

IMPAIRMENT OF URIC ACID EXCRETION IN GOUT *

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The urinary excretion of uric acid in individuals with primary gout has been shown to be approximately the same as, or in a minority of instances greater than, that of normal subjects on comparable diets (2, 3). These observations, plus the failure to demonstrate significant differences in the renal clearance of uric acid in gouty and nongouty control subjects, have led to the conclusion that patients with gout excrete uric acid in a normal manner (2-5).

This view has, however, recently been challenged (6) on the ground that in the studies on which it was based, differences in the plasma urate concentrations of gouty and nongouty subjects were not taken into account. In order to eliminate such differences Nugent and Tyler (6) induced hyperuricemia in nongouty individuals by the oral administration of uric acid precursors and compared uric acid excretion in these subjects and patients with gout. Under these conditions an impairment in urate excretion was clearly evident in patients with gout; both the excretion and clearance of urate were significantly less than in nongouty subjects with equivalent plasma urate levels.

These observations of impaired uric acid excretion were fully supported by the present study, in which urate was administered intravenously to gouty and nongouty subjects in order to *a*) study urate excretion at equivalent and various plasma levels and *b*) examine the dynamics of the renal tubular transfer mechanisms for urate.

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METHODS

The urinary excretion and renal clearance of uric acid were determined in 10 nongouty control subjects and in 11 patients with primary gout. The nongouty subjects, all but two of whom (M.W. and D.B.) were males, varied in age from 33 to 65 years and were free of apparent renal, hematologic, cardiovascular, or endocrine disease. The serum uric acid concentration was normal in all of the nongouty subjects, varying in the group from 3.1 to 5.5 mg per 100 ml. The pertinent clinical features of the patients with gout, all but one of whom (A.C.) were males, are shown in Table I. All of the patients had elevated serum uric acid levels (Table II) and a history consistent with gouty arthritis. None had clinical or laboratory evidence of renal or hematologic disease, renal calculi, or cardiac failure. Three of the patients with gout (S.M., N.T., and B.P.) had been treated with probenecid. Medication was discontinued in these individuals 16 days, 5 days, and 24 hours, respectively, prior to the test. The remaining patients had received no uricosuric medication.

All subjects were allowed their usual ad lib diets. After an overnight fast each subject ingested 500 ml of water approximately one hour before the test. During the experiment water was given orally at 15- to 30-minute intervals as needed to replace urinary losses. Urine was collected through a urethral catheter, and arterial blood from an indwelling needle placed in the brachial artery. After the collection of from one to three 15- to 20-minute control clearance periods, a priming injection of 25 ml of inulin was given and an intravenous infusion containing lithium urate and inulin was started. The infusion was prepared by dissolving 4.0 g of uric acid in 1 L of hot 0.15 per cent lithium carbonate solution. After the solution had cooled, 50 ml of inulin and 15 ml of 50 per cent glucose were added. The infusion was given at a rate of 4.5 ml per minute for 90 to 120 minutes and was then increased to a rate of 8.0 ml per minute for an additional 60 to 90 minutes. All subjects tolerated the infusion well except for one control subject who became nauseated at the conclusion of the test.

During the infusion of lithium urate 8 to 14 clearance periods, each 10 to 20 minutes in duration, were obtained. A sample of arterial blood was collected at approximately the mid-point of each period and was mixed with heparin and centrifuged immediately. Urine was collected by standard renal clearance procedures.

Analysis of plasma and urine was usually made on the day of the test. Occasionally the samples were re-

TABLE I
Clinical data in patients with gout

Subject	Age	Urate excretion*	Duration of arthritis	Tophi
		mg/24 hrs	yrs	
A.C.	51		2	0
S.M.	37		6	0
W.B.	36	1,546	13	0
V.W.	39	613	8	0
R.Z.	46	635	6	+
N.T.	62		3	0
C.E.	63	290	6	0
W.H.	48	592	10	0
Z.H.	49	713	1	0
F.F.	48	768	2 mos.	0
B.P.	58	670	20	0

* Determined prior to lithium urate infusion.

frigerated and stored for 24 to 48 hours prior to analysis. Storage for this period of time resulted in no significant loss of uric acid from the samples. Plasma and urine were analyzed for uric acid by the uricase method of

Liddle, Seegmiller, and Laster (7), and for inulin by the method of Harrison (8).

In addition to these experiments, an *in vitro* study of the diffusion of urate from plasma was made in which we utilized the principle of equilibrium dialysis. In this study 5 ml samples of plasma obtained from a patient with gout before and after elevation of plasma urate concentration by the infusion of lithium urate were placed in cellophane bags and dialyzed simultaneously. Dialysis was carried out on a shaking apparatus at 26° C for 20 hours. All components of the system were analyzed in duplicate for uric acid before and immediately after dialysis. Three such experiments were performed with plasma from gouty subjects W.H., V.W., and R.Z.

RESULTS

Urate excretion and clearance

Control. The values obtained in nongouty and gouty subjects for uric acid excretion, plasma concentration, and renal clearance under control

TABLE II
The renal clearance of urate prior to lithium urate infusion *

Subject	P _{UR}	C _{IN}	U _{URV}	C _{UR}	$\frac{C_{UR}}{C_{IN}} \times 100$
	mg %	ml/min	mg/min	ml/min	
Nongouty					
N.T.	4.6	102	.37	8.0	7.9
C.H.	4.8	105	.34	7.1	6.8
W.S.	4.4	113	.41	9.4	8.3
M.W.	3.7	144	.29	7.8	5.4
D.B.	3.1	110	.16	6.6	6.0
W.M.	4.7	133	.34	7.3	5.5
W.W.M.	4.7	83	.35	7.5	9.1
L.B.	5.5	115	.42	7.6	6.7
J.P.	3.9	103	.24	6.1	5.9
S.M.	4.6	100	.33	7.4	7.4
Mean ± SD	4.4 ± 0.7	111 ± 17	.33 ± .08	7.5 ± 0.3	6.9 ± 1.3
Gouty					
A.C.	7.9	150	.38	4.8	3.2
S.M.	9.7	92	.49	5.1	5.5
W.B.	12.6	93	.63	5.4	5.8
V.W.	7.6	91	.23	3.0	3.3
R.Z.	7.3	144	.48	6.6	4.6
N.T.	8.2	113	.81	10.0	8.8
C.E.	6.7	117	.27	4.0	3.4
W.H.	7.5	128	.54	7.2	5.7
Z.H.	9.4	126	.59	6.2	5.0
F.F.	7.7	118	.85	9.4	7.9
B.P.	6.1	119	.28	3.9	3.3
Mean ± SD	8.2 ± 1.7	118 ± 20	.50 ± .21	6.0 ± 2.2	5.1 ± 1.9
p	<.001	<.4	<.02>.01	<.05>.02	<.02>.01

* All clearance values are corrected to 1.73 square meters body surface area. Apart from the inulin clearance, the values shown were obtained prior to the infusion of lithium urate during a single control clearance period or represent the mean values of from 2 to 4 control clearance periods. The inulin clearances tabulated were not determined during the control periods, but represent the mean values of subsequent periods obtained during the infusion of lithium urate.

Abbreviations: P_{UR} = plasma uric acid concentration; C_{IN} = inulin clearance; U_{URV} = uric acid excretion; C_{UR} = uric acid clearance; $\frac{C_{UR}}{C_{IN}}$ = uric acid/inulin clearance ratio.

TABLE III
 Representative experiments in a nongouty subject and a patient with gout *

Subject	Time	P _{UR}	C _{IN} †	Load	U _{URV}	T _{UR}	C _{UR}	$\frac{C_{UR}}{C_{IN}} \times 100$
	min	mg %	ml/min	mg/min	mg/min	mg/min	ml/min	
Nongouty N.T.	0-13	4.6	(102)	4.72	.37	4.35	8.0	7.9
Inulin prime, 25 ml Infuse intravenously at 4.5 ml/min: Uric acid, 4.0 g/L; Li ₂ CO ₃ , 1.5 g/L; inulin, 50 ml/L; glucose, 10 g/L								
	13-30	5.7	(102)	5.82	.40	5.42	7.0	6.9
	30-45	6.8	104	7.08	.73	6.35	10.7	10.3
	45-51	8.1	100	8.08	1.05	6.93	13.0	13.0
	51-65	9.4	98	9.18	1.52	7.66	16.2	16.5
	65-77	10.0	104	10.47	1.67	8.80	16.6	16.0
	77-84	11.3	103	11.65	2.07	9.58	18.3	17.8
	84-99	12.4	99	12.20	2.58	9.62	20.8	21.0
	99-115	12.7	98	12.40	2.64	9.76	20.8	21.2
Infuse lithium urate, inulin at 8.5 ml/min								
	115-131	13.7	103	14.10	3.73	10.37	27.2	26.4
	131-149	15.2	102	15.50	5.35	10.15	35.2	34.5
	149-161	16.2	101	16.35	6.21	10.14	38.4	38.2
	161-173	17.2	108	18.60	8.40	10.20	48.8	45.1
	173-186	18.3	105	19.20	9.30	9.90	50.8	48.4
Gouty W.H.	0-24	7.5	(128)	9.56	.54	9.02	7.2	5.6
Inulin prime, 25 ml Infuse intravenously at 4.5 ml/min: Uric acid, 4.0 g/L; Li ₂ CO ₃ , 1.5 g/L; inulin, 50 ml/L; glucose, 10 g/L								
	24-62	8.1	(128)	10.39	.34	10.05	4.2	3.3
	62-77	9.4	136	11.45	1.09	10.36	11.6	8.5
	77-93	10.5	125	13.10	1.02	11.08	9.7	7.8
	93-109	11.2	131	14.70	1.16	13.54	10.4	7.9
	109-126	11.9	126	15.00	1.26	13.74	10.6	8.4
	126-140	12.5	128	16.00	1.53	14.47	12.2	9.5
Infuse lithium urate, inulin at 8.5 ml/min								
	155-168	15.6	126	19.70	2.91	16.79	18.6	14.8
	168-183	16.9	131	22.15	3.34	18.81	19.8	15.1
	183-193	18.4	129	23.65	4.18	19.47	22.8	17.7

* Abbreviations: P_{UR} = plasma uric acid concentration; C_{IN} = inulin clearance; load = filtered load (P_{UR} × C_{IN}); U_{URV} = uric acid excretion; T_{UR} = net tubular reabsorptive rate of uric acid; C_{UR} = uric acid clearance; $\frac{C_{UR}}{C_{IN}}$ = uric acid inulin clearance ratio.

† The values in parentheses were not determined for the periods shown, but represent the mean of the values obtained in the subsequent periods.

conditions prior to the infusion of lithium urate are presented in Table II. The excretion of uric acid was somewhat higher in gouty subjects, averaging $0.50 \pm .21$ mg per minute, than in nongouty subjects, in whom the mean uric acid excretion was $0.33 \pm .08$ mg per minute.¹ How-

¹ The rate of uric acid excretion in gouty subjects under these conditions differed in a variable manner from that found in 24-hour collections (Table I). These differences may be attributable to the fact that the control and 24-hour samples were collected on different days and to variations in such factors as diet, urine volume, and activity.

ever, there was considerable overlap between the two groups and the difference between the means was of borderline significance ($p < .02 > .01$). Since the plasma concentration of uric acid was considerably higher in gouty than in nongouty subjects, the somewhat higher excretory values of gouty subjects were not reflected in a corresponding difference in the renal clearance of urate. There was no significant difference between the mean urate clearance of gouty subjects (6.0 ± 2.2 ml per minute) and nongouty subjects (7.5 ± 0.3 ml per minute). When the clearance of urate

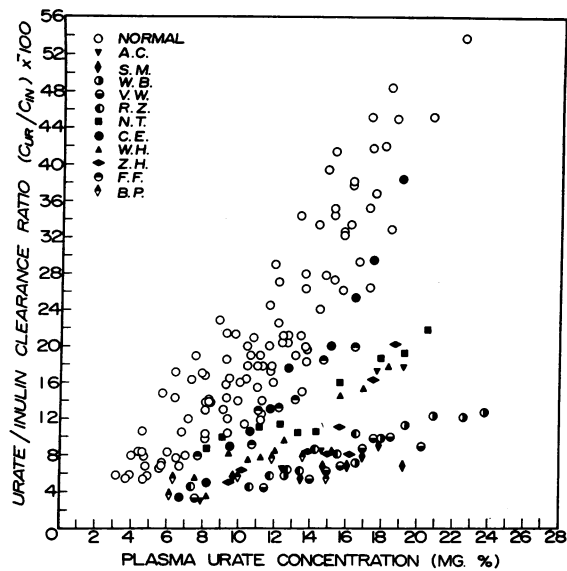


FIG. 1. THE RELATIONSHIP BETWEEN THE URATE/INULIN CLEARANCE RATIO ($C_{UR}/C_{IN} \times 100$) AND THE PLASMA URIC ACID CONCENTRATION. The open circles represent values obtained in individual clearance periods in nongouty subjects before and during the infusion of lithium urate. The various shaded symbols represent values obtained before and during the infusion of lithium urate in patients with gout.

was considered in relation to the clearance of inulin ($C_{UR}/C_{IN} \times 100$, Table II), slightly lower clearance ratios were found in patients with gout than in nongouty subjects. The means of the two groups were 5.1 ± 1.9 and 6.9 ± 1.3 , respectively. There was, however, overlap between the groups, and the difference between the means was of borderline significance ($p < .02 > .01$). The mean and range of values for the clearance of inulin were essentially the same in gouty and nongouty subjects, and all values were within two standard deviations of the normal mean as described elsewhere (9, 10). The control values for urate excretion and clearance in gouty and nongouty subjects were similar to those reported by others (2, 3, 6).

Lithium urate infusion. The results of representative experiments in a nongouty (N.T.) and gouty subject (W.H.) are presented in detail in Table III. The infusion of lithium urate resulted in a progressive increase in plasma urate concentration, uric acid excretion and clearance, and in the urate/inulin clearance ratio. The changes in plasma urate concentration were equivalent, and

the maximal level attained was approximately the same in the two subjects. However, the changes in uric acid excretion and clearance and in the urate/inulin clearance ratio with each increment in plasma level and filtered load were greater in the nongouty than in the gouty subject. Moreover, at equivalent plasma levels and filtered loads, the excretion and clearance of uric acid and the urate/inulin clearance ratios were significantly higher in the nongouty than in the gouty subject.

Similar differences were found in all of the patients with gout studied with the possible exception of patient C.E., in whom the results were equivocal. Figures 1 and 2 summarize the results in all ten nongouty subjects and the eleven patients with gout. In Figure 1 the urate/inulin clearance ratio is plotted against the plasma urate concentration. In Figure 2 this ratio is plotted as a function of the filtered urate load. These figures show that the urate/inulin clearance ratio was distinctly less in gouty subjects than in nongouty subjects when compared at equivalent plasma levels and filtered loads. In most patients this difference was evident at all levels and loads obtained, but was more pronounced at higher concentrations and loads. In gouty patients F.F. and N.T. the urate/inulin clearance ratio was indistinctly reduced at plasma concentrations below

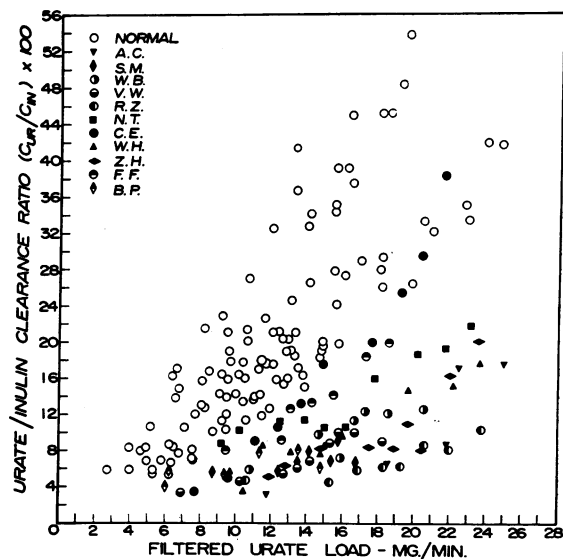


FIG. 2. THE RELATIONSHIP BETWEEN THE URATE/INULIN CLEARANCE RATIO ($C_{UR}/C_{IN} \times 100$) AND THE FILTERED URATE LOAD ($P_{UR} \times C_{IN}$). The symbols are the same as those used in Figure 1.

approximately 12 mg per 100 ml. At higher concentrations and at all filtered loads a distinct reduction in the clearance ratio was apparent. In gouty patient C.E. a reduced clearance ratio was evident at low plasma urate concentrations (below 10 mg per 100 ml) and loads, but at higher levels the clearance ratio was not significantly different from the values in nongouty subjects. In this subject, therefore, the evidence of impaired urate excretion was equivocal.

Reference to Tables I and II indicates that the reduction in uric acid clearance noted in Figures 1 and 2 was independent of the age of the patient, duration or severity of the disease, the level of 24-hour urinary uric acid excretion (high, patient W.B.; variable, others), the initial plasma uric acid concentration, and the glomerular filtration rate.

Equilibrium dialysis

In order to determine whether the reduced excretion of uric acid was the result of renal mechanisms or of plasma binding of urate, experiments employing equilibrium dialysis were performed with plasma from three (W.H., V.W., and R.Z.) of the gouty subjects studied. The results of one such experiment are shown in Table IV. In this experiment plasma obtained from patient R.Z. prior to and during the intravenous infusion of lithium urate (urate concentration, 7.3 and 14.4 mg per 100 ml., respectively) was placed in cellophane bags and dialyzed against normal (nongouty) plasma. Dextran served as a control. As a result of dialysis the concentration of urate in

TABLE IV
Effect of dialysis on plasma urate concentration *

Sample	Before dialysis	After dialysis
Inside bag		
Plasma, gout	7.3	3.7
Plasma, gout	14.4	3.9
Plasma, normal	3.1	3.8
Dextran, 6%	0.0	3.8
Outside bag		
Plasma, normal	3.1	3.8

* The plasma of the patient (R.Z.) with gout used in this experiment was obtained prior to and during the infusion of lithium urate (plasma urate concentration, 7.3 and 14.4 mg per 100 ml respectively).

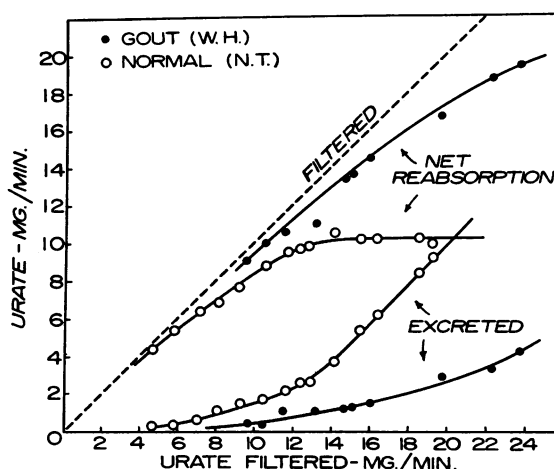


FIG. 3. TITRATION CURVES OF NET REABSORPTION AND EXCRETION OF URATE IN A NONGOUTY AND A GOUTY SUBJECT. The filtered load of urate is plotted along the abscissa and net reabsorption and excretion along the ordinate. Complete reabsorption is indicated by the dashed line. Data obtained in the gouty subject are represented by the shaded circles and those obtained in the nongouty subject by the open circles. Net reabsorption as used here is defined as the difference between the rates of filtration and excretion of urate.

the plasma of the gouty subject fell and was the same as that in all other components of the system: normal plasma in the bath (outside bag), normal plasma contained inside a cellophane bag, and 6 per cent dextran inside a bag. Similar results were obtained in other experiments with plasma from patients W.H. and V.W. These experiments indicate that reduced urate excretion in patients with gout cannot be explained by plasma binding. Impairment of excretion may therefore be attributed to renal mechanisms.

Tubular transport of uric acid

At all plasma levels and filtered loads obtained in gouty and nongouty subjects, the quantity of uric acid excreted was less than that filtered, indicating *net* tubular reabsorption of uric acid.²

Representative titration curves of net reabsorption and excretion of uric acid in a nongouty

² The fact that excretion was less than filtration does not indicate that reabsorption is the only tubular transfer operation involved. If tubular secretion of urate contributes significantly to the process of excretion (11), the differences between filtration and excretion describe only the predominant transfer operation (12), which in this instance was tubular reabsorption.

TABLE V
*Net renal tubular reabsorption of urate in nongouty subjects at highest plasma urate concentration attained during lithium urate infusion **

Subject	Highest plasma urate	Filtered load	Reabsorption		Apparent T_m	$\frac{\text{Load}\dagger}{T}$
	mg %		mg/min	mg/min		
N.T.	18.3	19.20	10.20	10.00	10.20	1.88
C.H.	16.7	18.20	12.84	11.80		1.42
W.S.	14.8	15.61	9.78	8.64	9.78	1.60
M.W.	17.2	24.75	14.39	9.92		1.72
D.B.	22.4	24.60	11.87	10.78	11.87	2.08
W.M.	18.0	24.00	14.30	10.78	14.30	1.68
W.W.M.	18.4	16.55	9.81	11.80		1.40
L.B.	17.3	19.90	14.61	12.71		1.36
J.P.	13.8	14.69	12.01	11.68		1.22
S.M.	15.3	16.10	11.83	11.83	11.83	1.36

* The values for reabsorption shown in those experiments in which an apparent T_m was demonstrable represent the mean of three or more periods during which net reabsorption was maximal and relatively constant.

† Mg of urate reabsorbed per 100 ml glomerular filtrate.

‡ Filtered load (mg/min)/net reabsorption (mg/min).

(N.T.) and gouty subject (W.H.) are shown in Figure 3. These curves were constructed from data presented in Table III. Three aspects of urate excretion and net reabsorption are illustrated in Figure 3. 1) At equivalent filtered loads, urate excretion was less and net reabsorption was greater in the gouty than in the nongouty subject. 2) With increasing filtered loads excretion increased less abruptly in the gouty subject, and hence the changes in net reabsorption were greater than in the nongouty subject. 3) Net reabsorption became constant in the nongouty subject at a maximal rate (T_m) of 10.2 mg per minute at filtered loads of 14 mg per minute and above; in the gouty subject, on the other hand, net reab-

sorption continued to increase and did not become constant with filtered loads as high as 23.8 mg per minute.

Data concerning net reabsorption for all 10 nongouty and 11 gouty subjects are summarized in Tables V and VI, respectively. In these tables net reabsorption has been calculated at the highest plasma urate concentrations and filtered loads reached during the infusion of lithium urate. An apparent T_m was assumed when net reabsorption remained relatively constant for three or more periods with increasing loads. Plasma concentrations and loads were comparable in nongouty and gouty subjects. In nongouty subjects the highest plasma urate concentration varied from 13.8 to

TABLE VI
Net renal tubular reabsorption of urate in patients with gout at highest plasma urate concentration attained during lithium urate infusion

Subject	Highest plasma urate	Filtered load	Reabsorption		Apparent T_m	$\frac{\text{Load}}{T}$
	mg %		mg/min	mg/min		
A.C.	19.2	25.00	20.60	13.75		1.21
S.M.	19.2	16.75	15.59	16.95		1.08
W.B.	23.8	20.60	18.00	19.35		1.14
V.W.	20.2	18.30	15.60	17.15		1.17
R.Z.	16.5	23.75	21.28	14.90		1.11
N.T.	20.5	23.15	18.09	16.00		1.28
C.E.	18.5	21.65	14.03	11.98	14.03	1.54
W.H.	18.3	23.65	19.47	15.10		1.21
Z.H.	18.7	23.55	18.80	14.90		1.25
F.F.	16.5	18.60	14.98	12.70		1.24
B.P.	14.8	17.57	16.54	13.90		1.06

22.4 mg per 100 ml; in gouty subjects the levels varied from 14.8 to 23.8 mg per 100 ml. Filtered loads varied from 14.69 to 24.75 mg per minute in nongouty subjects and from 17.57 to 25.00 mg per minute in gouty subjects. Net reabsorption, however, differed considerably in the two groups. In nongouty subjects net reabsorption varied between 9.78 and 14.61 mg per minute (8.64 and 12.71 mg per 100 ml glomerular filtrate). These values are somewhat lower than those reported by Berliner, Hilton, Yü, and Kennedy (13) in normal subjects. In gouty subjects net reabsorption was higher than in nongouty subjects, varying from 14.98 to 21.28 mg per minute or from 11.98 to 19.35 mg per 100 ml glomerular filtrate. Moreover, in five nongouty subjects an apparent maximal net reabsorptive rate (T_m) was demonstrated which varied from 9.78 to 14.30 mg per minute. In contrast, net reabsorption (T) became constant at a maximal rate (14.03 mg per minute) in only one (C.E.) of the patients with gout. Load/ T ratios exceeded 1.5 in all but one (S.M.) of the nongouty subjects in whom an apparent T_m was demonstrated, suggesting adequate saturation of reabsorptive capacity. The load/ T ratio in gouty subject C.E. was 1.54; in the remainder of the gouty subjects, load/ T ratios were below 1.3.

DISCUSSION

The results of the present study fully support the conclusions of Nugent and Tyler (6) that the renal excretion of uric acid is impaired in patients with primary gout. Under control conditions, in comparison of hyperuricemic gouty subjects with nongouty individuals whose plasma uric acid concentrations are normal, the impairment in uric acid excretion is not readily apparent. The reason for this is that both the excretion and plasma concentration of uric acid tend to be higher under these conditions in gouty subjects than in normal individuals, and hence the renal clearance of urate is approximately the same in the two groups.

Comparison in this way does not, however, take into account the fact that urate excretion and clearance are influenced by the plasma urate concentration, i.e., as the plasma level increases both excretion and clearance also rise. Thus, under control conditions, a higher renal clearance of

urate would be expected in hyperuricemic gouty subjects than in nongouty individuals with normal plasma levels, if there were no disturbance in renal excretory mechanisms. That this difference is not found therefore suggests that renal mechanisms are, in fact, altered in patients with gout.

The demonstration of an alteration in excretory mechanisms becomes conclusive when gouty and nongouty subjects are studied at equivalent plasma urate concentrations. Under such circumstances, when plasma urate levels are increased by the oral administration of ribonucleic acid (6) or by the administration of urate intravenously, as was done in the present study, a distinct impairment of urate excretion and clearance is apparent in individuals with gout.

The demonstration of impaired excretion in all eleven patients in the present study, with the possible exception of subject C.E., suggests that altered excretory function is a characteristic feature of the disease. Impaired excretion was evident in individuals who varied with respect to age, sex, duration and severity of the disease, the initial plasma urate concentration, and the quantity of uric acid excreted in the urine. The fact that impaired excretory function was evident in individuals who excreted both high and normal amounts of urate in the urine under control conditions (Tables I and II) serves to emphasize the widespread occurrence of the excretory disturbance in gout.

By demonstrating an equal distribution of urate between gouty and normal plasma during *in vitro* dialysis, an alteration in renal mechanisms rather than plasma binding was established as the mechanism of impaired urate excretion in patients with gout. The factors responsible for this alteration in renal function are, however, not known. Two mechanisms may be considered: augmented tubular reabsorption of urate, or decreased tubular secretion.

If we assume a filtration-reabsorption hypothesis as the mechanism of uric acid excretion (13), the results presented in Tables V and VI and Figure 3 may be interpreted as indicating that both the rate and capacity of tubular reabsorption of urate are augmented in patients with gout. If, on the other hand, urate excretion is conceived of as occurring by a process of tubular secretion (11),

the results of the present study can be explained on the basis of impaired secretory activity. The end result in either instance is the same, a reduction in urate excretion. With the present state of uncertainty concerning the precise mechanisms of urate excretion, there is no way to distinguish between these two possible functional alterations. Although it may be somewhat more comfortable to assume that disease acts by depressing rather than by augmenting function, it would be unwarranted on this ground alone to conclude that the functional alteration in gout involves an impairment of tubular secretion. There are precedents for augmented function in other diseases, and increased reabsorption of urate might develop in gout in a variety of ways. An adaptive response to chronic hyperuricemia, a genetically determined or acquired metabolic alteration in tubular transport activity, or a renal effect of some chemical or hormonal substance may be and have been mentioned (6) as possibilities. Such factors, with the possible exception of adaptation, might also be invoked to account for impairment of tubular secretion, if this can be shown to be the functional disturbance involved. At present, however, the respective roles of reabsorption and secretion are not sufficiently delineated to permit a definitive conclusion concerning the nature of the renal functional alteration in gout.

Despite this impairment of excretory function, a continuously positive balance between urate production and excretion is not necessarily required in patients with gout. As in normal individuals, the renal excretion of urate may be of sufficient magnitude to approximate net urate production—actual production minus extrarenal excretion and degradation (2, 14)—but to the extent that this occurs in patients with gout, it is accomplished by virtue of an elevated plasma urate concentration. In this respect an analogy may be made with urea excretion and equilibrium in individuals with azotemia due to renal failure (10). These considerations do not, however, establish a primary role for renal factors in the pathogenesis of hyperuricemia in gout. Although impaired excretion may play such a role, this remains to be established. Altered kidney function clearly serves, however, to maintain and contribute to the elevated plasma uric acid levels characteristic of this disease.

SUMMARY

The renal excretion and clearance of uric acid were determined in 10 nongouty subjects and 11 patients with primary gout before and during an intravenous infusion of lithium urate. Under control conditions prior to the infusion, the mean rate of uric acid excretion was somewhat greater and the mean urate/inulin clearance ratio was somewhat less in gouty than in nongouty subjects, but the renal clearance of urate did not differ significantly in the two groups. Under conditions of intravenous urate loading, however, an impairment in uric acid excretion was clearly evident in patients with gout. At equivalent plasma levels and filtered loads, the excretion and clearance of urate and the urate/inulin clearance ratio were significantly less in all of the patients with gout, with one possible exception, than in nongouty control subjects. The demonstration of this functional alteration with such regularity suggested that impaired urate excretion is a characteristic feature of primary gout.

In both gouty and nongouty subjects, the differences between the rates of filtration and excretion of urate during intravenous loading were indicative of net tubular reabsorption of this substance. However, net reabsorption was greater in patients with gout than in nongouty subjects at equivalent filtered loads, and with one exception, was not maximally limited with increasing loads. In contrast, a maximal net reabsorptive rate was demonstrated in five of the nongouty subjects studied.

On the basis of *in vitro* studies of urate diffusion, plasma binding was excluded as a cause of reduced urate excretion in patients with gout. Impairment of excretion was therefore attributed to an alteration in renal mechanisms. Whether this alteration involved augmented tubular reabsorption of urate or impairment of tubular secretion was not established.

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REFERENCES

1. Lathem, W., and Rodnan, G. P. Uric acid excretion in gout: evidence of an abnormality in renal

- transport (abstract). *J. clin. Invest.* 1961, **40**, 1056.
2. Gutman, A. B., and Yü, T. F. Renal function in gout with a commentary on the renal regulation of urate excretion, and the role of the kidney in the pathogenesis of gout. *Amer. J. Med.* 1957, **23**, 600.
 3. Wyngaarden, J. B. Gout *in* The Metabolic Basis of Inherited Disease, J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson, Eds. New York, McGraw-Hill, 1960, p. 679.
 4. Coombs, F. S., Pecora, L. J., Thorogood, E., Conso-lazio, W. V., and Talbott, J. H. Renal function in patients with gout. *J. clin. Invest.* 1940, **19**, 525.
 5. Talbott, J. H. Gout. New York, Oxford University Press, 1943.
 6. Nugent, C. A., and Tyler, F. H. The renal excretion of uric acid in patients with gout and in nongouty subjects. *J. clin. Invest.* 1959, **38**, 1890.
 7. Liddle, L., Seegmiller, J. E., and Laster, L. The enzymatic spectrophotometric method for determination of uric acid. *J. Lab. clin. Med.* 1959, **54**, 903.
 8. Harrison, H. E. A modification of the diphenylamine method for determination of inulin. *Proc. Soc. exp. Biol. (N. Y.)* 1942, **49**, 111.
 9. Davies, D. F., and Shock, N. W. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J. clin. Invest.* 1950, **29**, 496.
 10. Smith, H. W. The Kidney: Structure and Function in Health and Disease. New York, Oxford University Press, 1951.
 11. Gutman, A. B., Yü, T. F., and Berger, L. Tubular secretion of urate in man. *J. clin. Invest.* 1959, **38**, 1778.
 12. Weiner, I. M., Garlid, K. D., Romeo, J. A., and Mudge, G. H. Effects of tubular secretion and reabsorption on titration curves of tubular transport. *Amer. J. Physiol.* 1961, **200**, 393.
 13. Berliner, R. W., Hilton, J. G., Yü, T. F., and Kennedy, T. J., Jr. The renal mechanism for urate excretion in man. *J. clin. Invest.* 1950, **29**, 396.
 14. Sorensen, L. B. Degradation of uric acid in man. *Metabolism* 1959, **8**, 687.

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