Development of Renal Impairment in Laennec's Cirrhosis

JOHN F. MULLANE,* M.D., PH.D., MAJ., MC, MARVIN L. GLIEDMAN, M.D.

From the Departments of Surgery, Montefiore Hospital and Medical Center, and the Albert Einstein College of Medicine, Bronx, New York 10467; and the Kings County Hospital, Brooklyn, New York 11203

ABNORMAL renal function occurs in both the patient and the experimental animal with hepatic disease.[9, 13, 21, 26, 27, 29] The impaired renal function can occur in the absence of ascites [21, 26, 32] and has not been related to any consistent pathological renal lesion.[3, 5, 30, 33] A kidney from a patient with the hepatorenal syndrome will often improve its function after transplantation.[16] Multiple etiologies have been proposed for this hepatorenal relationship,[2, 9, 21, 26] but a hemodynamic basis appears the most likely cause.

In this study, we have analyzed the clinical course of two groups of patients with Laennec's cirrhosis. The first group, consisting of 45 patients with glomerular filtration rates less than 50 cc./min, was studied for the relations of systemic arterial pressure, abdominal caval pressure, the presence or absence of ascites, and the patterns of electrolyte excretion to their impaired glomerular filtration rate. Since bile pigments have been proposed as having an adverse effect on the kidney,[2, 28, 37] the second group, consisting of 78 patients was evaluated for the relationship of serum bilirubin to the glomerular filtration rate.

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*Present Address: Division of Surgery, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. 20012.

Methods and Materials

In the first group, patients were selected for study who had liver disease secondary to alcoholism and endogenous creatinine clearances (C_{Cr}) of less than 50 cc./min. All clearance studies were 24 hours in duration and a blood specimen was obtained at the start and end of each collection to be analyzed for creatinine, sodium and potassium. The urinary excretion of sodium and potassium were also studied when these patients were on standard hospital diets and were not receiving diuretics. The per cent of filtered sodium and potassium that was excreted was also calculated from the formula: $UV_E/C_{Cr} \cdot P_E \cdot 0.95$; where UV_E = urinary electrolyte excretion, C_{Cr} = endogenous creatinine clearance, P_E = plasma electrolyte concentration, and 0.95 = Donnan equilibrium factor. The endogenous creatinine clearance and fractional electrolyte excretion were also studied in 15 normal adult males who served as controls. The abdominal inferior vena caval pressure was measured in all patients on at least one occasion and values above 10.0 cm saline were considered abnormal.[21] The patients' weights, blood pressure, medications, intake and output, plasma creatinine, blood urea nitrogen, and the development of complications of liver disease were recorded and related to the impaired renal function.

The second group consisted of 78 pa-

tients who had simultaneous evaluation of the serum bilirubin and C_{Cr} on 115 occasions. The results among the 28 C_{Cr} in 20 ascitic patients and the 87 C_{Cr} in 58 non-ascitic patients were plotted separately and the statistical relationship determined by the correlation coefficient (r).

Results

Impaired glomerular filtration rate (first group).

At the time of the abdominal inferior vena caval pressure measurement, 29 patients clinically were non-ascitic and 16 were ascitic. Table 1 lists the endogenous creatinine clearance, fractional electrolyte excretion, plasma sodium, potassium and creatinine, blood urea nitrogen at the time of the caval pressure measurement and the morality. There were only two instances of a normal caval pressure in the presence of a decreased glomerular filtration rate (patients 6 and 24). In addition, only nine non-ascitic and three ascitic patients had caval pressures less than 15.0 cm. saline.

The cirrhotic patients had a similar fractional sodium and an increased fractional potassium excretion compared with the control patients. The mean endogenous creatinine clearance and its standard deviation in the 15 normal patients, was 112.8 ± 10.8 cc./min. The normal patients excreted $0.30 \pm 0.23\%$ of their filtered sodium and $6.03 \pm 3.11\%$ of their filtered potassium while on a standard hospital diet. Only three of the 31 cirrhotic patients had an increased fractional sodium excretion regardless of the degree of impairment of the C_{Cr}, while 12 of 14 cirrhotic patients with a C_{Cr} less than 20 cc./min. had an increased fractional potassium excretion.

Death occurred in 22 of the 45 patients. Hepatorenal failure was the primary cause of death in nine patients (patients 3, 7, 15, 20, 21, 26, 42, 44 and 45); liver failure and hepatic coma associated with upper gastrointestinal bleeding was the cause of death in eight cases; another five patients died in hepatic failure and hepatic coma. Autopsies were performed in only two of the nine patients dying in hepatorenal failure. Patient 3 had glomerulosclerosis,[5] cholemic nephrosis [30] and Laennec's cirrhosis with alcoholic hepatitis. Patient 15 had cholemic nephrosis and Laennec's cirrhosis.

Five of the nine patients dying of hepatorenal failure had intermittent hepatic coma and developed a gradual deterioration of renal function in the presence of a normal systemic blood pressure (patient 3, 7, 21, 44, and 45). Patient 15 had her C_{Cr} monitored over a 5-month period. The initial clearances were abnormal and gradually decreased till a precipitous fall in the C_{Cr} after a portal decompressive procedure. Three days before her death, when the plasma creatinine was 6.8 mg./100 ml., a generalized bleeding diathesis occurred. Patient 26 developed renal failure following an emergency exploratory laparotomy for biliary disease. At operation, she had a fatty liver and a normal extrahepatic biliary system. Her liver biopsy was reported as Laennec's cirrhosis with alcoholic hepatitis. Patient 42 developed renal failure while on diuretic treatment for ascites. The systemic blood pressure was normal till a few hours before death. Patient 20 developed oliguria and a rising blood urea nitrogen in association with a normal systolic but low diastolic blood pressure and a high caval pressure. There was no clinical hemorrhage associated with the low diastolic blood pressure. All these nine patients succumbing from hepatorenal failure had hypotension absent until 3 days before death when hypotension developed in patients 21 and 44; 2 to 24 hours of hypotension preceded death in patients 3, 7, 15, 20, 42 and 45. Table 2 presents the level of deterioration of renal function within 24 hours of death in the nine patients with hepatorenal failure. Patients 3 and 15 had

TABLE 1. *Abdominal Caval Pressure and Renal Function*

Case	Age	Sex	C_{Cr} cc./min.	IVC Pressure cm. saline	$\frac{UV_{Na+}}{F_{Na+}}$ %	$\frac{UV_{K+}}{F_{K+}}$ %	Plasma Na+ mEq./l.	Plasma K+ mEq./l.	Creat. mg./100 ml.	BUN mg./100 ml.	Died
Non-ascitic											
1	49	M	48.0	12.2	—	—	126	4.7	1.4	25	−
2	65	F	48.0	16.2	0.60	19.04	126	3.6	0.9	29	−
3	45	M	48.0	18.5	0.10	4.82	139	2.3	1.2	28	+
4	59	M	47.0	19.2	0.86	11.09	133	4.1	1.0	13	+
5	35	M	46.2	19.2	0.60	0.70	137	3.6	0.9	16	−
6	56	M	45.0	9.6	0.31	6.09	140	4.0	1.0	13	−
7	45	M	41.0	28.4	0.03	49.34	137	3.7	2.7	54	+
8	68	F	37.3	12.4	0.22	6.70	135	3.8	0.8	14	−
9	32	M	36.0	17.6	0.51	9.13	140	4.2	1.1	14	−
10	70	M	35.0	12.0	0.45	7.83	148	4.0	1.0	—	+
11	48	F	35.0	14.2	0.98	13.89	129	4.8	0.9	9	−
12	50	F	34.7	24.2	0.10	8.15	130	3.1	1.1	26	+
13	47	M	30.0	15.0	—	—	—	—	1.7	—	−
14	44	M	30.0	19.2	0.54	64.63	129	3.8	1.0	—	+
15	49	F	22.2	16.0	—	—	133	5.2	1.5	25	+
16	40	M	21.4	15.2	—	—	—	—	1.7	—	−
17	54	M	21.3	16.8	0.79	66.80	140	3.3	2.0	—	−
18	78	M	20.7	16.5	2.24	33.70	140	3.5	2.3	70	+
19	58	M	19.2	18.0	0.22	21.50	133	5.7	4.0	67	−
20	32	F	17.5	21.4	—	—	148	4.0	2.6	70	+
21	45	F	17.0	12.6	0.45	43.52	125	3.4	2.8	45	+
22	47	F	15.8	12.5	0.17	40.78	134	4.3	1.5	12	−
23	52	M	15.0	13.8	0.45	5.40	140	2.6	2.0	15	−
24	69	M	15.0	9.6	0.77	72.40	137	3.2	2.0	15	−
25	65	M	12.5	13.4	—	—	135	3.6	1.7	13	−
26	68	M	10.9	14.0	—	—	141	6.1	4.0	61	+
15	49	F	10.9	23.0	1.02	25.86	128	5.1	2.9	—	+
3	45	M	10.2	21.4	0.65	118.63	124	2.6	5.8	120	+
27	29	F	9.5	20.6	0.00	11.45	131	3.2	2.2	11	−
28	68	M	8.0	15.2	2.32	282.00	142	2.8	2.7	—	+
29	56	F	3.0	20.5	—	—	136	3.9	4.2	70	+
3	45	M	1.6	28.0	0.84	105.21	131	3.9	6.7	140	+
Ascitic											
30	41	F	49.5	23.4	0.00	9.03	144	5.4	0.7	8	+
31	48	F	44.0	16.4	—	—	138	3.0	1.0	12	−
32	56	M	43.7	24.2	—	—	132	4.3	1.4	—	+
33	38	M	42.2	13.0	—	—	140	4.2	1.0	—	−
34	41	M	40.1	14.2	—	—	133	3.4	1.0	12	−
35	47	F	40.0	25.8	—	—	128	5.2	1.8	20	−
36	55	M	39.8	15.6	0.09	4.70	126	2.8	0.9	8	−
37	63	M	32.3	23.0	—	—	132	4.3	1.4	—	+
38	58	M	29.0	33.0	—	—	125	3.3	1.5	—	−
39	32	F	29.0	18.2	—	—	131	5.1	1.4	5	−
1	49	M	24.0	20.4	0.00	19.38	125	4.4	1.1	49	−
40	53	F	23.8	14.2	—	—	133	3.4	1.0	12	+
41	40	M	19.0	22.0	—	—	130	3.3	2.0	19	+
42	33	M	16.2	24.2	—	—	133	4.7	2.6	—	+
43	70	F	12.3	24.8	0.00	18.49	143	5.4	1.7	48	+
40	53	F	11.0	19.2	0.24	111.87	132	3.5	1.8	—	+
44	65	F	5.2	19.4	0.63	22.74	125	2.6	3.2	—	+
45	49	F	3.4	20.0	0.14	52.41	130	5.8	4.2	77	+

TABLE 2. *Terminal Hepatorenal Failure*

Case	Hospital Stay	Plasma Na+ mEq./l.	Plasma K+ mEq./l.	Creat. mg./100 ml.	BUN mg./100 ml.
3	19 days	131	3.9	6.2	140
7	12 days	147	4.1	—	93
15	31 days	142	4.3	8.0	135
20	31 days	141	6.7	—	160
21	57 days	123	3.0	—	98
26	9 days	136	4.9	10.2	92
42	27 days	116	5.2	7.4	196
44	19 days	124	6.3	5.8	73
45	17 days	110	5.8	4.8	92

serial measurements of renal function and their data are presented in Tables 3 and 4. The course of patient 3 is presented graphically in Figure 1.

Patient 3 was a 45-year-old alcoholic man. His liver biopsy 9 months prior to admission was reported as "fatty liver." He was hospitalized 18 days prior to his death with weakness and melena. Plasma creatinine was 2.0 mg./100 ml. and the blood urea nitrogen was 27 mg./100 ml. He was transfused because of anemia and the melena stopped spontaneously. Varices were demonstrated on upper gastroin-

TABLE 3. *Serial Studies of Renal Function*

Case 3

Days Prior to Death	U cc./min.	C_{Cr} cc./min.	$\frac{UV_{Na+}}{F_{Na+}}$ %	$\frac{UV_{K+}}{F_{K+}}$ %	Plasma Na+ mEq./l.	Plasma K+ mEq./l.	Creat. mg./100 ml.	BUN mg./100 ml.	B.P. mm. Hg	I.V.C. cm. saline
18 days	—	—	—	—	138	3.7	2.0	27	120/80	—
12 days	0.625	35.4	0.14	18.6	131	2.2	1.8	22	110/70	—
10 days	0.556	35.0	0.17	23.3	136	3.3	2.0	31	110/70	18
5 days	0.486	11.8	0.03	32.9	134	2.5	3.5	71	110/70	—
4 days	—	—	—	—	133	3.2	—	—	120/80	—
3 days	—	—	—	—	—	—	—	72	110/70	—
2 days	0.771	10.2	0.64	115.9	124	2.6	5.8	120	110/70	21
1 day	0.139	1.6	0.84	105.2	131	3.9	6.2	140	90/60	—
0 day	—	—	—	—	—	—	—	—	90/50	28

TABLE 4. *Serial Studies of Renal Function*

Case 15

Days Prior to Death	U cc./min.	C_{Cr} cc./min.	$\frac{UV_{Na+}}{F_{Na+}}$ %	$\frac{UV_{K+}}{F_{K+}}$ %	Plasma Na+ mEq./l.	Plasma K+ mEq./l.	Creat. mg./100 ml.	BUN mg./100 ml.	B.P. mm. Hg	I.V.C. cm. saline
143	0.451	19.2	—	—	134	3.5	2.0	—	130/70	—
140	0.833	30.5	—	—	136	3.7	1.5	—	110/70	—
87	0.729	43.2	0.26	18.2	135	3.0	1.3	30	130/100	—
85	0.746	47.9	0.27	13.4	138	3.2	1.2	22	120/80	—
78	1.042	54.3	—	—	138	4.0	1.0	—	100/70	6.0
64	0.625	42.5	—	—	139	4.6	1.0	39	120/70	—
59	0.694	36.0	—	—	—	—	1.1	43	110/70	—
53	0.625	26.0	—	—	133	4.5	1.8	55	100/70	—
43	0.590	29.5	—	—	134	4.2	1.5	31	120/80	—
23	0.833	22.2	0.27	9.38	130	5.2	1.5	—	110/80	16.0
17	—	—	—	—	—	—	—	—	—	23.0
15	0.538	10.8	1.02	25.8	128	5.1	2.9	40	130/80	—
9	0.601	22.8	0.89	22.8	134	4.6	2.1	33	110/70	—
8	0.451	7.4	—	—	134	5.2	2.2	42	130/80	—
7	0.635	2.9	—	—	133	5.7	3.0	65	120/80	—
4	0.799	3.9	—	—	131	5.2	5.9	73	100/65	—
3	0.805	3.8	—	—	142	4.3	6.8	89	100/65	—
2	0.208	1.1	—	—	146	4.9	7.5	123	100/60	—
1	0.000	—	—	—	148	4.6	7.3	135	120/80	—
0	0.000	—	—	—	142	4.3	8.0	—	100/70	—

testinal barium roentgenograms. Hepatic coma developed 10 days prior to death without evidence of gastrointestinal bleeding. Coincident with this, there was a rapid, progressive elevation of plasma creatinine and blood urea nitrogen. This was not associated with any fall in blood pressure or weight gain and accumulation of ascitic fluid. The caval pressure was elevated at this time and rose progressively.

Patient 15 was a 49-year-old alcoholic woman who was admitted to the hospital 149 days prior to her death because of jaundice, ascites and ankle edema. The patient was placed on diuretics and a low salt diet and she became non-ascitic by the 138th day prior to death. Varices were demonstrated on upper gastrointestinal barium roentgenogram. She was discharged and re-admitted 88 days prior to death because of melena and hematemesis. The bleeding stopped spontaneously but the patient was discharged after refusing portal decompressive operation. She was re-admitted 30 days prior to death with melena and hematemesis of one days' duration. The bleeding stopped and 17 days prior to death a portal decompressive shunt was performed. Following uncomplicated operation, the patient developed hepatic coma and rapid deterioration of renal function. Three days prior to death, the patient's downward course was complicated by a generalized bleeding diathesis. The caval pressure was initially normal in this patient but was elevated during the last month of life.

Bilirubin and glomerular filtration rate (second group).

In the presence of ascites, there was no significant correlation ($r = -0.21$) of the endogenous creatinine clearance with the serum bilirubin. In four patients, the C_{Cr} was greater than 80 cc./min. (mean 91) while the total serum bilirubin was greater than 6 mg./100 ml. (mean 10.0). In one instance, the patient was in renal failure

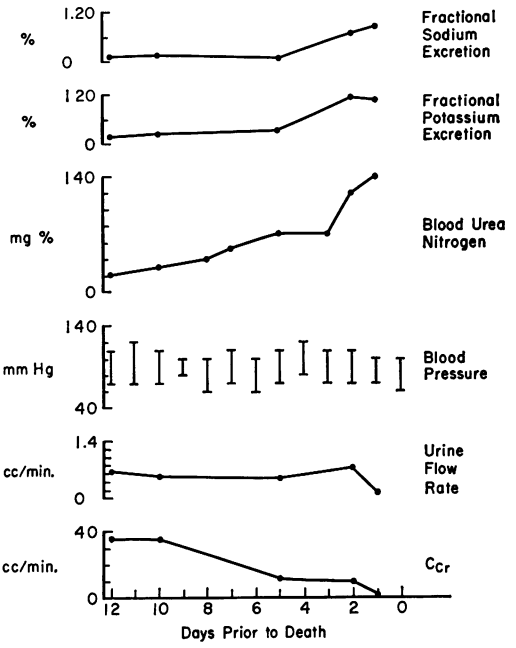

FIG. 1. Renal function deteriorated in patient 3 without accompanying hypotension. This was accompanied by marked sodium retention and increased potassium excretion.

with a serum bilirubin of 0.9 mg./100 ml.

There was an excellent correlation of the C_{Cr} with serum bilirubin in the 58 non-ascitic patients (Fig. 2). Below a serum bilirubin of 4.0 mg./100 ml., there appeared to be a random distribution of the C_{Cr}; above this value, the C_{Cr} was always abnormal.

Discussion

Patients with advanced liver disease were observed to have a decreased glomerular filtration rate without accompanying ascites or hypotension. Even with marked deterioration of glomerular filtration rate, their kidneys were capable of retaining sodium and markedly increasing potassium excretion. The plasma potassium was rarely elevated and plasma sodium tended to be low.

Renal tubular sodium reabsorption in these patients with hepatorenal dysfunction appeared to differ from that of the

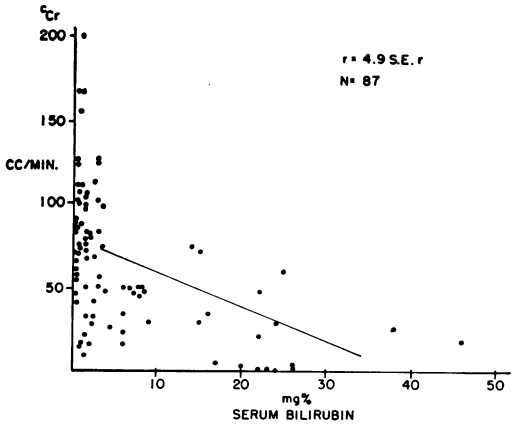

FIG. 2. The 58 non-ascitic patients had excellent correlations of serum bilirubin with the glomerular filtration rate when the serum bilirubin values were above 4.0 mg./100 ml.

patient with chronic disease due to glomerulonephritis, pyelonephritis, or polycystic renal disease.[35] The latter group tend to increase the per cent of filtered sodium excreted as the glomerular filtration rate decreased while patients with hepatorenal dysfunction did not. This renal sodium retention occurred even in non-ascitic cirrhotic patients and may possibly be independent of aldosterone secretion. This finding suggests that a portion of the sodium-losing mechanism is controlled or influenced by the liver but is ineffective in the presence of advanced hepatic disease.

We have previously observed abnormalities of sodium balance and excretion in the non-ascitic dog with hepatic damage due to common bile duct division.[13, 27] Exchangeable sodium increased prior to ascites formation[13] and when the non-ascitic dog was given a saline load, renal sodium excretion was impaired despite the presence of normal renal plasma flow and glomerular filtration rate.[27] These experimental observations, together with the derangement of a sodium-losing mechanism in the non-ascitic patient in the present study, leads us to believe that renal and total body sodium retention can precede the hemodynamic events that lead to ascites formation. The earliest event in the hepatorenal syndrome may be the redistribution of blood flow to the juxtamedullary glomeruli[14] at a time when glomerular filtration rate is normal. The neurogenic, humoral or hemodynamic basis for this redistribution of renal blood flow may then cause a decrease in both the cortical and juxtamedullary flow and lead to hemodynamic failure of the kidney.

The liver may have a direct humoral control on the renal sodium-losing mechanism. Experimental infusion of small quantities of sodium into the portal vein will increase renal sodium excretion when similar systemic quantities of sodium will not.[6, 20, 36] It is possible that this receptor mechanism is weakened by the cellular destruction with cirrhosis. It is also possible that in patients with hepatorenal dysfunction, the liver is ineffective in de-activating circulating sodium retaining factors.

The liver also may influence renal sodium excretion because of an increased sympathetic activity in response to the portal hypertension or because of encirclement of the vena cava by the caudate lobe.[21] Although renal vein hypertension alone may cause an increase in renal sodium excretion,[22, 23, 25] the accompanying congestion of the extremities with the caval hypertension may more than offset this and produce sodium retention.[10, 11]

The renal tubular handling of potassium in the patient with hepatorenal dysfunction was similar to that of the patient with chronic renal failure from other causes.[8, 15] Both were able to maintain a normal or near normal plasma potassium while markedly increasing renal fractional potassium excretion. The decreased body stores of potassium usually seen with advanced liver disease[17] may have aided the renal and extra-renal mechanisms of adaptation to the potassium load associated with the marked fall in glomerular filtration rate.[1, 4, 24]

The renal tubules were capable of normal fractional sodium reabsorption and of secreting large amounts of potassium into the tubular fluid at a time when the glomerular filtration rate had virtually ceased. This suggests that tubular function was intact when the glomerular membrane, or filtration pressure, or intrarenal blood flow distribution were markedly abnormal. The glomerulosclerosis described in some patients with the hepatorenal syndrome may have hindered filtration.[5] In addition, the rise in vena caval pressure may have caused a decrease in the net driving pressure across the kidney and altered intrarenal blood flow patterns.

If the elevated caval pressure with liver disease were to have a similar effect on the kidney as experimental elevation of renal vein pressure, a severe decrease in glomerular filtration rate would not be expected.[22, 23, 25] However, a compensatory mechanism for the renal vein hypertension, an increased renin release and angiotension II production, may be blunted by a diseased liver.[7] The patient with hepatic disease had an impaired conversion of angiotension I to the pharmacologically potent angiotension II [17] and this may account for the tendency to a reduced arterial pressure in hepatic disease.[18, 31] A reduced renal arterial pressure combined with an increased renal vein pressure might, in some instances, cause a severe reduction in filtration pressure and account for the renal failure of hepatic disease.

The severe glomerular changes seen early in the dog with the experimental cholemia[2] are not found as consistently in the dog or human with liver damage. Only 35% of the dogs with experimental biliary obstruction develop some deterioration of renal function.[13] Hyperbilirubinemia also did not appear to be a major etiological factor for the deterioration of the glomerular filtration rate in this study. In 53 cases of advanced cirrhotic glomerulosclerosis, only 58% of patients were jaundiced.[5] In the same study, the patients with biliary cirrhosis had the lowest incidence of glomerulosclerosis when compared with other etiologies for cirrhosis. Since experimental renal vein hypertension can produce a form of glomerulosclerosis,[34] it is possible that in the human, caval hypertension and hyperbilirubinemia could both contribute to this lesion.

Caval hypertension can not be the only cause of the abnormal glomerular filtration rate in the patient with liver disease. The caval pressure is rarely normal in advanced human liver disease [26] but may be only minimally elevated in the dog with experimental liver disease.[12, 13, 27] Renal dysfunction in these instances must be due to causes entirely distinct from caval hypertension. Since the abnormal renal hemodynamics are reversed when the kidney is transplanted to a patient with a normal liver,[16] it is possible that the diseased liver has a humoral control over both the intrarenal vascular resistance and intrarenal blood flow distribution that can cause failure. This possible humoral factor coupled with an elevated caval pressure, decreased arterial pressure, ascites formation, a deranged sodium control mechanism, renal excretion of bile salts, and other metabolic abnormalities of cirrhosis make the renal dysfunction of liver disease a syndrome of multiple etiologies.

Summary

Forty-five patients with Laennec's cirrhosis and a glomerular filtration rate (GFR) less than 50 cc./min. were studied for the relations of systemic arterial pressure, abdominal caval pressure, the presence or absence of ascites, and the patterns of electrolyte excretion to their impaired GFR. Another group of 78 patients with Laennec's cirrhosis had serum bilirubin levels correlated with the GFR.

The caval pressure was abnormal in 43 of the 45 patients with impaired GFR and in all nine patients with hepatorenal failure. The impaired GFR and hepatorenal failure were not related to systemic hypotension or the presence of ascites. The same renal abnormalities occurred in 29 of the 45 patients who were non-ascitic. The non-ascitic patient had an impaired ability to increase the fractional urinary sodium excretion with decline in GFR. The serum bilirubin had no correlation with the GFR in the 20 ascitic patients. In the 58 non-ascitic patients, below a serum bilirubin level of 4.0 mg./100 ml. there was no correlation of bilirubin and GFR but above this value, their correlation was significant.

Impaired GFR can be accounted for in many instances by elevated caval pressure but it is possible that the liver has some humoral influence on the renal circulation. The pattern of sodium excretion in non-ascitic patients suggests that the renal sodium-losing mechanism is impaired before the development of ascites. Hyperbilirubinemia does not appear to be essential for the development of abnormal renal function in hepatic disease.

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