Special Article

Cirrhosis of the Liver in Japan*

Tsuneo YOSHIDA, M.D.

Professor of Medicine, Osaka University Medical School

During the past several years, the number of patients with liver disease has been increasing not only in Japan but also in many other countries of the world.

The World Health Organization's statistics¹⁾ of the mortality rate of cirrhosis of the liver shows that Japan is number 11 in the world. From the statistical report of the causes of death in Japan during the past three years, cirrhosis was 14th. The corrected mortality rate of cirrhosis per 100,000 of the population has increased from 6.8 in 1952 to 9.8 in 1961. These figures and statistics, however, deal with mortality rate and little has been known about the present number and status of patients with cirrhosis of the liver in Japan.

An attempt has been made to analyze the number of patients with cirrhosis and their status in Japan. The present report deals with the result of this study as well as some data of the dietary analysis and of the biochemical studies done by the Liver Research Division of the First Department of Medicine, Osaka University Medical School.

A) Statistical observation of cirrhosis in Japan.

The statistical study was based on information obtained by questionnaire from 255 hospitals all over Japan. This study revealed that 330,349 patients.

Table 1. Number of Patients Analyzed

Total Number of Patients	330,349	
Number of Patients with Hepatobiliary Diseases	13,823	
Acute Hepatitis	2,706	20%
Chronic Hepatitis	4,168	30%
Cirrhosis	1,435	10%
Neoplasma	388	3%
Biliary Diseases	5,072	37%

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Table 2. Geographical Distribution of Cirrhosis

	Total number of patients	Number of cirrhosis	Cirrhosis/1,000 patients
Hokkaido	12,432	39	3.1
Aomori	3,999	8	2.0
Iwate	6,974	19	2.7
Akita	2,305	6	2.6
Yamagata	2,634	9	3.4
Miyagi	3,264	13	4.0
Fukushima	16,740	32	1.9
Ibaragi	5,627	11	2.0
Tochigi	3,001	10	3.3
Gunma	2,563	10	3.9
Saitama	2,858	17	5.9
Chiba	5,324	27	5.1
Tokyo	48,409	174	3.6
Kanagawa	24,259	93	3.8
Yamanashi	518	0	0
Shizuoka	4,902	28	5.7
Nagano	3,578	19	5.3
Niigata	14,345	44	3.1
Toyama	4,880	23	4.7
Ishikawa	2,555	16	6.3
Fukui	875	2	2.3
Aichi	15,546	62	4.0
Gifu	4,074	18	4.4
Mie	1,087	3	2.8
Shiga	8,794	8	0.9
Kyoto	12,114	69	5.7
Osaka	33,246	150	4.5
Nara	2,241	6	2.7
Wakayama	3,917	8	2.0
Hyogo	18,770	100	5.3
Tottori	1,728	9	5.2
Okayama	3,880	34	8.8
Simane	2,300	11	4.8
Hiroshima	5,731	54	9.4
Yamaguchi	2,902	13	4.5
Kagawa	2,451	21	8.6
Tokushima	5,105	55	10.8
Ehime	4,146	26	6.3
Kochi	994	6	6.0
Fukuoka	10,276	69	6.7
Saga	1,852	13	7.0
Nagasaki	6,238	49	7.9
Oita	3,358	33	9.8
Kumamoto	4,022	10	2.5
Miyazaki	2,431	0	0
Kagoshima	1,004	8	8.0
Total	330,249	1,435	4.3

visited these hospitals during one month arbitrarily selected in 1962. Out of these patients, 13,823 patients were diagnosed as having hepatobiliary diseases. This was 4.2% of the total number. Among these cases, 1,435 patients were diagnosed as having cirrhosis, corresponding to about 10% of all those diagnosed as having hepatobiliary diseases (Table 1).

Table 2 shows the geographical distribution of the number of cirrhotics per 1,000 patients with various diseases. The incidence is highest in the areas surrounding the Inland Sea of Japan. In general, the incidence is higher in the southern part of Japan than in the northern.

The geographical distribution of the mortality rate shows a similar tendency, being higher in the southern part and lower in the northern.

B) Clinical features of cirrhosis in Japan.

From the above mentioned hospitals, 3,550 reports on the clinical findings of patients with various liver diseases were collected. There were 902 cases of cirrhosis. The ratio between male and female was 2.3:1 which was almost the same ratio of 2.0:1 found in literature.²⁾⁻¹⁰⁾ The age distribution showed the highest peak to be in the sixth decade in men and in the fifth decade in women.

Table 3. Classification of Cirrhosis

Type	Male	Female
Portal	407 (72.9%)	142 (69.3%)
Postnecrotic	110 (19.7)	36 (17.6)
Biliary	26 (4.7)	13 (6.2)
Hemochromatosis	2 (0.4)	2 (1.0)
Cardiac	7 (1.3)	12 (5.9)
Parasitic	6 (1.0)	0 (0)
Total	558	205

Table 3 shows the types of cirrhosis classified according to the reports obtained from the hospitals. About 70% of cirrhotics were considered to have portal type while about 20% were of postnecrotic type. Miyaji¹¹⁾ reported that 56.5% of 726 cases of cirrhosis including Wilson's disease and Banti's syndrome were portal in his series of 23,254 autopsies. This discrepancy is thought to be partly due to the difference between pathological examination and clinical impression. We can not deny the possibility that there might be a considerable number of patients who had postnecrotic or other types of cirrhosis, but which were classified as portal on the basis of the clinical impression. In the present study the diagnosis of cirrhosis was

confirmed by biopsy in about 15% of patients, 3.7% by peritoneoscopy and 10.7% by a combination of biopsy and peritoneoscopy, and 3.3% by surgery or necropsy. The remaining patients (about 70%) were diagnosed by clinical findings and laboratory data.

Predisposing factors and/or cause of cirrhosis could be analysed in 848 cases. In about one-half of the cases, no definite predisposing factor relating to the present illness could be found. In the 848 cases, about 20% of cases were thought to be secondary to viral hepatitis, 8.1% were due to malnutrition and another 8% were secondary to other organic diseases such as diabetes mellitus and thyroid disease.

The previous history of these 848 patients showed that about one-third of the cases had an episode of ascites. About 7% of the cases have had hematemesis and/or melena and 4.6% had a history of hepatic coma. There was a previous history of jaundice in about one-third of the cases.

Fig. 1. Frequency of subjective complaints.

About 50% of patients had noticed dark urine and 40% complained of fat intolerance. The incidence of other complaints are summarized in Fig. 1.

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In the physical findings, 72% of cases had hepatomegaly. Splenomegaly was seen in 22% and hepatosplenomegaly was observed in 17%. Vascular spiders were seen in one-third of the patients. Ascites was present in 42%, including slight ascites in 16, moderate in 14 and marked in 11%. During the period of observation for one month, about one-third of the patients showed neither ascites nor jaundice, while one-fourth of the cases had both ascites and jaundice.

The incidence of abnormal liver function tests was as follows. Serum total protein of less than 6 g./dl. was seen in only 13%. Almost all patients showed an abnormally elevated zinc sulfate reaction. About 60% had a reaction of 13-24 units and about 20% had more than 25 units. 75% of the patients had a cobalt reaction of more than R_6 . About the same per cent of patients had an icteric index of less than 15. Only 5% of patients had an icteric index of over 61. Serum transaminase activity was less than 40 units in about 50% of cases and an activity of more than 80 units was seen in only 25%

of cases. BSP retention was prolonged in 95% of cases. About 23% of patients who had vascular spiders, gynecomastia or red palms had ascites and hepatosplenomegaly.

The more abnormal the liver function tests, the more frequently patients developed ascites. In more than 50% of patients who had marked BSP retention, high zinc sulfate and cobalt reactions, ascites was demonstrated. No definite relationship was found between BSP and zinc sulfate reaction and the presence of vascular spiders, gynecomastia and/or red palms.

C) Analysis of environmental, nutritional factors and alcohol history.

1) Climate and social background.

In order to analyze the relation between environment, climate and social background and cirrhosis, the author divided Japan into 14 districts. In each of the districts, the number of patients was of the same magnitude. The incidence of cirrhosis per 1,000 patients was highest in the areas surrounding the Inland Sea of Japan followed by northern Kyushu, Nankai areas including Wakayama and Kochi Prefectures. The incidence was lowest in the northern section of Honshu facing Pacific Ocean.

Table 4 shows the distribution of various types of cirrhosis in these 14 districts. The incidence of the portal type was high in Hokkaido and Nankai areas where the incidence was more than 85%.

A mass examination was undertaken in three different areas, Osaka, Nara and Miye Prefectures, in order to evaluate the relationship between the socio-economical background and liver disease. This study revealed that the incidence of liver disease was higher in low income class, being 22.4%, whereas the incidence was 3.5% and 10.3% in high and medium income classes, respectively.

2) Diet.

The analysis of the diet by questionnaire showed that about 40% of patients with portal cirrhosis ate a relatively protein deficient diet. It was also found that almost all patients lived on rice and that about 70% of patients took 2-3 bowls (300-450 grams) of cooked rice two to three times daily. A survey on healthy individuals showed that about 55% of them took the same amount of rice daily. On the basis of the questionnaire, 58% of the cirrhotics seemed to have taken a balanced diet. On the other hand, 14% of patients with cirrhosis did not take meat, fish, or eggs whereas in healthy controls, such a deficient diet was found in only 2%. From these data, it seemed likely that an unbalanced diet was more often taken in cirrhotics than in healthy individuals.

According to the statistics from the Department of Health and Welfare,

Table 4. Types of Cirrhosis in 14 Districts

Districts	Number of patients	Portal		Postnecrotic		Hemochromatosis	Cardiac	Biliary	Parasitic
		Number	%	Number	%				
Hokkaido	26	23	88.5	0	0	0	1	0	2
East-Ou	32	23	71.9	4	12.5	0	2	3	0
West-Ou	13	7	53.9	2	15.4	0	2	2	0
North-Kanto	26	18	69.3	6	23.1	1	1	0	0
South-Kanto	157	105	67.0	40	25.5	1	2	8	1
Hokuriku	42	35	83.4	6	14.3	0	0	1	0
Chubu	26	16	61.5	6	23.1	2	2	0	0
Tokai	33	22	66.6	8	24.2	0	0	3	0
Kinki	214	151	70.4	40	18.6	0	7	16	0
Setouchi	85	62	72.9	20	23.5	0	0	3	0
Sanin	12	6	50.0	6	50.0	0	0	0	0
Nankai	23	20	87.0	1	4.4	0	1	1	0
North-Kyushu	34	24	70.6	6	7.7	0	2	1	1
South-Kyushu	8	8	100.0	0	0	0	0	0	0
Total	731	520	71.1	145	19.8	4	20	38	4

Table 5. Comparison of Diet between Japan and U.S.A.

Protein Intake (grams)				Composition of Essential Amino Acids				
Vegetable		Japan	U. S. A.		Japan		U. S. A.	
					Grams of Daily Intake	%*	Grams of Daily Intake	%*
	Grains	31.2	21.4	Isoleucine	3.44	111	4.90	120
	Potatoes	1.3	2.6	Leucine	5.43	155	7.43	159
	Beans	8.5	4.8	Lysine	3.97	129	6.28	153
Animal	Vegetables & Fruit	5.4	5.2	Phenylalanine	3.23	157	4.25	155
	Fish & Shell-fish	17.1	2.7	S-containing amino acids	2.39	77	3.50	85
	Meat	3.7	35.6	Threonine	2.81	137	3.76	137
	Egg	1.9	7.6	Tryptophan	0.77	74	1.20	88
	Milk	1.1	15.3	Valine	4.04	131	5.21	127
Total (animal)		70 (34%)	95.2 (64.3%) <th>Total</th> <td>26.08</td> <td></td> <td>36.53</td> <td></td>	Total	26.08		36.53	
				Protein Score	74		85	

* Percent of F. A. O. pattern

Japan: According to the Statistics from the Department of Health and Welfare in 1958

U.S.A.: According to the Statistics from the Department of Agriculture in 1950

the average Japanese person eats 70 grams of protein daily. About 66% of the protein intake is of vegetable origin, mainly rice protein. Of the 34% from animal protein, 72% is from fish sources (Table 5). The average Japanese obtains 57% of his daily protein from rice and fish sources.

On the other hand, in the U.S.A., 64% of the total daily dietary protein is reported to be from animal sources. The daily intake is 4 times as much in eggs and 15 times as much in dairy products when compared to the Japanese people. An analysis of the protein score shows more clearly the qualitative difference in protein between the two nations; the average value is 74 in Japan and 85 in the U.S.A.

The first limiting amino acid in Japanese food is tryptophan. Using the statistics of the Department of Health and Welfare, an analysis of the protein score in 21 prefectures in Japan showed that the protein score ranged from 73 to 78. There was no clear-cut relationship between the protein score and the mortality rate of cirrhosis in these 21 areas.

The protein score was also individually analyzed in 25 cases of cirrhosis, 41 cases of chronic hepatitis and 16 cases of miscellaneous liver disease by recording and measuring all food eaten during a three day period.¹²⁾ The average protein score was 76.7 and tryptophan was always the first limiting amino acid. Only 10% of the patients took diet where the protein score was

more than 85, while 21% took diet with a protein score of less than 74.

From these data, it seems that quantitative and qualitative improvement of dietary protein is one of the most important things in the treatment of cirrhosis in Japan.

3) Alcohol

The relation between alcohol consumption and cirrhosis is an old but still remained a controversial problem. The facts that the incidence of cirrhosis in Paris dropped sharply when wine was rationed during the World War I and II, and that the frequency was reduced to one-half when alcohol beverages were prohibited in the U.S.A., seem to favor the pathognomotic role of alcohol in the pathogenesis of cirrhosis.

The present survey revealed that 55% of cirrhotics had no or little alcohol history and 5% were social drinkers. Of the remaining 40%, about one-third of cases had been drinking for ten years or more, in the amounts of 4.5 liters of Japanese "sake" per week (Table 6). "Sake" contains approximately 15% of ethanol.

Table 6. Alcohol History in Cirrhotic Patients

Duration of History			Amounts of "Sake" Consumption		
Years	Number of Cases	%	Liters per week	Number of cases	%
0	345	54.4	0	345	54.6
0-5	33	5.2	0-1.8	32	5.1
5-7	6	0.9	1.8-2.7	49	7.7
7-10	14	2.2	2.7-4.5	10	1.6
10-15	48	7.6	4.5-6.3	113	17.9
15-20	32	5.1	more than 6.3	83	13.1
20-30	69	10.9			
more than 30	86	13.6			
Total 633			Total 632		

Japanese "Sake" contains approximately 15% of ethanol.

A relationship was observed between the incidence of portal cirrhosis and the number of drinkers who had been drinking 1.8 liters or more of "sake" per week for more than five years in Kochi, Tokushima and Hokkaido.

Alcohol history was investigated to see what effect it had on the clinical status and on the liver function tests. There was no significant difference between drinkers and non-drinkers in the degree and frequency of hepatomegaly, splenomegaly, ascites, serum total protein, zinc sulfate or cobalt reac-

tions, icteric index, GPT or BSP. The only difference demonstrated was that the patients who had a combination of vascular spiders, gynecomastia and red palms were found more often in drinkers than in non-drinkers. These data seem to differ from the statistics in the U. S. A. where the incidences of ascites, splenomegaly and the rate of abnormal liver function tests were higher in drinkers.¹³⁾⁻¹⁵⁾

D) Biochemical study of the cirrhotic liver

The most characteristic change in the cirrhotic liver is abnormal proliferation of connective tissue in which acid mucopolysaccharide metabolism is closely involved.

The amount of collagen in the liver increased gradually in rats given thioacetamide, reaching about three times more than the normal level at the end of six months. In these animals, the hepatic mucopolysaccharide was increased in the early stage of the damage. Alkaline soluble collagen which has been thought to be a precursor of collagen also showed an early increase (Fig. 2).

Fig. 2. Changes of total and soluble collagen and mucopolysaccharide in the liver of rats with chronic thioacetamide damage.

The mucopolysaccharides were increased not only in the liver but also in the urine of cirrhotics. The urinary acid mucopolysaccharides were separated by cellophane membrane into dialyzable and non-dialyzable components, and it was found that the dialyzable component was increased in patients with cirrhosis.

It was also found that the increase of mucopolysaccharide in the liver of

Fig. 3. Rate of increase of hexosamine, glucosamine and galactosamine in the liver of rats with thioacetamide damage.

rats with thioacetamide damage was due mainly to the increase of galactosamine-containing mucopolysaccharides (Fig. 3).

The molar ratio, hexosamine to glucuronic acid in the urinary mucopolysaccharide was found to shift to abnormally high values in cirrhotics ($1.06 \pm$

Fig. 4. Serum β -glucosaminidase activity.

0.1) than in normals (0.65 ± 0.1). The abnormal metabolism of mucopolysaccharide in cirrhotic animals could also be demonstrated by radioisotope study: the biological half life of intraperitoneally injected S^{35} became shorter as the fibrosis of the liver proceeded.

β -Glucosaminidase activity which has been thought to play a role in mucopolysaccharide metabolism¹⁶⁾ increased in the serum and liver. This enzyme was also increased in the serum of patients especially in those who had early cirrhosis (Fig. 4). It was interesting that in animals with cirrhosis, the amounts of collagen and β -glucosaminidase activity were increased in the granuloma proliferated in the polyvinylpyrrolidone, "Ivalon", transplanted in the subcutaneous tissue of the back, as compared with non-cirrhotic animals. These findings suggest that in cirrhosis, mucopolysaccharide metabolism changes qualitatively as well as quantitatively.

Culture of fibroblasts of the liver of animals and patients with cirrhosis has been successfully carried out. By use of conventional microscope, there was no significant difference in morphology between fibroblasts obtained from cirrhotic and normal livers. However, by interference phase-contrast microscope, fibroblasts from cirrhotic liver contained more granules and they were larger in size than normal hepatic fibroblasts. It was also found that β -glucosaminidase activity and the amounts of collagen per cell were lower in the culture medium containing a cirrhotic liver specimen than in those containing a normal liver specimen.

Although no definite conclusion could be drawn from these findings, they seem to suggest that the presence of abnormal fibroblasts is an important factor in the development of cirrhosis. The tissue culture method seems to be one of the useful tools in the study of cirrhosis.

E) Treatment

In the treatment of cirrhosis, a study of dietary protein was attempted.

Since Patek's report, the effectiveness of a high protein diet has been well known and established. However, little attempt has been made to evaluate the importance of amino acid composition of the diet in the treatment of cirrhosis.

The comparative effect of eight kinds of diet which had various amino acid compositions on the recovery of body weight of rats with and without acute carbon tetrachloride damage was studied. The most beneficial effect was seen in rats fed on a diet containing 16 amino acids, both essential and non-essential. Although the amino acid requirement in hepatic damage has not been established yet, it seemed likely that the supplementation of non-essential amino acids to the eight essential amino acids was desirable.

The effect of five different diets, containing different amounts of protein

Table 7. Composition of Diets

	Protein	Carbo- hydrate	Fat	% of 1st limiting amino acid	Salts	Vitamins
High protein well balanced	30%	58%	8%	100%	4%	0.5%
Medium protein well balanced	20	68	8	100	4	0.5
Medium protein poorly balanced	20	68	8	33	4	0.5
Low protein well balanced	10	78	8	100	4	0.5
Low protein poorly balanced	10	78	8	72	4	0.5
Irregular feeding	Given medium protein well balanced diet and low protein poorly balanced diet alternatively every other week

Fig. 5. Effect of various diets on hepatic collagen of rats given thioacetamide for 4 months.

with different amino acid compositions (Table 7) on the amounts of collagen of rat livers with thioacetamide damage was also studied. As shown in Fig. 5, the hepatic collagen showed little increase in rats given a well balanced high protein diet whereas the rats given a diet of poorly balanced amino acid composition showed an increase of hepatic collagen even though the amount of protein was sufficient. A marked increase of hepatic collagen was observed in rats fed a low protein diet (10%) regardless of the amino acid

composition. It was interesting to note that rats given a medium protein well balanced diet and low protein poorly balanced diet alternatively every other week, showed a marked elevation of collagen in their livers. The hepatic mucopolysaccharide showed a similar pattern of change.

The same five different diets were given to rats with chronic carbon tetrachloride poisoning. The hepatic collagen was increased gradually in all groups. However, the increase was most marked in rats given the poorly balanced high protein diet.

In short, it was demonstrated that a high protein well balanced diet was effective in preventing the development of cirrhosis as well as an increase of hepatic collagen and mucopolysaccharides. It was also shown that irregular dietary habit may have deteriorating effect in the pathogenesis of cirrhosis as Davies¹⁷⁾ suggested.

As mentioned above, in Japan, most patients with cirrhosis of the liver have taken a diet deficient in tryptophan and the effect of supplementation of tryptophan to the diet was studied. Eighteen patients were given 300 mg. of tryptophan daily for 4 months. Six out of 18, showed an improvement in the liver function tests studied: BSP, zinc sulfate, cobalt, thymol turbidity, A/G ratio, serum bilirubin and Gros' reaction. Four cases showed an improvement of one or more liver function tests. No change and even deterioration were seen in four cases respectively. As a control, glycine was administered to 8 cases of cirrhosis where no effect could be observed.

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