A Clinical Observation of Renal Lesion in Liver Diseases

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It is an ordinary clinical experience that a slight degree of renal lesion may be accompanied in a majority of the patients suffering from the liver disease. The causality of the renal lesion has been attributed to such agents originating from the damaged liver tissue and/or hepatic dysfunction as a hepatotoxin[1], vasodepressor material[2,3], immunological agent[4], bilirubin[5], metabolic toxic material and metabolic disorder[6], especially dysproteinemia[7]. Controversy has still remained, however, to the elucidation of this mechanism.

In attempting to lay the foundation for further experimental studies on the mechanism of the renal lesion, a clinical observation on the kidney was carried out among the patients suffering from the liver disease.

MATERIALS AND METHODS

The materials examined were the patients with liver disease who have admitted to our clinic during past ten years.

The concentration of urine albumin was expressed as follows; negative (0 mg/dl, $-$), slightly positive (less than 9.9 mg/dl, $\pm$), and positive (more than 10 mg/dl, $+$). The red cell count in the urine sediment was expressed as positive when more than five cells were detected in a 400 magnification microscopic field.

Some of the methods of clinical biochemistry adopted for our use were Bodansky's method for alkaline phosphatase[8], Shibata-Takahashi's methed for cholinesterase[9], Zak-Henly's method for total cholesterol[10], together with Mizobe's method for glutamic pyruvic transaminase[11]. Antidiuretic substance in the serum, urine, and bile was assayed by the modification of Birnie's method[12].

RESULTS

1) Incidence of albuminuria and hematuria

Among the patients with liver disease the incidence of positive albuminuria was 33.0 per cent and that of slightly positive albuminuria was 9.1 per cent, while among the patients suffering from such gastrointestinal disease as gastric ulcer,

Table 1. Frequency of albuminuria and microscopic hematuria in the patients with liver disease.

Patients suffering from:	Numbers of the examined	Albuminuria (male and female)			Microscopic hematuria (male)	
		Frequency (%)			Numbers of the examined	Frequency (%)
		+	±	−		
Acute viral hepatitis	116	30.2	20.7	49.1	67	4.5
Chronic viral hepatitis	40	20.0	37.5	42.5	35	14.3
Liver cirrhosis	108	25.9	19.4	54.7	74	35.2
Liver cancer	80	33.8	8.8	57.4	57	15.8
Disease of gall bladder or extrahepatic bile duct	88	45.5	20.5	34.0	32	34.4
Acute liver atrophy	11	63.6	0.0	36.4	4	50.0
Leptospirosis	4	75.0	0.0	25.0	3	0.0
Total	449	33.0	9.6	57.4	272	20.6
Disease of gastro-intestinal tract	100	36.0	33.0	61.0	63	8.0

Albuminuria: 0 mg/dl (−), below 9.9 mg/dl (±), above 10 mg/dl (+).

gastritis, and duodenal ulcer, it was 6.0 and 33.0 per cent, respectively. Such tendency was noted more distinctly among the patients with leptospirosis, acute liver atrophy, cholelithiasis and cholecystitis (Tab. 1). Among the patients with liver disease there was some elevation of the frequency of albuminuria with the increase of ages, but it was more important that there was no distinct rise of the frequency with the increase of ages (Tab. 2). There was no sex difference in the frequency of albuminuria.

Table 2. Age-wise distribution of albuminuria in the patients with liver disease.

Ages	Numbers of the examined	Frequency of albuminuria (%)		
		+	±	−
10—19	16	37.5	12.5	50.0
20—29	64	22.4	25.0	51.6
30—39	84	34.5	28.6	36.9
40—49	84	31.0	21.3	47.7
50—59	124	31.5	18.5	50.0
60—69	59	39.0	27.1	33.9
70—79	18	38.9	22.2	38.9

In summary, the incidence of albuminuria among the patients with liver disease was higher than that of gastro-intestinal disease.

The incidence of microscopic hematuria in the patients with liver disease was 20.6 per cent and the incidence in the gastrointestinal disease was 8.0 per cent. The incidence of hematuria in the patients with acute liver atrophy, liver cirrhosis and the disturbances of the biliary tract was extremely high.

2) Correlation between albuminuria and the values of clinico-biochemical examinations.

The incidence of albuminuria in the patients suffering from the liver disease was high when they have either hypoproteinemia with hypoalbuminuria or hyperglobulinemia (Tab. 3, 4). The serum of renal diseases indicated a low concentration of albumin, somewhat high concentration of α_1-globulin and β-globulin; the similar tendency was noted among the patients with liver disease who have albuminuria (Tab. 4).

The direct proportion was detected between bilirubinuria and albuminuria, but the direct proportion could not be found between the elevated serum bilirubin concentration and the positive albuminuria (Tab. 5).

Table 3. Relationship between the frequency of albuminuria and the concentration of serum protein in the patients with liver disease.

Serum protein		Numbers of the examined	Frequency of albuminuria (%)		
			+	±	−
Protein	below 6.4 gm/dl	96	39.6	19.8	40.7
	* 65 - 8.0 gm/dl	304	30.3	26.4	43.4
	above 8.1 gm/dl	45	26.7	22.2	51.1
Albumin	below 2.4 gm/dl	118	36.4	19.5	44.1
	* 2.5 - 3.4 gm/dl	167	33.5	24.0	42.5
	above 3.5 gm/dl	151	26.4	25.8	47.8
Globulin	* 2.5 - 4.0 gm/dl	263	28.5	25.5	46.0
	above 4.1 gm/dl	169	37.3	20.7	42.0

* normal value

Table 4. Relationship between the frequency of albuminuria and the concentration of serum protein in the patients with liver disease.

	Albuminuria	Numbers of the examined	Albumin (%)	Globulin (%)	Globulin (%)	Globulin (%)	Globulin (%)	Total protein	Cloles-terol (mg/dl)
Liver disease	−	21	44.9 ±1.8	4.2 ±0.5	7.3 ±0.6	10.7 ±0.6	31.8 ±1.6	7.1 ±0.2	148 ±11
	±	9	43.1 ±2.5	4.2 ±0.7	7.4 ±1.0	10.3 ±0.6	35.4 ±3.8	6.7 ±0.2	159 ±11
	+	6	42.4 ±2.8	4.9 ±1.1	10.0 ±1.3	10.9 ±1.1	31.9 ±2.7	7.3 ±0.2	193 ±3
Renal disease	+	10	42.3 ±1.7	4.5 ±0.7	16.7 ±1.2	13.4 ±0.8	22.9 ±1.2	5.7 ±0.3	286 ±49

$$S.E. = \pm\sqrt{\frac{\sum(\bar{x}-x)^2}{n(n-1)}}$$

Liver disease: Liver cirrhosis, chronic hepatitis
Renal disease: Chronic glomerulonephritis

Table 5. Relationship between the frequency of albuminuria and the values of clinico-biochemical examination in the patients with liver disease.

Clinico-biochemical examinations		Numbers of the examined	Frequency of albuminuria (%)		
			+	±	−
Serum bilirubin	*below 0.4 mg/dl	109	32.1	19.3	48.6
	0.5-10 mg/dl	232	29.7	28.0	42.3
	above 11 mg/dl	87	31.0	23.0	46.0
Serum cholinesterase activity	below 0.49 -⊿pH	134	44.0	18.6	37.4
	0.50-0.74 -⊿pH	172	29.1	26.7	44.2
	* 0.75-1.10 -⊿pH	114	22.8	25.5	51.7
CCF test	* 0	57	28.2	25.8	46.0
	+1 - +2	162	34.5	19.2	46.3
	+3 - +4	120	34.2	24.3	41.7
Bilirubinuria	−	325	26.1	22.2	51.7
	±	79	45.6	25.4	29.1
	+	58	44.9	25.8	29.3

* normal value

Table 6. Relationship between the frequency of albuminuria and the values of clinico-biochemical examination in the patients with liver disease.

Clinico-biochemical examinations		Numbers of the examined	Frequency of albuminuria (%)		
			+	±	−
BSP-test (45 min.)	* 0 - 5 %	32	21.8	28.1	50.0
	6 - 20 %	84	31.0	28.6	40.4
	above 21 %	85	21.2	28.3	50.6
Serum GPT	*below 10 u.	84	25.0	32.2	42.8
	11 - 50 u.	111	30.6	27.0	42.4
	above 51 u.	69	25.5	31.9	40.6
Serum cholesterol	*130 - 200 mg/dl	229	27.5	25.3	47.2
	above 201 mg/dl	169	40.2	20.7	39.1
Serum alkaline phosphatase	*below 4 u.	253	29.6	22.6	47.8
	above 4.1 u.	182	32.4	28.6	39.0
Phenol turbidity test	*below 15 u.	301	33.2	20.2	46.6
	above 16 u.	135	34.8	25.2	40.0

* normal value

The high incidence of albuminuria was observed in the patients with low serum cholinesterase activity, positive cephalin-cholesterol flocculation test, high serum cholesterol concentration, and/or increased BSP retention (Tab. 5, 6).

There was no direct proportion between the positive albuminuria and the positive phenol turbidity test and increased activities of serum glutamic pyruvic transaminase and alkaline phosphatase (Tab. 6).

There was the direct proportion between both concentrations of serum non-protein nitrogen (NPN) and urea and albuminuria. There was no albuminuria when the concentration of serum NPN was below 40 mg per 100 ml and/or that of serum urea was below 30 mg per 100 ml (Tab. 7).

3) Correlation between albuminuria and other factors

The grade of hepatic parenchymatous damage in the patients with liver cirrhosis or chronic hepatitis was classified by calculating from the values of serum albumin to globulin ratio, cephalin-cholesterol flocculation test and serum cholinesterase activity[13]. The degree of hepatic damage was well correlated with the incidence of albuminuria (Tab. 8). No correlation was observed between the grade of

Table 7. Relationship between the frequency of albuminuria and the values of serum NPN and urea in the patients with liver disease.

Clinico-biochemical examinations		Numbers of the examined	Frequency of albuminuria (%)		
			−	±	+
NPN	*below 30 mg/dl	242	53.3	19.4	27.3
	31 - 40 mg/dl	57	43.9	24.6	31.5
	above 41 mg/dl	29	0.0	17.3	82.7
Urea	*below 15 mg/dl	212	50.9	24.2	24.9
	16 - 30 mg/dl	62	48.3	18.4	32.3
	above 31 mg/dl	16	0.0	25.0	75.0

* normal value

Table 8. Relationship between the frequency of albuminuria and the degree of liver parenchymal dysfunction (liver cirrhosis, chronic hepatitis)

Degree of liver parenchymal dysfunction	Numbers of the examined	Frequency of albuminuria (%)		
		+	±	−
Normal	7	14.3	28.6	57.1
Slight degree	36	16.7	25.0	58.3
Moderate degree	42	16.7	23.8	59.5
Distinct degree	42	31.0	19.0	50.0

hepatic parenchymatous damage and serum NPN and urea concentration (Tab. 9).

The cirrhotic patients with ascites showed the higher incidence of albuminuria than those who have no ascites. This tendency was revealed more prominently among the patients with hepatic cancer (Tab. 10).

4) Antidiuretic substances in the liver disease

Increment of antidiuretic substances (ADS) in the serum, urine, and bile were observed in the patients with liver disease. The urinary excretion of ADS in the patients with ascites was inclined to be higher than in those who have no ascites (Tab. 11).

5) Renal function tests in the liver disease

The incidence of decreased PSP excretion within 15 minutes were 34.1 per cent in the cirrhotics without ascites and 33.3 per cent in the cirrhotics with ascites, while that of the decreased PSP excretion within 2 hours was 15.2 per cent in the patients without ascites and 11.1 per cent in those who have ascites (Tab. 12).

Table 9. Relationship between the degree of liver parenchymal dysfunction and the concentration of serum NPN and urea in the patients with chronic liver disease.

	Degree of liver parenchymal dysfunction	Numbers of the examined	Albuminuria		
			+	±	−
NPN mg/dl	Normal	4	—	*33±0.0	*30±1.5
	Slight degree	28	*33±5.7	26±1.4	26±0.7
	Moderate degree	35	31±5.2	26±2.0	23±0.9
	Distinct degree	36	34±5.2	23±1.4	24±1.1
Urea mg/dl	Normal	4	—	20±0.0	17±1.2
	Slight degree	26	17±3.9	13±1.1	14±0.2
	Moderate degree	32	18±3.8	12±1.9	11±0.5
	Distinct degree	29	16±4.5	11±1.7	12±0.7

* mean ± S.E.

Table 10. Relationship between the frequency of albuminuria and ascites.

Patients with:	Ascites	Numbers of the examined	Frequency of albuminuria (%)		
			+	±	−
Liver cirrhosis	Ascites (−)	46	23.9	28.3	47.8
	Ascites (+)	55	32.7	21.8	45.5
Liver cancer	Ascites (−)	47	25.5	17.0	57.5
	Ascites (+)	22	63.7	13.6	22.7

Thus, there was no difference between the patients with and without ascites in the excretion of PSP.

In the patients with liver cirrhosis the frequency of the decreased urea clearance was 22.2 per cent, that of the decreased renal blood flow was 56.5 per cent and that of the decreased glomerular filtration rate was 20.8 per cent.

All kinds of renal function thus examined, especially renal blood flow, were decreased in a majority of the patients with liver cirrhosis.

6) Histlogical changes of the kidney in the liver disease

The histological changes of the kidney in the normal subjects and the patients with liver disease were divided into four groups according to the frequency and

Table 11. Antidiuretic substance of the serum, bile, and urine among the patients with liver disease.

ADS	Patients with:	Numbers of the examined	ADS index	
			Mean ± S.E.	Range
Serum	Normal liver	12	29±0.8	25 - 34
	Liver disease	7	15±3.3	2 - 28
Bile	Normal liver	8	16±1.0	8 - 19
	Liver disease	18	2±1.0	0 - 6
Urine	Normal liver	7	37±1.1	33 - 42
	Liver cirrhosis without ascites	20	21±2.5	6 - 37
	Liver cirrhosis with ascites	5	16±2.7	9 - 23

A decrease of ADS index shows an increase of antidiuretic activity.

Table 12. Renal functions in the patients with chronic liver diseases without ascites.

Renal function		Numbers of the examined	Frequency of the decreased (%)	Frequency of the normal (%)	Frequency of the increased (%)
PSP excretion test	15 min.	44	34.1	36.4	29.5
	120 min.	46	15.2	47.8	37.0
Urea clearance		31	32.3	51.6	16.1
Renal blood flow		23	56.5	34.8	8.7
Glomerular filtration rate		24	20.8	45.8	33.3
Filtration fraction		24	12.5	33.3	54.2
PSP excretion test in the patients with ascites	15 min.	9	33.3	44.4	22.2
	120 min.	9	11.1	44.4	44.4

Table 13. Microscopic findings of the kidney in the patients with liver disease. (score of renal histological lesions)

	Autopsied materials			Biopsied materials
	Liver cirrhosis (18 cases)	Liver cancer (7 cases)	Acute liver atrophy (6 cases)	Liver cirrhosis (12 cases)
(Glomerulus)				
Exudate into capsular space	2.9	2.8	1.8	5.6
Swelling of capsular epithelium	0.9	1.9	0.0	1.9
Increased cellularity of tuft	1.6	0.5	1.3	1.9
Thickening of lobular stalk	3.4	0.0	1.5	5.0
Epithelial desquamation	2.8	6.4	1.7	1.9
Epithelial crescents	0.0	1.4	0.0	0.0
(Proximal tubules)				
Dilatation of lumina	3.3	5.3	1.7	2.5
Pyknosis of nuclei	0.8	0.0	3.2	0.5
Casts	2.2	5.7	1.7	2.0
Epithelial desquamation	2.1	6.9	3.2	2.4
(Thin limb of loop of Henle)				
Casts	5.0	5.7	0.0	2.0
(Distal tubules)				
Dilatation of lumina	4.3	6.9	2.3	1.8
Pyknosis of nuclei	5.0	5.7	5.8	0.5
Cellular casts	1.7	0.0	3.3	5.4
Hyaline casts	1.3	3.1	0.0	2.3
Granular casts	1.8	5.7	3.3	0.0
Pigmented casts	3.7	5.4	0.7	1.8
Epithelial desquamation	0.0	0.9	3.0	1.3
Fatty vacuolation	1.1	0.0	1.7	0.5
Tubal rupture	0.0	1.4	0.8	0.0
Regeneration	0.0	0.0	0.0	0.0
(Collecting tubules)				
Casts	3.3	2.1	1.7	0.0
(Blood vessels)				
Angitis	0.0	0.0	0.0	0.0
Cortical collapse and medullary hyperemia	0.8	0.0	0.0	0.0
(Interstitium)				
Edema	2.6	3.8	2.3	0.0
Inflammatory reaction	3.6	0.0	3.8	0.1
Granulomatous reaction	0.0	0.0	0.0	0.1

the degree of the abnormalities. Each group was indicated as the following score; negative (+0), grade 1 (+5), grade 2 (+10) and grade 3 (+15), The grade of each histological change, then, was represented on an averaged value of the individual summary of each score.

To avoid the post-mortem histological changes, the changes of the kidney in the patients suffering from the liver disease were indicated as the score which was obtained in those who have liver disease minus, obtained in the normal subjects.

The histological changes in the glomerulus were more prominent in the patients with liver cirrhosis than in those with acute liver atrophy. The prominent glomerular changes were exudation into the intracapsular space, epithelial desquamation and thickening of the glomerular capillary wall. Tubular lesions such as luminal dilatation, epithelial degeneration and tubular rupture, furthermore, were more marked in the patients suffering from acute liver atrophy than in those with liver cirrhosis. The glomerular changes in the patients with liver cancer were remarkable and variable.

The renal biopsies in the patients suffering from liver cirrhosis showed various histological changes, these were mild as a whole, though.

Table 14. Erectrone microscopic findings of glomerulus in the patients with liver cirrhosis. (Averaged score of histological lesions in 12 cases)

(Bowman's capsula)	
Thickening of basement membrane	0.0
Loosing of basement membrane	0.0
Adhesion with tuft	0.5
Swelling of endothelium	0.0
Endothelial desquamation	0.0
Narrowing of capsular space	1.0
(Basement membrane of glomerulus)	
Thickening	7.0
Loosing	1.5
Thining	0.0
Distortion	2.0
Deposit of protein-like material	3.5
(Mesangium)	
Proliferation	0.5
Swelling	1.0
Degeneration	1.5
Increase of matrix	4.5
Invasion into sub-endothelial space	4.0
Granular deposition	1.0
(Specific findings in mesangium and basement membrane)	
Membrane-like material	2.5
Osmiophilic material	0.0
Osmiophilic body	1.5
(Epithelial cell)	
Proliferation	0.0
Swelling	2.0
Changes of organelles	1.0
Vacuolation	6.0
(Epithelial foot process)	
Disarrangement	1.5
Disappearance	0.0
Fusion	8.0
Flattening	3.0
Villous hypertrophy	0.5
Desquamation	0.0
(Endothelium)	
Proliferation	1.0
Swelling	1.5
Desquamation	0.0
Interruption	0.5
Disappearance of slit pore	3.5
Loss of pale layer	1.0
Changes of organelles	0.0
Vacuolation	5.0
(Blood vessel)	
Narrowing	1.5
Deposit of amorphous materials	0.5

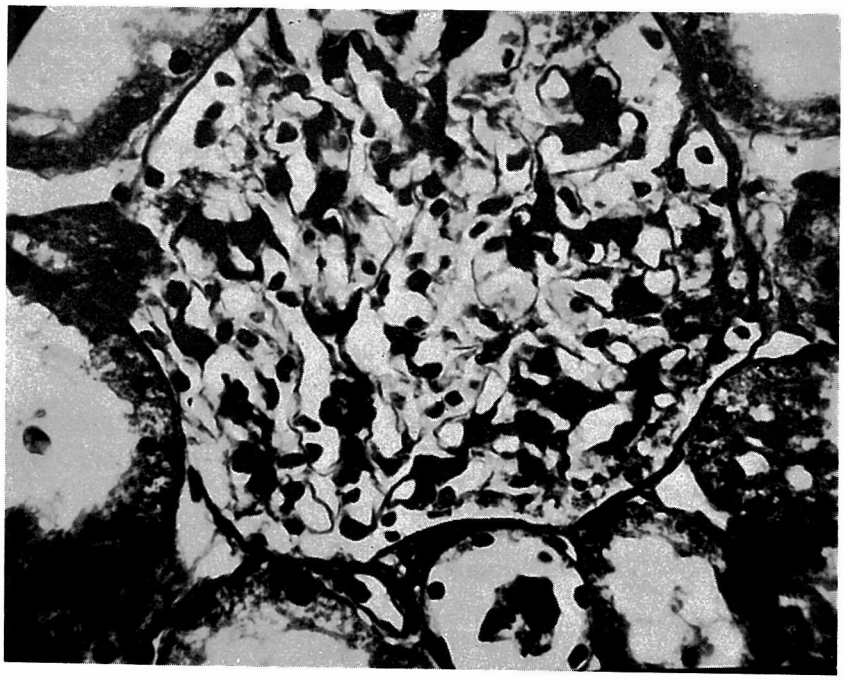

Fig. 1. Light micrograph of the glomerulus showing slight widening of the mesangium and thichening of the basal membrane. There is also the swelling of glomerular epithelial cells. ×920.

On the light microscopy, the glomerular changes were varying degree of diffused glomerular swelling which obliterated the Bowman's space, precipitation of proteinaceous material in the Bowman's space and thickening of the glomerular capillary wall (Fig. 1). The tubular changes were luminal dilatation and the varying degree of degeneration of the epithelial cells with the formation of amorphous casts.

Through the electron microscopy, the most significant findings in the glomerulus were thickening and coarseness of the basement membrane with the occasional deposition of proteinaceous material in the subendothelial space, the increase and degeneration of the mesangial matrix with the occasional small osmophilic granules, partial fusion and flattening of the epithelial foot process and the disappearance of the endothelial pores (Fig. 2).

DISCUSSION

Albuminuria with hematuria and/or cylinduria has been usually observed in the patients suffering from liver disease[14-17]. In our materials the incidence of

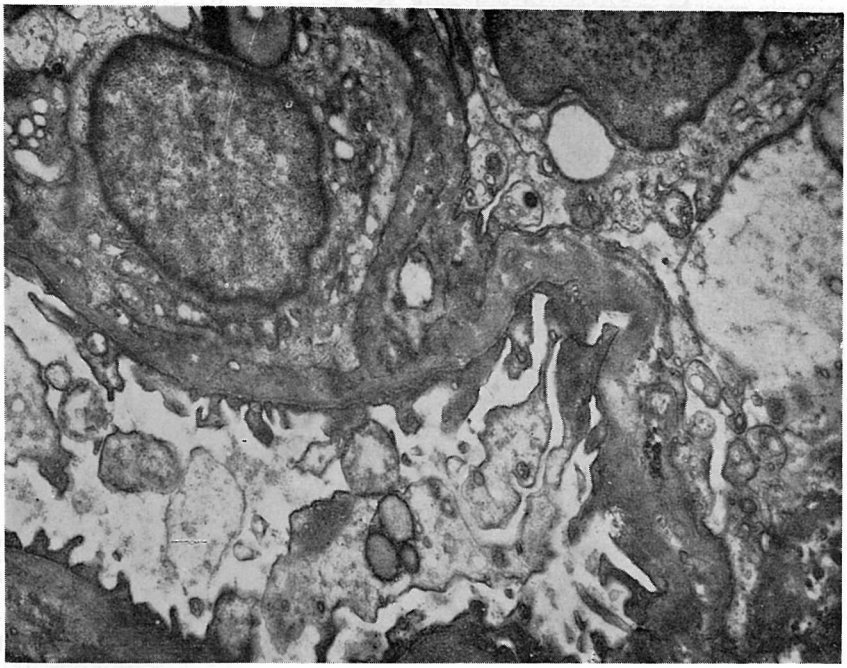

Fig. 2. Electron micrograph of the glomerulus showing moderate thickening of the basement membrane with subendothelial accumulations of amorphous material and osmiophilic granules. There is focal fusion of foot processes. ×13800.

albuminuria among the patients suffering from the liver disease was 5.6 times than those suffering from the gastrointestinal disease, and that of hematuria was 2.5 times. The high incidence of albuminnuria was demonstrated among the patients suffering from the liver disease. Those patients had hypoproteinemia, hypoalbuminemia, hyperglobulinemia, hyper-$\alpha_2$globulinemia, low A/G ratio, low serum cholinesterase activity, positive cephalin-cholesterol flocculation test, high serum cholesterol concentration and/or increased BSP retention. No distinct difference of the frequency of albuminuria was seen between the patients with and without abnormal alkaline phosphatase activity, phenol turbidity test, serum glutamic pyruvic transaminase activity and/or bilirubin concentration.

These abnormal values of clinico-biochemical examinations which have been demonstrated among the patients with albuminuria may indicate both changes induced from the renal lesion and the hepatic parenchymatous lesion. It, then, suggests that the same metabolic disorders of renal disease may have been preceded in the patients with liver disease who have albuminuria.

The fact that the incidence of albuminuria among the patients with liver disease did not distinctly correlated with the increase of ages suggests that the

albuminuria may be more correlated with the degree of hepatic parenchymatous lesion than the increase of ages.

It is not conclusive, though, it has been reported that such kinds of mechanical or physical factors of ascites as increased abdominal pressure, decreased cardiac output[18,19], on changes of hemodynamics in the kindney[20,21] and the portal vein[22,23] were participated in the mechanism of the renal failure. These concepts may be affirmative because albuminuria was more frequently demonstrated among the patients with ascites than among those without ascites.

Many investigators have reported that the glomerular filtration rate and renal blood flow are normal in the patients with the compensated cirrhosis and they are often reduced in those with the decompensated cirrhosis[16,24-31]. In our materials, however, it was noteworthy that, even in the patients without ascites, the decrease of renal clearance, renal blood flow and glomerular filtration rate was noted in considerably many cases.

It is a common opinion that the renal water tolerance in the patients with liver disease is not usually decreased, but it may considerably be decreased in the severe cases[14,32-40]. An endeavor has been done in order to clarify this phenomenon by the electrolytes imbalance, increased secretion of antidiuretic hormone, or decreased destruction of antidiuretic substance, and increased secretion of aldosterone.

It has been reported that antidiuretic substances in the serum, urine, and ascites as well were increased in the cirrhotic patients with ascites, and hepatitic patients in acute stage[41-46]. We had previously demonstrated an antidiuretic substance in the bile, and have confirmed that this substance has been increased during the active stage of acute hepatitis, and decreased to the normal range during the stage of convalescence[12,47].

It is the common picture that azotemia may appear in the late stage of the liver disease[48-51]. This phenomenon may be attributable not only to the hepatic failure but to the renal failure which is accompanied with the liver disease also. It may then be concluded that values of serum nonprotein nitrogen and the urea concentration can not increase beyond a limited level (40 mg per 100 ml for NPN and 30 mg per 100 ml for urea) by hepatic dysfunction alone and that when the values of the concentration are high beyond the levels described as above, there may be renal lesion as a complication of the liver disease.

In the patients with hepatorenal syndrome or acute liver atrophy, it has been assumed that the histological changes of the glomerulus are confined, to a slight degree, and the tubular changes resembling to that of biliary nephrosis, seasoned with acute nephrosis or shock kidney are more prominent[52-54]. In the patients suffering from liver cirrhosis, it has been assumed that the major histological changes are revealed in the glomerulus. The glomerular changes have been de-

scribed as glomerular nephrosis, cirrhotic glomerulosis, proliferative glomerulonephritis, and hepatic glomerulosclerosis and an intense attention has been paid to the thickening of the basement membrane and the proliferation of the mesangium[55-58]. The similar tendency as described above was observed in our material.

Various kinds of histological changes of the kidney were seen in the patients with liver cancer, which may have been brought out from a long standing of the disease and cachexia.

CONCCLUSION

An observation of the kindney based on the clinico-biochemical examination and biopsy of the patients suffering from the liver disease showed a high incidence of the renal lesions.

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