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Research Article

STUDY OF THE PARADOXICAL EFFECTS OF SALICYLATE IN LOW, INTERMEDIATE AND HIGH DOSAGE ON THE RENAL MECHANISMS FOR EXCRETION OF URATE IN MAN *

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Salicylate administered to man in sufficiently large dosage (5 to 6 or more Gm. per day) causes marked uricosuria, characterized by substantially increased urate/inulin clearance ratios attributable to inhibition of tubular reabsorption of the filtered urate. In smaller dosage (1 to 2 Gm. per day) salicylate exerts a contrary effect, retention of urate, associated with lower than normal urate/inulin clearance ratios (1–8). When small doses of salicylate are given concurrently with probenecid, the retention of urate caused by the salicylate is sufficiently pronounced to counteract, to a marked degree, the uricosuric effect of the probenecid (9, 10). Phenylbutazone and phenylbutazone metabolite I similarly cause marked retention of urate when administered in low dosage (7), and are uricosuric in large dosage.

Two explanations of this paradoxical effect have been offered (5, 7, 8). It is conceivable that the tubular transport system effecting reabsorption of urate might be stimulated by small doses and suppressed by larger doses of the drugs in question. Or, a postulated tubular excretory mechanism for urate (not apparent in the usual clearance measurements in man) might be inhibited by small doses, thus causing urate retention; and when larger doses are given tubular reabsorption of urate also is suppressed, the net effect then being uricosuric.

The present study documents the paradoxical action of salicylate by providing more detailed data on the effect of small, intermediate and large doses on the 24 hour urinary urate excretion, using analytical methods incorporating precautions to obviate errors due to the presence of a salicylate metabolite, gentisic acid. The relationships between the renal excretion of salicylate and of urate are then examined by means of simultaneous clearance techniques, including studies under conditions of urine pH made to vary from markedly acid to markedly alkaline. Clearance data on the antagonistic effect of small doses of salicylate on probenecid uricosuria, and vice versa, also are presented. Finally, the implications of the results as a whole are considered in relation to current concepts of renal mechanisms for the excretion of salicylate and of urate, with special reference to inferences regarding the possibility of tubular excretion of urate in man.

METHODS

The subjects selected for investigation were all adult, gouty males, in the intercritical phase of the disorder. Forty-four studies were made in 23 of these subjects to determine the effect of orally administered acetylsalicylic acid, in divided doses totaling 1.0, 2.0, 3.0 and 5.2 Gm. per day, respectively, on the 24 hour urinary urate excretion and the serum urate level. All subjects were maintained on a constant diet low in purines and restricted in protein (60 to 75 Gm. per day) for at least three days preceding study. Twenty-four hour collections of urine were then made for eight or 12 days, blood samples being secured at appropriate intervals. After a four day control period, the patient received the prescribed daily medication for four successive days. The mean daily urinary urate output during this four day medication period, and the serum urate level on the morning of the fourth day of medication, were taken to represent the response to salicylate. Determinations were made also in the four day postmedication period in most instances. Serum and urine salicylate levels were measured in representative cases during the medication period.

Simultaneous urate, salicylate, inulin and para-aminohippurate (PAH) clearance measurements were made in 38 studies in 35 gouty subjects. Standard renal clearance techniques were employed, as previously described in detail (11). In every experiment three premedication inulin and PAH clearance periods, each of 15 to 20 minutes' duration, were first obtained.

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Ten clearance studies were designed to determine the effect of slowly rising and declining plasma and urine salicylate concentrations on the urate clearance. Sodium salicylate was infused slowly at first (16 mg. per minute) for three 10 minute collection periods, then more rapidly for four to seven additional periods, each of 15 to 20 minutes' duration, until a total of 2 to 4 Gm. sodium salicylate had been delivered. Blood samples were procured at the midpoint of each urine collection period. After termination of the salicylate infusion, the collection of (spontaneous) voidings of urine was continued at two hour intervals during the day and four hour intervals during the night, over a period of 20 to 22 hours. Blood samples were taken at the beginning and end of the postinfusion period.

Two of the subjects of the preceding experiments (A. M. and M. M.) excreted a strongly acid urine and the results were included in a study of the effects of low urinary pH on salicylate uricosuria. To amplify these data two additional subjects (S. H. and M. L.) were given ammonium chloride, 16 Gm. in four divided oral doses on the day before the experiment, and 4 Gm. more one hour immediately preceding study. The protocol then followed was the same as in the previous experiments, except for omission of postinfusion urine collections.

Nine clearance studies were designed to determine the effect of alkalinization of the urine, by simultaneous injection of sodium bicarbonate, on salicylate uricosuria. Sodium salicylate was infused slowly in three instances (A. S., J. H., D. R.), as already described. In the six remaining subjects an initial priming dose of 3 Gm. sodium salicylate was given, followed by a sustaining infusion of 0.4 per cent sodium salicylate at a rate of about 4 ml. per minute for 30 to 60 minutes. Urine and blood samples were collected at appropriate intervals. Then, while the sodium salicylate infusion was continued, a priming dose of 7.5 per cent sodium bicarbonate was rapidly injected, the administration of sodium bicarbonate being sustained at a slower rate until a total of 15 Gm. had been delivered. Three or four 15 to 20 minute collection periods were obtained.

Five additional clearance studies were carried out similarly except that acetazolamide, 1.0 Gm., was substituted for sodium bicarbonate to alkalinize the urine.

To determine the effect on urate clearance of alkalinization of the urine *per se*, without prior administration of salicylate, three clearance studies were made with sodium bicarbonate alone, performed in the manner already described, and four with acetazolamide alone, given intravenously (two experiments) or by mouth (two experiments).

The interaction of salicylate and probenecid on urinary urate excretion was first investigated by concomitant oral administration of the drugs, then more precisely by clearance techniques. The latter experiments were initiated by establishment of premedication C_{urate}/C_{inulin} ratios. In four experiments probenecid was first administered by injection of 20 mg. per Kg. body weight within 20 minutes; then a small priming dose (0.3 Gm.) of sodium salicylate was given to establish low plasma salicylate levels, followed by a sustaining solution at accelerating rate until 2.0 to 3.0 Gm. sodium salicylate was delivered over a period of approximately two hours. In four additional experiments the order of drug administration was reversed so as to investigate the effect of probenecid on salicylate uricosuria. A priming dose of 2.0 Gm. sodium salicylate was first rapidly injected; then a sustaining solution of 2.0 Gm. was given more slowly over a period of two hours. At the end of the first hour, an increase in C_{urate}/C_{inulin} having already been established, probenecid, 20 mg. per Kg. body weight, was rapidly injected. Blood and urine samples were procured at appropriate intervals throughout the experiments.

The standard analytical techniques employed for inulin, PAH, urine pH and salicylate in plasma and urine have been indicated elsewhere (11). Plasma and urine urate concentrations were determined in part spectrophotometrically (12), in part by a modification (12) of the colorimetric method of Buchanan, Block and Christman. (13), which incorporates uricase digestion and the use of arsenophosphotungstic acid reagent and urea cyanide-carbonate. In this latter method the "true" urate content is determined by difference, the total chromogens minus residual (nonurate) chromogens persisting after incubation of the serum or urine with uricase in borate buffer at pH 9.3. Under ordinary circumstances in both gouty and nongouty individuals, 85 to 90 per cent of the total chromogens are found by this procedure to be "true" urate, and the results check satisfactorily with spectrophotometric methods of uric acid determination (12). However, in subjects receiving large doses of salicylate by mouth the "true" urate values thus obtained by the colorimetric method were found to be too high.

The cause of these discrepancies was investigated, incorporating an additional step into the procedure by incubating samples also in control tubes containing only borate buffer, pH 9.3, without uricase. Ordinarily, no significant difference in total chromogen results, the mean change in 13 urine samples being −0.7 per cent. However, in 12 urine samples from patients given salicylate by mouth the total chromogen content decreased 5.7 to 35.4 per cent (mean fall, 20 per cent). This finding suggested the presence in the urine of appreciable quantities of a chromogenic metabolite of salicylic acid which was unstable in alkaline solution and consequently ordinarily included in the "true" urate fraction. The metabolite in question was isolated by counter-current distribution techniques and identified as gentisic acid, which was found to give as much color with arsenophosphotungstic acid reagent as uric acid (14). Salicylic acid and salicyluric acid are not chromogenic.

In order to estimate the magnitude of the error involved by the presence of gentisic acid, 16 normal and gouty subjects were administered 5.2 Gm. per day of acetylsalicylic acid by mouth. The mean increase in total chromogens in the 24 hour urine, as compared with the premedication excretion, was 369 mg.; of this increase approximately 50 per cent was "true" urate, 42 per cent was in the ether-soluble chromogen fraction (chiefly gentisic acid), and 8 per cent in the aqueous-soluble nonurate chromogen fraction. In individual cases the ether-soluble chromogen constituted 9.5 to 34.4 per cent (mean,

TABLE I

Effect of oral administration of acetylsalicylic acid on urinary urate excretion and serum urate levels in gouty subjects. Potentiating action of sodium bicarbonate

Case	Urinary urate excretion (*mg./24 hrs.*)			Serum urate (*mg. %*)		
	Control	Medication	% Change	Control	Medication	% Change
	Medication: Acetylsalicylic acid, 1.0 Gm./day (0.32 Gm. t.i.d.)					
1. O. G.	648	596	− 8	11.4	12.1	+ 6
2. A. R.	766	669	−13	10.8	11.2	+ 4
3. E. M.	620	483	−22	11.2	11.2	0
4. T. T.	358	220	−39	10.9	12.2	+12
Mean			−21			+ 6
	Medication: Acetylsalicylic acid, 2.0 Gm./day (0.65 Gm. t.i.d.)					
1. A. R.	543	570	+ 5	9.9	10.4	+ 5
2. C. S.	250	252	+ 1	6.8	7.5	+10
3. J. J.	223	213	− 5	7.8	8.2	+ 5
4. W. L.	836	698	−17	9.0	11.0	+22
5. H. H.	466	378	−19	7.2	7.4	+ 3
6. O. G.	378	278	−26	8.7	8.7	0
7. D. R.	698	417	−40	11.0	11.8	+ 7
Mean			−14			+ 7
	Medication: Acetylsalicylic acid, 3.0 Gm./day (1.0 Gm. t.i.d.)					
1. J. J.	192	304	+58	8.7	7.4	−15
2. L. R.	452	675	+49	9.3	7.5	−19
3. J. S.	473	556	+18	8.8	7.3	−17
4. V. P.	224	258	+15			
5. W. L.	686	740	+ 8	8.3	8.5	+ 2
6. C. S.	170	177	+ 4	6.6	6.5	− 2
7. J. D.	999	996	0			
8. M. M.	860	848	− 1	5.0	4.9	− 2
9. L. C.	692	629	− 9	9.4	8.8	− 6
Mean			+16			− 8
	Medication: Acetylsalicylic acid, 5.2 Gm./day (1.3 Gm. q.i.d.)					
1. O. G.	343	701	+104	8.2	5.0	−39
2. J. J.	243	462	+ 90	7.7	5.9	−23
3. M. K.	645	1,093	+ 70	10.6	8.7	−18
4. D. R.	545	843	+ 55	10.7	7.4	−31
5. P. M.	547	818	+ 50	5.9	2.2	−63
6. J. D.	761	1,093	+ 44	11.1	9.1	−18
7. R. C.	519	714	+ 38	11.7	7.0	−40
8. V. P.	247	339	+ 37	10.8	10.4	− 4
9. N. W.	633	856	+ 35	10.5	5.3	−50
10. R. B.	357	459	+ 29			
11. R. M.	697	844	+ 21	10.8	5.4	−50
12. J. S.	473	556	+ 18	8.8	8.4	− 5
13. Y. F.	562	540	− 4			
14. P. C.	500	471	− 6	9.2	8.6	− 7
15. C. S.	146	115	− 21	7.0	8.0	+14
Mean			+ 37			−26
	Medication: Acetylsalicylic acid + $NaHCO_3$, each 5.2 Gm./day (1.3 Gm. q.i.d.)					
1. R. C.	416	974	+134	12.9	6.4	−50
2. O. G.	318	675	+112	8.8	3.7	−58
3. M. K.	764	1,572	+106	13.2	6.9	−48
4. V. P.	244	450	+ 85	11.5	10.2	−11
5. P. M.	527	892	+ 69	5.9	2.0	−66
6. C. S.	149	243	+ 63	7.0	5.0	−29
7. J. D.	999	1,307	+ 31	12.2	9.7	−20
Mean			+ 86			−40

19.5 per cent) of the total chromogen and was present in quantities representing 11.5 to 78.0 per cent (mean, 31.2 per cent) of the "true" urate. In view of these findings gentisic acid was removed from the urine by multiple extractions with ethyl ether prior to the colorimetric determination of urinary uric acid in all subjects receiving large doses of salicylate (14). The spectrophotometric method of determining uric acid was employed in the later studies since it obviates the need for this preliminary procedure.

The error involved is much smaller in patients receiving 2.0 Gm. per day of acetylsalicylic acid orally: In eight such instances the ether-soluble chromogen constituted a mean of 8.5 per cent of the total chromogen and 11.8 per cent of the "true" urate present. The gentisic acid content of the plasma was found to be too low to warrant correction, even in subjects receiving 5.2 Gm. per day of acetylsalicylic acid by mouth. The same applies to the gentisic acid excreted in the urine in experiments involving rapid intravenous injection of salicylate, as excretion is too rapid to permit of significant metabolic conversion to gentisic acid.

RESULTS

Effect of oral administration of salicylate in low, intermediate and high dosage on 24 hour urinary urate excretion and serum urate levels (Table I, Figure 1)

Acetylsalicylic acid in 1.0 Gm. daily oral dosage caused a decrease in urinary urate excretion per 24 hours of more than 10 per cent of the premedication excretion in three of four subjects studied; the mean *decline* was 21 per cent. This was usually associated with a slight rise in serum urate, the mean increase being 6 per cent. With 2.0 Gm. daily dosage, four of seven subjects showed a decreased 24 hour urinary urate excretion greater than 10 per cent of the control level, none showed a significant increase; the mean *decline* was 14 per cent, associated with a mean increase of 7 per cent in serum urate. In 3.0 Gm. daily dosage there was a distinct reversal of effect. Four of nine subjects excreted more than 10 per cent in excess of their premedication urinary urate output, only one excreted appreciably less urate than before; the mean *increase* was 16 per cent, associated with a mean decline of 8 per cent in serum urate. With 5.2 Gm. daily dosage there was a substantial further increase in urinary urate output per 24 hours, demonstrated in 12 of the 15 subjects tested; the mean *increase* was 37 per cent. The serum urate level was lowered in all but one instance, the mean fall being 26 per cent. Subjects studied at both small and large dosage levels strikingly illustrate the reversible effect of salicylate on urinary urate excretion. Thus D. R., O. G. and J. J. showed *decreases* of 40, 26 and 5 per cent, respectively, in urinary urate output per 24 hours on 2.0 Gm. daily dosage, and *increases* of 55, 104 and 90 per cent, respectively, when given 5.2 Gm. per day.

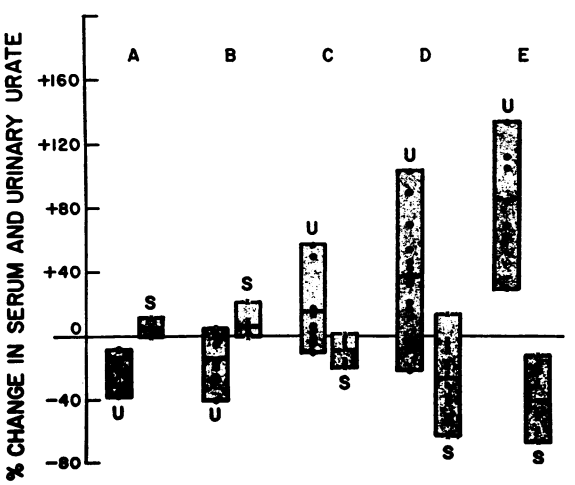

FIG. 1. DISTRIBUTION OF PER CENT CHANGE FROM PREMEDICATION LEVELS OF 24 HOUR URINARY URATE EXCRETION (U) AND SERUM URATE (S) AFTER ORAL ADMINISTRATION OF ACETYLSALICYLIC ACID IN DAILY DOSES OF: A, 1.0 GM.; B, 2.0 GM.; C, 3.0 GM.; D, 5.2 GM; E, 5.2 GM. ACETYLSALICYLIC ACID PLUS 5.2 GM. SODIUM BICARBONATE

The broken lines represent means.

Considerable variation was noted, however, in individual responses to orally administered acetylsalicylic acid at various dosage levels. Some subjects failed to exhibit significant urate retention in 24 hour urine collections on a divided dosage schedule of 1.0 or 2.0 Gm. per day, others failed to show any distinct uricosuric effect even after salicylate doses of 5.2 Gm. per day. A striking example is C. S., a gouty subject with marked renal damage, who showed 21 per cent retention of urate while taking 5.2 Gm. salicylate per day. (These individual variations may account in part for discrepancies in respect to dosage response reported by some prior investigators whose experimental subjects were very limited in number.) The general distribution of responses in 24 hour urinary urate excretion nevertheless indicates that most often in divided oral salicylate dosages between 2.0 and 3.0 Gm. per day there is a distinct reversal from urate retention to uricosuria. At such intermediate

TABLE II

Effect of sustained infusion of sodium salicylate on urate/inulin (respectively, urate/creatinine) clearance ratios

Case	Salicylate			Urate				
	Amount infused (cumulative)	P*	UV†	P	UV	C	C_{in}	C_{ur}/C_{in}
	Gm.	*mg. %*	*mg./min.*	*mg. %*	*mg./min.*	*ml./min.*	*ml./min.*	*%*
M. L.	0	0	0	9.1	0.88	9.7	129	7.5
	0.23	1.4	0.041	9.3	0.52	5.6	108	5.2
	0.69	2.8	0.24	9.3	0.32	3.4	112	3.1
	1.32	5.7	0.41	9.2	0.37	4.0	98.2	4.1
	1.78	9.0	0.59	8.9	0.62	6.9	102	6.8
	2.89	12.4	0.90	8.9	0.90	10.1	105	9.6
	4.23	17.7	1.73	8.8	1.65	18.8	106	17.7
Salicylate infusion stopped								
0– 4 hrs.		20.2	1.05	8.6	1.23	14.3	85.4‡	16.8§
4– 8 hrs.		18.2	0.98	8.0	1.32	16.5	113‡	14.6§
8–12 hrs.		14.8	0.49	7.8	0.54	6.9	94.0‡	7.4§
12–16 hrs.		12.0	0.41	7.9	0.40	5.1	121‡	4.2§
16–20 hrs.		8.0	0.33	8.4	0.42	5.0	97.2‡	5.1§
J. S.	0	0		11.5	1.69	14.7	128	11.5
	0.34	1.5		11.3	0.90	8.0	125	6.4
	0.53	3.1		10.9	0.77	7.1	125	5.7
	0.75	5.8		10.8	1.04	9.6	121	7.9
	1.05	9.0		10.9	1.46	13.4	118	11.4
	1.40	12.0		10.9	1.96	18.0	125	14.4
	1.81	15.0		10.8	2.34	21.6	116	18.6
	2.21	17.1		10.6	2.89	27.2	115	23.8
	2.71	21.0		10.7	3.37	31.5	119	26.5
Salicylate infusion stopped								
0– 4 hrs.		23.5		10.6	1.74	16.4	96.0‡	17.1§
4– 8 hrs.					1.15	10.9	87.7‡	12.4§
8–16 hrs.					0.61	5.8	91.5‡	6.3§
16–22 hrs.		6.5		10.6	0.33	3.1	118‡	2.6§
S. K.	0	0		11.4	0.71	6.2	120	5.2
	0.63	4.0		11.0	0.39	3.6	128	2.8
	0.92	8.8		11.0	0.49	4.5	112	4.0
	1.27	10.7		11.0	0.70	6.3	117	5.4
	1.62	12.0		10.6	1.11	10.5	114	9.2
	2.19	16.0		10.3	1.32	12.9	96.2	13.4
	3.36	21.8		10.7	2.42	22.6	117	19.4
Salicylate infusion stopped								
0– 4 hrs.		23.8		10.5	1.72	16.4	114‡	14.4§
4–10 hrs.					1.66	16.3	103‡	15.8§
10–16 hrs.					0.87	8.7	113‡	7.7§
16–20 hrs.		9.0		9.9	0.26	2.6	97.6‡	2.9§
M. S.	0	0		8.7	0.50	5.8	89.2	6.5
	0.59	4.5		8.9	0.35	3.9	89.2	4.4
	0.79	7.7		9.0	0.43	4.8	89.0	5.4
	1.22	10.5		8.8	0.68	7.7	97.0	7.9
	1.89	15.5		8.2	1.06	12.9	94.4	13.7
Salicylate infusion stopped								
0– 4 hrs.		19.8		8.3	0.93	11.2	95.8‡	11.7§
4–10 hrs.					0.39	4.6	85.1‡	5.4§
10–18 hrs.					0.48	5.4	85.4‡	6.4§
18–21 hrs.		4.7		9.2	0.35	3.8	88.3‡	4.3§
J. B.	0	0		9.3	0.70	7.5	147	5.1
	0.32	1.8		9.2	0.57	6.2	141	4.4
	0.64	5.3		9.0	0.69	7.7	142	5.4
	0.96	9.5		8.9	0.94	10.5	140	7.5
	1.85	14.9		8.9	1.65	18.6	153	12.2
	3.05	23.0		8.4	2.58	30.8	140	22.0
Salicylate infusion stopped								
0– 4 hrs.		24.2		7.8	1.94	24.8	177‡	14.0§
4– 8 hrs.					1.17	14.8	155‡	9.6§
8–16 hrs.					0.45	5.6	147‡	3.8§
16–21 hrs.		5.4		8.2	0.39	4.7	152‡	3.1§

* P salicylate represents plasma concentration of total salicylate.
† UV salicylate represents urinary excretion of free salicylate.
‡ Values represent C_{cr}.
§ Values represent C_{ur}/C_{cr}.

dosage levels (which, to be sure, may be higher or lower in individual instances) the net effect of salicylate on urinary urate excretion is apt to be negligible.

Upon discontinuance of salicylate medication the enhanced urinary urate excretion per 24 hours of those subjects receiving 5.2 Gm. per day fell sharply, transiently to below premedication levels. In most such cases urate retention in the first 24 hour postmedication period was 15 to 20 per cent of the control excretion (in some instances up to 40 to 50 per cent urate retention), with return to premedication excretion levels within the next 24 hours. In gouty patients with overt renal damage this urate retention phase was apt to be delayed, enhanced urinary urate excretion continuing for the first 24 hour postmedication period, urate retention following within the second 24 hour urine collection period. Patients who received lower oral dosages of salicylate, with no distinct salicylate uricosuria, did not in general exhibit significant urate retention upon discontinuance of medication.

In W. L., a daily regimen of 2.0 Gm. acetylsali-

TABLE III

*Effect of sodium salicylate infusion on C_{urate}/C_{inulin} ratios in the presence of an alkaline urine produced by administration of sodium bicarbonate**

Case	Salicylate			Urate					
	Amount infused (cumulative)	P†	UV‡	P	UV	C	C_{in}	C_{ur}/C_{in}	Urine pH
	Gm.	*mg. %*	*mg./min.*	*mg. %*	*mg./min.*	*ml./min.*	*ml./min.*	*%*	
A. S.	0	0	0	11.0	0.51	4.6	78.0	5.9	6.4
	0.29	2.4	0.19	11.1	0.37	3.3	77.0	4.3	6.4–6.5
	2.12	15.7	1.62	11.2	1.18	10.5	76.9	13.7	6.6–6.7
	4.34§	24.1	7.73	10.6	2.47	23.3	90.0	26.3	7.3–7.6
J H.	0	0	0	8.5	0.56	6.6	122	5.4	
	0.22	2.5	0.32	8.5	0.48	5.6	120	4.7	
	2.37	12.4	1.07	8.5	0.63	7.4	125	5.9	6.7
	4.33§	17.2	4.40	8.5	1.40	16.5	126	13.1	7.2–7.3
D. R.	0	0	0	11.2	0.95	8.5	140	6.1	
	0.23	2.6	0.26	10.9	0.85	7.8	140	5.6	
	2.03	14.8	1.71	10.4	1.87	18.0	138	13.6	6.9–7.1
	3.65§	18.7	8.47	9.6	4.28	44.6	128	34.9	7.6–7.7
S. L.	0	0	0	10.1	0.50	4.9	114	4.3	5.1
	3.48	27.0	1.04	9.7	1.41	14.5	107	13.6	5.7
	4.38§	26.6	9.19	8.4	2.21	26.3	98.5	26.7	6.9–7.9
L. C.	0	0	0	9.1	0.79	8.6	107	8.0	5.7
	4.00	26.2	1.95	8.9	2.04	22.9	102	22.4	6.3
	5.00§	25.4	10.40	8.4	3.04	36.2	100	36.2	6.9–7.7
B. R.	0	0	0	7.8	0.36	4.7	130	3.6	6.7
	3.54	26.6	3.86	6.0	1.91	31.9	146	21.8	6.7–7.1
	4.30§	25.4	11.52	6.2	2.49	40.2	138	29.1	6.8–7.2
H. W.	0	0	0	9.5	0.58	6.1	85.2	7.2	6.6
	3.58	15.1	3.10	8.7	1.56	17.9	86.2	20.8	6.5
	4.43§	18.9	9.45	7.8	2.43	31.1	85.2	36.5	7.3
H. G.	0	0	0	9.6	0.41	4.3	97.0	4.4	5.5
	4.00	32.4	4.45	8.5	2.21	26.0	94.5	27.5	6.4–6.6
	4.54§	25.2	7.23	8.0	2.12	26.6	93.2	28.6	7.5–7.6
J. S.	0	0	0	8.8	0.41	4.6	85.7	5.4	6.1
	3.67	34.5	3.94	8.5	1.28	15.1	85.3	17.7	6.4–6.5
	4.67§	31.4	11.00	7.7	2.42	31.3	84.5	37.0	7.0–7.3

* Each period indicated represents the mean of at least three urine collection periods.
† P salicylate represents plasma concentration of total salicylate.
‡ UV salicylate represents urinary excretion of free salicylate.
§ Sodium bicarbonate periods.

cylic acid resulted in serum salicylate levels of 3.0 to 5.5 mg. per cent; these low levels were associated with sustained urinary urate retention and a rise in serum urate. In L. C., 3.0 Gm. daily did not yield higher serum salicylate concentrations (3.8 to 5.2 mg. per cent over the four day medication period) and again there was some net urinary urate retention; whereas in J. S., given the same dosage, the serum salicylate rose successively each day from 8.7 mg. per cent (with urate retention on this first day) to 18.5 mg. per cent, the later high levels being associated with distinct uricosuria and fall in serum urate. In patients given 5.2 Gm. acetylsalicylic acid daily the rise in serum salicylate was more rapid and consistent. In O. G., for example, the serum salicylate level reached 12.0 mg. per cent on the first day and was associated on that day with a distinct increase in urinary urate excretion and fall in serum urate; these responses were sustained throughout the four day medication period as the serum salicylate further rose to 17.5 mg. per cent. R. M. responded the same way, although less markedly, as the serum salicylate level rose from 8.2 mg. per cent on the first day to 12.1 mg. per cent on the second day and to 18.0 mg. per cent on the fourth day. In P. C., on the other hand, the rise in serum salicylate was slower, from 9.3 to 10.9 mg. per cent in the first three days during which there was some urate retention, to 14.4 mg. per cent on the fourth day during which there was a substantial increase in urinary urate excretion and fall in serum urate level. The net change in urinary urate excretion over the four day period of medication in P. C. was a decrease of 6 per cent.

Urate/inulin clearance ratios at increasing plasma and urine salicylate levels produced by slow, sustained infusion of salicylate; postinfusion urate/creatinine clearance ratios at declining plasma and urine salicylate levels

The reversible effect of salicylate on urinary urate excretion was defined more precisely by simultaneous clearance measurements in eight slow, sustained salicylate infusion experiments. The results of five experiments are given in Table II; three others are briefly summarized in Table III.

The experiments uniformly revealed an initial

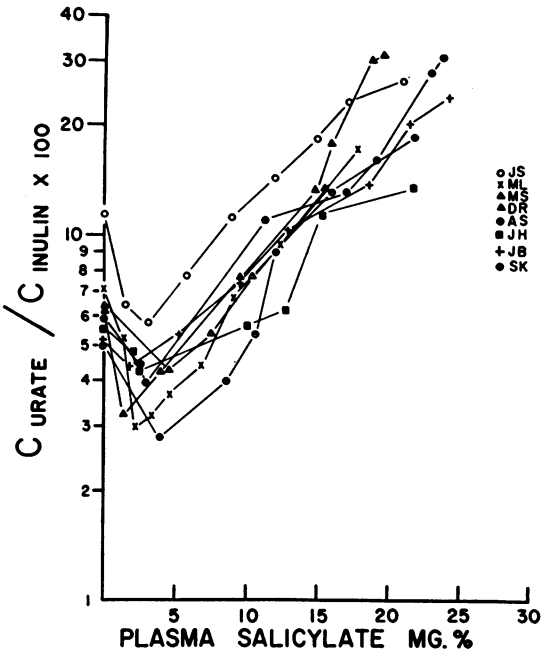

FIG. 2. SEMI-LOG PLOT OF RELATIONSHIP OF C_{URATE}/C_{INULIN} TO PLASMA SALICYLATE LEVELS IN EIGHT SUBJECTS SLOWLY INFUSED WITH SODIUM SALICYLATE

decline in the premedication C_{urate}/C_{inulin} as the plasma and urine salicylate levels slowly rose. This urate retention effect was demonstrable after injection of as little as 230 mg. sodium salicylate, with plasma salicylate levels as low as 1.4 mg. per cent and urinary excretion of free sali-

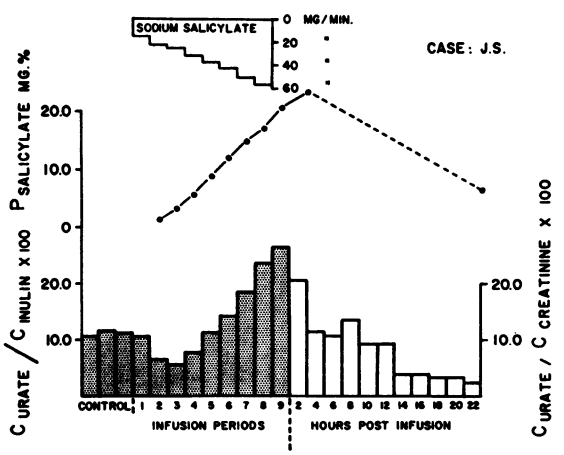

FIG. 3. C_{URATE}/C_{INULIN} (RESPECTIVELY, $C_{URATE}/C_{CREATININE}$) RESPONSE TO SLOWLY RISING PLASMA SALICYLATE LEVELS DURING SLOW INFUSION OF SODIUM SALICYLATE AND DECLINING PLASMA SALICYLATE LEVELS FOR 22 HOURS AFTER THE INFUSION WAS TERMINATED

cylate as low as 0.041 mg. per minute. The decline in C_{urate}/C_{inulin} persisted until the cumulative quantity of sodium salicylate slowly injected totaled a mean of approximately 1.0 Gm. (range, 0.6 to 1.5 Gm.), the plasma salicylate reached levels of 6 to 10 mg. per cent and sometimes more (Figure 2), and urinary excretion of free salicylate was 0.3 to 0.6 mg. per minute. The maximum reduction in C_{urate}/C_{inulin} noted in these experiments averaged 38.5 per cent (range, 13.7 to 58.8 per cent).

As the infusion of salicylate was maintained, C_{urate}/C_{inulin} returned to the control range, and continued to rise to uricosuric levels. Distinctly increased urate/inulin clearance ratios were noted after the cumulative injection of 1.5 to 3.0 Gm. sodium salicylate, with plasma salicylate levels of 10 to 12 mg. per cent or higher (Figure 2), and urinary excretion of free salicylate 0.4 to 0.9 mg. per minute or more. The infusion was terminated without attempting to attain a maximal uricosuric effect.

As the plasma salicylate and urinary excretion of free salicylate levels slowly declined after discontinuance of the salicylate infusion, the same sequence of events was observed in reverse order (Figure 3). For the first two to 10 hours the urate/creatinine clearance ratios remained excessive, then decreased to the premedication range, and continued to decline to values distinctly below the control figures. When observations were discontinued 20 to 22 hours after termination of the salicylate infusion, and the plasma salicylate levels were in the range 4 to 9 mg. per cent, the $C_{urate}/C_{creatinine}$ ratios invariably were still depressed. (The normally low nocturnal excretion of urate accentuates this trend.) These findings correspond with what has been designated "compensatory retention" of urate for a day or two after discontinuance of oral salicylate administration in uricosuric dosage.

These experiments again demonstrate the negligible net effect of salicylate in intermediate dosage on the renal excretion of urate. When salicylate is administered by slow infusion, this intermediate range of total dosage is variable but usually of the order of 1.0 to 1.5 Gm., with plasma salicylate levels usually of the order of 10 mg. per cent (Figure 2), and urinary excretion of free salicylate approximately 0.5 mg. per minute.

Influence of low urine pH on salicylate uricosuria (Table IV)

In subjects with distinctly acid urine, whether spontaneously developed (A. M., M. M.) or induced by administration of ammonium chloride (S. H., M. L.), the retention of urate produced by low dosages of salicylate was particularly pronounced and prolonged, as indicated by a comparison of the data on C_{urate}/C_{inulin} in Tables II and IV. The differences are well illustrated by M. M. (Table IV) whose urinary pH of 6 to 7 during the infusion of sodium salicylate was associated with the expected response in C_{urate}/C_{inulin} (Table II) but who spontaneously developed an unusually acid urine in the postinfusion period. It will be noted that the reduction in C_{urate}/C_{inulin} under these circumstances of distinctly acid urine was unusually marked, in the face of plasma salicylate levels ordinarily associated with a pronounced increase in C_{urate}/C_{inulin}.

The data in Table IV indicate that in subjects with low urine pH a larger than customary cumulative dose of injected salicylate is required to elicit a significant rise in urinary excretion of free salicylate, 3 or 4 Gm. to achieve urinary excretion of free salicylate levels of about 0.6 mg. per minute, whereas at pH levels within the usual range such doses result in UV salicylate levels of 1 to 2 mg. per minute. The corresponding plasma salicylate levels after infusion of 3 Gm. salicylate were 18 to 32 mg. per cent as compared with 12 to 20 mg. per cent. Larger than customary cumulative doses of salicylate, from 2 to more than 4 Gm., were required also to elicit a significant rise in C_{urate}/C_{inulin} above the premedication level. In the case of M. L. even 5.0 Gm. sodium salicylate failed to cause any appreciable increase in urate excretion. No concomitant rise in plasma urate was noted in most instances, presumably because of the short duration of the experiments.

In the systemic acidosis, with acid urine, produced by starvation and by high fat diets there is inhibition of urinary urate excretion (15, 16). In three subjects of this study (not receiving salicylate) given ammonium chloride by mouth to reduce the urine pH to 4.9 to 5.1, a maximal decline of 17 to 37 per cent was noted

TABLE IV

Effect of sodium salicylate infusion on C_{urate}/C_{inulin} ratios in the presence of an acid urine

Case	Salicylate: Amount infused (cumulative)	Salicylate: P*	Salicylate: UV†	Urate: P	Urate: UV	Urate: C	C_{in}	C_{ur}/C_{in}	Urine pH
	Gm.	*mg. %*	*mg./min.*	*mg. %*	*mg./min.*	*ml./min.*	*ml./min.*	%	
S. H.	0	0	0	13.0	0.90	6.9	96.0	7.2	4.5
	0.23	0.6	0.04	13.0	0.81	6.2	84.0	7.4	4.5
	0.35		0.12	13.0	0.47	3.6	105.0	3.4	4.5
	0.50	0.7	0.32	11.8	0.36	3.1	95.0	3.3	4.5
	1.04		0.38	11.8	0.66	5.6	81.0	6.9	4.5
	2.24	19.7	0.45	11.8	0.93	7.9	80.0	9.9	4.5
	3.43	18.1	0.63	11.8	1.30	11.0	92.5	11.9	4.6
	5.00	22.4	1.28	11.8	2.02	17.1	84.0	20.4	4.7
M. L.	0	0	0	9.1	0.84	9.2	135	6.8	4.5
	0.34		0.06		0.33	3.6	133	2.7	4.5
	0.50		0.22		0.27	3.0	125	2.4	4.5
	1.22		0.32		0.36	4.0	139	2.9	4.5
	1.72		0.48	9.1	0.42	4.6	136	3.4	4.5
	2.29		0.43		0.49	5.4	140	3.9	4.7
	2.94		0.43		0.52	5.7	114	5.0	4.7
	3.43	32.5	0.48	9.1	0.65	7.1	124	5.7	4.7
	4.00		0.43		0.66	7.3	130	5.6	4.7
	4.62		0.61		0.85	9.3	124	7.5	4.7
	5.00	31.7	0.61	9.1	0.83	9.1	123	7.4	4.7
A. M.	0	0	0	10.7	0.74	6.9	138	5.0	5.9
	0.15	2.9	0.12	10.7	0.39	3.7	150	2.5	5.6
	0.18	3.6	0.16	10.7	0.41	3.8	160	2.4	5.6
	1.26	9.5	0.24	10.1	0.31	3.1	157	2.0	5.2
	1.70	9.9	0.33	10.2	0.18	1.8	167	1.1	5.3
	2.10	10.3	0.43	10.2	0.56	5.5	179	3.1	5.4
	3.18	20.1	1.69	10.1	2.33	23.1	190	12.2	6.4
	4.10	20.3	2.53	9.7	2.76	28.5	188	15.2	6.7
	Salicylate infusion stopped								
	0– 5 hrs.		2.02	9.6	1.33	13.9	157‡	8.9§	
	5– 9 hrs.		0.81	9.4	1.80	19.2	219‡	8.8§	
	9–17 hrs.		0.35	9.2	0.48	5.2	180‡	2.9§	
	17–19 hrs.	4.0	0.27	9.0	0.34	3.8	152‡	2.5§	
M. M.	0	0	0	8.9	0.55	6.2	114	5.4	6.0
	0.32	1.8		8.8	0.28	3.2	104	3.1	6.5
	0.68	3.4	0.11	8.7	0.33	3.8	109	3.5	5.9
	1.14	6.5	0.26	8.7	0.53	6.1	108	5.6	6.2
	1.56	14.2	0.33	8.7	0.51	5.9	108	5.5	6.4
	2.28	17.5	0.48	8.7	0.66	7.6	108	7.0	6.0
	2.73	20.7	0.72	8.5	1.02	12.0	112	10.7	6.3
	3.57	25.4	1.15	8.3	1.28	15.4	112	13.8	7.0
	4.85	32.0	1.95	7.8	1.78	22.8	113	20.2	7.1
	Salicylate infusion stopped								
	0– 4 hrs.	26.1	0.19	7.7	0.54	7.0	111‡	6.3§	5.1
	4– 8 hrs.	18.5	0.20	7.4	0.50	6.8	112‡	6.1§	5.3
	8–14 hrs.	16.7	0.14	7.1	0.28	4.0	105‡	3.8§	5.2
	14–20 hrs.	15.1	0.23	7.3	0.16	2.2	89‡	2.5§	5.2

* P salicylate represents plasma concentration of total salicylate.
† UV salicylate represents urinary excretion of free salicylate.
‡ Values represent C_{cr}.
§ Values represent C_{ur}/C_{cr}.

in the 24 hour urinary urate output. This is substantially less than the decrease effected by acidification of the urine in subjects receiving salicylate.

Influence of alkalinization of the urine on salicylate uricosuria

a. Sodium bicarbonate. As shown in Table I, the uricosuric effect of acetylsalicylic acid ad-

ministered in 5.2 Gm. daily oral dosage is markedly increased by the simultaneous ingestion of 5 Gm. per day sodium bicarbonate. Except for J. D., the response was uniform, even in otherwise refractory C. S. The mean urinary urate output per 24 hours was increased 86 per cent after alkalinization, as compared with 37 per cent after salicylate alone, and the mean plasma urate level was 40 per cent lower, as compared with 26 per cent.

In two experiments (not included in Table I) a daily oral dosage of 2.0 Gm. acetylsalicylic acid was supplemented with 4 Gm. per day sodium bicarbonate. In J. J., who showed no significant change in urinary urate excretion per 24 hours with salicylate alone, there was no appreciable effect of supplementation with sodium bicarbonate. In D. R., retention of urinary urate decreased from 40.3 to 2.0 per cent, with a corresponding decline in serum urate.

In Table III are summarized the results of nine clearance studies in which a substantial increase in C_{urate}/C_{inulin} was first produced by infusion of sodium salicylate and, while maintaining the plasma salicylate at similar high levels by continued infusion, sodium bicarbonate was then simultaneously injected at rates sufficient to keep the urine pH at 6.8 to 7.9. In every case alkalinization of the urine with bicarbonate resulted in a marked increase in urinary excretion of free salicylate and, except in H. G., potentiation of salicylate uricosuria. The mean C_{urate}/C_{inulin} ratio in the control period was 5.6 per cent; following infusion of salicylate alone, 17.4 per cent; and following infusion of salicylate and bicarbonate, 29.8 per cent. Concomitant injection of sodium bicarbonate thus almost doubled the C_{urate}/C_{inulin} produced by salicylate alone.

b. Acetazolamide. Five similar clearance studies in which the urine was alkalinized with acetazolamide are summarized in Table V. The experimental conditions achieved in respect to increase in urine pH and augmentation of urinary excretion of free salicylate were comparable to those in the preceding studies with sodium bicarbonate (Table III). Except in B. C., however, no increase in C_{urate}/C_{inulin} beyond that produced by salicylate alone, prior to administration of acetazolamide, was obtained; on the contrary, the urate/inulin clearance ratios de-

TABLE V

*Effect of sodium salicylate infusion on C_{urate}/C_{inulin} ratios in the presence of an alkaline urine produced by administration of acetazolamide**

Case	Salicylate			Urate					
	Amount infused (cumulative)	P†	UV‡	P	UV	C	C_{in}	C_{ur}/C_{in}	Urine pH
	Gm.	*mg. %*	*mg./min.*	*mg. %*	*mg./min.*	*ml./min.*	*ml./min.*	*%*	
H. G.	0	0	0	9.5	0.92	10.1	131	7.7	6.0
	3.67	21.9	5.61	8.7	3.25	37.1	125	29.8	7.1–7.8
	4.96§	22.5	8.13	8.2	1.93	23.6	109	21.7	7.7–7.8
A. J. R.	0	0	0	8.6	0.55	6.3	136	4.7	5.6
	3.78	23.9	1.70	8.6	1.94	22.7	122	18.6	5.7–6.1
	5.24§	23.4	5.65	8.6	0.98	11.4	108	10.7	7.1–7.6
E. F.	0	0	0	5.4	0.68	12.6	143	8.8	6.4
	4.00	24.1	4.65	4.7	2.13	45.0	142	31.7	6.4–6.8
	4.92§	25.9	10.6	4.7	1.44	30.6	110	27.8	7.4–7.7
M. N.	0	0	0	11.5	0.69	8.9	92.9	9.5	6.6
	3.91	21.7	4.38	10.6	2.58	24.3	84.3	29.0	7.1–7.3
	4.93§	23.6	6.05	10.6	1.97	18.6	82.2	22.6	7.5–7.8
B. C.	0	0	0	9.7	0.57	5.8	152	3.9	5.1
	3.80	16.5	0.49	9.7	1.20	12.4	146	8.5	5.3–6.1
	4.92§	16.1	3.53	9.7	1.28	13.2	126	10.5	7.6–7.8

* Each period indicated represents the mean of at least three urine collection periods.
† P salicylate represents plasma concentration of total salicylate.
‡ UV salicylate represents urinary excretion of free salicylate.
§ Acetazolamide periods.

TABLE VI

*Effect of sodium bicarbonate or acetazolamide on C_{urate}/C_{inulin} ratios**

Case	Period	Urate P	Urate UV	Urate C	C_{in}	C_{ur}/C_{in}	Urine pH
		mg. %	*mg./min.*	*ml./min.*	*ml./min.*	%	
H. K.	Control	9.1	0.63	6.9	105	6.6	5.8–6.0
	$NaHCO_3$	9.2	0.90	9.8	112	8.7	7.3–7.4
M. L.	Control	10.0	0.71	7.1	104	6.9	5.6–7.7
	$NaHCO_3$	9.8	0.82	8.4	118	7.1	7.3–7.7
H. N.	Control	9.9	1.01	10.2	95.5	10.7	6.5
	$NaHCO_3$	9.6	1.37	14.2	106	13.4	7.2–7.4
A. L.	Control	9.8	1.03	10.5	106	9.9	6.7
	Acetazolamide (0.5 Gm. I.V.)	9.8	0.75	7.3	81.8	8.7	7.5–7.8
R. M.	Control	10.9	1.01	9.3	159	5.8	6.4
	Acetazolamide (1.0 Gm. I.V.)	10.9	0.72	6.6	123	5.4	7.3–7.6
M. W.	Control	9.5	0.52	5.4	128	4.2	4.9
	Acetazolamide (2.0 Gm. P.O.)	9.5	0.37	3.9	100	3.9	6.9–7.5
R. C.	Control	8.7	0.58	6.7	70.6	9.5	5.3
	Acetazolamide						
	(1.0 Gm. P.O.)	8.7	0.31	3.6	50.9	7.1	6.8–7.1
	(2.0 Gm. P.O.)	8.7	0.35	4.0	55.9	6.8	6.6–6.9
		8.7	0.25	2.8	71.0	4.0	7.1–7.8

* Each period indicated represents the mean of three to seven urine collection periods.

clined somewhat. The mean C_{urate}/C_{inulin} in the control period was 6.9 per cent; following infusion of salicylate alone, 22.5 per cent; and following joint administration of salicylate and acetazolamide, 18.7 per cent.

In order to dissociate the effects of alkalinization of the urine *per se* on the urinary excretion of urate, four clearance studies were made after administration of acetazolamide alone, without prior infusion of salicylate (Table VI). The results indicate a mean 32.5 per cent reduction in C_{urate}. This was associated with a decline in glomerular filtration rate (23.3 per cent), in part accounting for the fall in C_{urate}, to give a mean 14.6 per cent lowering in C_{urate}/C_{inulin}. Comparable studies in which sodium bicarbonate was rapidly injected to alkalinize the urine in three subjects (Table VI) revealed a mean rise of 20.8 per cent in C_{urate}/C_{inulin}, from a mean clearance ratio of 8.1 to 9.7 per cent. Sodium bicarbonate given alone in 5 Gm. oral daily dosage had no discernible effect on the 24 hour urinary excretion of urate.

Effect of salicylate in low and high dosage on probenecid uricosuria; effect of probenecid on salicylate uricosuria

The uricosuria induced by probenecid is markedly suppressed by small doses of salicylate (9). Thus L. G. excreted a mean of 486 mg. urate per 24 hours before medication, 824 mg. while taking 2.0 Gm. probenecid daily, 413 mg. during three days while 2.6 Gm. acetylsalicylic acid was added to the probenecid, and 850 mg. when salicylate was discontinued. The corresponding serum urate levels were 7.0, 3.0, 6.3 and 3.9 mg. per cent. In another representative patient, N. W., subjected to the first three phases of the same protocol, the respective figures for mean urinary urate per 24 hours were 399, 1,258 and 690 mg., and the serum urate levels were 9.5, 5.2 and 7.4 mg. per cent.

When large doses of acetylsalicylic acid, 5.2 Gm. per day, were added to the probenecid regimen the uricosuric response was but little affected, except for the first day when the serum

salicylate level was not yet fully established. Thus the basal urinary urate excretion in L. G. (previously cited) rose to a mean of 907 mg. per 24 hours with 2.0 Gm. probenecid daily, fell to 337 mg. on the first day after adding 5.2 Gm. per day salicylate to the regimen, averaged 846 mg. subsequently on combined medication, and 922 mg. when salicylate was withdrawn. The corresponding serum urate levels were 7.6, 4.6, 5.0 and 4.4 mg. per cent. In another representative patient, J. O., the respective figures for mean urinary urate per 24 hours were 483, 640, 480, 668 and 725 mg., and the serum urate levels were 11.5, 7.1, 6.8 and 6.8 mg. per cent.

The clearance studies summarized in Table VII delineate these effects more precisely. In O. G. and S. L., the initial C_{urate}/C_{inulin} ratios increased five- to sevenfold after rapid infusion of probenecid, fell sharply to approximately twofold values as sodium salicylate was slowly infused, then rose again as the plasma salicylate reached levels commonly associated with salicylate uricosuria. The reverse sequence, injection of probenecid after establishment of salicylate uricosuria, caused a modest but fairly consistent decrease in the augmented excretion of urate and a slight decline in the elevated C_{urate}/C_{inulin} ratios produced by salicylate. These changes were associated with a fall in urinary excretion of salicylate and rise in plasma salicylate. There was no indication of any additive effect of the two uricosuric agents.

TABLE VII

*Interaction of sodium salicylate and probenecid on urate/inulin clearance ratios**

Case	Salicylate			Urate				
	Amount infused (cumulative)	P†	UV‡	P	UV	C	C_{in}	C_{ur}/C_{in}
	Gm.	*mg. %*	*mg./min.*	*mg. %*	*mg./min.*	*ml./min.*	*ml./min.*	*%*
O. G.	0	0		8.0	0.42	5.2	106	4.9
	0§	0		7.0	2.06	29.5	82.0	36.0
	0.23	0.6		6.6	1.62	24.5	71.4	34.4
	0.50			6.5	0.97	14.8	92.0	16.1
	0.84	7.8		6.4	0.65	10.2	76.7	13.3
	1.45			6.4	0.64	9.9	67.3	14.7
	1.87	15.0		6.4	1.04	16.3	86.4	18.8
	2.57	20.9		6.4	1.34	20.9	85.0	24.6
S. L.	0	0		9.4	0.89	9.5	145	6.6
	0§	0		9.1	2.22	24.4	137	34.0
	0.20	1.3		8.8	3.24	36.7	112	32.9
	0.49	3.7		8.4	3.12	37.2	142	26.2
	0.80	6.1		8.4	2.59	30.8	167	18.4
	1.17	8.6		8.8	1.49	17.0	150	11.4
	1.55	13.4		8.8	1.32	15.0	150	10.0
	2.23	15.6		8.9	1.79	20.0	148	13.5
	3.00	20.6		8.6	1.57	18.3	107	17.1
I. S.	0	0	0	6.7	0.50	7.5	116	6.5
	2.88	20.5	2.50	6.8	1.82	26.9	123	21.9
	4.12§	23.9	1.98	6.4	1.17	23.3	117	19.9
R. S.	0	0	0	6.7	0.84	6.5	111	5.8
	3.32	21.0	1.37	6.8	0.93	13.7	107	12.8
	4.06§	25.0	1.15	6.7	0.90	13.5	106	12.7
N. B.	3.09	19.9	2.07	7.5	1.40	18.8	82.1	22.7
	3.79§	22.5	1.40	7.0	1.20	17.2	86.9	19.8
L. W.	3.98	24.1	4.30	7.0	2.00	28.6	96.5	29.7
	4.59§	24.7	2.62	6.2	1.68	27.1	97.8	27.7

* Each period indicated represents the mean of at least three urine collection periods for Cases I. S., R. S., N. B. and L. W.

† P salicylate represents plasma concentration of total salicylate.

‡ UV salicylate represents urinary excretion of free salicylate.

§ Probenecid, 20 mg. per Kg. body weight, intravenously as rapid injection.

DISCUSSION

The data define three distinct facets of the action of salicylate on the renal mechanisms for excretion of urate in man. The first discernible effect of salicylate is demonstrated to be suppressive, associated with relatively low concentrations of salicylate in the plasma and urine produced by small doses, such as are commonly employed for general analgesic purposes.[1] Large doses (high salicylate concentrations in the plasma and urine) have a markedly augmentative effect. Betwixt these, in an intermediate zone of dosage, the net effect of salicylate is apt to be negligible; the drug seemingly is virtually inactive in respect to the urinary excretion of urate. The absolute dosage of salicylate required to initiate this sequence varies somewhat from individual to individual, the urine pH being one important variable in this regard, but the relative dosage sequence appears generally to hold in normal and gouty man.

Before understaking an analysis of this paradoxical effect, it would be useful to summarize present knowledge of the mechanisms of renal excretion of salicylate and of urate in man.

Mechanisms of renal excretion of salicylate in man

Approximately one-third of the plasma salicylate is not bound to plasma proteins in man (11) and is presumed to be filtered at the glomerulus. The subsequent fate of the filtered free salicylate is modified by the urine pH. Under the ordinary circumstances of slightly acid urine, $C_{\text{free salicylate}}/C_{\text{inulin}}$ is of the order 0.2 to 0.4 (11), implying tubular reabsorption of the filtered free salicylate. Of the salicylate appearing in acid urine, only a small part (about 20 per cent or less, depending on the urine pH) is excreted as free salicylate. The major proportion is in conjugated form (18), combined with glycine as salicyluric acid (55 to 65 per cent) and with glucuronic acid as salicyl acyl and phenolic glucuronides (20 to 30 per cent) (18, 19). Approximately 20 per cent of ingested salicylate cannot be recovered in the urine as salicyl compounds because of metabolic conversion to gentisic acid and other degradation products (18).

If the urine is made distinctly alkaline, whether by administration of sodium bicarbonate (11, 19–25) or acetazolamide (25), or as a result of overbreathing (25), the rate of urinary excretion of salicylate is greatly enhanced, and the proportion of free salicylate increases to 60 to 90 per cent or more of the total urinary salicylate. This marked rise in $C_{\text{free salicylate}}$ is not due to any increase in the filtered load of free salicylate, and hence is ascribable to diminution of tubular reabsorption. $C_{\text{free salicylate}}/C_{\text{inulin}}$ may exceed 1.0 if the urine is made sufficiently alkaline, indicating tubular excretion of free salicylate in man (11, 19, 23, 25).

In view of the striking urinary pH dependence of the renal excretion of salicylic acid (pKa about 3.0), "passive" tubular transfer processes, dependent upon the pH gradient between the tubular urine and the peritubular fiuid, may be assumed to play an important role in both tubular reabsorption and excretion of free salicylate (25–27). However, tubular transfer of free salicylate is not altogether attributable to nonionic diffusion, since probenecid causes a substantial reduction in urinary excretion of free salicylate with a corresponding rise in plasma salicylate, irrespective of the urine pH (11, 19). This effect of probenecid is reminiscent of its action on the renal excretion of penicillin and other compounds "actively" secreted by the tubules. "Active" tubular secretion of free salicylate is further implied by transfer against an H^+ gradient, as indicated by its (limited) reabsorption in alkaline urine and suspected excretion in acid urine (11, 19, 23). Tubular secretion of salicyluric acid (28) and of salicyl acyl and phenolic glucuronides (19) has been clearly demonstrated by Schachter and Manis (19), and occurs at a rate independent of the urine pH, but determined chiefly by the rate of conjugation, largely in the liver (19).

Mechanisms of renal excretion of urate in man

The filtered urate load, calculated on the basis of complete filtrability of plasma urate at the glomerulus (29, 30), greatly exceeds the quantity of urate appearing in the urine. The deficit,

[1] As mentioned elsewhere (12), the hyperuricemia thus resulting from ingestion of salicylate in low dosage is not uncommonly encountered and is frequently misconstrued; when associated with joint pains it is sometimes attributed to gout. Even formal studies of the interpretation of hyperuricemia may neglect this iatrogenic etiology (17).

usually 90 to 95 per cent of the filtered load in normal and gouty man (31, 32), indicates tubular reabsorption. The tubular capacity for reabsorption of urate has been shown to be limited, of the order of 15 mg. per minute in normal man (31), but nevertheless much larger than the urate load delivered to the tubules in normal and most gouty subjects under ordinary circumstances (31, 32).

The conventional interpretation of urate clearance data in man limits the role of the kidney to glomerular filtration and tubular reabsorption of urate. The urate appearing in the urine is considered to represent that 5 to 10 per cent of the filtered urate load which has escaped reabsorption (Figure 4). Another possible interpretation, also consistent with the clearance data, considers tubular reabsorption of the filtered urate to be virtually complete under ordinary circumstances, and the urinary urate to be derived by tubular excretion (7, 32, 33) (Figure 4), *i.e.*, a mechanism similar to that postulated for potassium (34, 35) and thiosulfate (36). The processes of tubular reabsorption and excretion of urate both are conceived to be chiefly "active," in view of their limited capacity and the inhibiting effects of a variety of chemical agents. Nonionic diffusion of uric acid (pKa 5.4) appears to play a minor role in tubular transfer. While the excretion of urate is diminished in acid urine and slightly increased in urine made alkaline by the administration of sodium bicarbonate, alkalinization of the urine by use of acetazolamide leads to some decrease in renal excretion of urate (37). The contrary effects of alkalinization of the urine with bicarbonate and acetazolamide indicate that, in contrast to the nonionic diffusion of other weak acids (27), the tubular transfer of urate is not greatly influenced by alkaline urine pH alone.

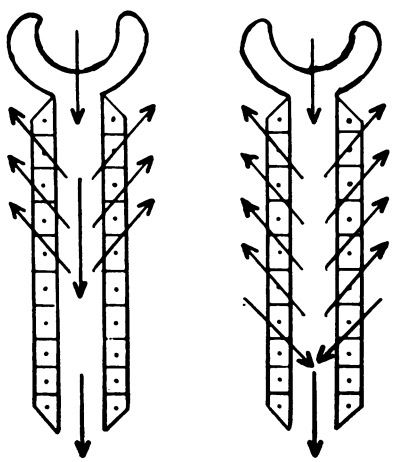

FIG. 4. SCHEMATIC REPRESENTATION OF TWO POSTULATIONS OF RENAL REGULATION OF URIC ACID EXCRETION IN MAN

On the left, the plasma urate is pictured as virtually wholly filtrable at the glomerulus, the filtered urate is largely but not completely reabsorbed in passage through the tubules, and the excreted urate represents that small fraction of the filtered urate which has escaped reabsorption. On the right, the plasma urate again is pictured as virtually wholly filtrable at the glomerulus, the filtered urate is completely reabsorbed in the tubules, and the urate appearing in the urine is secreted by the tubules. This figure originally appeared in Bull. N. Y. Acad. Med. 1958, **34**, 287 (33).

Relationship of concentration of free salicylate in the tubular urine to the tubular regulation of urate excretion

To return now, in the light of the foregoing résumé, to the primary consideration of this study, a critical point in interpretation of the paradoxical effects of low, intermediate and high dosages of salicylate is whether they are related to the corresponding salicylate concentrations in the plasma or in the tubular urine. This would be difficult to establish under ordinary circumstances, in which the rate of renal excretion of salicylate parallels the plasma salicylate concentration. However, dissociation of this relationship can be effected by rendering the urine distinctly acid or alkaline. In distinctly acid urine, urinary excretion of free salicylate remains lower than ordinarily, even after relatively large doses of salicylate, and the plasma salicylate rises inordinately. Under these circumstances the rise in C_{urate}/C_{inulin} is found to be delayed and less pronounced. This effect on C_{urate}/C_{inulin} ratios is distinctly greater than obtained by acidification of the urine *per se* without salicylate. When the urine is made distinctly alkaline with sodium bicarbonate, urinary excretion of free salicylate is greatly augmented and the plasma salicylate rapidly falls unless constantly replenished (as in the infusion experiments cited). Under these circumstances C_{urate}/C_{inulin} is found to increase, significantly above the ratios obtained solely by alkalinization of the urine

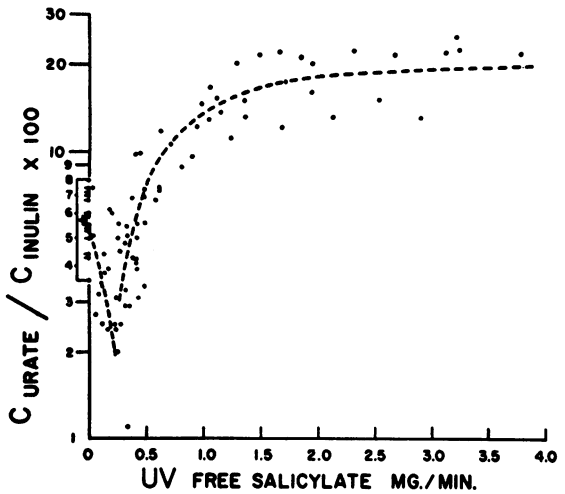

FIG. 5. SEMI-LOG PLOT OF RELATIONSHIP OF C_{URATE}/C_{INULIN} TO URINARY EXCRETION OF FREE SALICYLATE IN 14 SUBJECTS SLOWLY INFUSED WITH SODIUM SALICYLATE

The curves are schematically drawn by inspection. The points include measurements in subjects with markedly acid urine. Points representing measurements in markedly alkaline urine extend the abscissa to 14 mg. urinary excretion of free salicylate per minute and have therefore been omitted; the points lie slightly above the extended curve for urine alkalinized with sodium bicarbonate, slightly below for urine alkalinized with acetazolamide (see text).

with bicarbonate without prior administration of salicylate. When acetazolamide is used to alkalinize the urine in patients receiving salicylate, the excretion of free salicylate again is accelerated, and the plasma salicylate falls unless constantly replenished. However, C_{urate}/C_{inulin} is not increased in this instance, but declines somewhat below the levels reached by acetazolamide without prior administration of salicylate.

The combined results of experiments using ammonium chloride, sodium bicarbonate or acetazolamide indicate that salicylate exerts its various effects on urate excretion largely at the renal tubular level, although these effects seem to be modified by the state of metabolic acidosis or alkalosis. Further, the paradoxical effects of salicylate in varying dosage appear to be chiefly related to the correspondingly varied concentrations of free salicylate in the tubular urine (8). This relationship, illustrated in Figure 5, is represented by a discontinuous curve. Low ranges of urinary excretion of free salicylate are associated with decreased C_{urate}/C_{inulin} ratios, which at first decline further as urinary excretion of free salicylate slowly increases. The point of minimum inflection is formed by the intersection with another, sharply rising curve which represents increasing C_{urate}/C_{inulin} ratios, to markedly uricosuric levels, as urinary excretion of free salicylate further increases. The inexplicable apparent loss of drug potency at intermediate dosage levels clearly is the resultant of opposing suppressive and augmentative forces, in such relative proportions as virtually to nullify each other, and thus yield an insignificant net effect.

These results can be reconciled with the conventional concept of renal regulation of urate excretion only with some difficulty. The uricosuric effect of large doses of salicylate, associated with markedly increased urate/inulin clearance ratios, is readily understandable as due to inhibition of tubular reabsorption of urate, as in the case of other potent uricosuric agents (38–42). The suppressive effect of small doses of salicylate, however, requires the rather awkward assumption of *stimulation* of tubular reabsorption of urate by the same drug, and without any change in filtered urate load. A similar explanation presumably would apply to urate retention caused by phenylbutazone in low dosage (7) and by pyrazinamide (43) and lactate (44). The apparent impotency of intermediate doses of salicylate poses a dilemma. The single tubular transport system for urate would seem to be simultaneously stimulated and suppressed by the same drug in the same dosage.

The alternative concept of renal regulation of urate excretion, which postulates a tubular excretory as well as reabsorptive transport mechanism, supposes the suppressive effect of small doses of salicylate (and other agents with like action) to be due to inhibition of tubular secretion of urate (7, 8, 32, 33).[2] When the concentration of free salicylate in the tubular urine is sufficiently increased, it is assumed that inhibition of the reabsorptive mechanism also occurs. In the intermediate range of urinary excretion free salicylate, inhibition of urate secretion is marked whereas inhibition of urate reabsorption is so slight that the net effect is virtually to cancel out the effect of either action alone, the net result on the ex-

[2] The term "excretion" as employed in this discussion is used in a general sense, with no inferences as to whether excretion is "active," "passive" or both. "Secretion" here implies "active" tubular transfer.

cretion of urate being negligible. High concentrations of free salicylate in the tubular urine are considered markedly to inhibit both tubular reabsorption and secretion of urate (7, 8, 32, 33). The net effect of such marked dual inhibition would be expected to be uricosuric, since the quantity of urate normally reabsorbed from the glomerular filtrate in man is 10 to 20 or more times greater than the quantity eliminated in the urine.

The nature of the inhibition of the reabsorptive (and secretory) processes of tubular transfer of urate, by salicylate and the other drugs in question, must remain a matter of speculation for the present. Competition for some common component of the reabsorptive and secretory tubular transfer mechanisms may occur.

The interacting influences of salicylate and probenecid, when jointly administered, on the tubular regulation of urate excretion

The inhibition of probenecid uricosuria by small doses of salicylate poses a further dilemma for the conventional concept of the renal regulation of urate excretion, since here again there would seem to be simultaneous inhibition and stimulation of a single tubular transfer system, in this instance by two different drugs. A similar difficulty arises in connection with the inhibition of probenecid uricosuria by other drugs which, when given alone, cause marked retention of urate (for example, lactate) (44).

The explanation alternatively offered postulates that the inhibition of tubular reabsorption of urate produced by probenecid is partially counterbalanced by simultaneous inhibition of tubular secretion of urate by salicylate in low dosage (33). A similar dual mechanism is presumed to underlie the inhibitory effect of small doses of salicylate on the enhanced urate excretion produced by other potent uricosuric agents, such as zoxazolamine (42) and the phenylbutazone analogs, G-25671 and G-28315 (45, 46). It is interesting to note that salicylate, which has no effect on tubular secretion of penicillin, in no way influences the inhibition of penicillin secretion by probenecid (47).

It should be pointed out, however, that the observed counterbalance of probenecid uricosuria by small doses of salicylate is greater than anticipated by the postulated inhibition of tubular secretion of urate, since the quantity of urate secreted apparently is small in relation to that reabsorbed. Other factors, as yet obscure, must therefore be presumed also to be operative. Another discrepancy is the failure to observe an additive effect if salicylate in large (uricosuric) dosage is given when probenecid uricosuria is already produced, or if probenecid is administered when salicylate uricosuria already obtains (9, 48, 49). Such an additive effect is in fact noted when zoxazolamine and G-28315 are administered jointly, or with probenecid (42, 50).[3] However, in the case of salicylate uricosuria, probenecid exerts a moderate depressant effect, associated with a decline in the free salicylate concentration in the tubular urine. This response seems to be related to the inhibitory effect, already referred to (11, 19), of probenecid on the tubular secretion of salicylate.

SUMMARY

1. In 44 experiments in 23 gouty subjects the administration of acetylsalicylic acid in daily oral doses of 1.0, 2.0, 3.0 and 5.2 Gm. per day produced mean changes in 24 hour urinary urate excretion of −21, −14, +16 and +37 per cent, respectively. When 5.2 Gm. per day sodium bicarbonate was added to 5.2 Gm. per day salicylate dosage, the mean 24 hour urinary urate excretion rose to +86 per cent. Corresponding inverse changes were observed in serum urate levels.

2. Renal clearance studies in eight subjects slowly infused with sodium salicylate revealed that low levels of plasma salicylate (of the order of 1.5 to 10 mg. per cent) and of urinary excretion of free salicylate (of the order of 0.05 to 0.5 mg. per minute) were usually associated with a distinct fall in C_{urate}/C_{inulin} below premedication ratios. High levels of plasma salicylate (> 10 or 12 mg. per cent) and of urinary excretion of free salicylate (0.5 to 1.0 or more mg. per minute) were usually associated with a pronounced rise in C_{urate}/C_{inulin} above premedication ratios.

[3] Additive uricosuric effects are obtained with concurrent administration of uricosuric agents which do not cause urate retention, when given in low dosage, as in the case of zoxazolamine and G-28315. Probenecid in very low dosage may cause slight retention of urate [maximum observed, 27 per cent (7)] but this is not a constant finding.

Plasma salicylate levels and urinary excretion of free salicylate within a zone intermediate between those causing distinct urate retention and uricosuria were usually associated with little or no significant change from the premedication C_{urate}/C_{inulin} ratios.

3. Dissociation of plasma and urinary salicylate levels, by rendering the urine distinctly acid (ammonium chloride administration) or alkaline (sodium bicarbonate), indicated that the paradoxical effects of salicylate on C_{urate}/C_{inulin} were determined at the tubular level, largely by the concentration of free salicylate in the tubular urine. In subjects with distinctly acid urine, urinary excretion of free salicylate remained relatively low even after large sodium salicylate infusions, the plasma salicylate rose inordinately, the rise in C_{urate}/C_{inulin} was delayed and less pronounced than ordinarily. In subjects with urine made alkaline with sodium bicarbonate, urinary excretion of free salicylate increased sharply and the rise in C_{urate}/C_{inulin} was considerably greater than that produced by salicylate alone. In subjects with urine made alkaline with acetazolamide, urinary excretion of free salicylate again rose sharply but the increased C_{urate}/C_{inulin} produced by salicylate alone was somewhat depressed.

4. It is suggested that the paradoxical effects of salicylate on urinary urate excretion can be reasonably explained on the assumption that the filtered urate load in man is virtually completely reabsorbed by the tubules and that the urate in the urine, contrary to the conventional view, is derived largely by tubular secretion. It is postulated that low concentrations of free salicylate in the tubular urine depress tubular secretion of urate. Intermediate concentrations of free salicylate, it is suggested, depress tubular secretion, and also reabsorption of urate to a degree sufficient to give little or no net change in urate excretion. High concentrations of free salicylate in the tubular urine are believed to suppress tubular reabsorption of urate markedly (as well as tubular secretion), the net effect being uricosuric.

5. It is further suggested that probenecid uricosuria, which is produced by inhibition of tubular reabsorption of urate, is counteracted by small doses of salicylate in part because of concurrent suppression of tubular secretion of urate.

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