Discrepancy between Renal Plasma Flow Values Determined Simultaneously from PAH and Thiosulfate by the Fick Method and Its Significance for Renal Lymph

By

Keiichi Ito

*From the First Department of Internal Medicine, Tohoku
University School of Medicine, Sendai;
Director: Prof. T. Nakamura*

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Application of the Fick principle allows an accurate measurement of the total renal plasma flow when two parameters are actually determined, i.e. renal plasma clearance for substance X (C_x), and the extraction ratio for this substance (E_x). This calculation does not assume that the substance X is extracted nearly in hundred per cent by the kidneys, an assumption which is intrinsic to the older convention of equating the renal clearance value with the renal plasma flow.

Theory demands, then, that the same value of C_x/E_x will obtain irrespective of the nature of test substances used, e.g. p-aminohippuric acid (PAH) and diorast, i.e. substances having high ratios of renal extraction, or mannitol, sodium thiosulfate and inulin, i.e. substances having relatively low ratios of renal extraction.

This has been the subject of investigation by several authors: White & Heinbecker,¹⁾ Corcoran & Page,²⁾ Cargill,³⁾ and Reubi *et al.*⁴⁾ They compared C_x/E_x for PAH or diodrast with that for inulin, mannitol or thiosulfate at the same time. While the two values coincided beautifully in some cases, they showed discrepancy in other cases. Thus Reubi *et al.* found that the renal plasma flow determined with PAH (C_{PAH}/E_{PAH}) bore various ratios to the renal plasma flow determined with mannitol (C_M/E_M), which fell anywhere between 0.645 and 1.54. According to Corcoran & Page the renal plasma flow determined with diodrast (C_D/E_D) was consistently higher than the renal plasma flow determined with inulin (C_I/E_I), the ratio being 1.22.

If, then, significantly different renal plasma flow data should be obtained when the measurement is made with the Fick method but with two substances such

TABLE I. Values Obtained in the Cases of Low Plasma Arterial PAH Concentration

Dog no.	Body weight kg.	Blood pressure mm. Hg.	Urine volume cc./min.	PAH					Thiosulfate				$\frac{C_{PAH}}{E_{PAH}} \cdot \frac{C_T}{E_T}$
				Arterial plasma concentration mg./dl.	Clearance (C) cc./min.	Extraction (E) %	$\frac{C_{PAH}}{E_{PAH}}$ cc./min.	$\frac{C_{PAH}}{E_{PAH}}$ cc./min./kg. B.W.	Clearance (C) cc./min.	Extraction (E) %	$\frac{C_T}{E_T}$ cc./min.	$\frac{C_T}{E_T}$ cc./min./kg. B.W.	
D ₁	13			4.03	116	68.0	170	13.1	30.3	33.7	90	6.9	1.89
			3.85	97	76.7	127	9.8	30.3	35.9	85	6.5	1.50	
			3.85	63	71.5	110	8.5	23.4	31.6	74	5.7	1.49	
	Average						135.7			83.0		1.64	
D ₂	12		1.73	2.01	89	60.2	147	12.3	22.5	18.1	124	10.3	1.18
			1.50	2.25	77	66.2	115	9.6	20.2	23.9	85	7.1	1.35
			1.41	2.65	77	68.7	112	9.4	19.8	20.9	98	8.2	1.14
		Average						124.7			102.3		1.22
D ₃	16	120	1.54	9.95	111	57.0	195	12.2	33.1	21.7	152	9.5	1.28
		116	1.60	10.1	114	60.5	189	11.8	33.5	23.2	144	9.0	1.31
		Average						192.0			148.0		1.30
D ₄	40	148		9.91	157	71.7	219	5.5	59.1	35.1	168	4.2	1.30
		148		11.6	152	69.8	218	5.5	44.1	26.3	167	4.2	1.30
		Average						218.5			167.5		1.30
D ₅	18		1.50	3.50	156	75.6	203	11.2	38.5	17.1	225	12.4	0.90
			1.41	3.65	117	75.5	155	8.5	33.7	20.3	167	9.3	0.93
			1.42	3.75	122	77.0	159	8.8	36.5	20.6	171	9.7	0.90
		Average						172.3			189.7		0.91
D ₆	9	90	0.62	7.05	64	56.6	113	12.5	20.2	23.0	88	9.8	1.29
		84	0.53	6.52	63	56.9	110	12.2	20.9	23.1	91	10.1	1.21
		82	0.52	6.14	61	57.4	106	11.8	18.6	22.4	83	9.2	1.28
		82	0.55	5.52	68	58.2	117	11.9	19.2	22.0	87	9.7	1.34
		Average						111.5			87.2		1.28
D ₇	14	84	0.38	4.30	80	71.5	111	7.9	33.4	30.2	111	7.9	1.00
		92	0.44	4.30	92	71.6	128	9.2	37.4	33.3	116	8.3	1.10
		92	0.30	4.33	70	72.5	97	7.0	29.2	31.4	93	6.7	1.03
		90	0.34	4.42	74	74.0	100	7.2	29.9	34.4	87	6.2	1.16
		Average						109			101.8		1.07

TABLE I. (Continued)

D_8	15.5	88	0.46	3.35	67	79.2	85	5.5	16.5	23.3	71	4.6	1.20
		86	0.46	3.41	82	78.9	104	6.8	18.9	24.8	76	4.9	1.37
	Average						94.5				73.5		1.29
D_9	12	94		5.65	99	67.6	146	12.2	29.3	21.7	135	10.4	1.08
		106		6.40	95	72.5	131	10.9	22.0	19.3	115	9.6	1.14
	Average						138.5				125		1.11
D_{10}	14	84		10.3	53	45.8	116	8.3	22.8	24.0	95	6.8	1.22
		96		10.9	52	42.7	122	8.6	21.4	25.8	83	5.9	1.47
		96		11.1	56	41.0	136	9.7	22.5	26.7	84	6.0	1.64
		96		11.5	55	40.4	136	9.7	22.7	26.4	86	6.2	1.58
	Average						127.2				87		1.46
D_{11}	6	120	0.32	2.5	45	64.0	70	11.7	7.4	11.1	68	11.3	1.03
		102	0.38	2.5	44	64.0	69	11.5	7.4	10.3	72	12.0	0.96
	Average						69.5				70		0.99

* C_{PAH}/E_{PAH} = Renal plasma flow estimated with PAH by the Fick method.** C_T/E_T = Renal plasma flow estimated with thiosulfate by the Fick method.

Fig. 1. Comparison of C_{PAH}/E_{PAH} and C_T/E_T determined in the dogs where arterial plasma PAH concentration was kept low. (2.0 ~ 11.6 mg/dl.) It can be seen that the renal plasma flow estimated with PAH (C_{PAH}/E_{PAH}) in comparison with thiosulfate (C_T/E_T) had higher values.

as PAH and thiosulfate which differ in their mode of excretion from the kidneys, it may be worth investigating into the sources of the difference. Thus the author made the following experiments on dogs.

METHODS AND RESULTS

A) Experiment I and results (the case of low plasma arterial PAH concentration)

Adult dogs weighing 6 to 40 kg. and anesthetized with pentobarbital were used; a Cournand-catheter was advanced, from the jugular vein and under a X-ray control, till the tip was inserted into the left renal vein. Abdomen was opened and the urine from the left ureter was led out by a polyethylene tubing; femoral artery and vein were exposed bilaterally and the blood pressure was recorded from the femoral artery on one side; the contralateral femoral artery was used as the site of sampling the arterial blood. Through the femoral vein a mixture of sodium p-aminohippurate and sodium thiosulfate was infused at a constant rate. Sampling of the urine began 30 minutes after starting of infusion, taken from the left ureter at intervals of 10 minutes; at midpoints blood samples were obtained from the artery and renal vein at the same time and the blood pressure was read; and the above procedure was repeated several times with the same dog. The plasma level of PAH was kept below about 10 mg/dl. by adjusting the rate of infusion.

After the above experiment was over the samples of the arterial and renal venous blood and urine were analysed, as quickly as possible, for PAH by the method of Bratton & Marshall⁵⁾ as modified by Smith *et al.*⁶⁾ and for thiosulfate by the Brun's⁷⁾ method.

Thus a series of values were calculated, i.e. unilateral renal PAH clearance (C_{PAH}), unilateral PAH extraction ratio (E_{PAH}), unilateral renal plasma flow determined by PAH (C_{PAH}/E_{PAH}), unilateral renal thiosulfate clearance (C_T), unilateral thiosulfate extraction ratio (E_T), unilateral renal plasma flow determined by thiosulfate (C_T/E_T), and RPF ratio between PAH and thiosulfate (ratio of C_{PAH}/E_{PAH} to C_T/E_T).

Table I lists the values observed in 31 determinations on 11 dogs. The arterial plasma PAH concentration fell between 2.01 and 11.6 mg/dl and E_{PAH} ranged between 40.4 and 79.2%, with mean value of 67.6%. In contrast, E_T ranged between 10.3% and 35.9%, with mean value of 20.2%.

Fig. 1 shows the relationship between C_{PAH}/E_{PAH} and C_T/E_T . It can be seen on the left hand side of this Figure that the renal plasma flow estimated with PAH in comparison with thiosulfate had higher values; for convenience in comparison, all values are given in terms of a unit body weight (kg.) on the right hand side. Thus, the mean value of C_{PAH}/E_{PAH} was 9.60 cc/min/kg., while that of C_T/E_T was 8.02 cc/min/kg. The two mean value showed significant difference ($P < 0.05$). The ratios of C_{PAH}/E_{PAH} to C_T/E_T are shown on the left hand side of Fig. 3; thus the ratio ranged between 0.90 and 1.89, with mean value of 1.25.

B) Experiment II and results (the case of high arterial plasma PAH concentration)

Seven adult dogs weighing 4.5 to 16 kg. were used; the experiment was done in the same way as before except that higher plasma PAH concentrations were

used. A total of 21 determinations were done and values were calculated in the same manner as before, e.g. C_{PAH} , E_{PAH} , C_{PAH}/E_{PAH} , C_T , E_T , C_T/E_T , ratio of C_{PAH}/E_{PAH} to C_T/E_T , blood pressure.

TABLE II. Values Obtained in the Cases of High Plasma Arterial PAH Concentration

Dog no.	Body weight kg.	Blood pressure mm.Hg.	Urine volume cc./min.	PAH					Thiosulfate				$\frac{C_{PAH}}{E_{PAH}} / \frac{C_T}{E_T}$
				Arterial plasma concentration mg./dl.	Clearance (C) cc./min.	Extraction (E) %	C_{PAH}/E_{PAH} cc./min.	C_{PAH}/E_{PAH} cc./min./kg. B.W.	Clearance (C) cc./min.	Extraction (E) %	C_T/E_T cc./min.	C_T/E_T cc./min./kg. B.W.	
D ₁₂	11	112	1.70	37.5	28.8	24.0	120	10.9	24.0	13.6	176	16.0	0.69
		100	1.10	34.0	29.3	20.5	145	13.0	24.0	13.6	176	16.0	0.82
		96	1.25	32.5	28.5	15.8	180	16.5	20.5	11.7	139	12.6	1.29
	Average						148.3				163		0.91
D ₁₃	16	116		45.8	49.8	19.6	254	15.9	40.6	16.6	245	15.3	1.04
		116		44.4	48.0	19.0	252	15.7	36.6	15.8	232	14.5	1.08
	Average						253.0				238.5		1.06
D ₁₄	9	86	0.84	76.0	23.4	25.6	92	10.1	21.1	22.0	96	10.7	0.96
		80	0.88	65.0	27.4	23.1	118	13.1	23.2	20.7	113	12.5	1.04
		84	1.05	59.0	22.8	21.0	109	12.1	21.1	20.4	104	11.6	1.05
		84	1.02	55.5	23.0	20.4	113	12.6	19.9	16.8	118	13.1	0.96
		82	1.05	51.8	24.6	20.3	118	13.1	21.8	14.6	149	16.1	0.80
	Average						110				116		0.95
D ₁₅	4.5	76	0.48	87.0	9.91	25.3	39	8.2	7.45	24.0	31	6.8	1.26
		64	0.36	94.5	78.5	31.2	25	5.6	6.95	25.7	27	6.0	0.93
	Average						32				29		1.10
D ₁₆	14		1.08	50.4	34.0	71.5	48	3.4	25.9	40.4	64	4.6	0.75
		70	0.96	48.2	38.2	72.1	53	3.8	27.4	36.5	75	5.4	0.71
		50	0.94	44.1	34.2	74.0	46	3.3	23.6	34.5	68	4.9	0.68
	Average						49				69		0.71
D ₆	9	76	1.43	65.5	19.8	21.4	93	10.3	17.6	20.5	86	9.6	1.08
		76	1.05	71.0	16.5	21.3	78	8.6	14.9	21.0	71	7.9	1.10
		78	1.11	74.5	18.3	22.3	80	8.9	15.8	21.5	74	8.2	1.08
		68	0.91	79.5	15.6	22.1	71	7.8	13.7	21.7	63	7.0	1.13
	Average						80.5				73.5		1.09
D ₁₀	14	94	0.80	38.5	34.1	27.3	125	8.9	26.2	20.2	130	9.3	0.96
		94	0.76	38.5	34.5	29.8	116	8.3	25.5	22.4	114	8.2	1.01
	Average						120.5				122		0.99

Table II lists the values observed in 21 determinations on 7 dogs. In this case the arterial plasma PAH concentration ranged between 32.5 and 94.5 mg/dl; the mean value of E_{PAH} was 32.2%, a value close to the mean value of E_T , 21.6%, and suggesting that the plasma PAH concentration was at, or close to, the saturation limit.

Fig. 2 shows the relationship between C_{PAH}/E_{PAH} and C_T/E_T , and values of C_{PAH}/E_{PAH} and C_T/E_T in terms of unit body weight (kg.) as Fig. 1. It will be seen that the mean C_{PAH}/E_{PAH} was 10.00 cc/min/kg. and the mean C_T/E_T was 10.30 cc/min/kg., i.e. two values have no statistically significant difference. The ratio of C_{PAH}/E_{PAH} to C_T/E_T is shown on the right hand side of Fig. 3, i.e. 0.68 to 1.26, with mean value 0.98. This value, 0.98, was significantly different from the value previously found with lower plasma concentration of PAH, i.e. 1.25. ($P < 0.01$)

Fig. 2. Comparison of C_{PAH}/E_{PAH} and C_T/E_T determined in the dogs where arterial plasma PAH concentration was kept high. (32.5 ~ 94.5mg/dl.) It can be seen that the two values coincided in this case.

DISCUSSION

The author pointed out early in this paper that several attempts have been made in the past to compare the renal plasma flow data obtained with various substances, such as PAH and thiosulfate, which differ in their mode of excretion from the kidneys, but employing in all cases Fick principle. It was also pointed out that these attempts so far produced no consistent results. Neither was there any study where the arterial plasma PAH concentration was raised to its saturation limit, a condition under which extraction ratio for PAH was brought to the proximity of the extraction ratio for thiosulfate; the author compared C_{PAH}/E_{PAH} with C_T/E_T under such a condition for the first time.

Thus the author found that, with a low plasma PAH concentration, C_{PAH}/E_{PAH} gave a higher value than did the simultaneously observed C_T/E_T . Moreover, with a higher plasma PAH concentration, C_{PAH}/E_{PAH} gave practically the same value as C_T/E_T . It is suggested, then, that C_T/E_T gives a lower value than C_{PAH}/E_{PAH} in the presence of a low plasma PAH concentration because a certain fraction of the plasma thiosulfate leaks out of the renal blood vessel and is carried away by way of the renal lymph.

Reasonings which lead to this suggestion will be given, together with reference to previous papers, in the following paragraphs.

Fig. 3. Ratios of C_{PAH}/E_{PAH} to C_T/E_T obtained at low and high plasma concentration of PAH.

(1) Effect of analytic errors

In determination of the renal plasma flow by the Fick method, relatively small errors may arise in the assay of the test substance when its renal A-V difference is large, for example, when plasma concentration of PAH is below the level of self-depression; but errors of this nature may become appreciable when a substance with small A-V difference is used, e.g. thiosulfate. If it is actually the case and if C_T/E_T values contain large errors, the comparison of C_{PAH}/E_{PAH} with C_T/E_T is not free from errors. The author took a special caution in the measurement of thiosulfate concentrations; thus at least two measurements were repeated on the same sample and the mean value was used for later calculations. It was also to this end that a large number of determinations were made, such as 31 determinations of C_{PAH}/E_{PAH} and C_T/E_T , i.e. several determinations on each dog and on a total of 11 dogs. Moreover, the results were treated statistically to show that the difference was significant. After all this, it was concluded that C_{PAH}/E_{PAH} gave a higher value than the simultaneously measured C_T/E_T .

Previous authors did not find any consistent relation between the two, while they admitted that the two values were discrepant; this may be due, at least

partly, to the small number of materials these authors used.

Parenthetically, the same caution as this was taken by the author in comparing C_{PAH}/E_{PAH} with C_T/E_T in Experiment II.

(2) Right-to-left difference in renal extraction ratio

In this experiment the value of C/E was calculated on the basis of unilateral measurements, i.e. C from the urine samples collected in the left ureter, and E from the left kidney. It is recalled that Cargill and Reubi *et al.* calculated C/E on the basis of the clearance determination from the bladder urine (representing both kidneys) and extraction ratio measurement in unilateral kidney, with assumption that the extraction ratio is the same in both kidneys. Cargill and Reubi *et al.*'s result will be incorrect, if it happens that the hemodynamic pattern undergoes a certain change on the side, or on the contralateral side of the kidney the venous vein is catheterized.

(3) Correction factor for the urine flow

The author equated the renal plasma flow with $U_x V / A_x - R_x = C_x / E_x$. This treatment obviously neglects the fact that all the solute concentration becomes higher in the renal vein than renal artery, owing to the loss of fluid into urine. This fact may be neglected in the case of a test substance with high extraction ratio, e.g. PAH as used below the concentration of self-depression; however, contribution of this factor will be great in the case of substances with low extraction ratios, such as thiosulfate; in such cases Wolf's⁸⁾ formula will be useful: $U_x - R_x \cdot V / A_x - R_x$. Use of Wolf's formula, however, aggravated the difference between C_{PAH}/E_{PAH} and C_T/E_T ; namely, substituting $U_T - R_T \cdot V / A_T - R_T$ for $U_T V / A_T - R_T$ ($= C_T/E_T$) gave a value still lower than C_T/E_T . Obviously, the observed difference between C_{PAH}/E_{PAH} and C_T/E_T at a low plasma PAH concentration can not be ascribed to the fact that fluid is lost into the urine.

Note: V , urine flow from a unilateral kidney, per minute

A_x , arterial plasma concentration of substance X

R_x , concentration of substance X in the renal venous plasma

U_x , concentration of substance X in urine

(4) Effect of PAH diffusion from red cells to plasma

Phillips *et al.*^{9,10)} reported that there occurred diffusion of PAH from the red cells into plasma after samples of the renal venous blood were withdrawn, and this caused the PAH concentration in the renal venous plasma to increase with course of time, making E_{PAH} erroneously low. According to Phillips *et al.*, E_{PAH} is low, erroneously, by 5% even when plasma is separated from cells immediately after sampling of the renal venous blood; when 40 minutes are allowed to intervene between the blood sampling and cell-plasma separation, the observed E_{PAH} is 15% lower than the truth. It follows that the neglect of this fact (i.e. use of the erroneously low E_{PAH}) will make C_{PAH}/E_{PAH} higher than the true renal plasma flow. At the first glance, then, this observation of Phillips *et al.* appears

to account for the author's observation that, with low plasma concentration of PAH, C_{PAH}/E_{PAH} gave a higher value than C_T/E_T .

However, Phillips *et al.* noted also that such an artificial decrease in E_{PAH} had no bearing on the arterial blood concentration of PAH. If such is the case, "apparent" decrease in E_{PAH} with time should take place also with high arterial blood concentration of PAH. It is expected, then, that C_{PAH}/E_{PAH} gives a higher value than C_T/E_T at high blood concentrations of PAH as well as at low blood concentrations. Evidently this is not the case in the author's experiment; the truth is that C_{PAH}/E_{PAH} coincides well with C_T/E_T when arterial blood PAH concentration is high, a fact which Phillips *et al.*'s observation cannot account for. Furthermore, Sellwood & Verney¹¹⁾ did not note diffusion of PAH from cells into plasma when samples of the renal venous blood were obtained under the circumstance of low arterial blood PAH concentration.

(5) Admixture of extrarenal venous blood into the renal venous blood

The renal vein often communicates with the spermatic (ovarian) vein, a branch of suprarenal vein, subdiaphragmatic vein, and a branch of the lumbar vein. A strict application of the Fick principle demands that these extrarenal veins be ligated. However, this complication does not affect the validity of the ratio of C_{PAH}/E_{PAH} to C_T/E_T , for the following reason. Suppose that the extraction ratio for PAH in the purely renal circulation is E'_{PAH} ; this differs from E_{PAH} , i.e. PAH extraction ratio such as measured by the author and which is a function of both renal and extrarenal blood flow. Thus,

$$E_{PAH} = RPF / (RPF + SPF) E'_{PAH}$$

In the same way:

$$E_T = RPF / (RPF + SPF) E'_T$$

where RPF represents renal plasma flow and SPF represents extrarenal plasma flow of the admixing channel. Then,

$$C_{PAH}/E_{PAH} \div C_T/E_T = C_{PAH}/E'_{PAH} \div C_T/E'_T$$

It will be evident that the admixing of the extrarenal venous blood into the renal venous blood does not affect the validity of the ratio of C_{PAH}/E_{PAH} to C_T/E_T .

(6) Leakage of PAH and thiosulfate into the interstitial space or lymph of the kidneys

In order to account for the fact that C_{PAH}/E_{PAH} determined at a low plasma PAH concentration gave a higher value than C_T/E_T , a possibility must be invoked that a certain fraction of thiosulfate, brought to the kidney, is lost from the blood stream in some way other than the loss into the urine and drain into the renal vein. Should one invoke the decomposition, or conversion into other substances, of thiosulfate in the kidneys?

It is not likely, however, because there is a fact that the ratio of C_{PAH}/E_{PAH} to C_T/E_T approaches unity at high concentrations of PAH; in order to explain this fact along the line of the last-mentioned possibility, one would have to invoke

another possibility that PAH becomes subject to intrarenal decomposition at a high blood concentration of PAH, to the same extent that thiosulfate is decomposed.

A more tenable explanation will be that a fraction of thiosulfate, brought to the kidneys, is carried out of this organ other than by way of the urinary pathway or renal vein; firstly, this explanation is compatible with the first experiment described above. This channel, bypassing the renal vein, is presumably the renal lymphatics which carry a fraction of thiosulfate away.

The author tried to establish this point by measuring the concentration of thiosulfate and PAH in the renal lymph; however, it was difficult to obtain the renal lymph in such a large quantity as to enable the measurement of PAH and thiosulfate; the determination of PAH concentration in the renal lymph was possible only in one dog where arterial blood PAH concentration was high. In this instance arterial plasma PAH concentration was 21.7 mg/dl., renal venous plasma PAH concentration was 10.0 mg/dl.; the observed renal lymph concentration of PAH was 17.6 mg/dl., i.e. a value lower than the arterial plasma concentration but higher than the renal venous plasma concentration.

Sugarman *et al.*¹²⁾ studied the renal lymph of dogs and found that the urea concentration was higher than both arterial and renal venous plasma concentrations.

Kaplan *et al.*¹³⁾ succeeded in collecting renal lymph from dogs under the drip infusion of inulin and found that the renal lymph inulin concentration was 68% of the arterial plasma concentration.

Assuming that the fluid running out of the renal vein following the ligation of the renal artery represents a mixture of the intrarenal vascular blood and interstitial fluid (lymph), Swann *et al.*¹⁴⁾ estimated the possible inulin and diodrast concentration of the renal interstitial fluid, while blood concentration of these substances was kept constant; thus it was suggested that the interstitial fluid contained inulin and diodrast at concentrations lower than the arterial plasma concentration but slightly higher than the renal venous plasma concentration.

These observations suggest that PAH and thiosulfate, traversing through glomeruli, leak out of capillaries into the interstitial fluid and exist in the interstitial fluid in equilibrium with the blood in capillaries. In the case of PAH, the fraction lost ultimately into the renal lymph is small, since this substance is vigorously taken up by the tubular epithelial cells and excreted into urine; thus a straightforward application of the Fick principle will cause a negligible amount of errors in the case of PAH. In contrast, a considerable amount of thiosulfate may remain in the interstitial fluid and this will be carried away by way of renal lymph. Situations being like this, the extraction ratio for thiosulfate which one observes is higher than the truth, and the C_T/E_T value which one obtains is lower than the true renal plasma flow.

Thus it is possible to account for the fact that C_T/E_T gives a lower value than C_{PAH}/E_{PAH} determined at a low plasma PAH concentration.

Explanations such as given above also account for the second fact that C_{PAH}/E_{PAH} determined at a high plasma PAH concentration agrees well with C_T/E_T . In the presence of PAH in such high plasma concentration as its saturation limit, the capacity of tubular epithelial cells is exceeded; under such circumstances a large fraction of PAH which has leaked into the interstitial space may remain there and this will be carried out of the kidneys, as it is the case with thiosulfate, by renal lymph, a situation where one would logically expect that the ratio of C_{PAH}/E_{PAH} to C_T/E_T will approach unity; the value actually found was 0.96.

If it is really the case that the presence of the renal lymph compartment caused the observed discrepancy between C_{PAH}/E_{PAH} and C_T/E_T at a low plasma concentration of PAH, the observed ratio of C_{PAH}/E_{PAH} to C_T/E_T , 1.25, should allow a rough estimation of the renal lymph flow. Calculations show that the renal lymph flow must be considerable, i.e. about 6% of the renal plasma flow.

A few words on the magnitude of the renal lymph flow. Schmidt & Hayman¹⁵⁾ reported that the total lymph flow from a unilateral kidney of dog was 0.04–0.6 cc/min. It has been generally assumed, in the past, that the renal lymph flow was something very small as compared with renal blood flow.

In the author's dogs the urine flow was generally large, as shown in Tables I and II. It may be that these dogs had a tendency towards over-hydration and this has caused the renal lymph flow to increase. However, Schmidt's value can hardly be accepted as the normal value under physiological conditions, since surgical intervention was great in his series. That the intrarenal lymph or extravascular fluid of the kidney amounts to a large quantity as compared with other organs, was shown recently by several authors, such as Swann *et al.*,¹⁴⁾ Babics & Renyi-Vamos,¹⁶⁾ Goodyer *et al.*¹⁷⁾ and Lilienfield *et al.*¹⁸⁾

The author's observations suggest that the renal lymph flow, as well as the intrarenal fluids volume, is something larger than that previously assumed by early investigators, such as Schmidt and Hayman.

SUMMARY

(1) A comparative study of the renal plasma flow was carried out with the Fick principle, employing PAH and sodium thiosulfate at the same time and firstly, keeping the the plasma PAH concentration low, i.e. between 2.01 and 11.6 mg/dl. in normal dogs whose renal vein has been catheterized. Thus C_{PAH}/E_{PAH} and C_T/E_T were determined in a total of 31 measurements on 11 dogs and the results were compared. It was found that C_{PAH}/E_{PAH} did not agree with C_T/E_T ; while C_{PAH}/E_{PAH} per unit body weight gave a mean value of 9.60 cc/min/kg., C_T/E_T per unit body weight gave a mean value of 8.02 cc/min/kg., and the two values

were significantly different on statistical basis. The ratio of C_{PAH}/E_{PAH} to C_T/E_T was 1.25 on the average.

(2) A similar experiment was performed with the same plasma concentration of thiosulfate but with higher PAH concentrations, i.e. 32.5~94.5 mg/dl. A total of 21 determinations of C_{PAH}/E_{PAH} and C_T/E_T were done on 7 dogs. C_{PAH}/E_{PAH} per unit body weight gave a mean value of 10.00 cc/min/kg. and C_T/E_T per unit body weight gave a mean value of 10.30 cc/min/kg.; two values were not significantly different on statistical basis. In this case C_{PAH}/E_{PAH} bore a ratio of 0.98 in respect to C_T/E_T on the average.

(3) The two ratios were significantly different on statistical basis, i.e. 1.25 obtained at low plasma concentrations of PAH on one hand, and 0.98 obtained at higher plasma concentrations of PAH.

(4) From these observations the author infers that a considerable fraction of the administered thiosulfate is carried out of the kidneys other than by way of the glomerulus into urine, i.e. postglomerular loss by way of the renal lymph. According to this view, the observed C_T/E_T does not represent the real renal plasma flow; it should give a value lower than C_{PAH}/E_{PAH} determined at low plasma PAH concentration.

This view seems to be supported by the fact that the ratio of C_{PAH}/E_{PAH} to C_T/E_T approaches unity, when plasma concentration of PAH is high, i.e. where extraction ratio for PAH approaches the extraction ratio for thiosulfate.

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