

TRANSHEPATIC TREATMENT OF RENAL FAILURE

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Matsuo, Mizuta and associate¹⁾ demonstrated both in animal and human experiments that the hepatic functions are enhanced when the renal functions are seriously impaired, and they postulated that this phenomenon is the manifestation of the liver activities compensating the loss of kidney functions. In order to confirm this assumption and to investigate the clinical use of this phenomenon, an attempt was made using patients in which the liver was employed as a substitute for the impaired kidneys. As actual procedures, duodenal lavage or surgical drainage of the bile duct was applied to anuric or oliguric patients, and the bile, which was expected to contain some of the elements normally excreted in the urine, was drawn out of the body. Some of the results so far obtained are presented here.

METHOD OF EXPERIMENT

1. Duodenal lavage. A duodenal sound was inserted per os or per nasi and was left in the duodenum as long as possible. The duodenal fluid was syphoned out without suction. Twenty to forty ml. of 20-30% magnesium sulfate solution was given occasionally through the tube in order to keep the Oddi's sphincter open, and in addition, five to ten ml. of twenty per cent sodium dehydrocholate solution (DHC) was given intravenously as a cholagogue.

2. Biliary fistulation. When the duodenal sound was not applicable, a fistula of the gall-bladder was made surgically and a rubber tubing was inserted deeply into the bile duct for securing a maximum amount of the bile.

2. Animal experiment. Under laparotomy, a glass cannula was inserted into the bile duct in a rabbit in which both kidneys had previously been removed.

CLINICAL RESULTS

1. Cases

Case 1, uremia.

I. T., a seventy-eight year old man who had had chronic hypertrophy of the prostate was hospitalized on March. 3, 1953 with a chief complaint of anuria. He had had difficulties in urination for years and was in an absolute anuric state for the last five days. This was

activity which was lowered, and BSP elimination from the blood stream and azorubin S appearance in the duodenal fluid also remained normal. Liver biopsy revealed slight degenerative changes of the parenchymatous cells.

The patient received the duodenal lavage treatment from the 6th day of anuria. The duodenal fluid flowed smoothly and the B-bile was also demonstrated (Fig. 1). Intravenous administration of DHC resulted in a two- or three-fold flow of bile for half an hour. Chlorine, sodium, potassium, NPN and urea were also excreted in great amount resulting from the accelerated flow-rate of bile. The total amount of fluid eliminated was 3033 ml. during an intubation period of twenty hours and a quarter. Compared to the amount of these components normally excreted in urine per day, more electrolytes and about twenty-five to fifty per cent of nitrogen were estimated to have been removed through the tube (Table II). The patient felt much more comfortable, and a striking diuresis (2720 ml. a day) ensued.

TABLE II
Daily Analysis of Urine and Bile* (Anuria, Case 1)

Day**	6			7			8			Normal value
	urine	bile	total	urine	bile	total	urine	bile	total	
Volume (ml)	106	0	106	100	3033	3133	2720	418	3138	1500
NPN (gr)	0,1	0	0,1	0,1	5,1	5,2	3,5	0,7	4,2	10-17
UN(gr)	0,1	0	0,1	0,1	3,4	3,5	2,5	0,4	2,9	14
Cl(gr)		0		0,5	10,7	11,2	11,0	3,7	14,7	6-9
Na(gr)		0		0,2	6,7	6,9	5,7	0,5	6,2	3-6
K(gr)		0			0,6			0,1		2-4

* Bile means duodenal fluid.

** Days subsequent to the onset of anuria, March 6.

With the results of these procedures, the level of azotemia was kept almost constant without aggravation during the three day period of treatment. The kidneys, in this case, were incapable of eliminating more than one tenth of the normal nitrogen excretion, and a continuous transhepatic removal of nitrogen was required. Unfortunately, however, the patient was too weak to continue the treatment and left the hospital in a state of aggravated azotemia.

Case 2, anuria due to acute sulfanilamide poisoning.

M. F., a thirty-two year old man, was admitted to the hospital on Nov. 22, 1950 because of anuria and vomiting. These complaints resulted from an oral dose of three grams of mono-sulfanilamide taken two days before. On admission, eight ml. of bloody urine was obtained by catheterization, and the blood pressure was 124/72. Urinalysis revealed positive urobilinogen and porphyrin. Elevated NPN level (59.2 mg%), normal Takata's colloidal reaction, and normal BSP elimination (5% at 15 min. and none at 30 min.) were also demonstrated.

The duodenal intubation could not be carried out because of persistent vomiting, and a biliary fistula was made in the gall-bladder instead, with simultaneous capsulotomy of the kidneys on the third day of anuria. As shown in Table III, about 250 ml. of bile per day was removed through the fistula for three days following the operation. The bile revealed a high bilirubin index, and a positive diazoreaction which is compatible with the presence of aromatic amides. Despite the fact that anuria continued for three more days, the serum NPN level was not increase, and after six days of anuria the NPN level returned to normal indicating recovery of the renal functions. We would like to name this method as applied

TABLE III
Daily Output of Urine and Bile in a Case of Anuria due to acute
Sulfanilamide Intoxication. (Anuria, Case 2)

* Day	1	2	3**	4	5	6	7	8	9	10	11	
Urine	volume (ml)	0	0	8	0	0	4050	3650	3580	2720	2340	2000
	spc. grav.						1014		1014			1015
Bile	volume (ml)			positive	positive	240	59	8	6	20	40	
	Meulengracht index			—	900	675	562	450		450	225	
	NPN mg/dl			226	209	212						
Serum	protein %			7,0			6,9	7,5	7,5		5,9	
	NPN mg/dl			59,2			58,5		38,4		38,0	

* Days subsequent to sulfanilamide intoxication, Nov. 20.

** Operation for biliary drainage, Nov. 22.

in renal failure, in which biliary drainage is surgically performed, "Mizuta and Okamura's transhepatic treatment of anuria."

Case 3, nephrosis.

T.I., a twenty-eight year old man, was admitted to the hospital on Jan. 30, 1953 with edema and oliguria which he had for the past six months. Laboratory examinations revealed daily urinary excretion of 200-400 ml. of water, 2.5 gm. of NaCl, 7 and 8 gm. of NPN and UP respectively, suggesting impaired kidney functions; proteinuria of 2.8-3.0 %; blood pressure, 130/90; serum protein, 5.0 %; A/G ratio, 0.43; positive Gros' reaction; slightly elevated NPN (54 mg%) and UN (32 mg%); normal serum Na and K; increased serum cholesterol (490 mg%); positive phenol turbidity test and normal or slightly increased elimination of BSP (3 % at 15 min., none at 30 min.) and azorubin S (first appearance in bile, 6 min. and 25 sec. after intravenous administration). Liver biopsy showed nothing to be noted.

The patient was treated with the duodenal lavage method for eight days beginning Feb. 25th (Table IV). The tube was inserted per os every day, and was left for 10 to 18 hours

TABLE IV
Daily Output of Urine and Bile. (Nephrosis, Case 3)

**	Volume in ml	Cl		Na		K		NPN		UN	
		mg/dl	gr	mg/dl	gr	mg/dl	gr	mg/dl	gr	mg/dl	gr
Urine	630	258	1,6	129	0,8	—	—	1270	8,0	1020	6,4
Bile*	425	314	1,4	229	1,1	20,9	0,1	87	0,3	19	0,1
Total	1055		3,0		1,9		—		8,3		6,5
Note: In serum		311		250		17,0		54		32	

* The bile means duodenal fluid.

** Averaged daily volume for 7 days, from February 2 to March 2.

with occasional administrations of DHC. A considerably large quantity of bile, rich in Cl and Na and containing certain amounts of NPN, urea, and K was removed. It must be emphasized in this case, however, that the total amount of elements excreted both through the bile and the urine was almost the same as that in the normal urine. As a matter of fact, the patient lost 3.5 kg in weight and the edema was gone within seven days of treatment.

Case 4, nephrosis.

H.M., a man of twenty-eight years of age, was admitted to the hospital on Sept. 5, 1951 with a chief complaint of edema of two months' duration. Physical examinations revealed severe edema, and pleural fluid on the left side. The blood pressure was 128/90, serum protein, 5.8%, and urinalysis showed 2.6% of protein and 200 mg.% of chlorine, with daily excretion of 400-800 ml. of urine.

Beginning Nov. 26th the duodenal lavage was applied in this case for 10 to 18 hours every day. As shown in Fig. 2, a vigorous flow of duodenal fluid resulted, and the fluid

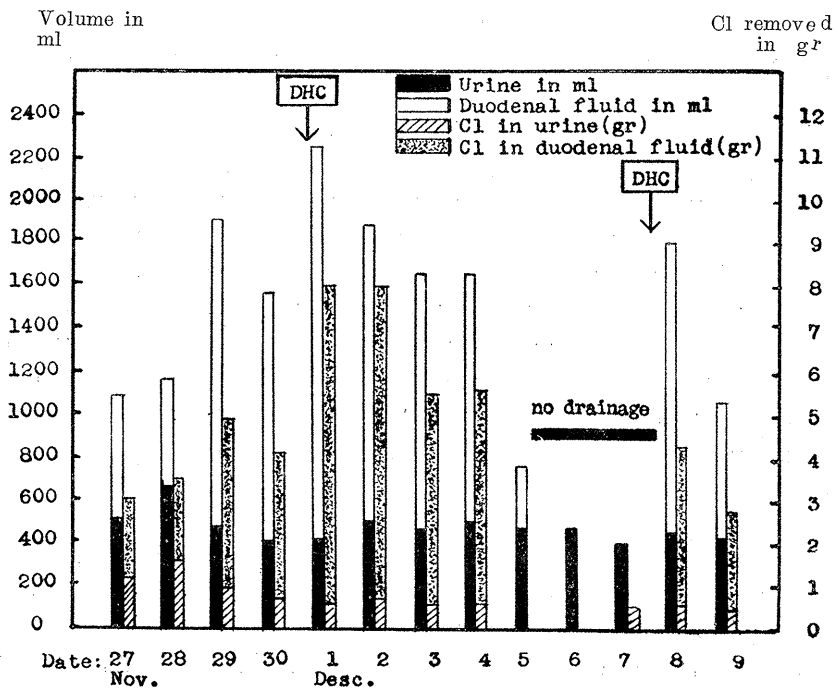


Fig. 2. Daily Output of Urine and of Duodenal Fluid in Nephrosis, Case 4. (DHC: Sod. dehydrocholate, 20%-5 ml)

volume exceeded the urine volume. It was striking that after DHC administration the duodenal fluid output became four times or more greater than the urine excretion. In a day when 2250 ml. of water were removed, 1850 ml. being duodenal fluid, 7.5 gm of total 8.0 gm chlorine was eliminated through the tube.

After having had the duodenal drainage for eight days, the patient lost weight by 5 kg, and also the edema disappeared quickly. The choleric effect of DHC in this case was much more remarkable than in the previous patient, who did not have extensive edema. The maximum outflow of duodenal fluid following administration of this choleric was 240 ml.

per hour and 540 ml. in four hours.

2. Discussion of the clinical results.

a) Amount of duodenal fluid. The amount of the bile, or more precisely "duodenal fluid", is 40-90 ml. per hour if drawn by means of duodenal lavage, and this amount is almost the same as that of the normal urine. The liver, therefore, seems to be capable of substituting for the kidneys as far as the elimination of water is concerned, and DHC meets this end with its remarkable choleric action.

b) Electrolytes. There is little difference between urine and bile in the chlorine concentration in normal subjects. In nephrosis, however, chlorine is usually decreased in urine and is increased in bile. The same relationship is also obtained between sodium and potassium of bile and urine. It is obvious, therefore, that in renal failure such as nephrosis, the liver is suitable for replacing kidneys in excreting electrolytes from the tissues and eliminates them through the liver, which also favors our objective.

c) NPN and UP. In normal conditions, the ratio of NPN level of serum to that of bile and urine is 1 : 1.5-3.0 : 20-50, and the ratio of UN levels is 1 : 0.6-1.0 : 20-30. In other words, the concentration of each nitrogen in bile is 1/50 to 1/20 that of urine, and the liver does not completely compensate for the diminished elimination of nitrogen through the kidneys. In case 1, however, 25-50 % of the normal output of nitrogen was eliminated from the liver with the help of DHC, and further aggravation of azotemia was prevented. In the peritoneal irrigation procedures developed by Fine et al.²⁾, 10-15 % of the normal renal urea clearance was the required efficacy for prevention of azotemia. Our procedures, in this respect, are comparable to their method.

RESULTS OF ANIMAL EXPERIMENT

In order to confirm the clinical results, animal experiments were carried out in nephrectomized rabbits, and the bile collected through a canula inserted in the common bile duct was investigated.

1. Chemical elements of bile. The ability of the liver to excrete water, chlorine, sodium, potassium, nonprotein nitrogen, and urea in nephrectomized rabbits was demonstrated to be as good as in man, and, under these conditions, the liver seemed to compensate the kidney functions exception of nitrogen (Table V).

2. Effect of DHC. Sodium dehydrocholate, if 2 ml. per kilogram body weight were given, was proved to be more effective in excreting the above mentioned elements from the liver one or two days after nephrectomy than immediately after operation. However, accumulation of nonprotein nitrogen and urea in the blood was not completely arrested and only retarded. If administered repeatedly to animals at intervals of a few hours, DHC became less effective. Ether extract

TABLE V
Effects of DHC (Sodium dehydrocholate, 20%-2 ml per kg body weight) upon Bile-Excreting Function of Liver in Nephrectomised Rabbits. (Average value)

Rabbits	Bile	For 2 hours before DHC				For 2 hours after DHC			
		Volume (ml)	Cl (mg)	NPN (mg)	UN (mg)	Volume (ml)	Cl (mg)	NPN (mg)	UN (mg)
Soon after nephrectomy		10,6	31,5	5,0	2,2	23,0	56,3	9,9	4,8
24 hrs after nephrectomy		20,6	71,0	23,1	16,7	36,3	109,8	34,5	28,8

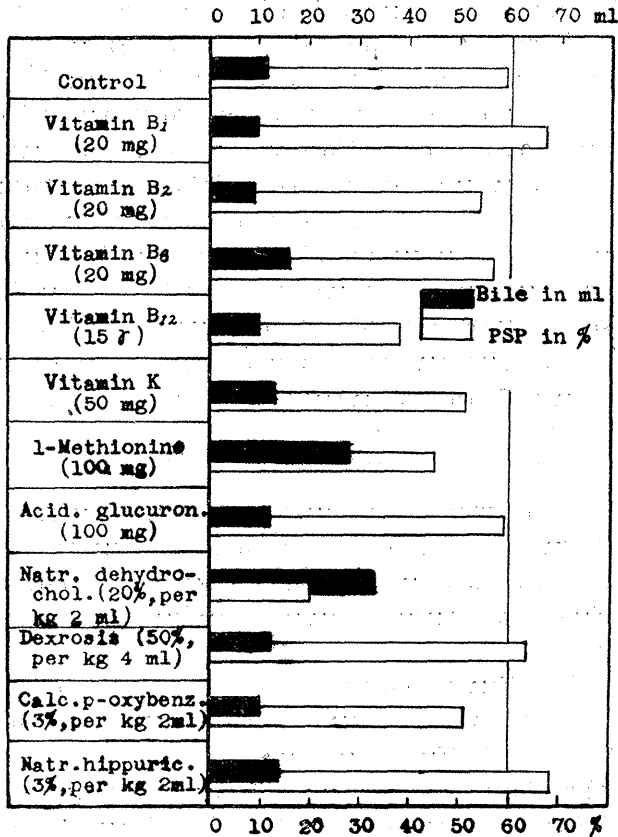


Fig. 3. Effect of Hepatotonics upon the Dyestuffexcreting Functions (PSP) of the Liver in Nephrectomized Rabbits. (Rabbits: 48 hours after nephrectomy. Two hours' observation.)

of cattle-bile or rabbit-bile itself, if infused directly into the intestine, seemed to modify the lowered cholaretic action of this drug.

EFFECT OF HEPATOTONICUM

The fact that the hepatic functions are enhanced after nephrectomy is primarily attributed to substances which appear in the blood stream and stimulate the liver to a great extent. Mizuta and Matsuura³⁾ who first discovered this phenomenon named those substances "Hepatotropin". In order to discover a substance which further affects the liver under such accelerated conditions, some of the commonly used hepatotonics were tested for their effect on PSP (phenolsulfonphthalein) excretion from the liver.

Vitamin B₁ (20 mg.), B₂ (20 mg.), B₆ (20 mg.), B₁₂ (50 γ), K (100 mg.), l-methionine (100 mg.), glucuronic acid (100 mg.), calcium paraoxybenzoate (3 %, 2ml. per kg), sod. hippurate (3 %, 2 ml. per kg) and glucose (50 %, 4 ml. per kg) were demonstrated to be more less stimulatory in PSP excretion if used immediately after nephrectomy. However, those gave negative results, and some of them even revealed the opposite effect if tested more than two days after the operation⁴⁾. These findings seem to be elucidated by the presence of "hepatotropin" which has supposedly stimulated the liver function to the utmost, and those drugs cannot further enhance the liver functions. Not only elimination of PSP but also elimination of chlorine, sodium, potassium and NPN were not modified by these substances. It must also be taken into consideration that DHC itself inhibits PSP elimination from the liver, and that injection of DHC results in dissociation of dye-excretion and choleresis of the liver.

SUMMARY

1. Duodenal lavage was performed in a case of renal anuria with simultaneous administration of sodium dehydrocholate. The amounts of water, chlorine, sodium and potassium excreted in the drawn duodenal fluid were more than those in the normal urine, whereas nonprotein nitrogen and urea removed were half or less the normal.

2. Two nephrotic patients were also treated with the same procedure. Their water and electrolytes were excreted in sufficient quantity by the liver to compensate for their impaired kidney functions.

3. In a case of acute anuria due to sulfamide intoxication, fistulation of the gall-bladder for bile removal and capsulotomy of the kidneys were carried out with satisfactory clinical results.

4. The liver of the rabbits, in which kidneys had been removed 24-48 hours previously, excreted enough water and electrolytes to compensate for the lost functions of the kidneys, whereas elimination of nonprotein nitrogen and urea was less marked.

5. Sodium dehydrocholate rendered a marked choleric action in nephrect-

omized rabbits, suggesting clinical usefulness of this drug in renal failure.

6. Hepatotnica, such as vitamin B₁, B₂, B₆, B₁₂, K, l-methionine, glucuronic acid, calcium paraoxybenzoate, sodium hippurate and glucose did not affect the eliminating function of the liver in rabbits if determined 24-48 hours after nephrectomy.

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