CARBON TETRACHLORIDE POISONING IN MAN. I. THE MECHANISMS OF RENAL FAILURE AND RECOVERY [1]

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Carbon tetrachloride poisoning in man, whether by inhalation or ingestion, is frequently associated with anatomical and clinical evidence of renal damage. Smetana (1) has shown that the distal tubule appears to bear the brunt of the renal pathological processes resulting in oliguria or anuria, and Woods (2) has demonstrated the identity of the renal pathology in this disease with that of the crush syndrome. This type of acute renal failure has therefore been included among the subclassifications of lower nephron nephrosis by Lucké (3). This author believes that the scant urine flow in this syndrome is adequately explained by the back-diffusion of the glomerular filtrate through the damaged tubular walls. This concept was first promulgated by Dunn, Haworth and Jones (4) working with experimental oxalate nephritis. Bywaters and Dible (5) concluded this to be the mechanism of anuria in the crush syndrome on the basis of morphology alone. A. N. Richards (6) was able to observe this phenomenon directly in the frog kidney poisoned with mercuric chloride. He noted the absence of urine formation in spite of normal or augmented glomerular filtration. Additional evidence cited for the occurrence of abnormal tubular permeability is the finding of negative Tm_D's [3] by Bobey *et al.* (7) and of decreased creatinine/inulin clearance ratios by Richards, Westfall, and Bott (8) in experimental uranium poisoning in dogs; the demonstration of negative Tm_{PAH} values by Redish, West, Whitehead, and Chasis (9) in a child with oliguria due to sulfathiazole intoxication and by Marshall and Hoffman (10) in two patients with post-shock uremia; and the demonstration by Phillips and Hamilton (11) of markedly reduced renal creatinine extraction ratios in dogs with near normal renal blood flow following renal ischemia.

Recently attention has been directed toward the possible contribution of renal hemodynamic factors in the maintenance of the oliguria during the post-shock phase, when the full-blown picture of uremia becomes manifest. Trueta *et al.* (12) have demonstrated in man as well as other mammalian species the presence of juxtamedullary glomeruli with large efferent arterioles draining directly into the venous circulation through the vasa recta, thereby avoiding the usual peritubular capillary circuit. As an explanation for the oliguria in the crush syndrome these authors postulate a neurogenic mechanism resulting in the shunting of blood from the active filtering and secreting cortical zone to the poorly functioning juxtamedullary region of the kidney.

Phillips and Hamilton (11) demonstrated rapid recovery of renal blood flow, as measured by the Fick principle, in dogs following two hours of complete renal ischemia. It is unfortunate that they did not perform renal blood flow studies on their dogs with three and four hours of renal ischemia, since it was these animals which subsequently developed progressive uremia, thus more nearly simulating the human material. Bobey *et al.* (7) observed immediate and maintained normal renal blood flow values in dogs with uranium poisoning for periods as long as 14 months. However, since uranium exerts its maximum toxic effects upon the proximal tubule (13) and the dose used was insufficient to cause oliguria, neither the histological nor usual clinical manifestations of the human syndrome under discussion were simulated in this series of experiments.

Corcoran, Taylor and Page (14) performed serial inulin and diodrast clearances upon one pa-

[1] Indebtedness is gratefully acknowledged to the U. S. Standard Products Co., of Woodworth, Wisconsin, for furnishing inulin in generous amounts for parenteral use in this work.

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[3] Abbreviations used will be as follows: D = diodrast, IN = inulin, CR = endogenous creatinine, PAH = p-aminohippurate, C = clearance, thus C_{IN} is clearance of inulin, Tm_{PAH} and Tm_D = tubular maximal excretory capacity for p-aminohippurate and diodrast respectively. E = renal extraction ratio, RBF = renal blood flow, U/P ratio = ratio of urine concentration to plasma concentration.

tient with carbon tetrachloride poisoning during the recovery phase and found values for C_{IN}, C_D and Tm_D of 5.8 cc./min., 67.8 cc./min. and 3.7 mgm./min. respectively on the 10th day of the disease. By the 64th day these values had returned to the normal range. On the basis of the clearance data these authors concluded that in addition to tubular back-diffusion depressed renal blood flow, caused by renal swelling, plays an important role in the production of oliguria. Marshall and Hoffman (10), using mannitol and PAH, performed similar studies upon two cases of post-shock uremia and one case of carbon tetrachloride poisoning. The clearance values were all markedly depressed during the early recovery phases with a gradual return to normal. Burnett *et al.* (15) studied renal clearances in wounded soldiers. They found significant depressions of mannitol and PAH clearances and Tm_{PAH} in those patients who had suffered moderate to severe shock even though the studies were undertaken from 14 hours to 30 days after recovery from shock.

With the severe tubular damage and probable tubular back-diffusion of the test substances that occur during the early recovery phase of this syndrome it would seem that the estimation of hemodynamic factors on the basis of uncorrected clearance measurements yields data of dubious significance. Certainly when a marked decrease in the renal extraction of PAH occurs, as has been adequately shown to be the case following total renal ischemia in the dog by Selkurt (16) and Phillips and Hamilton (11), the clearance of this substance cannot be used as a significant measure of effective renal plasma flow. These limitations of the clearance methods were early emphasized by Smith (17).

We have therefore studied the renal extraction ratios of PAH and inulin together with their clearances and other aspects of renal function in four patients with acute carbon tetrachloride poisoning during various stages of the disease. The results indicate that a marked reduction in renal blood flow is in fact important in the maintenance of the oliguria, if not in its initiation.

METHODS

Studies of renal function were performed on four male patients with acute renal damage due to inhalation of carbon tetrachloride.[4] These studies were started between the eighth and 11th day from the onset of oliguria and continued periodically for as long as 60 to 320 days. Simultaneous inulin, p-aminohippuric acid, urea, endogenous creatinine and chloride clearances and the measurement of Tm_{PAH} were performed according to the standardized techniques of Smith, Goldring, and Chasis (18). The technique of Warren, Brannon, and Merrill (19) and Bradley and Bradley (20) was utilized for the renal vein catheterizations in order to determine the renal extraction of PAH, inulin and oxygen.[5] Renal blood flow was calculated by the formula $RBF = (UV/A\text{–}R) \times (1.00/1.00\text{–}H)$, where A, R, and U represent arterial, renal venous and urine concentrations respectively of PAH or inulin in mgm./cc., V represents urine flow in cc./min., and H is the hematocrit expressed as a fraction of 1.00. Since repetition of renal vein catheterization in any one individual during the early recovery phase was thought unwarranted this procedure was performed once on each individual at times representing different phases of the recovery process. In each case the final position of the catheter was checked by means of roentgenograms.

On the days intervening between the standard clearance studies, when the 24 hour urine flow exceeded 1000 cc., endogenous creatinine clearances alone were obtained using two to four hour periods and voided urine specimens. One blood specimen was drawn at the midpoint of the urine collection period. In two of the subjects with severe oliguria, inulin and PAH clearances were determined, each on one occasion, by giving one intravenous injection which acted as both the priming and sustaining doses. Blood was drawn approximately every six hours and urine was collected at the end of a 24 hour period by catheterization and bladder washout. Total PAH (free and acetylated) and inulin analyses were performed on these specimens. The urine of the preceding day was used for the determination of the rate of excretion of the inulin blank (UV_o).

The other studies of renal function consisted of the usual clinical measurements for urine concentrating capacity, urinary acidity, efficiency of phenol red excretion, examination of the urinary sediment, plasma creatinine and urea nitrogen determinations and the semiquantitative estimation of albuminuria.

Inulin was determined by a modification of Harrison's method as described by Goldring and Chasis (21), with the exception that 2 cc. of undiluted plasma were added to 6 cc. of 20 per cent yeast and 1.0 N NaOH was substituted for 1.1 N NaOH in the precipitation of proteins. PAH, both free and total, was determined by the method of Smith *et al.* (22); creatinine by the Brod and Sirota modification of the Bonsnes and Taussky method (23);

[4] These patients were on the 1st and 2nd Medical Services of Mt. Sinai Hospital. The clinical details will be presented elsewhere.

[5] Drs. Sigmund Brahms and Irving Kroop collaborated with the author in the performance of the renal vein catheterizations.

TABLE I

The renal extraction ratios of PAH and inulin and renal plasma flow in four cases of carbon tetrachloride poisoning

Patient	Number of days of oliguria	Day from onset of oliguria	Renal extraction ratio $\frac{A-R}{A}$		Renal plasma flow*		Renal blood flow	$1.08 \times C_{PAH}$	C_{IN}
			PAH	Inulin	PAH $\frac{UV}{A-R}$	Inulin $\frac{UV}{A-R}$			
					cc./min.	*cc./min.*	*cc./min.*	*cc./min.*	*cc./min.*
F. M.	10	8	0.034	0.00	24.5	0	40.8	0.944	0.00
F. H.	2**	13	0.106	0.045	160	167	232	21.4	7.84
H. Z.	11	24	0.895	0.133	640	708	896	618	97.2
W. M.	17	37	0.594	0.149	592	434	897	392	56.0

* U, A and R represent urine, femoral arterial and renal venous plasma concentrations of PAH or inulin respectively, in mgm./cc., and V represents urine flow in cc./min. These values were obtained from averages of three extraction ratios and three urine collection periods, except for F. M. in whom one urine collection period was used.

** The occurrence of oliguria is questionable in this case because of difficult anamnesis. Its duration, if present, was definitely no longer than two days.

blood oxygen by the method of Roughton and Scholander (24); chlorides by Van Slyke and Hiller's adaptation of Sendroy's method (25); and urea by the aeration technique of Van Slyke and Cullen (26). All colorimetric determinations were performed on the Coleman Jr. spectrophotometer.

RESULTS

1. *Renal extraction ratios and renal blood flow*

Control PAH renal extraction ratios performed on four patients without renal disease yielded values of 0.904, 0.890, 0.910 and 0.895. The values for PAH and inulin extraction ratios and the renal plasma flows calculated therefrom in the four patients with carbon tetrachloride poisoning are presented in Table I. It is evident that during late oliguria and early diuresis there was a marked reduction in renal blood flow, and that the perfused tissue extracted PAH with poor efficiency, so that $1.08 \times C_{PAH}$ yielded values much lower than $\frac{UV}{A-R}$ for PAH, the true renal plasma flow.[6] Thus, patient F. M. on the eighth day following the onset of oliguria had a renal plasma flow of only 24.5 cc./min. and his kidney extracted PAH with only 3.4 per cent efficiency.[7] The value for $1.08 \times C_{PAH}$ was reduced to 0.94 cc./min. Patient F. H. on the 13th day had a renal plasma flow of 160 cc./min. in spite of a diuresis of over 3000 cc. in 24 hours. His PAH renal extraction efficiency was 10.6 per cent; $1.08 \times C_{PAH}$ was 21.4 cc./min. Patient H. Z. had both a normal renal plasma flow and PAH extraction ratio by the 24th day, so that $1.08 \times C_{PAH}$ closely approximated the true renal plasma flow. In contrast, W. M., who suffered oliguria for 17 days, still had a reduced PAH extraction (59.4 per cent) on the 37th day even though his renal plasma flow was normal (592 cc./min.). The low renal blood flow figures of 896 and 897 cc./min. for H. Z. and W. M. respectively are merely expressions of low hematocrits.

The use of the inulin extraction ratio for the calculation of renal plasma flow is fraught with error because of the comparatively low arterio-

[6] $\frac{UV}{A-R}$ represents the application of the Fick principle to the determination of renal plasma flow, and as long as a measurable quantity of PAH is present in the urine it is an expression of true renal plasma flow, being independent of the efficiency with which the tubules extract PAH from the plasma. C_{PAH}, the clearance of PAH, or $\frac{UV}{A}$ in the normal kidney is a measure of renal plasma flow to effective functioning renal parenchyma and is therefore dependent upon the efficiency of renal extraction. It normally is about 92 per cent of the total plasma flow, the remaining 8 per cent representing plasma flowing to non-functioning tissue such as capsule, interstitium and perirenal fat. Hence $1.08 \times C_{PAH}$ should approximate $\frac{UV}{A-R}$ closely. A discrepancy between these values merely reflects the deviation of renal extraction of PAH from the average 92 per cent value.

[7] Technical errors in the withdrawal of renal venous blood, such as too much suction causing the admixture of inferior vena caval blood with renal venous blood, would yield an erroneously low extraction ratio. However, this would also yield an erroneously high plasma flow, since the value A–R in $\frac{UV}{A-R}$ would be smaller than the true value.

TABLE II

*Serial renal clearance studies in four patients recovering from carbon tetrachloride poisoning**

Patient	Number of days of oliguria	Day from onset of oliguria	Urine flow	Plasma clearances				Clearance ratios		U/P ratios		Effective renal blood flow	T_{mPAH}	Filtration fraction	$\frac{C_{IN}}{T_{mPAH}}$	$\frac{C_{PAH}}{T_{mPAH}}$	Plasma creat.	Plasma urea N
				Inulin	Creat.	Urea	PAH	$\frac{\text{Creat.}}{\text{In.}}$	$\frac{\text{In.}}{\text{Urea}}$	Inulin	Chloride							
			cc./24 hrs.	*cc./min.*	*cc./min.*	*cc./min.*	*cc./min.*					*cc./min.*	*mgm./min.*				*mgm./100 cc.*	*mgm./100 cc.*
F. M.	10	8**	240	0.00	0.79	0.35	0.81			0.00	0.71						22.4	58.0
		10	1500		0.28	0.16					0.92						24.6	123
		11	2010		3.79	2.28					0.87						26.5	128
		17	1440		10.4	6.48					0.19						11.7	106
		20	1592		23.6	11.6					0.09						6.00	78.0
		23	1830		48.4						0.37						2.80	101
		26	2715	43.5	52.2	31.5	410	1.20	1.38	18.7	0.40	568	33.3	0.106	1.30	12.2	2.00	29. 0
		31	1790		60.8						0.35						1.68	18.0
		38		50.6	64.0		397	1.26		10.3		592	52.6	0.127	0.96	7.53	1.52	
		60		74.0	81.0		512	1.10				854	71.3	0.145	1.04	7.18	1.20	
F. H.	2(?)	10	2290	3.78	4.34	4.00	14.4	1.15	0.944	2.61	0.21		1.85	0.261	1.94	7.82	16.2	146
		12†	3700	3.55	3.95	2.62		1.11	1.16	2.51	0.20						16.9	166
		13†	3370	6.74	7.26		17.4	1.06		3.24	0.27			0.389				
		21	2250	37.7	38.3	20.5	169	1.02	1.84	14.6	0.26		17.0	0.223	2.22	9.96	3.70	81.0
		34		57.3	83.8	53.0	370	1.46	1.08	8.34	0.35	532	51.6	0.155	1.11	7.16	1.32	20.0
		47		70.1	90.3		390	1.11		8.94		600	72.2	0.180	0.97	5.40	1.24	
		61		78.2	93.0		389	1.25		9.10		627	83.9	0.201	0.93	4.64	1.16	14.0
		132		90.3			388			7.00		669	75.7	0.232	1.18	5.04		13.0
		220		110	158		583	1.43		15.2		980	76.2	0.190	1.45	7.66	1.16	
		307		117	131	84.2	502	1.12	1.39	14.0		816	78.4	0.232	1.49	6.50	0.99	14.0
H. Z.	11	10	880		1.42	1.54					0.47						30.7	166
		13	1180		4.50						0.66						32.0	189
		18	1965		14.1						0.08						13.8	193
		20	1460		26.6						0.18						4.80	
		21	2575		35.2	8.54					0.30						3.50	168
		24	1311	86.5	79.6	46.3	510	0.92	1.97	74.3		712		0.170			1.40	21.0
		29	3945		73.2												1.18	
		35		94.4	89.9		433	0.96		12.9		660	85.3	0.218	1.11	5.08	1.10	15.0
		106		99.7	107		603	1.07		20.4		1075	84.4	0.165	1.12	7.15	1.16	
		250		97.0	99.6		473	1.03				910	76.2	0.205	1.27	6.22	1.15	
W. M.	17	11**	95	0.49	0.48	0.14	2.38	0.97	3.43	7.50	0.54			0.208			18.6	71.0
		19	2272	1.66	4.06		9.91	2.44		1.38	0.51		2.54	0.167	0.65	3.90	20.9	98.0
		26	2378	25.2	31.0	21.6	143	1.23	1.16	12.3	0.20		12.9	0.176	2.13	11.5	4.20	68.0
		37	2975	57.6	78.6	48.8	362	1.37	1.18	17.3	0.20		30.8	0.152	1.79	11.8	1.08	16.0
		48		71.0	85.6	60.2	452	1.20	1.18	43.1		698	57.4	0.157	1.24	7.90	1.04	19.0
		63		74.6	89.0		570	1.19		7.97		926	71.3	0.132	1.05	8.00	1.06	
		96		91.0	100		470	1.10		8.84		824	83.2	0.194	1.10	5.60	1.07	14.0
		175		97.2	104		538	1.04		7.78		1020	130	0.181	0.75	4.12	1.08	
		331		108	117		618	1.08				1125	86.6	0.175	1.25	7.14	1.00	
Normal Values				131±21.5		697±136						77.5±13						

* All clearance figures represent the average of three clearance periods and are corrected for a body surface area of 1.73 sq. m.
** These clearances were of the 24 hour type, as explained under methods.
† The plasma and urine blanks for inulin on these days were assumed to be the same as those found on the 10th day.

venous difference, high plasma and urine inulinoid blanks and the relative insensitivity of the analytical method as compared to the PAH method. The good check in the calculations of the renal plasma flow by the two methods in patient F. H. was surprising. The poorer checks obtained in the other three subjects were expected. The C_{IN} and E_{IN} of 0.00 may be due to lack of filtration or tubular back-diffusion of the inulin molecule or a combination of both.

A urea extraction ratio determined in F. M. simultaneously with PAH yielded a value of 0.149 and a calculated renal plasma flow of 24.1 cc./min., affording an excellent check on the figure 24.5 cc./min. as obtained by means of the PAH extraction ratio.

A renal arteriovenous oxygen difference of 3.0 volumes per cent with an oxygen utilization of 26.8 cc./min. obtained in subject W. M. on the 17th day are within the normal range. The oxygen utilization was not determined in the other three patients.

2. *Renal clearance studies*

The results of the renal clearance studies are presented in Table II. There was a marked reduction in the clearance values of all the substances studied during oliguria and early diuresis. The following points are of special interest:

a. With the onset of diuresis the increment in the clearances of inulin, creatinine or urea were extremely small or even in the negative direction in patients F. M. and F. H. on the 10th and 12th days respectively. This suggests that the initial diuresis may be a reflection of tubular repair rather than an increase in glomerular filtration. However, since active water reabsorption appears to be markedly impaired at this stage, an increase in glomerular filtration, *per se,* of a magnitude small enough to be undetected with present methods, may result in a large increment in daily urinary output.

b. The U/P ratio for chlorides was always significantly less than 1.00, indicating preservation of selective tubular reabsorption of chlorides. During early diuresis the U/P ratio for inulin reached minimum values of 1.38 and 2.51 in patients W. M. and F. H. respectively, with simultaneous chloride U/P ratios of 0.51 and 0.20. Since the kidney is unable to do osmotic work at this stage, the urine being isosmotic with plasma (sp. gr. 1.010), water must follow the actively reabsorbed chloride in order that osmotic equilibrium be maintained. Such low inulin U/P ratios, therefore, in the presence of considerable selective chloride reabsorption, is suggestive of abnormal back-diffusion of inulin.

c. The clearance of PAH, though reaching very low figures during the early recovery phase, was always greater than C_{IN} and C_{CR}. In addition, Tm_{PAH} values were never negative, indicating continued active tubular secretion of PAH.

d. In patient H. Z., who sustained the least renal damage as judged by recovery rate, the CR/IN clearance ratio remained close to unity between the 24th and 250th days. The other three patients revealed high CR/IN clearance ratios during the early recovery period with gradual declines towards unity as recovery neared completion.

3. *Recovery of function*

The recovery of the inulin, creatinine and PAH clearances and the Tm_{PAH} values together with declining plasma creatinine levels are plotted against days following the onset of oliguria for the individual patients in Figure 1.

From Figure 1 it is evident that the recovery process may be arbitrarily divided into three functional phases. The first phase was initiated with the onset of diuresis and lasted from one to eight days. In spite of diuresis the plasma creatinine concentration continued to rise for one to three days apparently because of the absence of or very slight improvement in the clearance values. The second phase, starting between the second and ninth days, was initiated by a rapid fall in plasma creatinine concentration and a rapid increase in all the clearance values, reaching 40 to 70 per cent of the expected norm by the 40th day from the onset of oliguria. During this phase the relative C_{CR} increment was greater than the C_{PAH}, which in turn was slightly greater than the C_{IN} increment. The third phase, starting from about the 40th day was associated wtih gradual rises in C_{IN}, C_{PAH} and C_{CR}, the lower limit of normal (80 per cent of the statistical norm) being reached between the 100th and 200th day. Except for one C_{CR} value in patient F. H. on the 220th day the clearance values remained well under 100 per

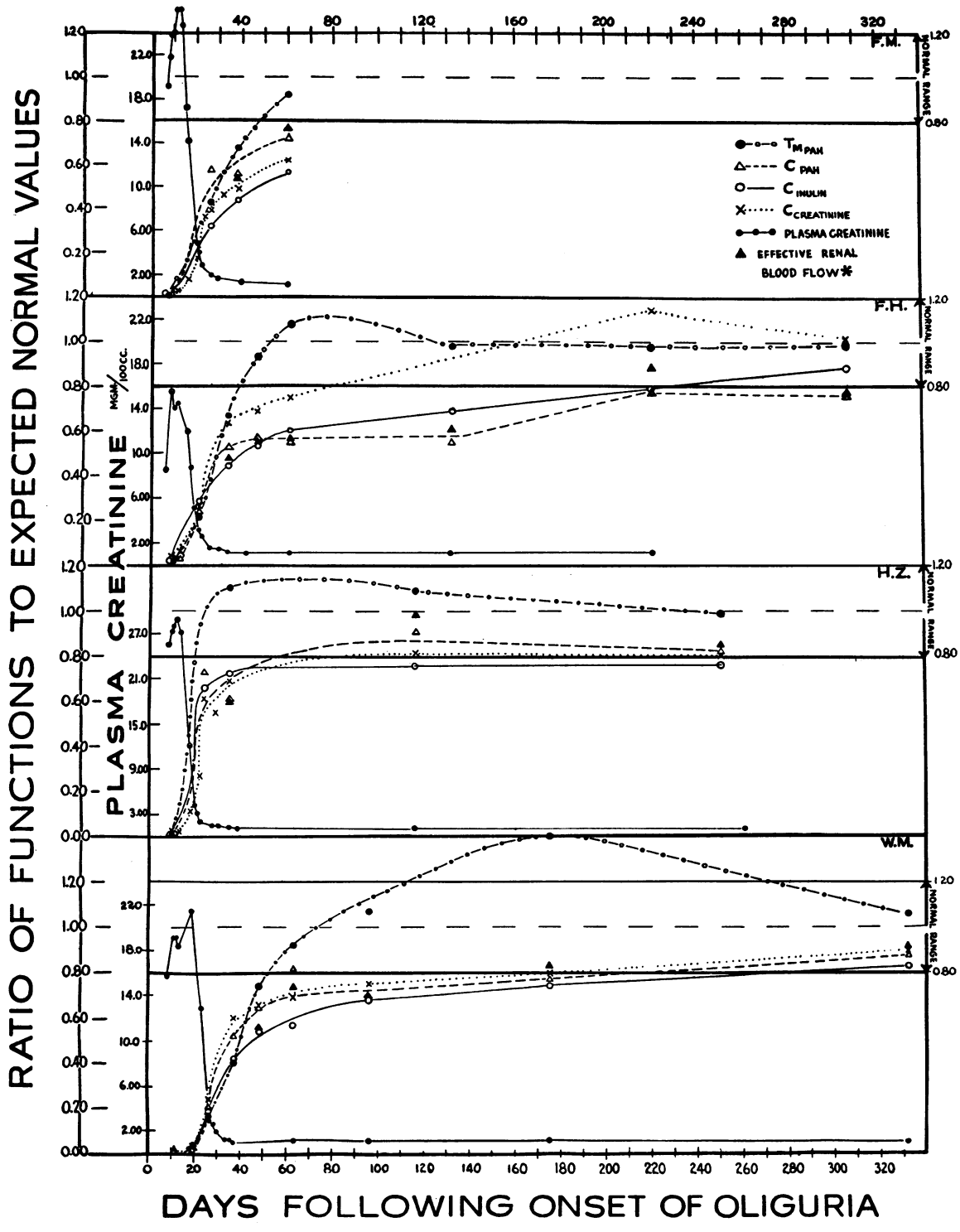

FIG. 1. INDIVIDUAL RECOVERY CURVES FOR C_{IN}, C_{CR}, C_{PAH}, Tm_{PAH}, AND PLASMA CREATININE CONCENTRATIONS IN FOUR SUBJECTS RECOVERING FROM CARBON TETRACHLORIDE POISONING

Cessation of oliguria occurred in F. M. on the 10th day, in F. H. on the third day, in H. Z. on the 11th day and in W. M. on the 17th day.

* Effective renal blood flow, calculated by $\frac{C_{PAH}}{1-H}$ where H is the hematocrit expressed as a fraction of 1.00, is not recorded before the 30th day because of poor renal PAH extractions.

cent of the statistical norm throughout the period of observation. Patient W. M., who suffered the most severe functional renal damage with oliguria for 17 days, had a C_{IN} of 108 cc./min. and a C_{PAH} of 618 cc./min. on the 331st day from the onset of oliguria.

In marked contrast, Tm_{PAH} for all four patients rapidly reached high normal values in the third phase of recovery, with patient W. M. obtaining the supernormal value of 130 mgm./min. per 1.73 sq. m. by the 175th day. With the further passage of time all the Tm_{PAH} values declined, leveling off at the expected normal value in F. H. by the 132nd day, in H. Z. by the 250th day and in W. M. by the 331st day. Because of the continued relative depression of C_{PAH} and C_{IN} the ratios C_{IN}/Tm_{PAH} and C_{PAH}/Tm_{PAH} in all four subjects remained lower than normal.

There was no correlation between the speed of recovery and the number of days of oliguria or the maximum plasma concentration of creatinine or urea. Thus, patient H. Z., the most critically ill of the four because of severe pulmonary edema, who suffered marked oliguria for 11 days and had peak plasma concentrations for creatinine and urea nitrogen of 32.0 and 226 mgm./100 cc. respectively, recovered most rapidly. Conversely, although F. H. had questionable oliguria for two days the renal damage sustained by him was as severe as the two with oliguria 10 and 11 days.

The sequence in which the usual clinical tests of renal function returned to normal is presented in Table III. The relatively low peak values for plasma urea nitrogen and creatinine concentrations in patient W. M. in spite of 17 days of severe oliguria is due to two runs on the artificial kidney.[8] The time of return to normal values of the plasma urea nitrogen concentration (8 to 18 mgm./100 cc.) was from the 24th to the 36th day from the onset of oliguria; for the plasma creatinine concentration (0.80 to 1.20 mgm./100 cc.) from the 29th to the 61st day.

All four patients had proteinuria. During oliguria the urine protein concentration was roughly between 1.5 to 3.0 gms./1000 cc. in three patients. W. M. spilled about 3 to 6 gms./1000

[8] Drs. H. E. Leiter and I. G. Kroop placed this patient on the Kolff artificial kidney for six hours on the ninth day, during which time his plasma urea nitrogen concentration dropped from 108 to 69 mgm./100 cc. A second dialysis on the 15th day caused a drop from 98 to 57 mgm./100 cc.

TABLE III

The sequence in which the clinical tests of renal function returned to normal in four cases of carbon tetrachloride poisoning

Patient	Number of days of oliguria	Plasma urea nitrogen			Plasma creatinine			Proteinuria		Specific gravity			Phenol red excretion		Day of disappearance of abnormal urine sediment
		Maximum conc.	Day of max. conc.	Day of return to normal*	Maximum conc.	Day of max. conc.	Day of return to normal*	Severity	Duration	Duration of fixation	12 hour water deprivation		Day	Per cent of 6 mgm. in 2 hours	
		mgm./100 cc.			*mgm./100 cc.*				*days*	*days*	*day*	*value*			
F. M.	10	131	15	30	26.5	11	40	1–2+	30	22	33	1.018	25 33 60	38 45 75	20
F. H.	2**	166	12	26	16.9	12	61	1–2+	30	26	27 132 220	1.011 1.019 1.025	23 28	41 70	20
H. Z.	11	226	14	24	32.0	13	29	1–2+	29	20	31 106 252	1.012 1.020 1.020	30	55	26
W. M.	17	108	8	36	20.9	19	37	2–4+	37	35	33 96 175	1.014 1.025 1.026	33	70	23

* Arbitrary maximum normal values for plasma urea nitrogen and creatinine concentrations were chosen as 18 and 1.20 mgm./100 cc. respectively.

** The occurrence of oliguria is questionable in this case because of difficult anamnesis. Its duration, if present, was definitely no longer than two days.

cc. during this stage. With the onset of diuresis the daily proteinuria gradually decreased in quantity so that by the 30th day it had disappeared in all except W. M. In the latter it did so by the 37th day. All four exhibited occasional faint traces of proteinuria for two to three months thereafter with eventual complete subsidence.

Following the onset of oliguria the urinary specific gravity gradually became fixed between 1.009 and 1.011 in all four patients and remained so for 20 to 35 days. The ability to concentrate urine to a minimum specific gravity of 1.025 after a 12 hour water fast returned relatively late, varying between 96 and 220 days.

The ability to secrete an acid urine was only slightly impaired from the onset of oliguria in three of the subjects, who had urine pH's ranging from 5.4 to 6.7. In patient W. M., however, up to the 13th day urine with an average pH of about 6.0 was passed. From the 13th through the 23rd day the urine pH ranged between 7.0 and 8.0 in spite of mild clinical acidosis. Acid urine was again excreted on the 24th day when urine with a pH of 5.5 was passed.

DISCUSSION

The marked reduction of renal blood flow during late oliguria and the early recovery phase in carbon tetrachloride poisoning may be a sequela rather than the initial cause of the renal failure. Adequate explanation for this depression of blood flow is found in the development of severe interstitial edema and inflammatory swelling of the kidneys as described by MacMahon and Weiss (27), Smetana (1), Woods (2) and Lucké (3). Unfortunately, because of the nature of the methods, it has not been possible to measure renal blood flow in man at the onset of oliguria. The experimental results of Richards (6) and Bobey *et al.* (7) with nephrotoxins suggest that renal blood flow may be normal during the initial phase of acute renal failure.

The morphological and clinical similarities of the post-shock and the nephrotoxic anurias have been well established (2, 3). The common denominator appears to be tubular injury. The occurrence in man of severe and prolonged renal anoxia during shock has been demonstrated by Lauson, Bradley, and Cournand (28), and Badenoch and Darmady (29) found identical tubular lesions in men who died of post-shock uremia and in rabbits which developed uremia following two-hour ligation of the renal arteries. Thus, prolonged renal anoxia simulates the nephrotoxic action of carbon tetrachloride.

On the basis of the available information it is possible to formulate a working hypothesis concerning the pathogenesis of anuria and the mechanism of recovery from the acute renal failure of carbon tetrachloride poisoning. During the first 24 to 48 hours after exposure, because of nausea and vomiting, dehydration may be present. During this phase of gastro-intestinal irritation the urine, although scant, may be of normal composition and of high specific gravity. The tubules, still intact functionally, respond to the needs of the organism by maximally reabsorbing water. Between the first and third days after exposure the nephrotoxic action becomes manifest with severe oliguria or anuria and rapidly rising plasma urea and creatinine concentrations. Because of abnormal glomerular permeability considerable protein and gross blood may be present in the scant urine that is passed. Until studies of *early* anurias are performed in man we must tentatively accept the findings of the experimentalists and explain the scant urine flow of this stage by back-diffusion of the glomerular filtrate across the damaged tubule wall. "The organism urinates into the kidney instead of the bladder." [9] There is now convincing evidence to minimize the role of pigmented casts in the production of oliguria by mechanical blockage (3).

As oliguria progresses renal blood flow becomes markedly diminished. The resultant anoxia added to the initial toxic insult causes maximal depression of tubular function. Some of the small amount of filtrate now formed appears to be lost by back-diffusion. It is of some interest that during this phase and that of early diuresis, although there is fixation of urinary specific gravity and markedly depressed phenol red excretion, Tm_{PAH} and E_{PAH}, the ability to retain chloride and to secrete an acid urine may be only slightly diminished.

Tests used for the secretory activity of the proximal tubular system during this phase may yield erroneously low values because of back-diffusion through the severely disorganized distal tubular

[9] This simile originated with Dr. Paul Klemperer.

system. Apparently carbon tetrachloride poisoning causes less injury to the proximal tubules than other circumstances leading to acute renal failure, as in all the published cases in which functional studies were performed (six including the four presented herein) Tm_{PAH} was never negative and returned to normal values with relative rapidity.

Diuresis initiates the recovery process. It occurs without significant changes in the clearance values and in the presence of low renal blood flow, and probably represents reestablishment of the tubular barrier to the indiscriminate back-diffusion of the filtrate. The rapid increase in tubular and glomerular function of the second stage of recovery is the result of tubular regeneration, diminishing renal interstitial pressure and rising renal blood flow. The gradual increase in filtration and blood flow of the third stage of recovery probably represents gradual reabsorption of inflammatory tissue and reestablishment of the finer vascular channels. Burwell, Kinney, and Finch (30) present autopsy findings of a case of renal injury three months after an episode of intravascular hemolysis, with death due to an unrelated cause, revealing cortical scarring. In a patient with acute carbon tetrachloride poisoning causing four days of oliguria who died 10 months later from an unrelated cause, Simon (31) failed to demonstrate significant renal pathology.

The high values for Tm_{PAH} obtained soon after the 40th day may represent transient compensatory hyperfunction of the proximal tubular system. The ability to concentrate urine maximally is the last tubular function to return to normal, probably representing final complete functional integrity of the distal tubule. These functional aspects of tubular recovery reflect the morphological pattern of mild proximal tubular damage and severe disorganization of the distal tubules.

Since a severe absolute reduction in renal blood flow has been demonstrated in the late oliguria of carbon tetrachloride poisoning, the shunt described by Trueta and his colleagues, if operative at the time of measurement, could not have been of great functional significance, since such a mechanism implies little reduction in total renal blood flow, but merely cortical bypassage. There has been no evidence to show that such a mechanism is responsible for the initiation of anuria in man. All data so far available indicate that this juxtamedullary bypass is of little physiological import in normal man (32, 33), in man with increased intra-abdominal pressure (20), in essential hypertension (34) and in congestive heart failure (32, 35) by the demonstration of continued normal renal extraction of PAH in these conditions.

CONCLUSIONS

1. By means of the Fick principle the renal plasma flow was determined in four male subjects with acute carbon tetrachloride poisoning. Renal venous blood was obtained by catheterization of the right renal vein. P-aminohippurate was used as the test substance. In two of the subjects there was a marked reduction in the renal plasma flow and PAH renal extraction ratio. On the eighth day of oliguria the renal plasma flow in one of these subjects was 2.45 cc./min. and the PAH extraction ratio 0.034. On the 13th day from the onset of a questionable two-day oliguric period the second subject had a renal plasma flow of 160 cc./min. and a PAH extraction ratio of 0.106 in spite of a urine flow of over 3000 cc./24 hrs. In a third subject both the renal plasma flow and the PAH extraction ratio were normal on the 24th day. The fourth subject, who had suffered oliguria for 17 days, had a renal plasma flow of 592 cc./min. on the 37th day and a continued depression of the PAH extraction ratio to 0.594. Because of low PAH extraction ratios C_{PAH} is not a valid measure of renal plasma flow during oliguria and early diuresis following carbon tetrachloride poisoning.

2. The oliguria and anuria of carbon tetrachloride poisoning and the markedly depressed renal clearances of all substances during early diuresis are the results of a marked reduction in renal blood flow and glomerular filtration as well as abnormal tubular back-diffusion of the filtrate. It is probable that back-diffusion plays the most important role during early oliguria as decreased renal blood flow does during late oliguria and early diuresis.

3. The recovery of renal function following acute renal failure due to carbon tetrachloride poisoning is characterized by three clinical phases. The first phase starts with the cessation of oliguria and is associated with rising plasma creatinine and urea concentrations in spite of an adequate urine flow. It lasts from one to three days, during which

time there is little change in C_{IN}, C_{CR} and C_{PAH}. The second phase starts with a rapid decline in the plasma urea and creatinine levels and a simultaneous rapid rise in C_{IN}, C_{CR} and C_{PAH} which reach 40 to 70 per cent of normal by the 40th day from the onset of oliguria. The third phase, starting about the 40th day, is characterized by gradual improvement in renal blood flow and glomerular filtration, so that the lower limit of normal is reached between the 100th and 200th day. During this phase the ability to elaborate a maximally concentrated urine is recovered.

4. During the early part of recovery phases Tm_{PAH} reached high normal or supernormal values in three of the patients, ranging between 83.9 and 130 mgm./min. per 1.73 sq.m. These gradually declined to the expected norm. The ratios C_{IN}/Tm_{PAH} and C_{PAH}/Tm_{PAH}, however, were significantly lower than normal in all four patients when last determined on the 60th, 250th, 307th and 331st day, respectively, suggesting some residual vascular damage.

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