EFFECT OF BENEMID (p-[di-n-PROPYLSULFAMYL]-BENZOIC ACID) ON URATE CLEARANCE AND OTHER DISCRETE RENAL FUNCTIONS IN GOUTY SUBJECTS [1]

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Benemid, (p-[di-n-propylsulfamyl]-benzoic acid), is a potent inhibitor of the renal tubular transport systems responsible for tubular secretion of the penicillins (1–3), p-aminohippurate (1), phenolsulfonphthalein (1) and p-aminosalicylic acid (4). It was initially introduced as an agent more effective than carinamide in sustaining high therapeutic blood levels of penicillin and p-aminosalicylic acid.

Benemid also is a potent uricosuric agent, of low toxicity (5). Gutman and Yü (6), in studies on 39 patients with chronic gout maintained on a low purine, restricted protein diet, found that Benemid consistently caused a rapid and marked increase in urinary urate excretion and a sharp decline in serum urate levels. The mean rise in urinary urate excretion in the first week of Benemid administration was 67%, 52% and 46% with daily doses of 2 gm., 1 gm. or 0.5 gm., respectively, resulting in corresponding falls in serum urate of 42%, 33% and 27%. Talbott, Bishop, Norcross, and Lockie (7) have reported similar results. The drug appears to have an important place in the management of chronic gout (8).

In the present study the renal mechanisms whereby the uricosuric action of Benemid is effected have been investigated. Simultaneous renal clearance studies of urate, inulin or endogenous creatinine, p-aminohippurate, sodium, potassium and chloride were carried out in 10 male gouty subjects before and after oral administration of 2 gm. of Benemid. In some of these subjects the effects of Benemid on phosphate clearance, urinary excretion of hydrogen and ammonium ion, and on urine and blood pH were also

studied. The implications of our findings in respect to the renal mechanisms for regulation of urate excretion by the kidneys in normal and gouty man are discussed.

METHODS

The subjects, whose ages ranged from 38 to 54 years, were all known to have had gout for several years. Only patients without overt cardiovascular and renal disease (no albuminuria, cylindruria, nitrogen retention) were used for these experiments. All had been on low purine, restricted protein (50–80 gm./day) diets preceding study and were in the morning post-absorptive state at the time of the experiment. Water was ingested in liberal quantities to maintain urine flow rates above 4 ml./min. throughout the experiment.

After drawing blood for inulin and p-aminohippurate plasma blank values, priming and sustaining infusions of these substances in 0.89% saline were administered by means of a Bowman constant infusion pump at rates calculated to maintain plasma concentrations of inulin at 30 mg.% and p-aminohippurate at 2 mg.%. Thirty minutes were allowed for equilibration. Bladder catheterization was then performed with multi-eyed hard rubber catheters and three 10- to 15-minute urine collections were obtained for the control clearance values. Bloods were drawn midway between the first and third clearance periods. Following the third control period 2 gm. of the drug were administered orally (19.3 to 29.5 mg./kg.). Six 20-minute post-Benemid clearance periods were then obtained. Three bloods were drawn approximately 30, 70 and 110 minutes after drug administration and representative plasma concentrations of inulin, urate and p-aminohippurate were obtained by plotting the concentrations semilogarithmically against time and by extrapolating back to 2.5 minutes (approximate urine delay time) from the mid-time of each urine collection period. Bladder washouts with 20 ml. of distilled water, followed by air, effected complete emptying at the termination of each urine collection period. With slight modifications the clearance techniques employed were those recommended by Goldring and Chasis (9).

In two additional subjects simultaneous endogenous creatinine, urate, sodium, potassium and chloride clearances were obtained at 30-minute periods for two hours preceding and two hours following administration of Benemid. In this manner intravenous infusions were

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avoided and urine could be collected by spontaneous voiding.

In two gouty subjects the effects of a single 2 gm. oral dose of Benemid upon simultaneous inulin, urate, endogenous creatinine and p-aminohippurate were studied over 24 hours. The drug was administered to these subjects following three 10- to 20-minute control periods, during which time urine was collected by catheter and bladder wash. Following administration of the drug, urines were collected by spontaneous voiding at two-hour intervals during the day and at two four-hour intervals at night. Intravenous infusions of inulin and p-aminohippurate

were maintained for 24 hours employing the technique of Sirota, Baldwin and Villarreal (10). Two bloods were drawn during the control periods, and six at strategically spaced intervals for 24 hours after drug ingestion. In a third subject the diurnal variations of endogenous creatinine, urate, sodium, potassium and chloride clearances were studied for 48 hours preceding Benemid and for 48 hours following a single 2 gm. oral dose. This patient was hospitalized and maintained on a constant protein (50 gm.), constant salt (3.5 gm.) diet for three days preceding the control study. Water was allowed *ad lib.* throughout.

TABLE I

The acute effect of oral Benemid upon the renal clearances of inulin, urate and PAH in 10 subjects with non-tophaceous gout

Subject Age	Period	Renal clearances‡					Plasma uric acid
		C_{IN}	C_{URATE}	C_{PAH}	C_{URATE}/C_{IN}	C_{IN}/C_{PAH}	
		ml./min.	*ml./min.*	*ml./min.*			*mg. %*
	Control*	100	5.02	557	0.050	0.179	6.7
	Benemid 24.6 mg./kg.						
	20 min.	103	5.39	618	0.052	0.167	
A. R.	40 min.	108	14.5	590	0.135	0.183	6.8
41	60 min.	109	24.3	632	0.223	0.173	
	80 min.	109	25.8	455	0.237	0.239	6.6
	100 min.	116	29.9	395	0.258	0.294	
	120 min.	107	27.3	520	0.255	0.205	6.2
	Control	117	8.30	529	0.071	0.221	11.0
	Benemid 19.3 mg./kg.						
	20 min.	131	9.00	508	0.069	0.242	
H. G.	40 min.	112	8.00	576	0.071	0.195	11.1
38	60 min.	119	18.1	638	0.152	0.187	
	80 min.	119	33.6	634	0.282	0.188	10.3
	100 min.	113	27.2	341	0.241	0.332	
	120 min.	104	13.2	311	0.127	0.335	10.3
	Control	119	11.0	610	0.092	0.195	8.2
	Benemid 25.9 mg./kg.						
	20 min.	119	11.8	579	0.099	0.220	
L. G.	40 min.	122	28.8	538	0.236	0.230	8.1
54	60 min.	121	36.7	516	0.303	0.209	
	80 min.	115	36.6	463	0.318	0.268	7.5
	100 min.	122	40.2	480	0.330	0.214	
	120 min.	113	42.1	414	0.373	0.261	6.8
	Control	99.9	9.14	621	0.092	0.161	7.3
	Benemid 27.5 mg./kg.						
	20 min.	92.0	10.1	640	0.110	0.144	
H. H.†	40 min.	94.0	16.3	582	0.174	0.162	7.2
47	60 min.	77.7	13.6	520	0.175	0.149	
	80 min.	85.4	31.3	522	0.367	0.164	6.4
	100 min.	67.8	27.4	388	0.404	0.175	
	120 min.	82.4	35.3	502	0.428	0.164	6.2
	Control	137	13.2	623	0.096	0.220	8.0
	Benemid 23.2 mg./kg.						
	20 min.	132	13.8	656	0.105	0.201	
W. L.†	40 min.	136	21.2	632	0.156	0.215	7.8
42	60 min.	121	32.0	510	0.265	0.237	
	80 min.	130	51.0	504	0.393	0.258	7.2
	100 min.	129	51.3	377	0.398	0.343	
	120 min.	110	51.2	299	0.465	0.369	6.5

* The control clearance values represent the averages of three 10- to 15-minute urine collection periods. The control plasma urate values represent the averages of three separate determinations before administration of Benemid.
† Endogenous creatinine clearances were substituted for inulin clearances in these instances.
‡ Not corrected for surface area (values in text so corrected are indicated there).

TABLE I—*Continued*

Subject Age	Period	Renal clearances					Plasma uric acid
		C_{IN}	C_{URATE}	C_{PAH}	C_{URATE}/C_{IN}	C_{IN}/C_{PAH}	
		ml./min.	*ml./min.*	*ml./min.*			*mg. %*
	Control	83.7	7.68	332	0.092	0.253	9.6
	Benemid 25.5 mg./kg.						
	20 min.	90.7	12.2	343	0.135	0.264	
	40 min.	92.6	45.7	328	0.493	0.282	8.7
N. W.	60 min.	88.8	48.0	244	0.541	0.364	
54	80 min.	72.0	39.4	203	0.547	0.355	8.5
	100 min.	103	50.9	125	0.493	0.825	
	120 min.	69.4	28.7	355	0.413	0.195	7.6
	Control	76.0	6.62	485	0.087	0.157	6.3
	Benemid 29.5 mg./kg.						
	20 min.	76.6	7.50	448	0.098	0.171	
M. M.	40 min.	81.0	11.5	457	0.142	0.177	6.5
53	60 min.	84.0	14.3	434	0.170	0.194	
	80 min.	68.5	13.7	380	0.200	0.180	6.1
	100 min.	72.4	14.1	383	0.195	0.189	
	120 min.	79.3	18.1	426	0.228	0.186	5.8
	Control	128	13.2	650	0.103	0.197	9.5
	Benemid 23.3 mg./kg.						
	20 min.	138	14.0	664	0.100	0.208	
A. L.	40 min.	124	23.0	584	0.184	0.213	9.6
45	60 min.	123	33.6	446	0.270	0.363	
	80 min.	113	31.1	566	0.272	0.200	
	100 min.	108	31.4	518	0.307	0.208	
	120 min.	116	29.6	524	0.252	0.221	8.0
	Control	98.5	4.98	526	0.051	0.187	8.0
	Benemid 22.7 mg./kg.						
	20 min.	110	4.60	516	0.042	0.213	
J. R.	40 min.	95.8	3.79	489	0.040	0.196	8.3
39	60 min.	90.1	4.34	443	0.048	0.203	
	80 min.	95.6	4.84	462	0.051	0.207	8.1
	100 min.	91.2	6.29	469	0.069	0.197	
	120 min.	87.9	10.4	432	0.118	0.203	8.0
	Control	75.1	6.32	316	0.084	0.238	13.9
	Benemid 26.2 mg./kg.						
	20 min.	78.2	7.80	342	0.100	0.229	
R. C.	40 min.	76.2	12.1	348	0.159	0.219	12.6
47	60 min.	71.2	23.6	268	0.332	0.266	
	80 min.	73.0	16.6	251	0.228	0.291	12.4
	100 min.	70.1	17.1	253	0.244	0.277	
	120 min.	67.7	20.6	238	0.304	0.284	11.2

Inulin in plasma and urine was determined by the method of Schreiner (11), p-aminohippurate by the method of Smith and his associates (12), "creatinine" by the method of Bonsnes and Taussky (13), phosphate by the method of Fiske and SubbaRow (14) as modified for spectrophotometry, and chloride by either the method of Schales and Schales (15) or Van Slyke and Hiller's modification of the Sendroy method (16). Sodium and potassium analyses were performed by means of the Perkin-Elmer internal standard flame photometer, Model 120 A. Urine ammonia determinations were performed by the method of Van Slyke and Cullen (17), urine titratable acidity by the technique of Pitts and Alexander (18), and blood and urine pH by means of the Cambridge pH meter. Plasma and urine urate concentrations were determined by a modification of the method of Buchanan, Block and Christman (19), using uricase digestion, urea cyanide-carbonate and arsenophosphotungstic acid. With this method inulin and p-aminohippurate, in the concentration ranges present in these studies, were found not to interfere with the recovery of urate from plasma and urine. For estimating filtrable plasma urate, ultrafiltrates of plasma were obtained by means of the Simms-Sanders "surge" ultrafiltration apparatus (20). In this device negative pressures are applied and rapidly varied by 10–15 mm. Hg so as to remove the serum protein film which would otherwise soon occlude the surface of the collodion sac. Thus the rate of ultrafiltration is greatly increased and a minimum of urate is retained by adsorption on the protein film.

RESULTS

Acute experiments. Table I summarizes observations on the acute effects of 2 gm. Benemid given orally on the renal clearances of inulin (C_{IN}), urate (C_{URATE}) and p-aminohippurate (C_{PAH}) in 10 gouty subjects. Despite the absence of gross manifestations of renal damage in these patients, the control C_{IN} and C_{PAH} values were found to be slightly to moderately depressed. Thus the mean C_{IN} was 92.5 ml./min./1.73 M^2 with a range of 73–111; the mean C_{PAH} was 472 ml./min./1.73 M^2 with a range of 307–596.

As indicated in Table I, Benemid in this dosage consistently caused a striking increase in C_{URATE} which was sustained over the two-hour period of observation. C_{URATE} rose from a mean control value of 8.55 ml./min. (range 4.98–13.2) to peak values averaging 32.9 ml./min. (range 10.2–51.3). In eight of the 10 subjects this rise was apparent within 40 minutes of ingestion of the drug. In six instances an accompanying fall in plasma urate of 1 mg.% or more was noted by the end of two hours.

Significant changes in C_{IN} did not occur. Consequently, the ratio C_{URATE}/C_{IN} rose, from a mean control value of 0.071 (range 0.050 to 0.103) to peak values averaging 0.337 (range 0.118 to 0.547). In two cases (not included in Table I) in which the clearance of endogenous creatinine was used as a measure of glomerular filtration and intravenous infusions thus avoided, C_{URATE}/C_{CR} rose from control values of 0.066 and 0.046 to 0.510 and 0.252, respectively, after Benemid. The C_{CR}/C_{IN} ratio was found to average 1.03 ± 0.03 before Benemid and 0.965 ± 0.048 after Benemid in eight gouty subjects, a correspondence which justifies use of C_{CR} for GFR under these circumstances.

TABLE II

The effect of oral Benemid upon the renal clearances of sodium, potassium, chloride and phosphate in gouty subjects

Case	C_{IN}			$100 \times \frac{C_{Na}}{C_{IN}}$			$100 \times \frac{C_{Cl}}{C_{IN}}$			$100 \times \frac{C_K}{C_{IN}}$			$100 \times \frac{C_{PO_4}}{C_{IN}}$		
	Control	After Benemid	% Change	Control	After Benemid	% Change	Control	After Benemid	% Change	Control	After Benemid	% Change	Control	After Benemid	% Change
R. C.	75.1	72.7	−3.3	4.26	4.15	−2.6	5.51	5.19	−5.8	20.0	18.7	−6.5	9.64	9.29	−3.6
L. G.	119	119	0.0	2.98	3.66	+22.7†	3.35	4.14	+23.6†	11.1	17.3	+55.8	19.0	22.6	+19.0
J. R.	98.5	95.1	−3.6	1.46	2.01	+37.7	1.95	2.57	+31.8	29.0	25.2	−13.1	21.0	22.1	+52
A. L.	128	120	−6.2	2.67	3.09	+15.9†	2.19	2.89	+32.0	22.0	17.6	−20.0	17.0	14.9	−12.3
H. H.*	99.9	83.2	−16.8	6.33	5.87	−7.3	8.03	5.70	−29.0	38.4	24.1	−37.2	8.34	6.36	−23.8
W. L.*	137	126	−8.0	1.98	2.84	+43.5†	1.56	2.18	+39.6†	25.8	24.2	−6.2	10.9	10.9	0.0
H. G.	117	113	−3.4	1.71	1.85	+8.2	2.57	2.62	+2.0	34.7	31.0	−10.7			
M. M.	76.0	77.1	+1.5	2.30	2.79	+21.3	3.05	3.38	+10.8	25.2	26.6	+5.6			
A. R.	100	108	+8.0	1.05	2.41	+130†	1.64	3.24	+97.2†	47.4	29.2	−38.4			
N. W.	83.7	86.1	+3.0	3.26	6.76	+107†	3.46	5.15	+48.8	20.5	23.0	+12.2			
O. G.*	83.5	70.6	−15.4	0.27	0.59	+119	0.78	1.50	+92.5†	24.8	32.0	+29.0			
A. R.*	120	111	−7.5	2.10	1.70	−19.0	1.38	1.12	−18.8	10.9	14.2	+30.3			
Mean			−4.3			+39.7			+24.1			+.07			−2.6
S.D.			±2.1			±14.7			±11.4			±8.1			±5.9

The control values represent the averages of three 10- to 15-minute periods. The values after Benemid represent the averages of six 20-minute periods starting immediately after oral ingestion of 2 gm. of the drug.

* C_{CR}, endogenous creatinine clearance, used instead of C_{IN} in these subjects.

† These changes considered significant (p <.02). The t test of significance for the $\frac{C_{Na}}{C_{IN}}$ and $\frac{C_{Cl}}{C_{IN}}$ ratios was applied to the six post-Benemid clearances as compared to the three control periods for each of the subjects.
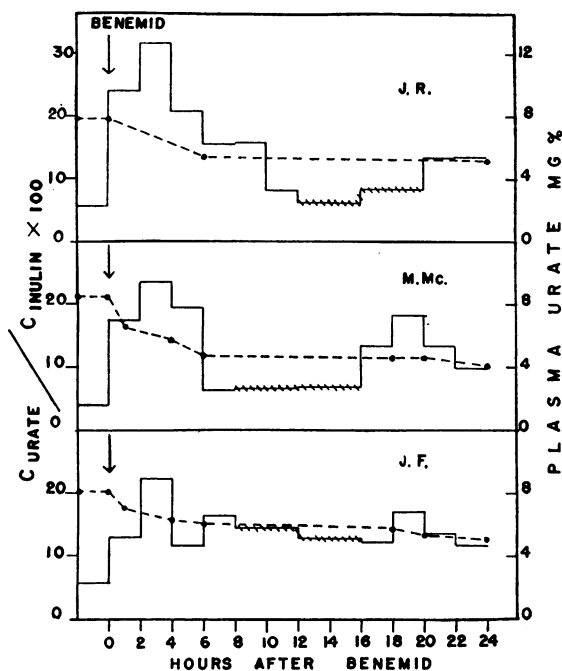
FIG. 1. C_{URATE}/C_{IN} RATIOS AND PLASMA URATE CON-
CENTRATIONS IN THREE SUBJECTS FOR 24 HOURS FOLLOW-
ING A SINGLE ORAL DOSE OF 2 GM. BENEMID (ARROW)

C_{CR} was substituted for C_{IN} in subject J. R. The pre-
Benemid control C_{URATE}/C_{IN} ratios represent the average
of three 10- to 15-minute periods. The solid lines repre-
sent the C_{URATE}/C_{IN} ratios, the interrupted lines plasma
urate concentrations and cross-hatches the sleeping hours.

There was a general moderate decline in C_{PAH}
usually evident after one hour. The clearance
ratios C_{IN}/C_{PAH} rose from a mean control value
of 0.201 (range 0.157 to 0.253) to peak values
averaging 0.333 (range 0.175 to 0.825).

Table II summarizes observations on the clear-
ances of sodium (C_{Na}), potassium (C_K), chloride
(C_{Cl}) and phosphate (C_{PO_4}) in these gouty sub-
jects. Benemid was found to have negligible ef-
fects on C_K and C_{PO_4} and on the ratios C_K/C_{IN}
and C_{PO_4}/C_{IN}; the mean per cent changes during
the two-hour period following drug administra-
tion for C_{IN} were $- 4.3 \pm 2.1\%$; for C_K/C_{IN},
$+ 0.7 \pm 8.1\%$; for C_{PO_4}/C_{IN}, $- 2.6 \pm 5.9\%$. The
mean per cent changes for C_{Na}/C_{IN} and C_{Cl}/C_{IN}
were of much greater magnitude, $+ 39.7 \pm 14.7\%$
and $24.1 \pm 11.4\%$, respectively. Statistical analy-
sis indicates significant increases in both C_{Na}/C_{IN}
and C_{Cl}/C_{IN} ratios in four of the 12 subjects, a
significant rise in C_{Na}/C_{IN} only in a fifth subject,

and in C_{Cl}/C_{IN} only in a sixth subject after
Benemid.

In the two patients so studied there were no
significant effects of the drug upon urine or blood
pH, urine titratable acidity and ammonium ion ex-
cretion. However, these latter observations were
obtained without previously rendering the sub-
jects acidotic, and with low control values (2 to
10 μeq. hydrogen ion/min. and 10 to 19 μeq. am-
monium ion/min.).

Prolonged experiments. Since the two-hour
experiments lapsed before the uricosuric effect of
Benemid had worn off, observations were pro-
longed over a 24-hour period in three gouty sub-
jects in an attempt to establish the duration of in-
creased C_{URATE} following ingestion of a single 2
gm. dose (Figure 1). The peak effect upon
C_{URATE}/C_{IN} or C_{URATE}/C_{CR} ratios was found
within the first four hours; in Case J. R. rising
from a mean control ratio of 0.056 to 0.320, in
Case M. Mc. from 0.034 to 0.235, and in Case
J. F. from 0.058 to 0.225. Significant elevations
of these ratios persisted for 24 hours with a diur-
nal depression during sleeping hours. At the end
of 24 hours the plasma urate concentrations had
fallen from 7.9 to 5.1, 8.4 to 4.2, and 8.2 to 4.1
mg. %, respectively.

The results of a four-day study of the excre-
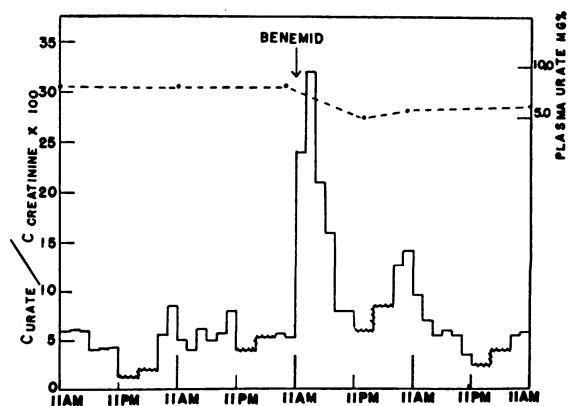tion of urate, water, sodium, potassium, chloride

FIG. 2. C_{URATE}/C_{CR} RATIOS AND PLASMA URATE CON-
CENTRATIONS IN ONE SUBJECT FOR 48 HOURS PRECEDING
AND FOLLOWING A SINGLE 2 GM. DOSE OF BENEMID WHILE
ON A CONSTANT DIET

The solid line represents the C_{URATE}/C_{CR} ratios; the in-
terrupted line plasma urate concentrations, and the cross-
hatches the sleeping hours.

and creatinine in one gouty subject before and after a single dose of Benemid while on a controlled protein (50 gm.), constant salt (3.5 gm.), water *ad lib*. regimen are presented in Figure 2. The subject was maintained on this constant diet for three days before obtaining the two-day pre-Benemid control data. The C_{URATE}/C_{CR} ratios during the two control days and the second post-medication day showed diurnal depressions during sleeping hours similar to those while under Benemid influence. The 24-hour urate excretion rose to 1143 mg. from control values of 543 and 502 mg. This was associated with depression in the plasma urate concentration from a premedication value of 7.9 mg. % to 5.1 mg. %, the greatest decrement occurring during the first four hours. There were no significant changes in the 24-hour excretion of sodium, potassium, chloride, water and creatinine following drug administration.

DISCUSSION

The current concept of renal mechanisms for urate excretion in normal man, recently summarized by Homer Smith (21), assumes complete filtration at the glomerulus and subsequent tubular reabsorption of all but a small fraction of the filtered urate, of which only 5–10% appears in the urine. The tubular transport mechanisms for reabsorption of urate have been shown to be of limited capacity (22) with a Tm_{URATE} of approximately 15 mg./min., and, while not identified, are presumed to be enzymatic. There is no evidence for tubular secretion of urate in normal man, although this is known to occur in birds and reptiles.

In connection with the question of tubular secretion of urate in man, Praetorius and Kirk (23) report the case of a young man, in apparent good health, who was found to have a very low plasma urate (0.2 to 0.6 mg.%) associated with elevated C_{URATE}/C_{IN} ratios averaging 1.46. The authors interpreted these high ratios as indicating tubular secretion of urate. Although the renal clearance of urate undoubtedly was very high in this individual, the C_{URATE}/C_{IN} ratios must be interpreted cautiously because of the analytical errors inherent in available methods for estimating such low plasma concentrations of urate and of inulin (9.03 to 9.77 mg.%) as were present during their study. The plasma blank for inulin averages 1 to 2 mg./ml., 10–20% of the total plasma value.

We have had opportunity to study an unusual case of marked glomerulo-tubular imbalance of the Fanconi type,

to be reported in detail elsewhere, which appears to throw light on this problem. In this subject C_{IN} was markedly depressed (26.1 ml./min.) but the functions attributed to proximal tubular activity were disproportionately and quite extraordinarily low: C_{PAH} 36.7 ml./min., Tm_{PAH} 4.9 mg./min., Tm_G 22.0 mg./min. The plasma urate (2.3 to 2.8 mg.%) was consistently below the normal range for the method we employ (4–6 mg.% in males) yet the urate clearance was consistently elevated (C_{URATE} 25.7 ml./min. as compared with the normal of about 8 ml./min.) and the urinary urate excretion was about twice normal (0.75 mg./min. instead of 0.30 to 0.40 mg./min.).

In view of the indications of severe tubular damage in this patient, and the evidences of impaired reabsorption of glucose (renal glycosuria), amino acids (amino aciduria) and phosphate (hyperphosphaturia), it seemed more rational to ascribe the high urinary urate excretion to impaired tubular reabsorption of urate than to enhanced tubular secretion of urate. This interpretation was supported by the finding in this patient of a C_{URATE}/C_{IN} ratio of approximate unity (0.984), as compared with a normal mean C_{URATE}/C_{IN} ratio of 0.067, which would indicate both complete filtrability at the glomerulus and virtual absence of urate reabsorption by the tubules. In view of the concurrent evidence in this patient of generally reduced function of the proximal tubules, it may be inferred that urate normally is reabsorbed wholly or in large part by the proximal convoluted tubules. The fact that C_{URATE}/C_{IN} did not exceed unity argues against tubular secretion of urate.

In accord with these inferences is the striking fact that of all the non-gouty and gouty subjects to whom we have administered Benemid, this patient was the only one in whom the drug failed to evoke increased urinary urate excretion and increased urate clearance.

The renal mechanisms for urate excretion in gouty subjects do not appear to differ in any essential from those of normal man (24, 25). However, in view of the often marked hyperuricemia in gout, complete filtrability of urate at the glomerulus cannot be assumed. We therefore subjected the sera of four of these patients, before treatment with Benemid, to ultrafiltration. The results, in conformity with those obtained in 13 other cases of gout (26), showed the serum urate to be wholly filtrable, apart from variations within the limits of error of the method: in case A. R., serum urate 11.3 mg. % (expressed in terms of serum water), ultrafiltrate urate 11.6 mg. %; in Case O. G., serum urate 11.1 mg. %, ultrafiltrate 10.6 mg. %; in Case M. M., serum urate 8.7 mg. %, ultrafiltrate 8.8 mg. %; in Case H. H., serum urate 8.5 mg. %, ultrafiltrate 7.8 mg. %. In view of these findings tubular reabsorption of

urate and not non-filtrability of plasma urate must be assumed to explain the large discrepancy between urate clearance and glomerular filtration rate in these patients. The possibility of some tubular excretion of urate in gout is not excluded.

Saturation of tubule reabsorptive capacity for urate probably does not occur either in normal subjects (22) or in gouty patients with adequate renal function. According to Berliner, Hilton, Yü and Kennedy (22), a urate load/Tm_{URATE} ratio of 1.25–1.50 is necessary for saturation which, with a normal Tm_{URATE} of 15 mg./min., would require filtered urate loads between 18.9 and 22.5 mg./min.—at a normal filtration rate of 120 ml./min., necessitating plasma urate concentrations of 15.8–18.7 mg. %. Since the filtration rate was depressed in most of our gouty patients, even higher plasma urate concentrations would be required. The greatest filtered urate load recorded in our gouty subjects was 14.5 mg./min. (Patient H. G., Table I). Moreover, no increase in C_{URATE}/C_{IN} ratios was observed in the patients with greater filtered urate loads, such as might be expected if significant tubule saturation had occurred.

There is every indication that, as in its effects on penicillin and p-aminosalicylic acid, Benemid produces uricosuria primarily by altering renal excretory mechanisms. The rapidity of the uricosuric effect, within 40 minutes of ingestion in most instances, makes it highly improbable that it can be accounted for by increased breakdown of nucleic acids, which normally have a slow turnover rate, or by accelerated urate biosynthesis. Moreover, studies carried out in two of our gouty subjects before, during and after ingestion of 2 gm. of Benemid showed no concurrent increase in urinary total nitrogen or phosphorus excretion (26). Bishop, Rand and Talbott (27) have demonstrated a decrease in the miscible pool of urate after administration of Benemid, indicating a predominantly excretory effect of the drug.

Our data indicate clearly that the enhancement of renal excretion of urate by Benemid is not due to an increase in glomerular filtration but is attributable to inhibition of tubular reabsorption of urate. In none of the subjects studied by us was this inhibition complete, the highest C_{URATE}/C_{IN} ratio obtained being 0.547. Since the drug exerts its effect upon known proximal tubule function (PSP, PAH, PAS and penicillin secretion) it appears likely that the uricosuric effect is mediated at this level of the nephron. It is interesting that the uricosuria produced by Benemid is the result of inhibition of a reabsorptive process whereas its other known effects are based upon inhibition of secretory mechanisms. The drug appeared to exert no effect upon phosphate reabsorption, the only other reabsorptive process with a Tm mechanism studied by us. Beyer and his associates (1), working with dogs, demonstrated that the drug exerted no effect upon the reabsorptive mechanisms for glucose, arginine, sulfonamides, urea and phosphate. The precise mechanism of the inhibitory effect of Benemid on tubular urate reabsorption has not been determined. According to Beyer and co-workers (1), the drug, in concentrations which suppress PAH, PSP, PAS, penicillin and urate transport, will inhibit utilization of energy from high-energy phosphate bonds without interfering with oxygen uptake or phosphorylation.

Significant depression of C_{PAH} occurred following Benemid admininstration in eight of the 10 subjects so studied. From the data in Table I it is impossible to indicate to what extent these depressions resulted solely from inhibition of tubule secretory activity, since decrease in renal plasma flow might partially account for C_{PAH} depressions. Quantitative evaluation of the effect of the drug upon this tubule function is possible only by PAH renal extraction and Tm_{PAH} measurements. Beyer and his associates (1), employing Benemid in approximately twice the relative dosage used in our studies, were able to reduce Tm_{PAH} to almost zero in dogs. In one non-gouty subject without renal disease studied by us, Benemid in a dose of 20 mg./kg. produced a fall of Tm_{PAH} from 83.4 mg./min. to 26.4 mg./min. without influencing C_{IN}, suggesting that the depressions in C_{PAH} observed were primarily the result of inhibition of tubule secretory activity.

In the acute studies several of the subjects showed significant increases in the clearances of either sodium or chloride, or in both of these ions. However, the absolute magnitude of the renal clearances of these ions was so low that a slight increment would result in a marked increase in

their clearance when expressed as per cent change. Thus, the maximum per cent change in C_{Na}/C_{IN} noted, 130% (Case A. R., Table II), represents an actual increment of C_{Na} from 1.05 to 2.60 ml./min., and a change in urine excretion of 0.147 to 0.364 meq./min. The subjects who exhibited this increase in C_{Na} and C_{Cl} were among those who presented the most marked uricosuria. Significant water diuresis did not occur in these studies. However, the control urine flows before administration of the drug were maintained at high levels and may have masked a diuretic effect. The one subject studied on the controlled purine and salt intake and water *ad lib.* failed to exhibit an increase in either salt or water output for the 24-hour period following drug ingestion.

Beyer and co-workers (1) found that less than 2% of Benemid is excreted in dog's urine during 24 hours after a single intravenous dose, and that determinable plasma concentrations of the drug were present 48 hours after a single dose of 60 mg./kg. They found that approximately 75% of the drug was bound to plasma protein and 25% was freely filtrable. This latter fraction is presumably filtered at the glomerulus and is virtually completely reabsorbed by the tubules. This provides an explanation for the prolonged uricosuric effect following a single dose of the drug. An oral dose of approximately 20 mg./kg. produced elevations of C_{URATE}/GFR above control levels for 24 hours in the three subjects so studied. The complete tubular reabsorption of filtered Benemid presumably results in the maintenance of an effective concentration in or about the tubule cells for a prolonged period of time.

The diurnal variation of renal urate clearance noted in our cases is of some interest. Brøchner-Mortensen (28) reported a diurnal variation in urate clearances, with the lowest values occurring at night. Leathes (29) studied the diurnal urate excretion in a single individual on two different levels of purine ingestion and found decreased excretion during the sleeping hours on both levels of purine intake. Stanbury and Thomson (30) demonstrated a relatively greater depression of urate excretion than GFR in a single individual during sleeping hours. C_{URATE} was not determined in this subject. Since our studies demonstrated a fall in C_{URATE}/GFR ratios at night, the

decreased clearance of urate cannot be explained solely by the decreased glomerular activity which usually occurs at night (10). Benemid does not alter this diurnal pattern, even though the nocturnal C_{URATE}/GFR ratios, while under drug influence, are still higher than the control values. This pattern apparently reflects diurnal variation in tubule activity with respect to urate reabsorption. It is well established that a similar pattern occurs for the renal excretion of the major electrolytes and water (30).

Unless water diuresis is encouraged during Benemid uricosuria excessively high concentrations of urate may be encountered in the urine. Thus, in one of our subjects on the 24-hour study maintained on fluids *ad lib.*, a concentration of urine urate of 157 mg. % was obtained at a time when his urine flow was less than 1 ml./min. Talbott and Coombs (31) found a maximum urate solubility of slightly more than 100 mg./100 ml. in the urine of gouty subjects. Alkalinization and water diuresis would therefore appear to be important measures for the prevention of uric acid crystalluria during Benemid therapy. In a gouty subject with normal glomerular function and a plasma urate concentration of 8 mg. %, a urine flow of at least 4 ml./min. is necessary to maintain urine urate concentrations under 100 mg./100 ml. during the peak of Benemid uricosuria, which occurs within four hours after drug administration.

No indication of toxicity attributable to Benemid was observed in the course of these experiments, with the possible exception of one patient who developed an acute attack of gout the day after. The effects upon renal transport mechanisms are completely reversible following discontinuance of medication. Benemid appears thus far to be of a low order of toxicity (6, 32) and no overt signs of renal "irritation" (albuminuria, casts, red blood cells) unequivocally attributable to the drug have yet been reported.

SUMMARY

1. In 15 clearance studies carried out in 13 gouty subjects, Benemid given orally in a single 2 gm. dose consistently produced a marked rise in urate clearance, from a mean control level of 7.99 ml./min. to a mean peak value of 32.7 ml./

min. This rise was usually evident within 40 minutes of drug administration and lasted 24 hours in the subjects followed for this period. The plasma urate level fell concomitantly.

2. There was no significant effect on glomerular filtration rate. The ratio C_{URATE}/GFR consequently rose, from a mean control value of 0.0718 to peak values averaging 0.333.

3. Some depression of C_{PAH}, with consequent moderate rise in the ratio C_{IN}/P_{PAH}, was observed in most instances.

4. Phosphate and potassium clearances were unaffected by Benemid. Slight but significant increases in sodium or chloride clearance, or both, occurred in about half the subjects.

5. A marked diurnal variation in C_{URATE}/GFR ratios was noted in those subjects in whom these functions were studied over one or more 24-hour periods. The depression of these ratios noted during sleeping hours persisted in spite of continued overall Benemid uricosuria.

6. The data obtained support the complete filtration-partial tubular reabsorption concept of urate excretion in the normal and gouty subject and indicate that Benemid uricosuria is the result of a highly selective inhibition of tubular reabsorption of filtered urate. Corroboratory evidence for this conclusion was derived by clearance studies in one subject with glomerulo-tubular imbalance of the Fanconi type who was found to have a C_{URATE}/C_{IN} ratio of approximate unity, which was uninfluenced by Benemid.

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