Origins of the Uricosuric Response

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ABSTRACT The acute effects of intravenous (i.v.) probenecid and chlorothiazide on renal urate handling were investigated in paired studies in normal men. Uricosuric responses to these agents were compared in the same subjects, both without and with pyrazinamide (PZA) pretreatment. Assuming that PZA selectively inhibits the tubular secretion of urate and that uricosuric agents act by increasing the excretion of filtered urate, then the uricosuric responses (the increment in urate excretion or clearance) should have been unaffected by PZA. Defined in this manner, however, uricosuric responses to probenecid and chlorothiazide were significantly decreased after PZA pretreatment. In order to determine whether PZA diminished other renal actions of chlorothiazide, changes in sodium and inorganic phosphorus excretion were examined. Chlorothiazide produced equivalent natriuretic and phosphaturic responses after PZA pretreatment, indicating that PZA does not interfere with at least some of the renal actions of chlorothiazide. In separate studies, PZA depressed urate excretion by at least 68% during the maintenance of chlorothiazide-induced natriuresis and phosphaturia, suggesting that chlorothiazide does not diminish the antisecretory action of PZA.

The results suggest that probenecid and chlorothiazide may derive their uricosuric properties by facilitating the excretion of both filtered and secreted urate. Possibly, increased excretion of secreted urate might occur through modulation of urate reabsorption at a site distal to tubular secretion, rather than by the direct acceleration of secretory transport. However, PZA-induced interference with the actions of probenecid and chlorothiazide on renal urate transport mechanisms cannot be excluded as a possible explanation for the present results.

INTRODUCTION

The mechanism of action of uricosuric agents has been a matter of considerable theoretical and practical interest, but has been difficult to study in man. After the demonstration that pyrazinamide (PZA)[1] and pyrazinoic acid are potent and highly selective inhibitors of the renal tubular secretion of urate in several species (1–3), PZA subsequently was utilized to give a rough quantitative estimate of the relative magnitudes of urate reabsorption and secretion in man (4, 5). In the "PZA suppression test," the decrement in uric acid excretion produced by a maximally antiuricosuric dose of PZA is taken as an index of tubular secretion, while the residual amount of urinary urate after PZA usually is considered to represent urinary uric acid derived from glomerular filtration but escaping tubular reabsorption (6). This interpretation depends on the assumptions that: (*a*) PZA completely and specifically inhibits urate secretion, and (*b*) there is no interaction between urate secretion and reabsorption within the nephron. If the action of PZA were incomplete or nonspecific, or if a portion of the secreted urate subsequently were reabsorbed, the PZA technique would underestimate both tubular secretion and reabsorption.

The present studies were designed to further examine changes in renal urate handling in man during the uricosuric states immediately after the administration of probenecid and chlorothiazide. The increased uric acid excretion caused by uricosuric agents usually has been attributed solely to an increase in the fraction of filtered urate excreted. In contrast, the results of the present studies indirectly suggest that the increased excretion of secreted urate may contribute importantly to the uricosuric properties of probenecid and chlorothiazide.

METHODS

38 renal clearance studies were performed in 21 volunteers. All had been fully informed of the experimental nature of the studies and gave their informed consent. None had a history of gout. 19 subjects were normal males whose ages ranged from 20 to 35 yr. One female participant, R. O., age 54, had essential hypertension; while the other, J. S., age 46, had bilateral renal artery stenosis.

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[1] *Abbreviations used in this paper:* C_{inulin}, clearance of inulin; GFR, glomerular filtration rate; PAH, para-aminohippuric; PZA, pyrazinamide.

TABLE I

Responses to Probenecid, Without and With PZA Pretreatment

	Without PZA pretreatment					With PZA pretreatment				
	$U_{urate}V$	$U_{urate}V/C_{inulin}$ ×100	C_{urate}/C_{inulin} ×100	V	C_{inulin}	$U_{urate}V$	$U_{urate}V/C_{inulin}$ ×100	C_{urate}/C_{inulin} ×100	V	C_{inulin}
	μg/min	*μg/100 ml*	%	*ml/min*	*ml/min*	*μg/min*	*μg/100 ml*	%	*ml/min*	*ml/min*
J. O., control	607	444	10.0	9.0	138	132	92	1.5	11.3	144
probenecid	1,675	1,162	28.2	12.4	144	692	506	7.8	9.2	137
E. L., control	196	142	4.8	7.4	147	84	54	2.0	11.1	156
probenecid	825	549	20.8	13.0	150	347	226	8.4	9.0	154
G. U., control	1,016	842	10.2	14.1	121	270	246	4.8	14.6	110
probenecid	2,053	1,815	18.8	14.4	113	382	360	7.0	3.4	107
G. R., control	731	531	10.1	13.5	133	68	62	1.1	7.2	111
probenecid	1,460	1,495	29.1	6.6	98	192	187	3.5	5.7	103
H. A., control	382	316	6.8	5.6	111	66	63	1.2	7.7	105
probenecid	1,827	1,428	26.4	4.2	130	257	280	5.4	3.0	95
H. O., control	688	392	6.3	14.0	158	64	49	0.8	15.0	128
probenecid	2,459	1,889	31.2	12.5	127	285	249	4.3	8.4	114
G. O., control	895	591	10.2	16.1	122	70	59	1.4	10.5	117
probenecid	2,120	1,817	33.4	9.9	117	240	207	4.9	12.3	116
Control-mean	645	465	8.3	11.4	133	108	89	1.8	11.1	124
(SEM)	(107)	(84)	(0.9)	(1.5)	(6)	(29)	(27)	(0.5)	(1.1)	(7)
Probenecid-mean	1,774	1,451	26.8	10.4	126	342	288	5.9	7.3	118
(SEM)	(200)	(180)	(2.1)	(1.4)	(7)	(63)	(42)	(.7)	(1.3)	(8)
P	<0.001	<0.001	<0.001	NS	NS	<0.01	<0.05	<0.001	NS	<0.02

Control, mean of control periods; Probenecid, mean of periods during the hour after probenecid; 500 mg i.v.; $U_{urate}V$, urate excretion rate; C_{inulin}, inulin clearance (GFR); C_{urate}/C_{inulin}, urate-to-inulin clearance ratio, V, urine flow, NS, $P \geq 0.05$.

The subjects were studied as outpatients, and had been consuming their usual diets. None were taking medications. Studies commenced in the morning after an overnight fast. Venous blood specimens were drawn into heparinized syringes from an indwelling needle at the midpoint of each clearance period. Urine specimens were obtained by voiding; all exceeded 70 ml in volume. Participants remained recumbent throughout, except while voiding. Initial hydration was accomplished with tap water, 10–15 ml/kg orally, as well as the intravenous (i.v.) administration of 1,000 ml of 0.45% NaCl during a 40–60 min equilibration interval preceding the onset of clearance periods. After the administration of a suitable priming dose of inulin, a sustaining infusion of inulin in 0.9% NaCl was maintained at 3.5 ml/min, utilizing an infusion pump. Four subjects also received para-aminohippurate (PAH) in amounts sufficient to establish plasma concentrations at 5–10 mg/100 ml, levels which do not affect urate excretion in man (7). Clearance periods were 20 min in duration. Specimens for 3 or 4 control clearance periods were collected at the beginning of each experiment.

In 34 experiments in 17 normal participants, subjects received 500 mg of probenecid or chlorothiazide as a single i.v. pulse. Specimens for three additional clearance periods then were collected. After an interval ranging from 3 to 31 days, the studies were repeated in an identical manner in the same participants, except that each received PZA, 3 g orally, 90 min before onset of the control periods for the second study. In four other studies with chlorothiazide, participants received 3 g of PZA orally after completion of the above experimental sequence without PZA. The format then was repeated, beginning with infusion of 1,000 ml of 0.45% NaCl during another equilibration interval, during which the antiuricosuric action of PZA developed.

Inulin (8) and inorganic phosphorus (9) were analyzed by automated methods. Uric acid was measured by an ultraviolet enzymatic spectrophotometric procedure (10) or an automated differential enzymatic colorimetric procedure (11). The latter method does not require dialysis of samples or precipitation of plasma proteins. Both methods gave substantially identical results and complete recoveries of uric acid in plasma and urine. Sodium was measured with a flame photometer, utilizing lithium internal standardization.

The clearance of inulin (C_{inulin}) was used as an estimate of glomerular filtration rate (GFR). Values for GFR, urine flow rate, and solute excretion rates were normalized to a standard body surface area of 1.73 m^2. In each study, results from all control periods and all posturicosuric periods were averaged separately. Comparisons were made utilizing paired *t* tests (12). Mean control values were compared with mean posturicosuric values as pairs in each experiment. In addition, paired comparisons were made between similar phases for experiments in the same participants, without and with PZA pretreatment.

RESULTS

Uricosuric responses to probenecid, 500 mg i.v., were measured in paired experiments in seven normal men without and with PZA pretreatment (Table I). Without PZA, urate excretion averaged 645±107 μg/min (mean ±SEM) in control periods and increased by a mean of 1,129±150 μg/min after probenecid. When the same individuals were restudied after PZA pretreatment, control urate excretion values averaged 108±29 μg/min, but probenecid increased urate excretion by only 235±58

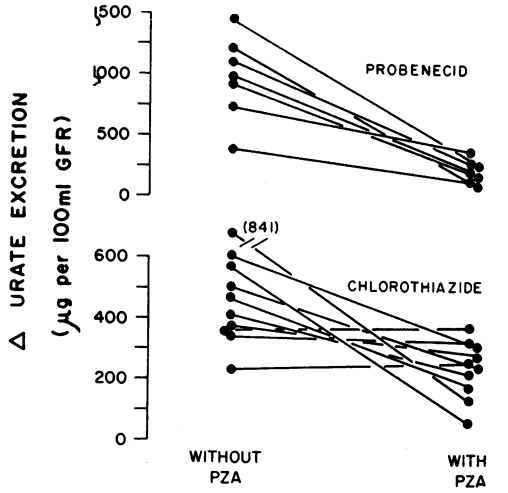

FIGURE 1 Increments in urate excretion (per unit GFR) produced by probenecid or chlorothiazide. In the studies with PZA, probenecid, and chlorothiazide always produced an increase in urate excretion, although this usually was less than that occurring when the same subjects were studied without PZA pretreatment.

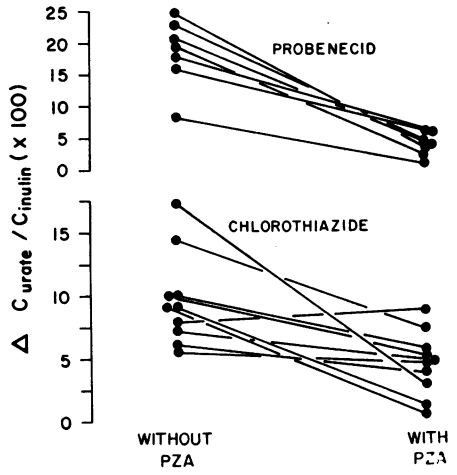

FIGURE 2 Changes in the urate-to-inulin clearance ratio ($\Delta C_{urate}/C_{inulin}$) after probenecid or chlorothiazide. Probenecid and chlorothiazide produced significantly smaller changes in C_{urate}/C_{inulin} after PZA pretreatment ($P < 0.02$). Plasma urate concentrations were not significantly different in the paired studies.

TABLE II

Uricosuric Responses to Chlorothiazide, Without and With PZA Pretreatment

	Without PZA pretreatment					With pretreatment				
	$U_{urate}V$	$U_{urate}V/C_{inulin}$ ×100	C_{urate}/C_{inulin} ×100	V	C_{inulin}	$U_{urate}V$	$U_{urate}V/C_{inulin}$ ×100	C_{urate}/C_{inulin} ×100	V	C_{inulin}
	μg/min	*μg/100 ml*	%	*ml/min*	*ml/min*	*μg/min*	*μg/100 ml*	%	*ml/min*	*ml/min*
C. O., control	495	406	7.0	7.6	122	109	91	1.3	7.3	120
chlorothiazide	1,037	749	12.8	10.3	135	480	412	5.9	9.1	107
F. E., control	600	462	7.2	11.6	130	127	81	1.2	19.7	175
chlorothiazide	1,023	931	15.2	21.9	107	305	257	3.9	26.9	119
H. L., control	446	504	9.5	6.3	88	95	75	1.7	10.1	128
chlorothiazide	799	869	17.1	8.9	92	392	349	8.0	16.1	113
Z. O., control	535	361	5.8	12.1	148	45	31	0.45	14.8	144
chlorothiazide	1,086	926	14.7	9.6	122	117	104	1.4	9.6	116
V. O., control	530	392	8.9	15.7	139	159	111	2.3	15.8	142
chlorothiazide	1,200	1,007	23.4	15.1	119	525	428	9.6	17.8	121
H. F., control	553	385	8.0	20.1	152	147	155	2.8	14.5	94
chlorothiazide	865	1,226	25.7	12.2	90	378	318	5.7	14.2	112
S. A., control	453	380	6.7	13.8	119	78	67	1.1	9.9	117
chlorothiazide	869	860	16.8	12.4	101	360	340	5.7	24.8	110
E. L., control	443	413	9.8	13.3	110	38	30	0.75	17.8	133
chlorothiazide	732	810	19.8	19.8	101	268	271	6.8	19.6	100
M. A., control	512	407	7.5	10.9	126	186	141	2.4	14.0	133
chlorothiazide	1,159	643	12.6	17.5	150	779	404	7.3	19.1	139
C. V., control	719	577	11.6	8.5	129	208	159	3.6	17.8	132
chlorothiazide	942	922	19.3	19.9	107	658	554	12.7	21.7	114
Control-mean	529	429	8.2	12.0	126	119	92	1.8	14.2	132
(SEM)	(27)	(21)	(0.6)	(1.3)	(6)	(18)	(14)	(0.3)	(1.3)	(7)
Chlorothiazide-mean	971	894	17.7	14.8	112	426	319	6.7	17.9	115
(SEM)	(49)	(49)	(1.4)	(1.5)	(6)	(61)	(43)	(1.0)	(1.9)	(3)
P	<0.001	<0.001	<0.001	NS	NS	<0.001	<0.001	<0.001	NS	<0.05

Studies and abbreviations are similar to Table I, except that chlorothiazide, 500 mg, was administered instead of probenecid.

TABLE III

*Plasma Solute Concentrations in Paired Experiments**

	Plasma urate	Plasma sodium	Plasma phosphorus
	mg/100 ml	*meq/liter*	*mg/100 ml*
Probenecid studies			
Without PZA	5.4	138	2.6
(7 studies)	(0.7)	(1)	(0.1)
With PZA	5.1	141	2.7
(7 studies)	(0.5)	(1)	(0.1)
Chlorothiazide studies			
Without PZA	5.3	140	2.7
(10 studies)	(0.2)	(1)	(0.1)
With PZA	5.6	142	2.7
(10 studies)	(0.4)	(1)	(0.1)

* Experiments reported in Tables I and II. Values are mean of means, with SEM in parentheses. Paired differences in each group, between studies without and with PZA, were not significant.

μg/min. A roughly similar degree of disparity occurred for changes in urate excretion per unit GFR (Fig. 1) and C_{urate}/C_{inulin} (Fig. 2). Changes in urine flow and GFR usually were small and variable (Table I).

Similar paired studies utilizing chlorothiazide, 500 mg i.v., were performed in 10 other normal men and are summarized in Table II. Without PZA, urate excretion averaged 529±27 μg/min in control periods, and increased by an average of 443±49 μg/min during the hour after chlorothiazide. When the same individuals were restudied after PZA pretreatment, urate excretion averaged 119±18 μg/min in control periods and increased by only 306±46 μg/min, a value significantly less than the increase without PZA ($P < 0.05$). Uricosuric responses, taken as magnitudes of the absolute increases in uric acid excretion, were greater in the experiments without PZA in 9 of the 10 participants. Roughly similar changes occurred in urate excretion per unit GFR (Fig. 1) and C_{urate}/C_{inulin} (Fig. 2). GFR tended to diminish and urine flow increased after chlorothiazide (Table II).

In the probenecid studies without PZA, the increase in urate clearance ($\Delta C_{urate}/C_{inulin}$) averaged 18.4±2.1 ml/100 ml GFR (mean difference ±SEM of the paired differences), in contrast to a $\Delta C_{urate}/C_{inulin}$ of 4.1±0.6 ml/100 ml GFR in the probenecid studies with PZA ($P < 0.001$ for the paired comparisons of $\Delta C_{urate}/C_{inulin}$). Similarly, in the chlorothiazide studies without PZA, $\Delta C_{urate}/C_{inulin}$ averaged 9.6±1.2 ml/100 ml GFR, in contrast to 4.9±0.8 ml/100 ml GFR with PZA ($P < 0.02$ for paired comparisons). In the experiments without PZA pretreatment, the mean uricosuric response to probenecid ($\Delta C_{urate}/C_{inulin}$) was 92% greater than to chlorothiazide. After PZA, the uricosuric responses to both agents were similar. Thus, chlorothiazide appeared to be as potent a uricosuric agent as probenecid when comparisons were made after PZA pretreatment (Fig. 2).

Plasma urate values in both types of paired studies were comparable (Table III). In G. U. (Table I), the plasma urate was 8.4 mg/100 ml in the study without PZA, but unaccountably had diminished to 5.2 mg/100 ml 3 days later when the PZA study was performed. In all other participants, plasma urate concentrations were less than 7 mg/100 ml. Likewise, plasma sodium and inorganic phosphorus values did not vary significantly between the groups (Table III).

The suppression of uricosuric responses to probenecid and chlorothiazide after PZA pretreatment could have resulted from some type of interference by PZA with the renal transport or actions of these compounds. In the case of chlorothiazide, its natriuretic and phosphaturic actions were compared, both without and with PZA pretreatment (Table IV). Changes in fractional sodium excretion ($\Delta C_{Na}/C_{inulin}$) and fractional inorganic phosphorus excretion ($\Delta C_{phosphate}/C_{inulin}$) were essentially equivalent in the paired studies (Fig. 3). Control values for both parameters were similar, without and with PZA pretreatment (Table IV). $\Delta C_{Na}/C_{inulin}$ after chlorothiazide averaged 5.1±0.8 ml/100 ml GFR without PZA and 6.3±0.4 ml/100 ml GFR with PZA values which did not differ significantly (Fig. 3). Similarly, $\Delta C_{phosphate}/C_{inulin}$ averaged 13.2±1.0 ml/100 ml GFR without PZA and 14.5±0.9 ml/100 ml GFR with PZA (Fig. 3). Although the uricosuric action of chlorothiazide was sharply diminished after PZA pretreatment, its natri-

TABLE IV

*Summary of Natriuretic and Phosphaturic Properties of Chlorothiazide in 20 Paired Studies**

	$U_{Na}V$		C_{Na}/C_{inulin} ×100		$C_{phosphate}/C_{inulin}$ ×100	
	Without PZA	With PZA	Without PZA	With PZA	Without PZA	With PZA
	μEq/min		%		%	
Control-mean	321	332	1.9	2.0	14.9	14.7
(SEM)	(47)	(33)	(0.3)	(0.3)	(1.1)	(1.7)
Chlorothiazide-mean‡	1,041	1,254§	7.1	8.3	28.1	29.1
(SEM)	(70)	(77)	(0.8)	(0.6)	(1.6)	(1.4)

$U_{Na}V$, sodium excretion rate; C_{Na}/C_{inulin}, fraction of filtered sodium excreted; C_{phos}/C_{inulin}, fraction of filtered inorganic phosphate excreted.

* Studies of Table II.

‡ All chlorothiazide values significantly exceeded their respective paired controls ($P < 0.001$).

§ $U_{Na}V$ after chlorothiazide was significantly greater in the studies with PZA pretreatment ($P < 0.05$); otherwise, values with and without PZA did not differ significantly.

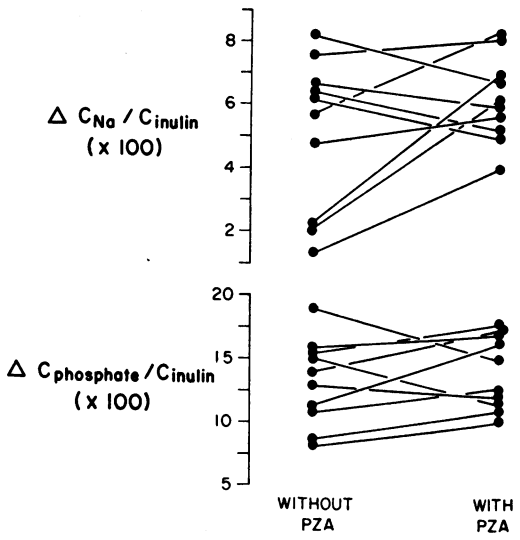

FIGURE 3 Changes in fractional sodium excretion ($\Delta C_{Na}/C_{inulin}$) and fractional inorganic phosphorus excretion ($\Delta C_{phosphate}/C_{inulin}$) after chlorothiazide. In contrast to uricosuric responses, the natriuretic and phosphaturic responses to chlorothiazide were unaffected by PZA pretreatment.

uretic and phosphaturic properties were unaffected (Table IV).

Since the uricosuric responses to chlorothiazide in PZA pretreated subjects might have resulted from interference by chlorothiazide with the antiuricosuric properties of PZA, the peak antiuricosuric effect of PZA after receiving chlorothiazide was investigated in four additional combined studies (Table V). At the time of the peak antiuricosuric action of PZA, fractional sodium excretion (C_{Na}/C_{inulin}) and fractional phosphorus excretion ($C_{phosphate}/C_{inulin}$) had declined somewhat from their respective peak values after the initial dose of chlorothiazide, but still greatly exceeded their original control values. Concomitantly, however, urate excretion (per unit GFR) decreased to values ranging from 68% to 90% less than control, comparing favorably with values reported previously in the absence of chlorothiazide (4). When a second dose of chlorothiazide was administered, the peak increment in uricosuric response was less than that after the first dose of chlorothiazide in all the subjects except S. T., although there always was a definite uricosuric response after the second dose. Likewise, fractional sodium and phosphorus excretion increased after the second dose of chlorothiazide. The PZA-induced discrepancies in peak uricosuric responses, with both experimental phases performed during the same day, suggest that the data of Table II did not arise from a

TABLE V

Chlorothiazide Action, Before and After Treatment with PZA

	$U_{urate}V/C_{inulin}$ ×100	C_{urate}/C_{inulin} ×100	V/C_{inulin} ×100	C_{Na}/C_{inulin} ×100	$C_{phosphate}/C_{inulin}$ ×100
	μg/100 ml	%	%	%	%
P. R., Control	461	10.8	12.1	0.66	9.6
First chlorothiazide peak	1,568	23.5	19.2	5.72	22.8
PZA peak	145	2.4	15.0	4.54	25.6
Second chlorothiazide peak	342	5.8	13.9	7.65	27.8
S. T., control	363	5.1	8.4	0.77	16.1
First chlorothiazide peak	880	13.0	10.1	3.19	24.8
PZA peak	86	1.5	4.4	3.06	30.1
Second chlorothiazide peak	575	9.7	9.1	5.65	42.0
J. S., control	374	9.9	7.3	1.7	9.5
First chlorothiazide peak	951	24.4	9.4	11.6	24.2
PZA peak	99	2.3	8.7	5.8	19.4
Second chlorothiazide peak	263	6.4	14.4	12.4	27.8
R. O., control	444	11.4	8.5	3.04	5.3
First chlorothiazide peak	973	24.4	11.1	9.11	11.1
PZA	43	1.1	15.2	6.19	8.3
Second chlorothiazide peak	150	3.3	11.9	8.47	9.7

Control, mean values during control periods; First chlorothiazide peak, values during peak uricosuric action of first dose of chlorothiazide; 500 mg i.v.,; PZA peak, values during peak antiuricosuric action of PZA (between 60 and 120 min after administration of PZA, 3 g.p.o.); Second chlorothiazide peak, values during peak uricosuric effect of second dose of chlorothiazide, 500 mg i.v., administered 120 min after PZA. Subjects received 1,000 ml 0.45% NaCl during the hour preceding the onset of control periods and during the 1st h after PZA administration.

systematic error incurred in performing the paired experiments on different days.

DISCUSSION

These data indicate a striking diminution in uricosuric effects of probenecid and chlorothiazide in paired studies after PZA pretreatment. Assuming that PZA specifically and completely inhibited the tubular secretion of urate, only 22% of the uricosuric response to probenecid could be ascribed to an increase in the excretion of filtered urate, although nearly 70% of the response to chlorothiazide could be attributed to filtered urate. Although uricosuric agents may lessen the binding of urate to plasma proteins at low temperatures, the available data indicate that this protein-binding becomes negligible at normal body temperature (13). Therefore, it seems unlikely that the results could be explained on the basis of PZA-induced alterations in the effects of chlorothiazide or probenecid on bound urate.

Evidence obtained in various species has suggested that the predominant effect of PZA or its active metabolite, pyrazinoic acid (14), is to inhibit the renal tubular secretion of urate (1–3). Fanelli, Bohn, and Stafford (15), in contrast, have suggested that pyrazinoate may increase the tubular reabsorption of urate rather than diminish its secretion. This possibility, however, seems unlikely in view of more recent observations in the dog (14) and chimpanzee (G. M. Fanelli, Jr., personal communication) wherein very large doses of pyrazinoic acid were uricosuric, in sharp contrast to the usual antiuricosuric action of the compound in those species (1, 3). In addition, microinjection studies in the rat by Kramp, Lassiter, and Gottschalk (16) have indicated that pyrazinoate diminishes the proximal tubular outflux of [^{14}C] uric acid, although the total amount of uric acid present was not measured in those experiments. Therefore, it appears that PZA potentially could inhibit urate reabsorption in man, although in the doses used in these studies the predominant net effect is to inhibit secretion.

In addition to a lack of complete specificity of PZA, the PZA suppression test suffers from two other potential sources of inaccuracy. The dose of PZA (or the amount of pyrazinoic acid generated) might be insufficient to inhibit maximally the tubular secretion of urate. In that case, both urate secretion and reabsorption would be underestimated. If PZA simultaneously inhibited reabsorption in the doses utilized for the test, both parameters again would be underestimated. Another potential source of error, originally proposed by Gutman, is that a portion of the secreted urate might subsequently be reabsorbed (17). Greger, Lang, and Deetjen (18) have reported net secretion of urate by proximal tubules of superficial nephrons in the rat while simultaneous urinary clearances of uric acid showed net reabsorption. The same authors have made measurements of unidirectional urate influx and efflux for the rat proximal tubule (19). Again, the secretory flux was predominant in that nephron segment. If nephron homogeneity for uric acid handling in the rat is assumed, then those studies suggest that uric acid undergoes secretion before subsequent reabsorption in that species. Data supporting the proximal tubular secretion of uric acid also have been obtained in the mongrel dog, utilizing the stop-flow technique (20, 21).

Recent evidence utilizing the PZA suppression technique suggests that a group of diverse uricosuric substances, disease states, and physiologic maneuvers, may increase the amount of secreted uric acid appearing in the urine. In man, glycine (22), certain iodinated radiographic contrast agents (23), ethacrynic acid (24), and benziodarone (25) all have uricosuric actions which are diminished sharply or ablated entirely after pretreatment with PZA. In that respect, these diverse compounds affect renal urate handling similarly to probenecid and chlorothiazide. Also, the hyperuricosuric states accompanying certain cases of Wilson's Disease (26) and Hodgkin's Disease (27) have been counteracted by PZA. More recently, Diamond, Lazarus, Kaplan, and Halberstam (28) have reported that the increased urate excretion accompanying hydration can largely be ablated by PZA. In contrast, if urate secretion and reabsorption did not affect one another, then any increment in uric acid excretion produced by inhibiting reabsorption should be unaffected by the simultaneous inhibiton of urate secretion.

Discrepancies in uricosuric responses to probenecid and chlorothiazide, without and with PZA pretreatment, could have resulted from some type of interference by PZA with the renal actions of probenecid and chlorothiazide. Speculatively, PZA might have inhibited the secretion of probenecid and chlorothiazide, thereby preventing their access to luminal surfaces of renal tubular cells. This possibility can neither be confirmed nor excluded by the present data. However, the fact that the natriuretic and phosphaturic properties of chlorothiazide remained essentially unchanged during PZA action, despite a concomitant decrease in its uricosuric response, militates against this possiblity. On the other hand, any relationship between sodium or inorganic phosphorus and uric acid reabsorption is uncertain and poorly characterized. If PZA does interfere with the renal action of chlorothiazide, however, the site of this interference must be highly specific for urate transport and must permit an unchanged degree of inhibition of inorganic phosphorus and sodium transport by chlorothiazide.

In addition to pharmacologic interactions, the present results canot exclude the possiblity that probenecid and chlorothiazide might directly accelerate the tubular se-

cretion of urate. However, a more likely explanation is that the amount of urate delivered to a reabsorptive site in the nephron, located distaly to the region where secretion occurs, might influence urinary uric acid excretion. Modulated reabsorption at a postsecretory reabsorptive site could explain the discrepancies in uricosuric responses produced by PZA pretreatment. Agents which inhibit earlier (presecretory) reabsorptive sites would produce an elevation in the intratubular urate load or concentration which, together with the considerable amount of urate normally added via tubular secretion, might surpass the reabsorptive capacity at a postsecretory reabsorptive site. The inhibition of tubular secretion could turn the balance and allow the subsequent reabsorption of a much greater fraction of the urate load simply by reducing the total load. Alternatively, depending upon the reabsorptive transport characteristics of a postsecretory site and the amount of reabsorption occurring before secretion, direct inhibition at the postsecretory site might produce a similar end result. Through such a mechanism, secretory inhibiton by PZA then could substantially diminish uricosuric responses to probenecid and chlorothiazide.

Several important implications arise from these data. First, past estimates of urate secretion and reabsorption, utilizing the PZA suppression test, may be falsely low. Urate secretion in man may be more highly developed than prevously suspected, but its magnitude could be masked by subsequent reabsorption. In keeping with this possibility is the recent observation by Fanelli, Bohn, and Reilly (29) that the administration of mersalyl to the chimpanzee results in net secretion of uric acid to the extent that urate clearances may approach values as much as twice the filtered load. Thus, renal urate handling in man might bear a rough analogy to PAH transport in the dog, where net PAH secretion evidently is modulated by a carrier-mediated reabsorptive component (30).

The data also are consistent with a diminished response to uricosuric agents in hyposecretory states—either induced pharmacologically or by disease. If diuretic-induced hyperuricemia is due partially to diminished net urate secretion (24), the uricosuric response to probenecid might be subnormal in that condition. Although previous data have suggested that probenecid is effective at ameliorating chronic diuretic-inducing hyperuricemia, no comparisons of uricosuric responses in normals and hyperuricemic patients were made (31).

In far advanced chronic renal disease, net urate secretion per nephron usually appears to be severely compromised, as judged by the PZA suppression test (32). The increased fraction of filtered urate excreted (after PZA) suggests that reabsorption also is impaired. In chronic lead nephropathy, however, PZA suppression has suggested a rather selective preservation of urate reabsorption—even in far advanced disease (33). In view of the present data, it would be of considerable interest to compare uricosuric responses to probenecid in patients with lead nephropathy to responses in patients with other types of advanced renal disease. Similar studies also would be of interest in certain patients with gout who manifest a tendency toward sluggish excretion of urate, in contrast to other gouty patients with over-production of uric acid who do not exhibit this tendency (34).

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