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THE COMPETITION BETWEEN P-AMINO-HIPPURIC ACID (PAH) AND DIODRAST FOR RENAL EXCRETION AND EXTRACTION IN MAN [1]

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The competition between two substances for tubular excretion has been demonstrated repeatedly with orthodox clearance techniques. Smith, Goldring, and Chasis (1) found that raising the plasma concentration of diodrast depressed the excretion of phenol red. They concluded that both substances were excreted by the same mechanism. Similarly, it has been reported that intravenously administered diodrast (2) or PAH (3) retard the excretion of penicillin, that hippuric acid depresses the tubular excretion of glucuronic acid derivatives in the chicken (4), and that the amide of methyl-nicotinic acid depresses the tubular excretion of guanidine (5). Recently, it has been demonstrated that PAH in sufficient concentrations excludes phenol red from the cells or lumen of fish tubules suspended in appropriate salt solutions (6).

Smith, Finkelstein, Aliminosa, Crawford and Graber (7) found that diodrast and PAH given simultaneously had approximately the same renal clearance in man when the plasma concentration of both was low. They concluded that the two substances were excreted by the same mechanism. In none of these previous studies has the simultaneous renal extraction of the examined substances been investigated by analysis of renal vein blood. In fact, although it has been reported that renal extraction of diodrast is lower than that of PAH (8), there have been no published reports of simultaneous measurements of extraction of the two substances.

In the present study, the renal percentage extraction (E) and the tubular excretion (T) of diodrast and PAH in man were simultaneously compared in experiments during which the plasma concentration of one or both was varied over wide limits.

By "renal extraction," E, is meant the percentage of a solute removed from the plasma during the passage of blood through the kidneys. Thus,

$$E = \frac{A_c - V_c}{A_c} \cdot 100,$$

where A_c is the concentration of a solute in the arterial plasma and V_c is the concentration of the same solute in the renal venous plasma.

By the tubular excretion, T, is meant the difference between the total amount of a solute excreted per minute in the urine and the amount of this solute filtered through glomeruli. The filtered quantity is calculated as the product of the inulin clearance and the filterable fraction of the plasma diodrast or PAH, which generally are considered to be 73 and 83 per cent of the total plasma concentrations, respectively.

MATERIAL AND METHODS

Seventeen healthy young volunteers—medical students and nurses—were studied in the morning in the post-absorptive state. In fifteen of the experiments, a Goodale catheter was placed in the right renal vein under fluoroscopic control. An indwelling needle was placed in a brachial artery and a catheter placed in the bladder. After each clearance period the bladder was emptied and rinsed twice with distilled water and subsequently with air. At the beginning and end of each clearance period, blood samples were simultaneously collected from the brachial artery and the renal vein, transferred to heparinized tubes, and centrifuged within 5 minutes.

In experiments 1 and 2 (Table I, Figure 1), by first giving an intramuscular injection of PAH, a low and comparatively steady plasma concentration was achieved (9). After one or two control periods, by giving an intramuscular injection of diodrast,[2] a low and fairly

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[2] We are indebted to A. B. Astra Co., Södertälje, Sweden, for generously supplying us with 35 per cent Umbradil (diodrast).

TABLE I

Results of renal vein catheterization experiments 1 to 4

Exp. no.	Subject	Minutes	In.‡	PAH A_e‡	PAH E‡	PAH Cl‡	PAH RPF‡	PAH T‡	PAH $\frac{10T}{A_e}$‡	Diodrast A_e	Diodrast E	Diodrast Cl	Diodrast RPF	Diodrast T	Diodrast $\frac{10T}{A_e}$	$\frac{Cl_D}{Cl_{PAH}}$	$\frac{E_D}{E_{PAH}}$	
1*	Man,	13	106	60	92	592	644	27	4,5									
	26 y.,	27	120	67	91	590	649	33	4,9									Diodr. intramusc.
	b.s.a.	15	116	72	91	616	671	37	5,2	40	72	568	789	27	6,9	0,92	0,78	
	2,01	26	109	86	63	456	724	31	3,6									Start diodr. infus.
		14	101	80	61	536	880	36	4,5	544	59	508	861	221	4,1	0,95	0,97	
2*	Woman,	32	133	61	87	806	926	42	6,9									Diodr. intramusc.
	26 y.,	14	133	52	85	746	877	33	6,2	87	81	673	832	49	5,5	0,90	0,95	
	b.s.a.	29	164	51	58	715	1,233	29	5,7									Start diodr. infus.
	1,73	15	190	46	61	792	1,298	29	6,3	418	54	687	1,270	229	5,5	0,87	0,88	
		16	142	38	62	720	1,161	23	6,0	323	57	665	1,166	185	5,7	0,92	0,92	
3†	Man,	24	116							189	83	726	874	25	1,3			
	21 y.,	31	142							110	89	945	1,060	29	2,7			PAH intramusc.
	b.s.a.	18	122	76	93	652	700	41	5,4	83	86	772	897	27	3,2	1,18	0,92	
	1,92	29	147							79	70	557	796	18	2,3			Start PAH infus.
		13	137	1,010	61	505	827	392	3,9	71	67	463	691	14	2,0	0,92	1,10	
4†	Man,	17	134							141	85	722	848	88	6,2			
	24 y.,	26	131							124	86	583	678	60	4,9			PAH intramusc.
	b.s.a.	12	124	150	91	604	654	74	5,0	80	81	669	827	46	5,7	1,11	0,89	
	1,83	21	131							72	76	669	879	41	5,7			Start PAH infus.
		11	131	1,133	56	425	759	353	3,1	66	53	645	1,218	36	5,5	1,52	0,95	
		12	130	1,256	55	396	721	357	2,8	59	48	526	1,095	26	4,3	1,33	0,87	Illness

* In experiment 1–2, a low arterial plasma concentration of PAH was maintained and that of diodrast was increased to high levels.
† In experiments 3–4, a low diodrast concentration was maintained, and the PAH concentration increased.
‡ In = inulin clearance,
A_e = arterial plasma concentration in μ-mol./L.,
E = apparent renal percentage extraction,
Cl = renal clearance in ml./min.,

$$RPF = \frac{\text{clearance}}{E} 100,$$

T = calculated tubular excretion in μ-mol./min.,
y = years,
b.s.a. = body surface area in m^2.

steady plasma concentration of this substance was also attained (10). When the simultaneous excretion of the two substances had been observed for a sufficient time at these low plasma concentrations, the diodrast concentration was increased by giving a constant intravenous infusion until one or two more periods had been concluded.

In experiments 3 and 4 (Table I, Figure 1), the experimental design was the same but the order in which the substances were given was reversed, diodrast being given first and at low concentrations only.

In the experiments 5 to 9 (Table II), both substances were given simultaneously in equimolecular quantities. In experiment 5 (Figure 2), intramuscular injections were supplemented by constant, sustained intravenous infusions of both. At first, only a comparatively high concentration was effected, followed by a very high one of both substances. In experiments 6 to 9 (Table II), PAH and diodrast were given in equimolecular amounts by intravenous infusion only. Thus, initially, the concentrations were comparatively high and subsequently very high. In experiments 6 and 7, the renal vein was not catheterized.

In eight other experiments (Table III), a comparison was made between the simultaneous renal extractions, E, and clearances, Cl, of diodrast and PAH at low plasma concentrations only, which were sustained by simultaneous intramuscular injections.

In five experiments, the influence of the time interval between sampling and centrifugation was studied by a method similar to that described by Phillips, Dole, Hamilton, Emerson, Archibald, and Van Slyke (11). A large renal venous blood sample was drawn rapidly in subjects given both PAH and diodrast. An aliquot of each sample was centrifuged within 40 to 80 seconds and others after longer intervals up to 20 min. By using an angle centrifuge with accelerations up to 8,000 r.p.m., the blood was separated in a few seconds so that the time of centrifugation was negligible. Then, the plasma was analyzed for diodrast and PAH by the usual method, slightly modified for the small concentrations.

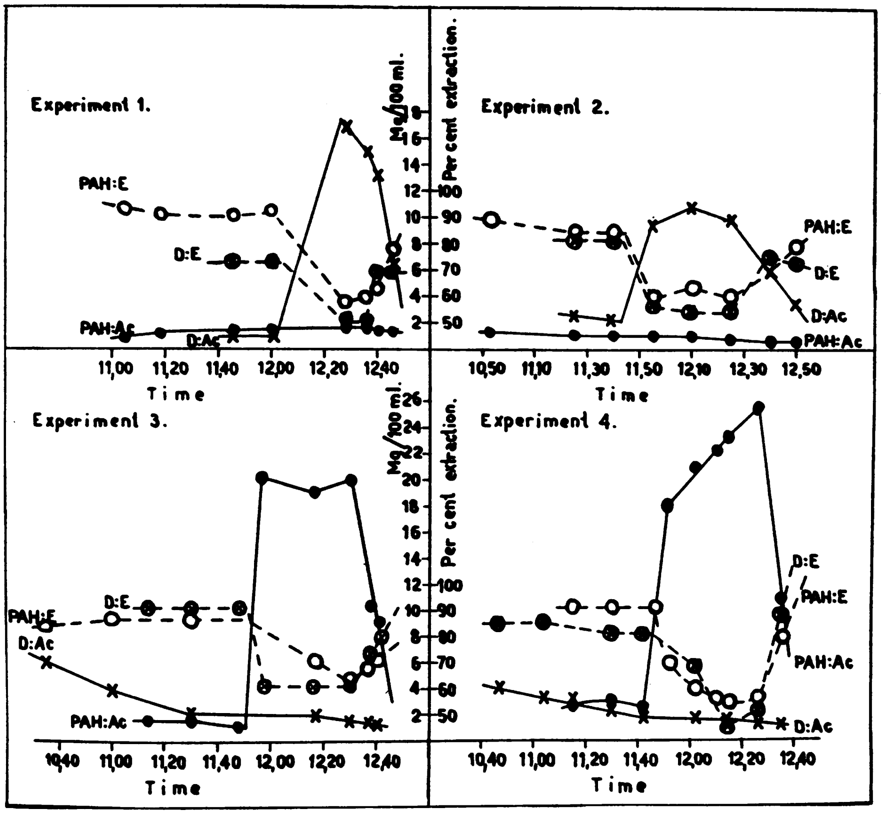

FIG. 1. RESULTS OF RENAL VEIN CATHETERIZATION-EXPERIMENTS 1–4

● = arterial plasma PAH concentration (PAH: Ac); ○ = apparent percentage PAH extraction (PAH: E); × = arterial plasma diodrast concentration (D: Ac); ⊗ = apparent percentage diodrast extraction (D: E).

The details of the methods used, abbreviations and calculations, are described in previous publications from this laboratory (12, 13, 14).

RESULTS

Table I contains the interpolated concentration in arterial blood plasma (A_c), the interpolated renal extraction (E), the renal clearance (Cl), the estimated renal plasma flow ("RPF") and the tubular excretion (T) for both PAH and diodrast for the experiments, in which the concentration of only one substance was increased. In Figure 1, the corresponding actual extraction values and arterial plasma concentrations are presented. It is evident that when the concentration of both was low, the extraction of diodrast was slightly lower than that of PAH. When the concentration of either test substances was increased, the extraction of both decreased, although the arterial content of the other was actually lower than during the control period.

In Table II and Figure 2, the results obtained during administration of high, equimolecular concentrations of PAH and diodrast are presented. When the concentrations were increased, there generally was a parallel fall in the extraction of both substances. When calculated on the usual basis of a filterability of 83 per cent for PAH and 73 per cent for diodrast, the tubular excretion, T, did not remain constant. The ratio T/A_c for PAH and diodrast is included as a comparative index of affinity for tubular excretion in the mutual competition.

In Table III are summarized the results of the first simultaneous and complete period from each low concentration experiment. The ratio of the PAH clearance to the diodrast clearance varied considerably in some of the experiments, but the

TABLE II*

Results of experiments 5 to 9 with high equimolecular plasma concentration of PAH and diodrast

Exp. no.	Subject	Minutes	In.	PAH A_a	PAH E	PAH Cl	PAH RPF	PAH T	PAH $\frac{10T}{A_a}$	Diodrast A_a	Diodrast E	Diodrast Cl	Diodrast RPF	Diodrast T	Diodrast $\frac{10T}{A_a}$	$\frac{E_D}{E_{PAH}}$	$\frac{T_D}{T_{PAH}}$
5†	Woman,	17	102	74	92	450	490	27	3,67	104	88	546	623	49	4,71	0,96	1,79
	26 y.,	22	84						Steep concentr. increase								
	b.s.a.	14	97	516	43	260	605	93	1,80	623	37	238	644	98	1,57	0,86	1,05
	1,69	21	92	697	40	236	591	119	1,71	799	40	239	597	141	1,76	1,00	1,18
		12	91						Steep concentr. increase								
		9	80	3,200	24	94	391	78	0,24	3,030	19	90	473	95	0,31	0,79	1,21
		12	83	2,530	23	112	448	103	0,41	2,360	20	119	595	137	0,58	0,80	1,33
6	Man,	19	170	896		213		66	0,74	878		272		131	1,49		2,01
	21 y.,	15	144	950		174		50	0,53	930		212		105	1,13		2,13
	b.s.a.	21	142						Steep concentr. increase								
	1,75	20	130	1,327		181		98	0,74	1,338		177		109	0,82		1,11
		22	155	1,427		141		27	0,17	1,453		153		72	0,49		2,88
7	Man,	21	113	797		259		131	1,65	854		268		158	1,80		1,21
	24 y.,	25	105	891		219		118	1,33	994		220		147	1,48		1,25
	b.s.a.	34	105						Steep concentr. increase								
	2,07	22	101	1,475		168		121	0,82	1,490		185		164	1,10		1,36
		16	94	1,835		134		103	0,56	1,865		148		149	0,80		1,43
8†	Man,	14	162	560	37	394	1,072	146	2,61	570	53	423	824	173	3,04	1,43	1,18
	20 y.,	12	158	680	41	327	802	134	1,97	610	48	403	841	177	2,90	1,17	1,32
	b.s.a.	13	141	770	44	281	642	128	1,67	680	46	350	763	167	2,46	1,04	1,30
	1,95	35	142	1,080	36	244	680	137	1,27	1,000	34	269	796	166	1,66	0,95	1,21
		11	186	1,410	27	249	934	134	0,95	1,280	29	277	956	181	1,41	1,07	1,35
		15	197	1,510	29	201	683	56	0,37	1,350	31	235	757	122	0,91	1,07	2,18
		10	182	1,640	27	211	776	87	0,58	1,460	29	241	840	160	1,10	1,07	1,84
9†	Man,	18	156	700	43	235	547	74	1,06	680	42	245	587	89	1,31	0,98	1,20
	24 y.,	16	133	820	36	216	596	86	1,05	840	42	231	547	112	1,34	1,17	1,30
	b.s.a.	15	115	900	29	220	716	112	1,24	950	40	223	579	132	1,39	1,38	1,18
	1,98	44	86	1,290	23	160	696	113	0,88	1,300	26	160	621	127	0,98	1,13	1,12
		24	108	1,950	18	138	760	95	0,49	1,970	19	147	779	133	0,68	1,06	1,41
		14	102	2,180	18	125	705	88	0,40	2,230	20	127	636	118	0,53	1,11	1,34
		13	88	2,320	17	99	583	60	0,26	2,380	19	99	517	83	0,35	1,12	1,38

* Abbreviations as in Table I.
† In 5, 8, 9, the renal vein was catheterized.

TABLE III

Comparison between the simultaneous renal clearance (Cl) and renal extraction (E) of PAH and diodrast at low plasma concentrations of both substances

Exp. no.	Sex	Age *year*	PAH Cl	PAH RPF	PAH E	Diodrast Cl	Diodrast RPF	Diodrast E	$\frac{Cl_D}{Cl_{PAH}}$	$\frac{E_D}{E_{PAH}}$
1	M	26	529	577	92	488	679	72	0,92	0,78
2	F	26	746	877	85	673	832	81	0,90	0,95
3	M	21	587	630	93	695	807	86	1,18	0,92
4	M	26	571	627	91	632	780	81	1,11	0,89
5	F	26	460	501	92	559	637	88	1,21	0,96
10	M	25	—	—	89	585	720	81	—	0,91
11	M	23	598	673	89	658	794	83	1,10	0,93
12	M	25	440	490	90	410	470	87	0,93	0,97
13	M	23	618	672	92	939	1,064	87	1,52	0,95
14	M	23	492	557	89	525	627	84	1,07	0,94
15	F	21	467	511	91	—	—	86	—	0,95
16	M	22	544	594	91	525	610	86	1,04	0,95
17	M	25	506	566	90	482	570	85	1,05	0,94
Mean			547	606	90,3	598	716	83,6	1,09	0,926
σ			85,2	105,2	2,06	138,0	154,2	4,20	0,175	0,0505
$\frac{100\sigma}{M}$			15,6	17,4	2,3	23,1	21,5	5,0	16,0	5,5

proportionality between PAH extraction and diodrast extraction was much more stable. As previously reported, the renal extraction of PAH was somewhat higher than that of diodrast, the difference between the means being highly significant (P = 0.001) by Student's "t" test. Statistically, the difference between the means of the clearance values was not significant. As a consequence of the lower renal diodrast extraction and the higher diodrast clearance, the calculated figures for the renal plasma flow (RPF), calculated from the diodrast data, were higher than the corresponding figures, based on PAH.

The analysis of PAH and diodrast in the renal venous samples, centrifuged after different time intervals, demonstrated that the shift of diodrast and PAH from erythrocytes to plasma after the first 40 seconds following sampling could influence the calculated extractions and RPF's only slightly (Figure 3). However, the shift during the first 40 seconds, which we were unable to study, may have been considerable.

DISCUSSION

The calculation of the tubular excretion, T, at high plasma concentrations of diodrast or PAH is subject to error from several sources. Because T represents the small difference between the large amounts filtered and the larger total urinary excretion, analytical errors are of great significance. Variations in the percentage of the plasma diodrast or PAH filterable through the glomerular membranes are probably of even greater significance. In experiments on ultrafiltration of fresh human plasma containing high concentrations of diodrast and PAH, we have obtained filterability factors which vary from 1 to 5 per cent in both directions from the classical figures of 73 per cent and 83 per cent. However, because in some experiments the filterable fraction slowly decreased, it may be that the duration of ultrafiltration is of some influence, since filtration in the capsula of Lavietes or in the centrifuged cellophane bag of Rehberg (15) took 5 to 10 hours. Moreover, filterability varied with the age of the sample. In some subjects, the changes did not exceed 1 to 2 per cent, but occasionally, after 24 hours, we found 2 to 6 per cent decreases in the ultrafilterability, and, at times, after 48 hours, decreases as great as 10 per cent. However, in fresh plasma, the proportion between the ultrafilterability of diodrast and of PAH remained reasonably steady.

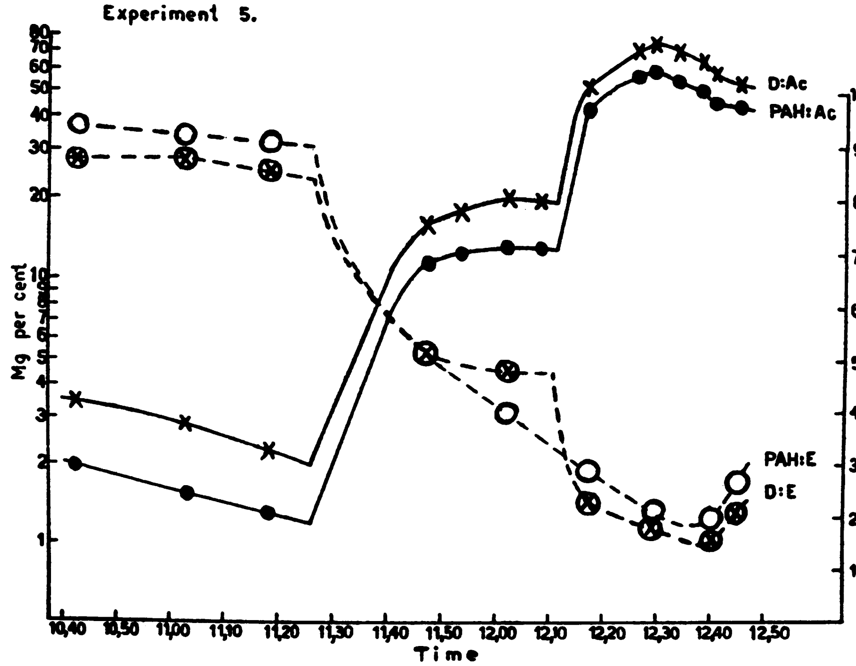

FIG. 2. RESULTS OF RENAL VEIN CATHETERIZATION-EXPERIMENT 5
Symbols and abbreviations as in Figure 1.

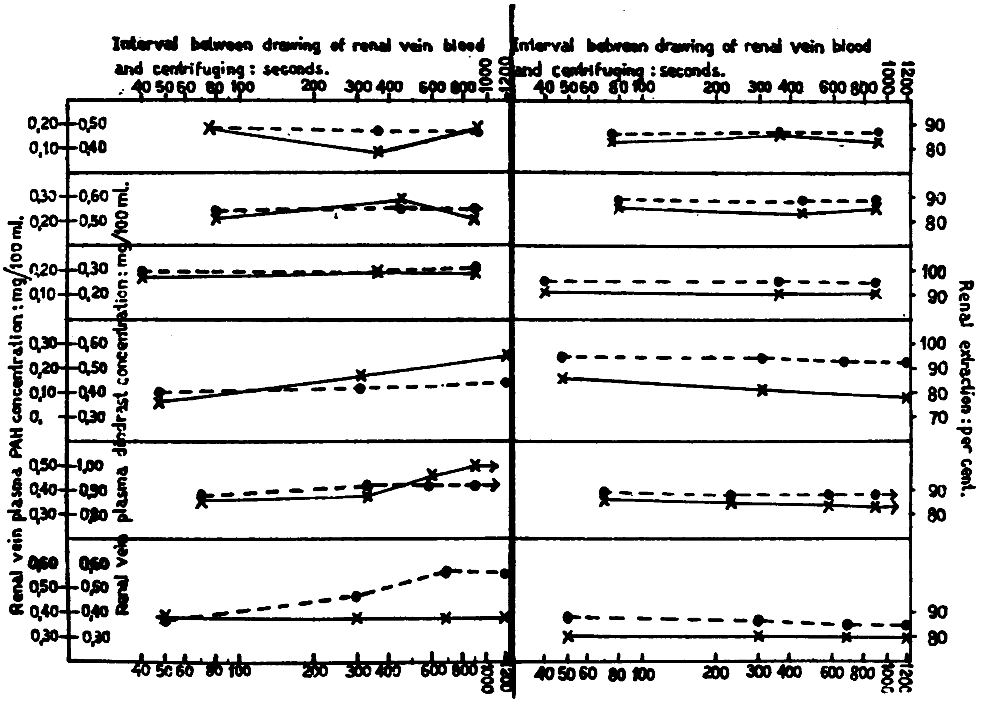

FIG. 3. RENAL VENOUS PLASMA CONCENTRATIONS (LEFT-HALF OF CHART) AND RENAL EXTRACTIONS (RIGHT-HALF OF CHART) FOR DIODRAST (×) AND PAH (●) BLOOD CENTRIFUGED 50 TO 1,200 SECONDS AFTER COLLECTION

In the experiments recorded in the tables, the ultrafiltration was performed on 1 to 2 day old samples. Hence, we have preferred to calculate T values, with reservations, on the basis of the usual ultrafilterabilities of 73 per cent and 83 per cent.

When calculated in terms of molecules, the T-values for diodrast and PAH were essentially the same when plasma concentrations were below the saturation limit; *i.e.*, the proportion between the tubular excretion and the arterial plasma concentration, T/A_c, was of the same order of magnitude for both substances (Table I). However, at plasma concentrations above the saturation limit, the tubular excretion of diodrast exceeded that of PAH; *i.e.*, its T/A_c ratio was higher even if it were assumed that both substances were completely filterable.

The data in Table III demonstrate that at low plasma concentrations the renal plasma flow, calculated on the basis of diodrast, was significantly higher than the corresponding PAH value, although there was no significant difference between the corresponding clearances.

At low plasma concentrations, the ratio of diodrast extraction to PAH extraction was slightly below 1 and remained remarkably steady, whereas the corresponding clearance ratio was above 1 but had a high standard variation. When the plasma concentration of both substances was very high, the percentage extractions were nearly identical, with a few exceptions (Table II). If the arterial plasma concentration of one of the substances was maintained at a constant low level when the concentration of the other was suddenly increased, there resulted simultaneous and equivalent depression of both E_{PAH} and E_D (Table I).

The accumulation of diodrast in the renal tubular cells, found by Engstrom and Josephson (16), could not have induced the higher tubular excretion and renal venous concentration of diodrast. As shown with PAH by Josephson, Bucht, Ek and Werkö (13), such accumulation can influence the tubular excretion and the renal vein plasma concentration only when the plasma concentration is rapidly increased or decreased. The differences found here remained fairly steady over a long period and represented much larger amounts of diodrast than could be explained by this process.

White, Findley, and Edwards (17), and Corcoran, Smith, and Page (18) have suggested that diodrast may shift from the erythrocytes to the plasma during the passage of the blood through the kidneys. This shift may explain the observed differences in the renal percentage extractions of diodrast and PAH.

The fact that these substances mutually depressed each other's tubular excretion indicates that either they are excreted by the same transferring mechanism, as postulated by Smith, Finkelstein, Aliminosa, Crawford, and Graber (7), or that the energy required for their excretion is provided by a common source. The fact that at higher plasma concentrations more molecules of diodrast than of PAH are excreted should result in a higher renal extraction for diodrast than for PAH under these conditions. However, the anticipated difference may be negated by the shift of diodrast from the erythrocytes to the plasma. At low plasma concentrations, when the two substances are almost equally excreted, the shift of diodrast may increase the renal vein plasma concentration, and thereby produce the apparent, lower renal extraction of diodrast with the consequent, apparent, higher renal plasma flow. The suggested shift must be so rapid that it cannot be prevented by almost immediate centrifugation of the renal venous blood. At high plasma concentrations, the percentage of plasma diodrast excreted by the tubules is small. Consequently, the plasma/erythrocytes concentration ratio is only slightly changed and the influence of the shift not measurable.

SUMMARY

Injections of PAH and diodrast were given simultaneously to 17 healthy human subjects. In 15 of these, renal venous blood for repeated analyses was obtained by venous catheterization.

When the plasma concentrations of PAH and diodrast were low, the proportions between both their respective percentage renal extractions from the plasma and their respective tubular excretions were remarkably steady.

When the plasma concentration of one of the substances was increased, the percentage renal extraction of both was equally depressed. With increasing plasma concentration, the tubular excretion of diodrast increases relative to the PAH excretion. It is concluded that the two substances are probably excreted by the same mechanism, which, at high plasma concentrations, can transport more diodrast molecules than PAH.

It is suggested that a shift of diodrast from the erythrocytes during the passage through the kidney may increase the renal venous plasma concentration. At high plasma diodrast concentrations, the influence of this shift is not measurable, but at low concentrations it leads to a lower, apparent value of renal percentage extraction for diodrast as compared to PAH.

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