field Branch who had not been inoculated with icteriogenic plasma. Fifteen occurred in the group of 1017 individuals who had received the influenza vaccine and 15 in the group of 791 individuals who had received no inoculation. Since only about 60% of the 1808 individuals not inoculated with plasma were still attached to the unit at the close of the

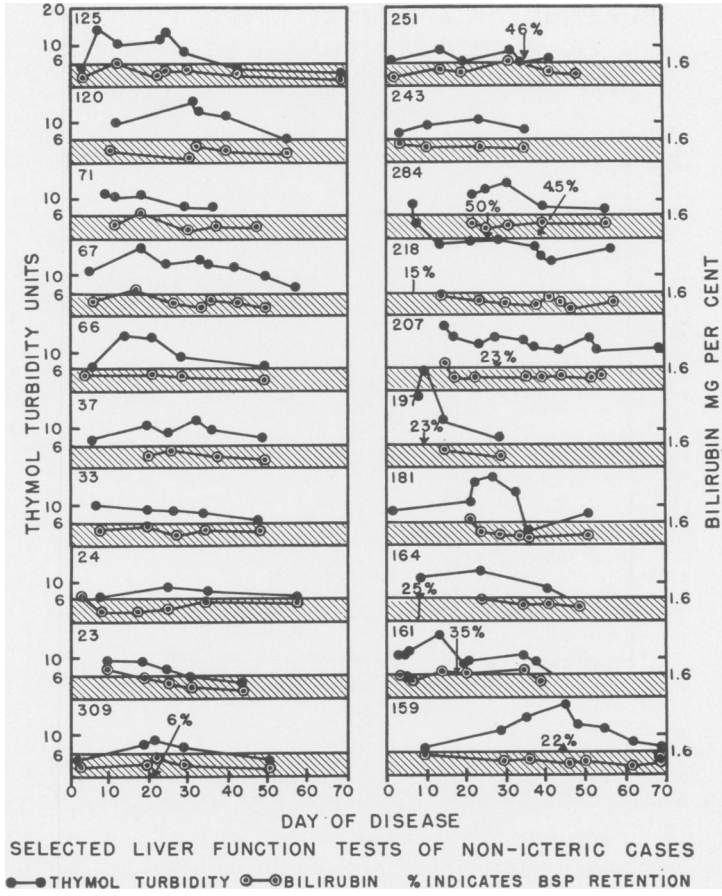

FIG. 4

hepatitis study (Fig. 2), this represents an attack rate of 2.8% in the observed uninoculated group. It was shown (Fig. 1) that these cases of hepatitis tended to occur toward the end of the epidemic. Their average incubation period after the date of vaccination was 90 days as compared with 78 days in the plasma inoculated group. The symptoms of over two thirds of these patients began after the 79 day average incubation period of the whole epidemic.

No hepatitis had been recognized in the personnel of the Field Branch during the three preceding years. There was no increased incidence of hepatitis in the civilian population of Cleveland at the time of or preceeding the epidemic. The plasma-inoculated and other naval personnel of

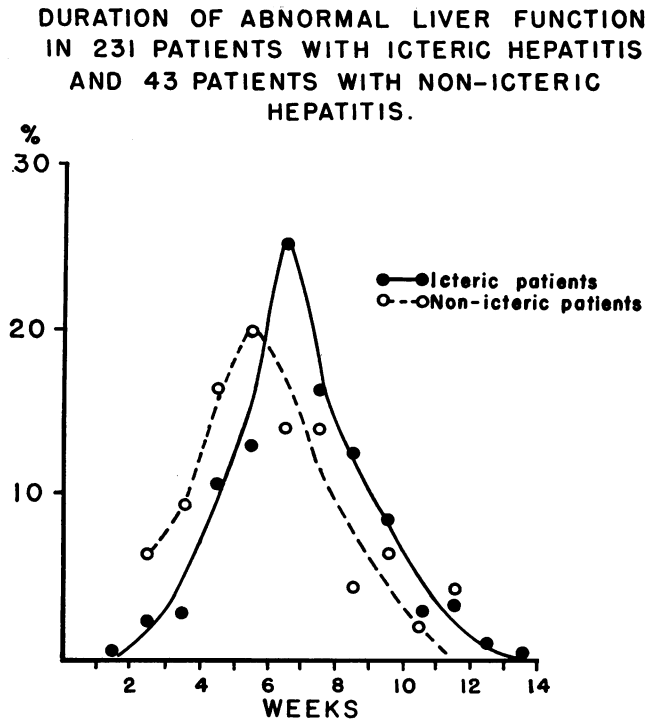

FIG. 5

the Field Branch were in intimate contact both at work and, in general, in their living conditions. Five had room mates with hepatitis, eight had known close contact with patients who developed hepatitis. The other 17 denied known close contact but each worked in a unit with a number of patients with the disease.

Jaundice was present in 80% of the plasma-inoculated and in 70% of the "contact" cases and in other respects the disease was indistinguishable. Fever was rarely observed in either group.

In 1942 Hawley et al[7] reported an epidemic of hepatitis in soldiers who had been inoculated with mumps-immune human plasma. That epidemic was characterized too by a high incidence (42.5%) of allergic symptoms. It can be seen in Table III that in our epidemic these symptoms were about equally common in the plasma-inoculated and "contact" patients with hepatitis and more common than in the 241 patients without hepatitis. This suggests that the "contact" patients were infected by the strain of hepatitis virus which was in the plasma. It is of interest that a comparable incidence of allergic symptoms was present in the plasma-inoculated group without hepatitis suggesting a possible sub-clinical infection in this group.

TABLE III

Allergic Symptoms

Group	Plasma Inocul.	Total No.	Total	% Allergic Symptoms			
				Arthralgia	Hives	Rash	A.E.*
Hepatitis	+	272	50.0	24.6	20.9	14	4.4
Hepatitis	0	30	46.6	30.0	10.00	15	3.3
Total		302	49.6	28.5	20.0	13.9	4.3
Non-hepatitis	+	56	48.2	26.8	25.0	3.5	7.1
Non-hepatitis	0	185	30.0	15.6	9.7	9.7	1.1
Total		241	38.8	18.3	13.3	8.3	2.4

* A.E. = Angioneurotic Edema

For these reasons then, the late appearance in the epidemic of hepatitis in uninoculated individuals, the absence of previous hepatitis at the unit, and the similarity of the disease in the two groups, it is thought that the hepatitis in uninoculated persons resulted from their close contact with those who had been inoculated with the icterogenic plasma.

The Influence of Respiratory Infections during the Incubation Period on the Incidence of Hepatitis

As previously stated, a careful study was made of the incidence and nature of the respiratory infections which occurred in the influenza control group of patients as well as in those vaccinated against influenza during the 38 days following vaccination. Thus, it is possible to evaluate any possible effect respiratory infection in the incubation period might have had on the subsequent development of hepatitis in individuals inoculated with hepatitis virus. Two hundred fifty-five of the 934 influenza-control patients developed respiratory infections during this 38 day period. Ninety-three cases of hepatitis were subsequently diagnosed in this group, or an incidence of 36.4%. Forty-four of these 93 patients had influenza, 30 rhinitis, 16 pharyngitis and 3 bronchitis. In the group of 679 influenza-control patients who remained free of respiratory infection, hepatitis was subsequently diagnosed in 179, or an incidence of 26.3%. When analyzed by the X^2 test, it is found that these differences are highly significant ($p = <0.003$). This strongly suggests that the occurrence of some respiratory infection during the incubation period of hepatitis may potentiate the latter disease. An alternate hypothesis is that these individuals were inherently more susceptible to all infections, but nothing in their medical histories supported this idea.

The duration of abnormal liver function of 216 patients with hepatitis, where sufficient data were present to determine this point with some ac-

curacy, was compared with the occurrence of respiratory infection in the incubation period. Only 27.6% of the 181 patients whose liver function had returned to normal by the ninth week of disease had respiratory infections during the incubation period of the hepatitis, whereas 48.6% of 35 patients with more protracted hepatitis had been so infected. This suggests that the severity of the hepatitis as well as its incidence was enhanced by the preceding infection.

Discussion

The epidemic of hepatitis described, with a long incubation period (average 79 days) is typical of serum hepatitis. The circumstances of this epidemic in a mixed urban population, part of which had been inoculated with human plasma as a part of a controlled study of influenza vaccine, allowed comparison which has not usually been possible in other epidemics. Plasma-inoculated individuals could be compared with uninoculated controls; differences between icteric and non-icteric patients could be noted; male and female patients could be contrasted; and finally, the possible influence of intercurrent infection in the incubation period of hepatitis could be evaluated. Serum hepatitis is usually considered to be different clinically, immunologically and epidemiologically from infectious hepatitis. Some skepticism concerning the validity of these differences has been expressed.[8] Some observations made in the present epidemic, which most will agree is serum hepatitis, tend to support this skepticism. The argument has been presented that secondary cases due to contact occurred in the present epidemic. Similar observations have been made by others.[9-14] This implies that the serum hepatitis virus must have been shed at some time during the course of the infection. This is contrary to the evidence obtained from experiments in volunteers[15] but these experiments have, of necessity, been limited.

Fox et al[16] indicated that some unknown factor or factors possibly dietary toxins may influence the occurrence of hepatitis in plasma inoculated individuals. Havens[17] has shown that concurrent salmonella infection may greatly enhance the severity of hepatitis. There is evidence that malnutrition also increases susceptibility to hepatitis and the enhanced severity of hepatitis in pregnant women is well recognized.[18-20] The circumstances under which the present epidemic was studied made it possible to demonstrate that respiratory infection during the incubation period of hepatitis increased the incidence and the severity of the latter disease. Since several types of respiratory infection were involved, it seems probable that this effect was non-specific and merely represents a stressful situation. The adrenal cortico-steroids, which may be beneficial in treating established hepatitis,[21] have been shown to increase susceptibility to most virus infections if administered during the incubation period.[22] It is therefore not

surprising that stress in the incubation period should be found to enhance hepatitis.

Summary

1. An epidemic of hepatitis was studied in 272 (36.3%) of 750 individuals who had been inoculated with human plasma. It is estimated that actually 70% of the plasma inoculated group was infected. The incubation period varied from 49–125 days and averaged 79 days.

2. Thirty additional cases of hepatitis occurred amongst 167 patients who were examined at sick call and had not been inoculated with plasma. This represents 2.8% of the entire uninoculated group under observation throughout the epidemic. These patients had been in intimate contact with the plasma-inoculated personnel throughout the incubation period and the epidemic of hepatitis. They are thought to be secondary cases due to this contact because: they occurred toward the end of the epidemic; there had been no previous hepatitis in the environment and because of the clinical similarity of the two groups of patients.

3. Forty-three or (14.2%) of the 302 patients with hepatitis did not develop icterus. Non-icteric hepatitis resembled the icteric disease in all other respects except that it was, on the whole, somewhat less protracted. Women outnumbered men two to one in this non-icteric group, whereas the ratio of women to men was only 0.57 to 1 in the icteric cases and was 0.82/1 in the population studied. This difference is significant; $p = <0.001$.

4. Two hundred forty-one control patients without hepatitis were also studied. The symptoms of these patients resembled the presenting symptoms of hepatitis. Liver function tests were of great value in making an early diagnosis of hepatitis. The thymol turbidity was elevated in 91.3% of the first serum specimens obtained from the patients with hepatitis, and the serum bilirubin in 72.8%. Sixty-three and one half per cent of these sera were obtained before the seventh day, additional 23.7% before the fourteenth day of disease.

5. The incidence of hepatitis was 36.4% in 255 observed individuals who had been inoculated with the influenza-control material and developed a respiratory infection during the incubtaion period of hepatitis, and 26.3% in 679 observed individuals who had received the influenza-control injection and remained free of respiratory infection. This difference is statistically significant and suggests that non-specific stress in the incubation period may influence the incidence of this disease. The hepatitis was also more protracted in the former group.

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DISCUSSION

DR. DANIEL S. ELLIS (Boston): Dr. Mirick, I wonder if you have had the opportunity to do any late follow-up study on this group and if so, what is the incidence of residual liver disease at this time?

DR. MIRICK: I did try, Dr. Ellis, five years after the close of the study. All these patients had been demobilized. Most of the women had married. I found out that only

about 70 per cent of my letters ever reached their destination even though registered letters were sent. The replies I got, about 12 per cent, stated that they had symptoms that suggested they had chronic disease. As I remember, more women had these symptoms than men.

This is a pretty hard thing to analyze, though. I followed five of the officers who were stationed near Washington and had come over for a check-up at Hopkins. One of them had persistent hyperbilirubinemia, but no symptoms. None of the other four had anything.

I got a very interesting letter, however, from Dr. Patek, of Cleveland, five years after, who told me that one of these officers, that I had been following and had found perfectly well two years before, had had a replapse, a very mild one, at which time his wife contracted hepatitis. He recovered from this and about six months later, having in the meantime changed wives, his second wife developed hepatitis. This might mean either one of two things depending on which school of thought you are in. To Dr. Patek it meant that this is evidence that serum hepatitis is a different disease, that you can catch it and then have infectious hepatitis. It might, however, mean, that the patient had had a relapse, and be a further evidence that this was a contagious strain of virus that we had.

DR. LEMUEL C. MCGEE (Wilmington, Delaware): Did you go back to see if he was a so-called contact? In other words, did you go back to see if it was infectious hepatitis?

DR. MIRICK: Yes, he was not. He had gotten the injection.

One, there hadn't been any hepatitis there. There weren't any new people added to the unit. There was no increased hepatitis in Cleveland at the time. They occurred late in the epidemic, stopped at the time of the rest of the epidemic and the disease clinically in the 30 patients was not like viral hepatitis is usually described, that is, there was no fever. It began insidiously and had this high percentage of allergic symptoms, which made it seem to be the same strain of virus and I have thought, and Dr. Shank has thought, that this is another bit of evidence that the disease can be spread by contact.

There are six good examples of this in the literature, which are, for some reason, usually suppressed by the people who write on the subject. This is not an unusual occurrence, not at all.

DR. WATSON (Minneapolis): I think that point Dr. Mirick brought out is of great interest, because, as he just said, there is a widespread impression that Virus B cannot be transferred except by direct inoculation.

One point in this connection is always interesting to me. There is a superb report I think in 1882—in the 1880's—by a man named Learmont, who had a very large epidemic of what was undoubtedly serum hepatitis transmitted by vaccination with human lymph. It was well contained. There was no hepatitis in the surrounding country, nor even in the members of the families. These were all individuals in a very large industry who had been vaccinated in the plant. I think he had something like 300 patients with hepatitis and they all had a long incubation period, just about the same as you showed, so that it does appear, and even long before there was any use of blood transfusions. Certainly long before there was any widespread use of inoculation, this type of disease could and did exist, so this raises the question of how the virus gets into the body to begin with and it certainly does make one wonder whether it cannot be transferred from individual to individual. At the same time it seems to me that there has been no direct evidence of this by a feeding of known infected serum to volunteers. If I am not correct about this I hope that you will correct me.

There was one other point that I wanted to comment on and that is the relativity of

this business of non-icteric hepatitis. There are two rather important aspects of this. We have found that in all of the cases of non-icteric hepatitis that we have studied if we can get them early enough we find bile in the urine. Furthermore we find that there is invariably a distinct, although sometimes only mild, increase in the conjugated bilirubin.

It is interesting from an historical point of view that Dr. George Budd in his really classical work in 1846, "Diseases of the Liver," undoubtedly described what were the first recognized cases of hepatitis without jaundice, although he didn't call it hepatitis, but I am sure that that was what he was dealing with. These were individuals who became sick and who had all of the manifestations of hepatitis clinically but who never became jaundiced, but he noticed that the urine became dark if tested for bilirubin, if bilirubin was present, and he postulated that these individuals were able to excrete this bilirubin so rapidly that they never became jaundiced.

DR. WINKENWERDER (Baltimore): I would like to ask about the possibility of differentiating what has been known about jaundice of hepatitis versus your serum jaundice. During the war, for instance, in the Southern Pacific, we suddenly had a series of officers and nurses come down with acute hepatitis, a variable degree of fever, sometimes very high. In some of these individuals the total length of the disease was very short and all of them recovered very quickly. Soon thereafter we then ran into cases of serum hepatitis, which ran a much more prolonged course and I think much more serious and some of them became exceedingly severe and went into chronic forms.

In your slides here I didn't notice—I may have overlooked it—whether you included fever in your group of clinical characteristics, whether there is any way in which one can distinguish an individual with hepatitis and acute jaundice, whether it is jaundice of the old-fashioned type or whether it is serum-inoculated jaundice.

DR. MIRICK: Dr. Winkenwerder, we questioned all the patients for fever and took the temperature on all of them we found and characteristically this was very minimal or absent, not over 100 degrees in any one and it was not a symptom. That is why it didn't appear on the list. This is one of the reasons I think they were the same strain of virus.

As to Dr. Watson's remarks, I think you will remember that the complaint of dark urine was quite high on the non-icteric list. I think it was the fourth commonest symptom, even though we didn't examine the urine at that time, and I think it confirms what you have just said. It was the second commonest symptom in the icteric group and the fourth commonest in the non-icteric, even though they did not have jaundice.

There was another point you made, about the negative tests in volunteers. These have been limited to tests of faeces from SH patients or Virus B patients, and the sample tested was collected about the last ten days in the incubation period.

Now, in the present group, if you remember, the average incubation period in the inoculated patients was 79 days and that in the non-inoculated was only slightly longer, about 90-some days, which would, if we can speculate very freely, perhaps indicate that, if the virus is shed, this occurred in the first ten days after infection and that maybe the wrong type of sample has been tested in the past.

DR. WINKENWERDER: May I remind Dr. Mirick that he didn't answer my question whether or not you can differentiate between the two types of jaundice, or hepatitis.

DR. MIRICK: Whether you can differentiate between them? I don't think I can. Clinically and pathologically they are indistinguishable.