

ACUTE HEPATITIS

I. A STATISTICAL ANALYSIS OF 462 CASES OBSERVED DURING THE PAST TEN YEARS

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The early "catarrhal" concept of Virchow for the pathogenesis of this disease has been altered, and the terms "catarrhal jaundice", "infectious hepatitis", "hepatitis epidemica" and "acute yellow atrophy of the liver" seem to have been identified as descriptive appellations of a single disease entity¹⁾.

Because of the relative paucity of reports referring to the epidemiology, geographic distribution and seasonal relationship of this disease in our country, it seems justified to study the patients observed at our clinic during the past ten years which included two apparent epidemics. Despite the fact that many epidemics had been studied²⁾ during and after the First World War in the occidental countries, it is quite recently that the infectious character of this disease has attracted attention in Japan. Unfortunately, infectious hepatitis has not been required to be reported to public health authorities in most countries, Japan being no exception, and the only material available for statistical study is the clinical records made at medical clinics.

METHOD OF INVESTIGATION

The clinical charts of individual cases of infectious hepatitis observed from Jan. 1, 1943 to Dec. 31, 1952 inclusive were taken as material for statistical analysis, and specific cards designated for this survey were employed since Sept., 1951 for extensive clinical studies.

The criteria for diagnosis of infectious hepatitis were as follows: (1) Lack of previous or present history and clinical findings contributory to the diagnosis of obstructive jaundice such as cholelithiasis, parasitic diseases of the liver and the bile ducts, etc., (2) jaundice of comparatively short duration with somewhat acute onset, (3) lack of clinical and laboratory data supporting the possibility of other infections with jaundice as a clinical manifestation, such as leukocytosis, positive reaction for syphilis, enlargement of the gall-bladder, etc., and (4) lack of detectable cause of intoxication which could result in toxic hepatitis.

Notwithstanding these criteria, it is sometimes difficult to differentiate benign obstructive jaundice from this condition in older ages. Although there must have been not a few inapparent cases besides the apparent ones, none of the former was included in the case number except during the epidemic from Sept., 1951 to July, 1952.

RESULTS

AGE AND SEX. The rough incidence of the disease among the groups of the patients older than 13 is tabulated in Table I, which indicates that young adults up to thirty are very susceptible, and the age incidence decreases as the age advances. The oldest patient was a 79 year old man.

As regards the incidence in both sexes, the number of the male patients made up to 64.6 per cent of the total, a rate somewhat two times as great as the female, and this difference—a significant difference as examined by the level of significance of 0.01—is too great to consider to be due to the domestic circumstances which make females consult doctors less frequently, and the rates of each to the whole out-patients also revealed a statistically significant difference (see note of Table I).

TABLE I
Relation of age and sex to incidence

Sex	Male	Female	Total	Percentage
Total of outpatients	22103	19907	42010	
13-19y. of age	66	31	97	20.9%
20-29	134	83	217	46.9%
30-39	55	38	93	20.1%
40-49	24	10	34	7.4%
50-	20	2	22	4.8%
Total	299	164	463	100.0%
Percentage	70.7 \geq 64.6 \geq 57.7%*	42.0 \geq 35.4 \geq 29.3%*	100.0%	
Percent. to total out-patients	P ₁ =1.352 \pm 0.017%	P ₂ =0.824 \pm 0.014%	1.10%	

Note: $\frac{P_1 - P_2}{\sqrt{\sigma P_1^2 + \sigma P_2^2}} > 3$

* $\alpha = 0.01$

YEARLY INCIDENCE. As shown in Table II, the total of the acute hepatitis patients during the ten year period from 1943 to 1952 numbered 463, which was 1.102 per cent of the total out-patients. The yearly distribution as considered from the percentage of the cases to the out-patients' number disclosed two waves of occurrence, whose peaks came in 1944 and in 1952 with an interval of seven years.

Although the rate of incidence among the inhabitants in the Ube Area (near Shimonoseki, in the western part of Yamaguchi Prefecture) is not known, the yearly rates per 100 out-patients ranged from 0.28 to 2.99, suggesting endemicity in this area. It is apparent that acute hepatitis is one of the important conditions affecting the liver and the bile ducts, as manifested by the figure which illustrates that the

frequency of this condition is 15.1 to 77.0, averaging 48.9 per cent of the diseases of the liver and the bile ducts. The figure for acute hepatitis does not include the conditions of cirrhosis and atrophy of the liver or others that are regarded to be the sequelae of virus hepatitis.

TABLE II
Yearly incidence among the out-patients

Year	Number of hepatitis patients	Total of new out-patients	Percentage of hepatitis to out-patients	Patients of liver & bile-duct dis. (percent. to total)	Percent. of hepatitis to liv. & b.d. dis.
1943	109	9402	1.16	175 (1.86%)	62.3
'44	57	2023	2.81	75 (3.66%)	77.0
'45	69	3469	1.99	110 (3.18%)	62.7
'46	29	3300	0.88	69 (2.09%)	40.0
'47	24	4389	0.55	46 (1.05%)	49.0
'48	16	5485	0.29	93 (1.78%)	17.2
'49	11	3411	0.32	53 (1.55%)	20.8
'50	10	3524	0.28	67 (1.90%)	15.1
'51	37	3584	1.02	75 (2.09%)	49.4
'52	102	3423	2.99	181 (5.29%)	56.4
Total	463	42010	1.102±0.033	946 (2.25%)	48.9

EPIDEMICS There were two apparent epidemics experienced at our clinic, i. e., the one which is manifested as one of the peaks in the figures given in the column "percentage of hepatitis to out-patients" of Table II which prevailed from Aug., 1944 to Nov., 1945, and the other from Sept., 1951 to July, 1952. The number of the patients involved in those epidemics counted 113 and 99 respectively, the latter including 5 non-icteric cases.

It is to be noted that the duration of the epidemics were 11 to 16 months, and that the beginning and the end of each epidemic were quite inconspicuous, setting in with increasing incidence and expiring with gradual transition to sporadic occurrence. Also, there was between the two epidemics an intervening period of some seven years during which time only sporadic occurrence was seen and the yearly incidences declined gradually to the lowest in the year 1950, the preceding year of the latest epidemic.

The epidemic of 1943-1944 was the very first one ever recognized in Ube and Yamaguchi Area, but it is uncertain that there had actually been no epidemic before. The area where epidemics were noticed during those times included the cities of Ube, Onoda, Yamaguchi and Bofu and the counties around them, thus the extent of their prevalence seemed to be so wide as to involve at least the western half of Yamaguchi Prefecture. If the number of the patients who consulted practitioners or other hospitals were taken into account, the actual total of them must have been vast.

PREVIOUS HISTORY OF JAUNDICE. The history was checked in each individual for previous jaundice. The number of those who had had jaundice more than five years prior to the present illness was only four among 463, and the nature of icterus was not known.

ATTEMPTS TO ISOLATE THE PATHOGENIC AGENT FROM THE PATIENTS' MATERIAL. Mice were employed for this study. Six specimens of bile and three of blood obtained in the acute stage from patients involved in the latest epidemic were inoculated intraperitoneally or intrahepatically, and the observation was done for two weeks for the first generation. Although in some of the mice the liver had previously been damaged by administration of carbon tetrachloride for facilitating inoculation, the results were negative, and the further serial inoculations up to the fourth generation were not successful either.*

SURVEY OF THE SOURCE OF WATER SUPPLY, AND CONSIDERATION OF THE MODE OF TRANSMISSION. The survey card contained an inquiry on the source of water supply. In 82 cases where the inquiry was answered, 21 were using well-water for drinking and cooking, and the rest, tap water. No detectable relation was obtained between the kind of water supply and the beginning of the latest epidemic, as investigated from the distribution of the early patients in the epidemic. In other words, the source of water did not seem to have played an important role in transmission of the disease.

And also it is somewhat strange that not a single case of apparent familial outbreak was encountered during the latest epidemic. It was supposed in the case of a patient who was an intern, that he became infected while performing biliary drainage for a diagnostic purpose. As far as known to us, there was no apparent outbreak within a closed institution in this area, though there occurred sporadically a few cases both among the hospitalized patients and the nurses living in a dormitory.

MONTHLY INCIDENCE AND SEASONAL TREND. In Figure 1 is presented the cumulative number of the patients observed in each month. The monthly distribution of the patients revealed fluctuations of relatively small deviation, i. e., from 29 to 47 cases which count 6.3 to 10.1 per cent of the total. Shown by a curve (Curve A), this is turned into a curve with two waves, one of which had its peak in October and the other in February and April with an intervening drop in March. If the cases during epidemics were subtracted from the tabulated cumulative figures, and divided by the number of months counted, the incidence is modified (Curve B) to reveal a prominent peak in the early months from Jan. to Apr., and an inconspicuous wave in autumn which corresponds to the late peak in Curve A.

The largest number of patients seen in a month was 15, and the smallest was none. In the year preceding the latest epidemic, there was no case in five of the twelve months. It will be presumed from the mentioned data that the predisposed season of the beginning of epidemics is autumn, and the months of the lowest incidence in general are those of summer. The monthly ratio of the number of patients to out-patients ranged from 0 to 6.5 per cent, and the gradual onset and expiration

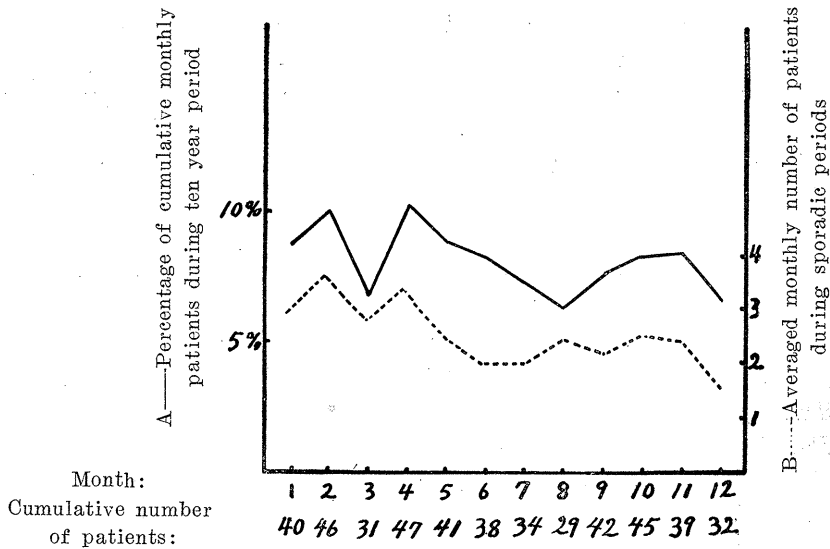


Figure 1 Monthly incidence of acute hepatitis

TABLE III
Epidemic and monthly incidence

Month	No. of hepatitis patients	Total of out-patients	Percentage of hep. patients
Aug. '51	2	375	0.53
Sep. '51	5	346	1.44
Oct.	5	310	1.61
Nov.	3	186	1.58
Dec.	8	199	4.02
Jan. '52	7	247	2.84
Feb.	15	231	6.50
Mar.	6	296	2.02
Apr.	11	303	3.63
May.	10	386	2.66
Jun.	15	267	5.75
Jul.	14	403	3.48
(Total)	(98)	(3271)	(3.03)
Aug. '52	4	318	1.26

of an epidemic will be comprehended by the figures both of the number of patients and of the percentage of that number to the total out-patients presented in Table III.

DISCUSSION

In view of the relative lack of known facts concerning epidemiology and immunology of this disease, it is interesting that the yearly incidence of acute hepatitis

observed at our clinic gradually decreased to the lowest rate in 1950, and which was followed by an apparent outbreak of another epidemic. The intervening seven years of sporadic occurrence might have been necessary for the coming of another epidemic, assuming that the previous epidemic had conferred immunity widely among the inhabitants of that area. Though it is not clear if those two epidemics were parts of the reportedly³⁾ world-wide pandemics, some correlation between the incidence or epidemic and immunity of the people is presumed. Besides, the fact that there were only four among 463 cases that had previous history of jaundice suggests the role of an active immunity in not acquiring the disease twice. The gradual transition of the epidemic to the sporadic occurrence or vice versa seems to support the claim⁴⁾ that both are different patterns of occurrence of the same disease. We might in the future be able to anticipate another epidemic by investigating the annual rate of acute hepatitis.

There has been no unanimous agreement on the mode of transmission, but several reports⁵⁾⁶⁾ in occidental countries seem to be confirming the water-borne outbreak. Our investigation could not confirm the role of water in its propagation, so some unknown factors might be considered. However, the apparent higher frequency in men suggests a possibility of some sort of contact infection. The negative results in isolation of the pathogenic agent through mice do not deny the viral character of this disease, as experimental animals have been reported⁷⁾ insusceptible to this agent.

The monthly distribution or predilection of this disease in this area, which revealed two seasonal waves, differed definitely from those on the continent, where hepatitis was said⁸⁾⁹⁾ to have a conspicuously high incidence in cold months only. According to Hara⁹⁾¹⁰⁾ (1952), the warmer the climate, the later in autumn or in winter comes the beginning of an attack wave, whereas, in Formosa, the wave comes in summer. Our data seem to disclose an intermediate pattern which also suggests a relationship between the climate and the incidence. Another difference is that the duration of an epidemic is some one year, is much longer than that reported⁸⁾¹¹⁾ on the continent.

As acute hepatitis has not so far been handled as an infectious disease in Japan, the authors want to rouse general attention to its infectious characteristic, and to a possibility of person-to-person propagation supposedly including syringe-borne transmission.

CONCLUSION

The analysis of 463 cases of acute hepatitis observed during the past ten years at the First Medical Clinic of the Yamaguchi Medical School Hospital, Ube, disclosed the following conclusions:

- 1) There were two epidemic occurrences of acute hepatitis in Ube and the surrounding area in the periods 1944-1945 and 1951-1952.
- 2) Each epidemic, beginning in autumn, lasted about one year, and the onset and expiration were inconspicuous,

3) A correlation between the incidence and the immunity of the disease was presumed from the yearly frequency of the patients.

4) The monthly incidence of the disease revealed two peaks, which fell in the early months of the year and in the late autumn.

5) The frequency in men was higher than that in women, so some unknown mode of propagation might be considered.

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