

ACUTE HEPATITIS

II. CLINICAL STUDIES OF 99 CASES IN THE LATEST EPIDEMIC

KUNIO OKUDA AND FUKASHI ITO

First Medical Clinic of the Yamaguchi Medical School, Ube

Director: Prof. Nobuo Mizuta

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In the previous report we have presented a statistical analysis of the infectious hepatitis patients observed at the Medical Clinic of the Yamaguchi Medical School Hospital during the past ten years. Infectious hepatitis, which has come to be considered as a viral disease, seems to reveal some clinical aspects that contribute to clarifying its pathogenesis and relation to other related hepatic diseases.

This paper is concerned with the clinical findings of the patients involved in the latest epidemic from Sept., 1951 to July, 1952 inclusive, which counted 99 cases containing seven hospitalized and five non-icteric cases as well. Cases of acute and subacute atrophy of the liver were not included.

METHOD OF INVESTIGATION

1. Physical Examination.—The survey cards mentioned in the previous paper were employed for the investigation of subjective symptoms, and the physical examinations were made two or three times a week for the ensuing month or longer in individual cases.

2. Laboratory Examination.—Urine: albumin was tested by sulfosalicylic acid method, urobilinogen by Ehrlich's method, and bilirubin by Gmelin's method. Blood: the ordinary procedures were used for blood cell counts, and both Sahli's hemoglobinometric and the electrophotometric¹⁾ method were employed for hemoglobin amount. The various tests for hepatic functions were made according to Shibata's procedures¹⁾ (1951). Collection of the bile was done by Lyon's method, and for aspiration biopsy of the liver, Vim-Silverman's needle was employed.

3. Treatment.—Usually, the treatment consisting of high protein diet and injection of vitamin B₁, l-methionine and glucose solution was given. In selected cases, calcium para-oxybenzoate was given intravenously with a dose of 20 ml of 3% solution two times per day.

RESULTS

SUBJECTIVE SYMPTOMS. As presented in Table I. the most common major subjective symptoms the patients had were anorexia, fever, lassitude and fatigue, reddish or brownish colored urine, etc., and inappetency accompanied with epigastric or abdominal distress. The introductory complaints or heralding symptoms were the

first three or four listed in the table, which also presents the days when these symptoms were frequently complained of. The outstanding feature in general was the manifestation of gastrointestinal disorder, and the grippal complaints such as headache and cough came next, but were less intensive. The onset was usually heralded by fever, anorexia and grippal feeling, but sometimes jaundice was the first sign the patient noticed. Fever was oftentimes accompanied by chills and continued for a few days, and in a protractedly febrile case, even typhoid was suspected on the first examination.

TABLE I
Frequency of subjective symptoms

Symptom	99 cases in epidemic (1951-52)				96 cases of sporadic occurrence	
	No. of cases	%	Day of illness (from onset)	Day when pt. had complaint most frequently	No. of cases	%
Anorexia	93	93.9	1-35	2- 8	87	90.7
Fever	63	63.7	1-30	1- 7	55	57.3
Lassitude	59	59.6	1-15	1-10	49	51.0
Bile-colored urine	54	54.6	1-10	3- 6	23	24.0
Notice of jaundice	51	51.5	1-13	2- 7	21	21.9
Nausea	48	48.5	1-25	2- 7	35	36.5
Epigastric or right hypochondriac tenderness	40	40.4	1-15	1- 7	44	45.8
Vomiting	31	31.3	1- 9	2- 6	22	22.9
Headache	27	27.2	1-25	1- 3	19	19.8
Other abdominal distress	25	25.2	1-10	1- 5	16	16.7
Chill	23	23.2	1- 3	1- 2	18	18.8
Lumbago	22	22.2	1- 9	1- 5	8	8.3
Cough	6	6.1			18	18.8
Grippal feeling	21	21.2	1- 6	1- 3	9	9.4
Pruritus	18	18.2	3-15	7-10	8	8.3

In order to examine whether there is a difference in the frequency of symptoms between the patients involved in the epidemic and those of sporadic occurrence, the latter group was taken for comparison. As the figures indicate, there was little discrepancy between the frequencies of the principal symptoms in the two groups except for noticing of jaundice and change of the urine color, which are somewhat objective findings and possibly failed to be recorded often in the latter group. This difference in the five major subjective symptoms between the two groups is statistically insigni-

ficant ($\alpha=0.05$).

OBJECTIVE SYMPTOMS. (Table II). Jaundice.—All had jaundice except for five non-icteric cases which were otherwise typical hepatitis. The grade of icterus was grossly slight to moderate in most cases (89.9%), and the beginning of icterus was from three to six days from the onset, usually lasting about two to three weeks, and in chronic cases, more than one month.

TABLE II
Objective findings (99 cases in the latest epidemic)

Finding		No. of cases	%
Jaundice	Portion		
	Skin & conjunctiva	78	78.8
	Conjunctiva only	16	16.2
	Unrecognizable	5	5.1 (inapparent cases)
	Grade		
	Slight	54	54.5
Moderate	35	35.4	
Intensive	5	5.1	
Hepatomegaly	Size (maximum)		
	Impalpable	2	2.0
	within 1 fingerbr.	4	4.0
	1-1.5	32	32.3
	2-2.5	47	47.5
	Over 3 f. b.	14	14.2
	Tenderness upon press.	42	42.4
Firmness on palpation	39	39.4	
Splenomegaly	Size (maximum)		
	Within 1 f. b.	15	15.2
	1-1.5	2	2.0
	2-2.5	2	2.0
	3	1	1.0
Total	20	20.2	
Enlarged tonsils	6	6.1	
Inflammatory pharynx	6	6.1	
Acholic stool	6	6.1	
Herpes	2	2.0	
Subcutaneous hemorrhage	2	2.0	
Urticaria	1	1.0	

Hepatomegaly.—The liver was palpated in 97 cases (98.0%), and the maximum size was reached in one to two weeks. In about half of the cases, the liver was firm and tender in the acute stage. Although the liver diminished its size within a month, it was still palpable for a long period in the convalescence in some cases.

Splenomegaly.—Splenomegaly was demonstrated in 20 cases (20.2%), but the size, remaining within 1 fingerbreadth in the majority, did not exceed 3 fingerbreadths. With regard to the frequency of splenomegaly among several groups taken (Table III), not only was there a wide discrepancy between the figures in the first and the second epidemic, but also there was a difference of some twenty per cent between the early and the later period of the latest epidemic. The examiner was, of

course, the same through the entire period of investigation, and those differences are statistically significant.

TABLE III
Frequency of splenomegaly

Group	No. of patients	Cases with splenomegaly	%
Cases in the first epidemic	113	5	4.4
Cases in interepidemic sporadic periods	96	9	9.4
Cases in the latest epidemic			
Sep. '51-Mar. '52	49	15	30.6
Apr. '52-Jul. '52	50	5	10.0
			20.1 (average)
Cases in transitory period from epidemic to sporadic pattern	24	3	12.5

Other physical findings.—The frequency of the other objective findings was much lower, and the signs of upper respiratory tract involvement such as injected throat and swollen tonsils were encountered in six cases only. Conjunctival injection was not seen in any case.

Urine.—Urine was examined in 75 cases in various stages. In the early days (1st-4th day of disease) albuminuria, though mild, was positive in all of 5 cases examined, but disappeared in 89 per cent of the cases within two weeks. Bilirubin was demonstrated late in the first and through the second week, turning negative in the third or the fourth week. Urobilinogen, appearing in the first week, remained positive for the longest time and had a frequency of 45.5 % during the period from 21st to 30th day of illness.

Blood picture.—No detectable change was obtained either in the red cell count or the hemoglobin amount. The remarkable feature was the changes in the white cell count and its differential count. Figure I which presents the distribution of white cell counts through the course of disease reveals leukopenia in the acute stage with gradual recovery to the normal level in the fourth week or later. Monocytosis predominated in the change of stained films in the acute stage, and the maximum value of 31 per cent was obtained in a case during the second week. Relative lymphocytosis and appearance of plasma cells were also demonstrated in most cases.

Tests of hepatic functions (Table IV).—The acute stage was marked by high total serum bilirubin level, positive Gros' reaction, decreased serum albumin, increase in serum globulin, lowered A/G ratio, increased units of Popper's, zinc and thymol turbidity tests, and depressed serum choline-esterase activity which seem to reflect the impairment of the parenchyma, whereas somewhat high value for serum alkaline phosphatase and one-minute direct bilirubin in the acme of the disease suggest the additional involvement of the canaliculi or/and finer bile ducts. Although the total plasma protein level was not greatly reduced, the reversal of the A/G ratio corresponds to the parenchymatous damage. Phenol turbidity test and serum cholesterol level did

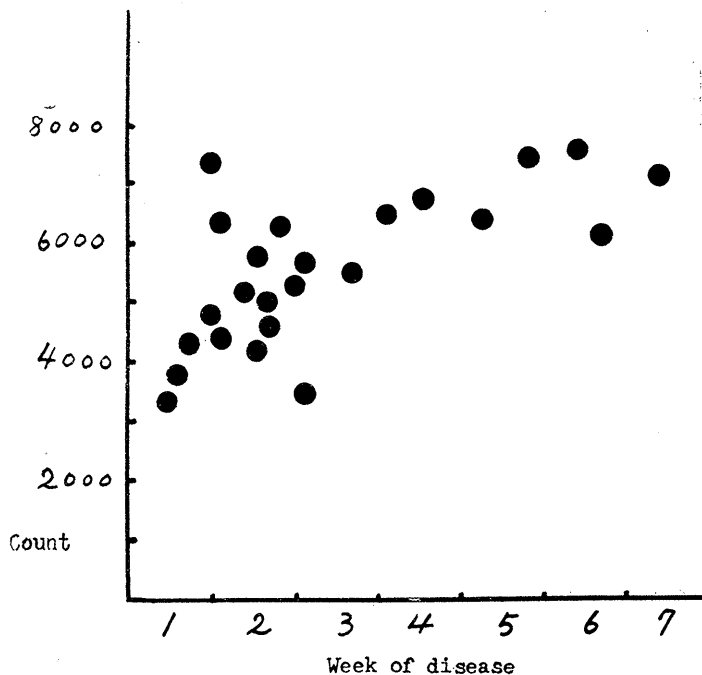


Fig.1 White cell count.

TABLE IV

Tests of hepatic functions (chronic cases are excluded).
The average values for each week.

Test	Week	I	II	III	IV
	No. of case	10	12	8	6
Total bilirubin (mg/dl)		4.82	6.37	4.71	2.43
1-minute bilirubin (mg/dl)		1.50	1.94	1.03	0.32
Gros' reaction (ml)		0.82	0.79	0.78	0.85
Total serum protein (gm/dl)		7.8	7.4	7.8	7.8
Serum albumin (gm/dl)		3.5	3.6	3.5	3.8
Serum globulin (gm/dl)		3.9	4.0	3.6	4.2
A/G ratio		0.88	0.90	0.97	0.90
Popper's test (Kunkel's unit)		16.1	18.0	16.7	13.9
Thymol turbidity t.(K.'s unit)		13.8	17.1	13.2	5.0
Zinc t.t.(K.'s u.)		13.9	14.2	15.7	11.2
Phenol t.t.(K.'s u.)		30.5	28.5	31.3	35.5
Serum cholineesterase (Δ pH)		0.71	0.54	0.54	0.68
Serum alkalinephosphase (B.'s u.)		6.5	6.7	6.9	5.0

not always yield pathognomonic findings. Pigment excretion was tested in seven cases for bromsulfalein and in four for azorubin S. The dye retention of slight to moderate grade was always encountered. In a case in whom dissociation of the liver activities—bilirubinemia and dye retention with negative turbidity tests—was obtained, the aspiration biopsy disclosed cholangiolitic involvement.

Blood sedimentation rate.— This was not markedly elevated, though slight acceleration was sometimes encountered during the acute stage as seen in Fig. 2.

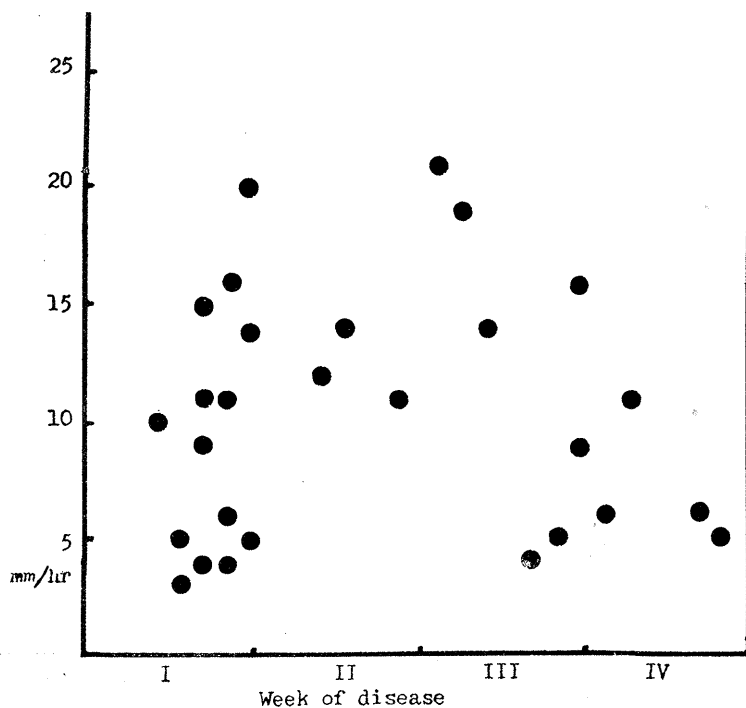


Fig. 2 Blood sedimentation rate

Duodenal drainage.— In fourteen cases in whom drainage was performed, B-bile with low Meulengracht index or no B (dark)-bile was obtained in ten instances, but otherwise the bile was normal. There were also three cases who passed clay-colored stools during the icteric phase.

Liver biopsy.— Seven cases were histologically examined. The predominating findings in the specimens taken from six cases during the acute stage were the infiltration of mononucleated cells in the portal spaces and the lobules, and moderate to serious damage of the liver cells such as necrosis, eosinophil patches, degeneration of the cytoplasm, changes of the nuclei, etc. The above stated case with function had clinically had persistent jaundice, and consecutive bioptic examinations revealed transition of hepatitis to pericholangiolitic infiltration with little change of the parenchymatous

cells. In a chronic case, periportal infiltration and moderate fibrosis, a finding of transition to cirrhosis, were obtained.

CLINICAL COURSE. Among the 94 manifest cases there were only six that had jaundice longer than two months, two of whom had been pregnant. In the majority of the rest, the icterus subsided within one month, and the subjective complaints within one and a half, though several had slight disability and mental instability somewhat persistently. There was encountered no complication, but for spontaneous nyctopia in one case and herpes in two.

TREATMENT. The standard treatment, which was mentioned before, did not seem to shorten the period of jaundice remarkably. Calcium para-oxybenzoate rendered beneficial effects both in two serious cases and one persistently jaundiced case in whom this drug was singly administered. The clinical course of one of the former is presented in Fig. III

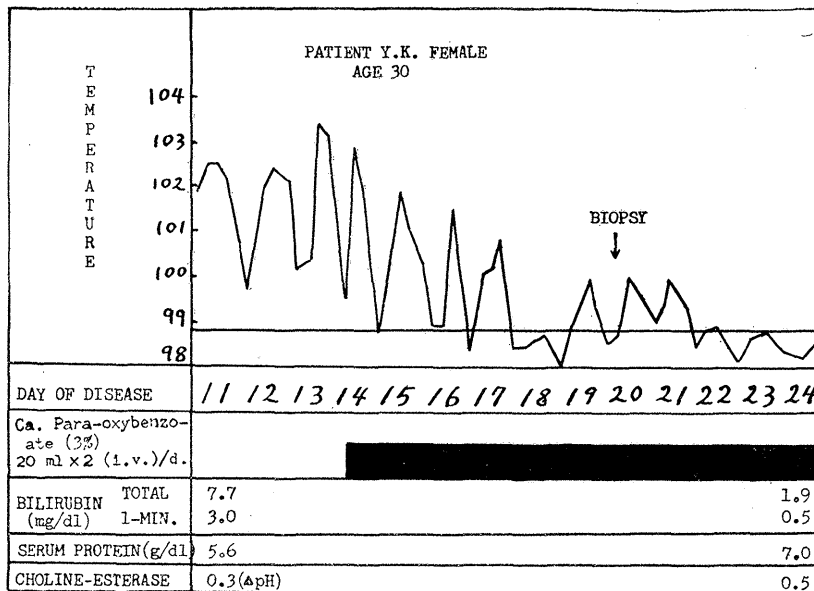


Fig. 3 Chart of results in a patient with fulminant hepatitis treated with calcium para-oxybenzoate

STATISTICAL NOTES ON PROGNOSIS. Not only of the 99 cases but of the whole 463 cases dealt with in the previous paper, none was fatal. However, there were six of acute or subacute atrophy of the liver during the ten year period, of which three died and the rest were cured by the treatment with calcium para-oxybenzoate (Mizuta et² al, 1951). No estimable correlation was obtained between the frequencies of acute hepatitis and liver atrophy. Lingering hepatitis that was apparently the eventuation of acute hepatitis, and which had prolonged symptoms, numbered 19 cases (4.1%) among the entire patients, three of which were of the type of recurrent jaundice (Post

et³⁾ al, 1950). The follow-up results are not available. It attracts attention that six of eight women who acquired hepatitis during pregnancy had icterus for more than one month, the longest being 4 months, and that a prompt improvement was gained in a case in which gestation had been interrupted.

Furthermore, relation of the frequency of acute hepatitis and that of cirrhosis of the liver was investigated by comparing the annual numbers of both of them, but no recognizable correlation was derived from this study.

DISCUSSION

As subjective and objective symptoms go, there was no particular finding that differed from those previously known⁴⁾⁵⁾. However, the fact that few of our cases had findings of the upper respiratory tract involvement differs greatly from the reports which appeared on the continent (Mochizuki⁶⁾, 1936, and others⁵⁾). This proposes a problem that will most likely be solved after the relation of the climate and the portal of entry of this disease are clarified. The pronounced symptoms of the digestive tracts are hard to explain by the ailment of the liver alone, but it is very likely that they are due to the involvement of the stomach and probably the intestine themselves which was demonstrated gastroscopically by Loughead et⁷⁾ al (1952).

Splenomegaly, chills and fever, and lumbago known as manifestations of acute generalized infection, seem to support the claim of Hara⁸⁾ (1952) who has pointed out the systemic involvement in this disease through viremia. It is of interest that the frequency of splenomegaly varied with the time of epidemic. This, with the fact that edema of slight degree was not infrequently encountered during the first epidemic whereas none in the second, causes us to understand that this disease does not always reveal the same clinical picture.

The blood picture, i. e., leukopenia and monocytosis, was not incompatible with the virus infection. The data of the tests for the liver functions disclosed the parenchymatous involvement, and, in the acme stage, damage in the finer bile ducts resulting in slight obstructive process. The problem proposed by Nishi⁹⁾ (1941) that dissociation of the hepatic activities is present in some instances was not investigated in particular, but in a case in which functional dissociation was obtained, the ailment of the liver was of the cholangiolitic type (Watson and Hoffbauer¹⁰⁾, 1946). However, in the majority of the cases, the parenchymatous condition evaluated chiefly by choline-esterase activity and turbidity tests was not greatly unproportional to the degree of hyperbilirubinemia. As was already pointed out by Weibren¹¹⁾ (1952), we must always keep in mind that this cholangiolitic form is not seldom encountered. The bioptic examination should, in this connection, not only have a momentous position in the diagnostic procedures, but also play an important role in estimating prognosis and the results of the treatment given, and thus in preventing cirrhosis of the liver from occurring. The difficulty of obtaining the B-bile in the patients may be partly due to insufficiency of the gall-bladder, which was demonstrated by Kalk and Buechner¹²⁾ (1949) who performed

laparoscopic examination in a number of patients.

As for the treatment, it is not always feasible to evaluate and compare the effects of several therapeutic regimens, as the clinical signs are not constant in each case and the course is mostly short. Although some of the antibiotics¹³⁾ and hormones¹⁴⁾ have been reported to be beneficial in some instances, they were not applied in our series, but calcium para-oxybenzoate proved worth while for employment in serious and prolonged cases. In order to prevent the development of the sequelae of infectious hepatitis, the longterm follow-up study is required in chronic cases, and also precaution must be taken against aggravation of the disease through pregnancy in women.

SUMMARY

1. Clinical pictures of 99 cases observed during an epidemic of acute hepatitis from Sept., 1951 to June, 1952 were presented.

2. The prevailing subjective signs were those of the digestive tract involvement and those conceivably due to the generalized infection.

3. The liver damage, particularly the parenchymatous involvement, predominated the objective findings; however, there were found five non-icteric cases also.

4. The frequency of splenomegaly varied with the year and the epidemic, and a slight deviation in the clinical feature was observed in individual epidemics.

5. Calcium para-oxybenzoate was demonstrated to be effective in fulminant and chronic cases.

6. Gestation most often aggravated the clinical course, and in the lingering cases, manifest or inapparet, bioptic observation as follow-up study is strongly required.

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