Changes in Renal Function and Intrarenal Blood Flow

T. VARGISH, M.D., R. LEVIN, B.S., J. COTTON, B.A., R. A. CUKINGNAN, M.D.
J. C. BOYD, M.D., W. M. STAHL, M.D.

From the Department of Surgery,
New York University-Bellevue Medical Center,
New York, New York 10016

THE PRESENCE of decreased vascular tone associated with hyperdynamic cardiovascular states has been described previously in patients with cirrhosis as well as septic shock.[4,16,17,18] The fall in vascular tone has been attributed to the opening of arteriovenous shunts by circulating vasoactive substances. [9,13,18] Because hepatic failure is an essential part of the pathophysiology of cirrhosis and may play a part in certain shock states as well, we have chosen an ischemic liver preparation to demonstrate the effect of compromised liver function on a target organ, the kidney. The model for this preparation was described by Stahl and Cukingnan,[19] and they also noted the presence of humoral factors in ischemic liver effluent which resulted in decreased renal function. We use this model to relate changes in renal function to intrarenal blood flow distribution using the ^{133}Xe washout technic.

Materials and Methods

A) Preparation of Dogs. Thirty acute mongrel dogs weighing 15–20 Kg. were divided into two groups: "A" donor dogs, and "B" recipient dogs. All dogs were anesthetized with 25–30 mg./Kg. of pentobarbital and received small amounts (1.5–2 mg./Kg.) of additional pentobarbital during the course of the experiment. Both groups were intubated and maintained on Harvard respirators throughout the experiment. "A" dogs were either bled 500 ml. immediately as controls or were prepared according to the method of Stahl and Cukingnan,[19] undergoing laparotomy and side-to-side portacaval shunt. The common hepatic artery and the portal vein above the shunt were snared isolating the blood supply to the liver. After 2 hours of hepatic ischemia, the shunt was occluded as was the vena cava below the renal veins. The hepatic artery and portal vein were unsnared and 500 ml. of hepatic vein effluent was collected through a PE-240 catheter in the left hepatic vein. This catheter had been placed there previously via retrograde passage down the inferior vena cava from the external jugular vein. After the 500 ml. of blood was collected in heparinized recipient blood bags, "A" dogs were sacrificed.

"B" dogs were divided into two groups—(1) those undergoing hemodynamic studies, and (2) those undergoing ^{133}Xe scans. All "B" dogs had simultaneous renal function studies performed. Dogs in Group I underwent bilateral groin cutdowns with isolation of both femoral veins and one artery. Both veins were cannulated with short PE-240 catheters for fluid administration and extra-corporeal venous return. The femoral artery was cannulated with a long catheter positioned so the tip was at the level of the renal arteries. This catheter was used for blood pressure monitoring and blood infusion. The dogs then underwent laparotomy for the placement of PE-205 catheters in both ureters and isolation of the left renal pedicle and aorta just below the renal arteries. A snare was placed around the aorta at this site. Occlusion of this snare, during cross-transfusion, directed most of the infused blood into the renal arteries. Following heparinization, 3 mg./Kg., the left renal vein was cannulated and left renal blood flow was then directed into a measuring reservoir before being returned to the femoral vein by a calibrated sigmamotor pump. During renal blood flow measurements the reservoir outflow was occluded. The occlusion time for the renal artery

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and vein during cannulation was always less than 60 seconds (Fig. 1.).

Group II dogs underwent laporotomies through small midline incisions for right and left ureteral cannulation. Catheters were brought out through the skin via flank stab wounds. Bilateral groin cutdowns were again performed and PE-240 catheters were placed in one vein and one artery. The second femoral artery was cannulated with 6.5 French radio-opaque, polyethelene catheter which, under direct fluoroscopic control, was placed in the left renal artery. Two to ten milliliters of 50% sodium diatrizoate was injected to confirm the positioning of the catheter and a skin clamp was positioned externally over the left kidney to facilitate proper placement of the monitor probe.

B) Analysis. Intra-renal hemodynamics were monitored with inert gas (in this case radioactive ^{133}Xe) according to the method originally described by Thorburn[20] and modified by Ladefoged[12] and Hollenberg *et al.*[8] Xenon in doses of 0.4–0.8 mCi in isotonic saline were injected directly into the left renal artery catheter and flushed immediately with 2½–3 ml. of isotonic saline. The volume of the Xenon bolus did not exceed 1 ml. The disappearance of activity was measured by a Picker multi-probe digital analyzer interfaced with a Franklin high-speed digital printer. The probe, with a ¾″ sodium iodide crystal, 3⅛″ from the 3¼ aperture of the colimater, was placed adjacent to the skin surface of the animal at the time of maximal inspiration over the clamp site. Activity was measured every second for 5 minutes and then over 30-second periods for an additional 35 minutes.

The 40-minute scans were plotted on semi-logarythmic paper, counts *vs* time. A straight line drawn through the tail of the curve was said to represent Component IV. Using the equation of this line with its slope and zero time intercept, the line was subtracted from the original curve resulting in a new curve. These curve analyses were performed by a semi-automated method using an Olivetti Programma 101. A line was then drawn through the tail of this new curve. This line was said to be Component III. In a similar fashion, lines representing Component II and I were derived. Using ^{85}Kr radiographs and scans of kidney. Thorburn and Hollenberg[8,20] documented that Component I represents blood flow to the renal cortex (Compartment 1), Component II represents the flow to the outer medullary compartment, Component III represents the flow to the inner medullary compartment and Component IV represents the flow

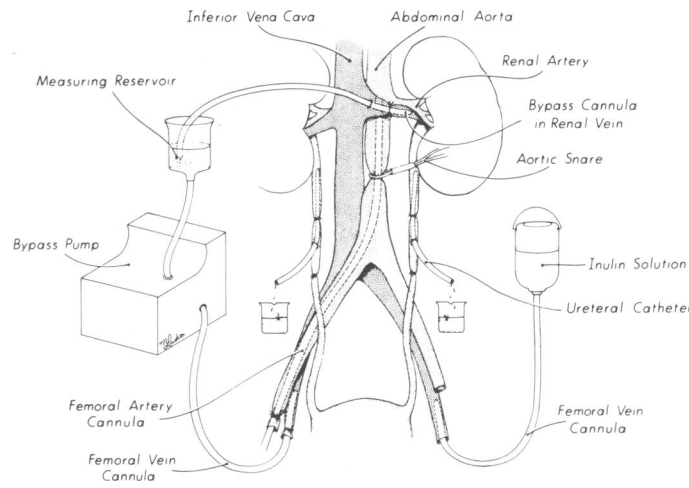

FIG. 1.

TABLE 1. *Renal Function Studies in Groups I and II*

	U_{flow}			C_{in}			C_{osm}		
	cc/min			cc/min			mosm/min		
	Pre Transfusion	Post	Post as % of Pre Values	Pre Transfusion	Post	Post as % of Pre Values	Pre Transfusion	Post	Post as % of Pre Values
Group I Controls									
Dog #1	0.17	0.09	54	5.2	4.5	86	0.39	0.12	30
2	0.21	0.36	171	14.5	13.5	93	0.49	0.65	134
3	0.22	0.47	213	18.2	24.2	133	0.47	0.55	117
4	0.16	0.45	281	13.8	17	123	0.38	0.63	168
Mean			180%			109%			112%
Group I Experimentals									
Dog #1	0.99	0.23	23	29.3	15.2	51	1.85	0.39	21
2	0.21	0.07	33	16.4	6.9	42	0.51	0.06	12
3	0.25	0.02	7	8.6	0.4	5	0.54	0.003	1
Group II Experimentals									
Dog #1	0.34	0.11	32.4	29.5	2.3	8	1.32	0.17	13
2	0.81	0.15	19	23.4	2.2	9	0.88	0.12	14
3	0.46	0.03	7	53.4	0.4	1	0.82	0.05	6
4	0.69	0.02	3	28.2	0.1	1	0.67	0.01	2
5	2.75	1.10	40	14.1	9.3	66	0.70	0.56	80
Mean			20%			23%			19%
p			<0.001			<0.005			<0.005

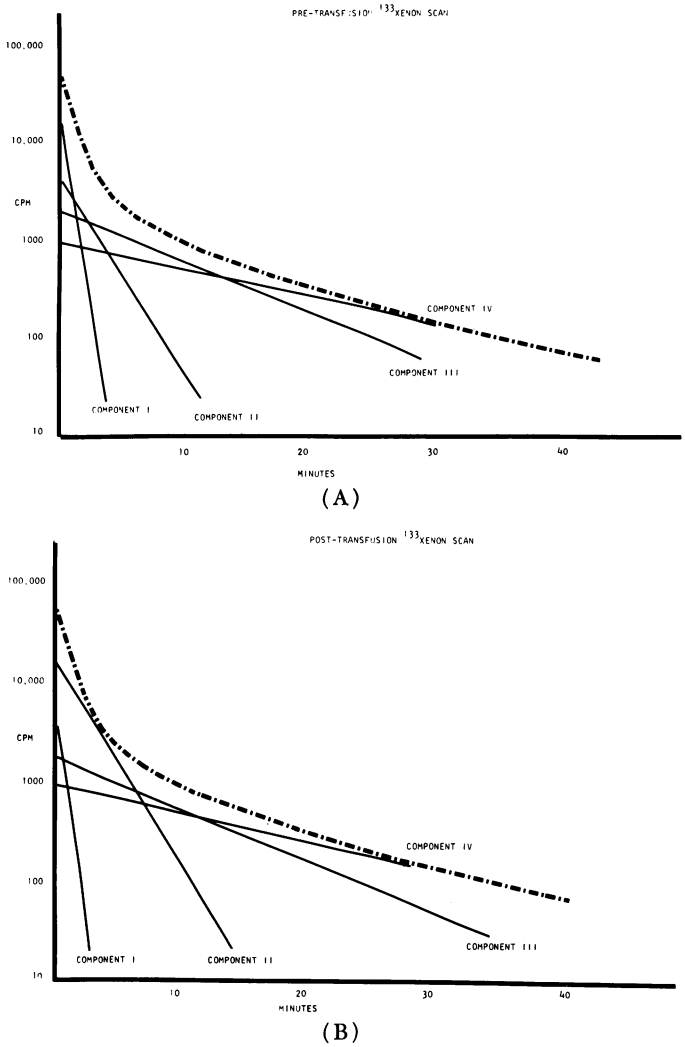

FIG. 2A, 2B. The results of ^{133}Xenon washout curve analyses in pre and post cross-transfusion periods. The slopes of C_I and C_{II} remain essentially the same while the zero time intercepts change significantly. C_{III} and C_{IV} do not change significantly in pre and post cross-transfusion periods.

to the peri-hilar fat. Flows were determined for each component using the formula: Flow (ml./min/100 Gm. of tissue) $= 0.893 \cdot \lambda \cdot 100 \cdot 60^{12}/(T_{1/2} \cdot \rho)$ where λ is the partition coefficient for ^{133}Xe, $T_{1/2}$ is the standard clearance of ^{133}Xe from the kidney, and ρ is the Xenon-tissue coefficient which for kidney is ≈ 1. The partition coefficient, λ, was corrected for hematocrit done at the time of each Xenon scan.[12] In experimental work done by others, a value for relative mass was derived from the initial activity and rate constant of Components I and II: $M_1/(M_1 + M_2) = A_1/K_1/(A_1/K_1 + A_2/K_2)$.[7] This value represents the relative masses of cortex and outer medulla which, together, are supplied by such a significant per cent to total renal blood flow that they have been designated essentially a two compartment kidney and given a total value of 1.0.

Osmolarity was measured by freezing point depression and sodium and potassium determinations were performed using flame photometry. Inulin values were determined by the method of Walser, MacKensie *et al.* Urine output from the individuals kidneys and renal blood flow were measured directly and the systemic blood pressure was measured using a Statham P23Db transducer and a Honeywell 906C Visicorder. Statistical analyses were performed using the methods of comparison between the differences of two means and calculation of values for Student's *T* distribution.

C) Experimental Protocol. All "B" dogs received a fluid load, following operation, consisting of 10 ml./Kg. of 5% dextrose in water and 10 ml./Kg. of 5% inulin solution in isotonic saline administered simultaneously at a rate of 20 ml./min. After the loading period, these dogs were maintained for the remainder of the experiment on a simultaneous constant infusion of 2 ml./min of each of the above fluids. Renal hemodynamics were recorded at 10-minute intervals. Renal function was monitored in both kidneys by measurement, over 20-minute periods, of urine volume, inulin and osmolar clearances, and sodium and potassium concentrations in both blood and urine. Cross-transfusion was performed when urine output was stable, defined as less than 3 ml. variation over 20 minutes for 2–3 collection periods.

In Group I dogs, baseline renal function studies were performed. Five-hundred ml. of blood was then cross-transfused into the femoral artery catheter above the snared aorta, as an equal amount of blood was removed simultaneously from the femoral vein. In four Group I dogs, the cross-transfused blood was drawn from normal dogs (these will be referred to as control dogs). In three Group I dogs the cross-transfused blood was drawn from "A" dogs following 2 hours of hepatic ischemia (experimental dogs). The experimental period, in these animals, began with the conclusion of blood infusion.

In Group II dogs, following stabilization, control ^{133}Xe scans were done. At the completion of the first 40-minute scan, 500 ml. of blood was cross-transfused directly into the renal artery catheter while another 500 ml. was simultaneously removed from the femoral artery. In all Group II dogs the cross-transfused blood was drawn from "A" dogs following 2 hours of hepatic ischemia. When the urine output of the left kidney dropped below control values after the blood transfusion, the second ^{133}Xe scan was performed. At the end of the scan in Group II dogs and at the end of 100 minutes of experimental time in Group I dogs (usually five collection periods), the animals were sacrificed.

In the early experiments, the infusion of blood was done as a bolus over 8–10 minutes, which led to a decrease in urine output 40–60 minutes after completion of the blood infusion. In later dogs, however, it was noted that the fall in urine output occurred much sooner if the

TABLE 2. *^{133}Xenon Scan Results in Group II*

		Initial Activity A_0		A_0 As % Of Total Activity		Relative Mass		Flow (cc/min/100 Gm. of tissue)	
Dog	Transfusion Period	C_I	C_{II}	C_I	C_{II}	C_I	C_{II}	C_I	C_{II}
1	Pre	47,000	5850	85	11	0.67	0.33	313	80
	Post	9300	3800	58	24	0.44	0.56	92	30
2	Pre	4000	580	79	12	0.56	0.44	392	71
	Post	405	470	31	36	0.10	0.90	627	80
3	Pre	21,000	910	94	4	0.82	0.18	224	44
	Post	33,000	4320	86	11	0.70	0.30	196	60
4	Pre	30,100	4100	86	12	0.74	0.26	184	73
	Post	3370	8200	27	65	0.17	0.83	241	123
5	Pre	7200	540	86	6	0.77	0.23	250	41
	Post	5500	2240	60	25	0.35	0.65	280	63
6	Pre	11,750	960	90	7	0.72	0.28	264	56
	Post	1925	1225	45	29	0.28	0.72	165	40
7	Pre	10,200	284	94	3	0.89	0.11	200	46
	Post	1075	365	32	11	0.31	0.69	437	66
8	Pre	20,400	680	93	3	0.86	0.14	298	60
	Post	6400	850	82	11	0.67	0.33	358	95
Mean	Pre Transfusion			88	7	0.75	0.25		
p	Post Transfusion			53	26	0.38	0.62		
				<0.001	<0.011	<0.001	<0.001		

infusion of blood was carried out over a 20-minute period. Consequently, we now advocate infusion of blood slowly over a longer period of time.

Results

In all, 15 experiments were performed using the methods described. Group I consisted of seven donor-recipient pairs, four control and three experimental. Group II consisted of eight donor-recipient pairs, all of which were experimental studies. The hemodynamic and excretory function data during the post-transfusion period are expressed in per cent of mean pre-transfusion values in order to eliminate the wide difference of pretransfusion values between dogs. The Xenon washout results are expressed as actual values (Tables 1 and 2).

Blood pressure, renal blood flow and renal vascular resistance did not differ significantly between post cross-transfusion studies using control blood and those using hepatic ischemia blood (p values ranged from < 0.30 to < 0.80). After cross-transfusion from control dogs, urine flow rose to a mean of 180% of pre-transfusion levels, while after cross-transfusion from experimental dogs, urine flow fell to 20% of pre-transfusion levels. Similarly, C_{in} measured 109% in control transfusions and 23% in experimental transfusions. C_{osm} changed from a mean of 112% after control transfusions to 19% after experimental transfusions ($p < 0.001$ for U_{flow} and C_{in}, $p < 0.005$ for C_{osm}). As described in an earlier section, the fall in urine volume occurred approximately 40–60 minutes after infusion of the hepatic effluent in those experiments where it was infused as a bolus, whereas the fall in urine output occurred immediately if the effluent was infused slowly over 20 minutes.

In the ^{133}Xe scan studies, the initial activity or counts per second at T_0, taken as representation of initial distribution of Xenon to the various compartments, varied inversely during the pre- and post-transfusion periods. Component I fell from a mean value of 88% to a mean of 53% during the post-transfusion period whereas component II rose from a mean of 7% to 26% during this same period ($p < 0.001$ for C. I and $p < 0.011$ for C. II). Similarly, the relative mass of kidney perfused by the flow in Component I and II also varied inversely. The relative mass of Component I fell from a mean pre-transfusion value of 0.75 to 0.38 while the relative mass of Component II rose from 0.25 to a mean post-transfusion value of 0.62 ($p < 0.001$ for both).

The flow as ml./min/100 Gm. of tissue in Components I and II was extremely variable both within the pre-transfusion period itself and between pre- and post-transfusion periods. We were unable to correlate a rise or fall in this flow parameter with changes in renal function, and feel at this time that flow in ml./min/100 Gm. of tissue is not as significant as the relative mass of kidney being supplied by that flow.

In sum, we have been able to demonstrate that with the cross transfusion of hepatic vein effluent from an ischemic liver preparation, there is a fall in urine output with a documented decrease in C_{in} and C_{osm} associated with a shift in distribution of intrarenal flow from Component I, the cortex, to Component II, the outer medullary compartment.

Discussion

Using the Stahl and Cukingnan model,[19] we have shown that changes in renal function were unrelated to

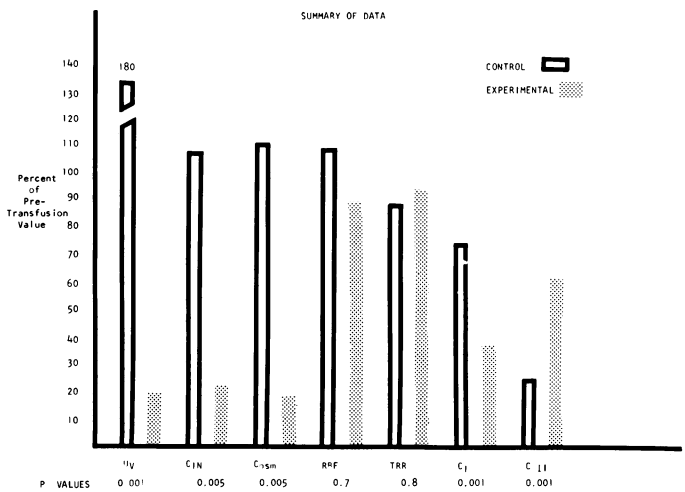

FIG. 3. Summary of data. Results are expressed as the mean per cent of pre transfusion values with (U_V) urine flow in ml/min, (C_{IN}) inulin clearance in ml/min, (C_{OSM}) osmolar clearance in milliosmoles/min, (RBF) renal blood flow in ml/min, (TRR) total renal resistance in mm Hg/ml/min, (C_I) relative mass of component I perfused and (C_{II}) relative mass oc component II perfused. P values were calculated to indicate the significance of the differences between control and experimental groups.

changes in systemic blood pressure, total renal vascular resistance or renal blood flow. Using the ^{133}Xe washout technic, we can demonstrate a shift of blood away from the cortex to the outer medullary regions with a resulting fall in urine output C_{in} and C_{osm}. The mechanism for this shift in intrarenal blood flow may be similar to what occurs in the peripheral circulation during the hyperdynamic states of septic shock and cirrhosis as described by Siegel, Del Guercio and Murray.[4,13,18] They noted that while the cardiac output and blood pressure were normal or slightly increased, there was a decrease in vascular tone which they attributed to the opening of arteriovenous shunts. Similarly, we theorize that the fall in urine output is related to the opening of medullary intrarenal shunts which allow blood flow to bypass the cortex. This is also compatible with the clinical picture seen in cirrhotic patients with varying stages of renal insufficiency described by Epstein and Kew.[5,9] They both noted the shift in blood flow away from the cortex into the medullary region and were able to document changes in renal function associated with this intrarenal blood flow shift. In both papers, moreover, the authors were unable to document any evidence of intrinsic renal disease in these patients at the time of autopsy. Koppel *et al.*[11] were able to demonstrate the prompt return of function in kidneys taken from cirrhotic patients and transplanted into recipients with normal liver function.

The presence of vasoactive humoral substances has been suggested in other papers by Rangel *et al*,[14] Kobold and Thal,[10] as well as work done in this laboratory. In Group II dogs we are able to how a marked change in C_{in} on the experimental kidney while simultaneous measurements in the contralateral kidney do not show the same degree of change. The substance infused has a much greater effect on the experimental kidney than it did on the contralateral kidney for several probable reasons: dilution of the substance decreased its effectiveness after complete mixing; much of the substance may have been removed by the experimental kidney on its initial pass through that kidney; finally, much of the substance may have been detoxified by the dog's own liver. This final explanation coincides with Rangel's experience[14] and raises the question of the origin of the humoral substance. At this time we are unable to answer whether the substance is a toxin released by damaged hepatocytes or whether it is substance produced in the GI tract which is not adequately removed or detoxified by these same hepatocytes. Kobold and Thal[10] have isolated vasoactive substance from the lumen of small intestine in animals subjected to hypotension and GI infarction. We plan to explore this area in experiments.

The properties of this vasoactive substance are unclear. Barnardo's[2] work suggested that perhaps the substance was vasoconstrictor which caused a constriction of pre-glomerular arterioles. Epstein *et al.*[5] reached the same conclusion but then found that phentolamine did not improve cortical flow in these patients when administered directly into the renal artery. Rangel[14] and Kobold[10] suggest that the vasoactive substance may be a vasodilator and our results seem to support this concept. We were unable to demonstrate a significant change in systemic blood pressure, renal vascular resistance or renal blood flow while renal function decreased markedly. We feel that this vasoactive substance is opening low resistance intra-renal medullary shunts rather than constricting pre-glomerular arterioles. The presence of these shunts is further supported by the work of Rector *et al.*[15] in 25 septic patients. He noted that while renal blood flow remained the same or increased, GFR and effective renal blood flow decreased. These results seem compatible with intrarenal shunts much like the shunts described in the peripheral and pulmonary circulations.

The site of activity for this substance has not yet been determined but at least one recent thesis suggests that presynaptic nerve endings may take up the substance from the passing blood stream.[6] We noted that a bolus infusion has less effect on the experimental kidney and requires a longer time lapse before giving a response whereas the slower infusion has an immediate, marked effect. The rate limiting step seems to be the ability of the presynaptic nerve ending to take up the substance as it passes. During hepatic failure certain amines, such as β-hydroxylated phenylethylamines and octopamine, which originate in the GI tract, may not be altered by

liver enzymes monoamine oxidase (MAO) and catechol-0-methyl transferase (COMT) and consequently circulating levels of these amines may be elevated. Levels of one of these-octopamine-was found to be elevated in the serum and urine of cirrhotic patients with hepatic coma.[6] It is postulated that these substances could then be taken up by presynaptic nerve endings in competition with norepinephrine. By displacing norepinephrine in the storage vesicles of these nerve endings, weak pressors like octopamine become false neurohumoral transmitters by diluting norepinephrine concentrations at the postsynaptic receptor sites.[1]

A second possible site of action for these circulating amines is suggested in the work of Berkowitz *et al.*[3] He noted that there were decreased renin levels in the renal vein effluent of cirrhotic patients with renal failure. Using an isolated canine kidney model, he demonstrated that decreased renin levels coincide with decreased cortical flow as measured with ^{133}Xe. By infusing large amounts of renin, it was possible to restore normal cortical flow. This data would be compatible with our results if one considers a mechanism of circulating amines blocking the renin binding sites thus resulting in a depletion of renin substrate and subsequently opening previously closed intra-renal shunts.

Finally, clinical trials have been attempted, to evaluate the use of metaraminal and dopamine in the treatment of "hepato-renal" syndrome. Fisher initially used metaraminal for its alpha-effect but found that it was the weaker beta-effect on the pre-glomerular arterioles that resulted in some improvement of renal function. He also used dopamine, primarily as a renal vasodilator.[6] Since dopamine is a norepinephrine precursor, it is possible that this drug may really be restoring proper norepinephrine levels in presynaptic storage vesicles and consequently normal renal function. These clinical trials have been unsatisfactory thus far and as long as the exact identity of the vasoactive substance and its mechanism of action remain a mystery, it seems unlikely that successful medical treatment will be possible.

We feel that our work presents a model of renal insufficiency which results from humoral vasoactive substances acquired in hepatic ischemia. This model satisfies the clinical picture seen in "hepato-renal" syndrome which occurs with severe hepatic decompensation and possibly certain shock states. Further work must be done to isolate the vasoactive substance and define its mechanism of action so that clinical steps can be taken to prevent its deleterious effect on renal function.

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