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THE RENAL EXCRETION OF URIC ACID IN GOUT

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The hyperuricemia of gout of necessity results from either an excessive production of uric acid or a diminished elimination of uric acid either by the kidney or by means of uricolysis. Behind the controversy of the past century as to which of these explanations is true has been the implicit assumption that only one of them could be correct and that all gouty subjects must carry the same basic metabolic defect if we could but detect it.

In a previous study the production of uric acid by 16 gouty patients was evaluated by determining both the extent to which isotopically labeled glycine was incorporated into urinary uric acid and the urate turnover as revealed by the simultaneous injection of uric acid labeled with a different isotope (1). The latter measurement also permitted a correction to be made for the extrarenal disposal of uric acid, as shown by the fraction of injected isotopically labeled uric acid that failed to be recovered in the urinary uric acid. Excessive uric acid production was found in a substantial number of the gouty patients studied, in some of whom all parameters of urate synthesis were elevated several-fold above normal. Five gouty patients were found, however, in whom the glycine incorporation values were in the same range as that found in nongouty control subjects even when corrections were made for the extrarenal disposal of uric acid. The normal urate turnover values of this group of patients provided an independent confirmation of a normal uric acid production. In addition, there was no evidence of a diminished uricolysis to account for the hyperuricemia of this group of patients. We were therefore left with the view, by exclusion, that a specific impairment in the renal excretion of uric acid must be responsible for the hyperuricemia of this group of gouty patients.

In the past, repeated attempts to demonstrate a characteristic difference in the renal handling of uric acid between groups of normal and gouty patients have been unsuccessful (2). Although a lack of specificity and precision of the colorimetric procedure for determining uric acid seriously hampered earlier studies (3), more recent studies with a more specific method have also failed to show significant differences in the urate/inulin clearance ratios between normal and gouty subjects (4). Only in a recent study, when normal subjects were given a diet high in purines in order to raise their serum urate to levels comparable with those of gouty subjects, were all of the six gouty subjects found to have urate/inulin clearance ratios significantly lower than those of normal subjects (5).

The present investigation was undertaken in an effort to confirm the postulated decrease in the renal excretion of uric acid in the group of five gouty patients in whom other causes of hyperuricemia had been excluded. In addition, we wished to evaluate the extent to which a diminished renal excretion of uric acid might be contributing to the hyperuricemia of the group of gouty patients in whom an adequate cause for hyperuricemia—i.e., excessive production of uric acid—had already been demonstrated.

METHODS

Control subjects consisted of six normal male volunteers, aged 18 to 22, who gave no family or personal history of gout or arthritis, and one 51 year old male with palindromic rheumatism of 3 years' duration. All of the gouty subjects were male patients in whom, with three exceptions, the extent of uric acid production had been evaluated in previous studies (1) by the incorporation of isotopically labeled glycine into uric acid as well as by the turnover rate of isotopically labeled uric acid. The classification of the three patients, R.J., T.J., and C.P., as excessive producers of uric acid was based on their excretion of large amounts of it in their daily urine (see Table II) in the absence of uricosuric agents and while consuming a standard purine-free diet.

All subjects were hospitalized during studies. Since the fat content of the diet is known to affect the renal clearance of uric acid (6), all patients consumed a standard 2,600 calorie diet essentially free of purines, containing 70 g protein, 350 g carbohydrate, and 100 g fat

for 1 to 5 days before the renal clearance studies were done.

A high purine diet was provided for the nongouty control subjects by adding 4 g of ribose nucleic acid per day in four divided doses to the above diet. Breakfast was postponed until completion of the studies. All patients had received no uricosuric drugs for at least 5 days prior to the study. Those patients receiving daily colchicine as prophylaxis against acute gouty arthritis continued to receive it except for the morning of the study when no medications whatever were given.

Renal clearance studies were performed in the conventional manner (3) after water loading to permit urine collections without catheterization; 0.3 per cent inulin in 5 per cent dextrose was infused at a rate of 5.5 ml per minute with a Bowman pump after a priming dose of inulin of 26 mg per kg, which was calculated to give plasma inulin levels of around 13 mg per 100 ml. After a 1-hour period of equilibration with two voidings at half-hour intervals, three clearance periods of one-half hour each were obtained. Heparinized blood samples were collected at the midpoint of each period. The inulin content of plasma and urine was determined by the method of Walser, Davidson and Orloff (7) and the uric acid content by the enzymatic spectrophotometric procedure (8). All clearances were corrected to a standard body surface of 1.73 m² (3).

RESULTS

In response to the RNA supplement in the diet, most of the nongouty control subjects more than doubled their daily production of uric acid in the urine and substantially increased their serum urate levels (Table I). The mean C_{urate}/C_{inulin} ratios of the control subjects were increased from 0.070 to 0.096 in response to the increased uric acid production.

In Table II the C_{urate}/C_{inulin} ratios of the gouty patients are grouped according to the degree of uric acid production that was manifest. The group having excessive urate production was separated from those with more modest degrees of overproduction quite arbitrarily by reason of a corrected cumulative glycine incorporation of over 0.38 per cent of the administered dose in a 7-day period (1) or a daily production of uric acid in the urine in excess of 700 mg per day under standard conditions.

The mean C_{urate}/C_{inulin} ratio in the five gouty subjects who produced normal amounts of uric acid was 0.055 ± 0.009, substantially lower than the values of 0.096 found for nongouty control subjects after production of hyperuricemia. Among the gouty patients who showed a moderate over-

TABLE I

Renal clearance of inulin and urate in nongouty subjects before and after RNA load *

Subject	Urinary uric acid		Mean plasma uric acid		Urine flow rate		$C_{uric\ acid}$		C_{inulin}		Filtered uric acid		Urine uric acid UV		Uric acid reabsorbed		$\frac{C_{uric\ acid}}{C_{inulin}}$	
	C	RNA	C	RNA	C	RNA	C	RNA	C	RNA	C	RNA	C	RNA	C	RNA	C	RNA
	mg/24 hr		*mg/100 ml*		*ml/min*		*ml/min*		*ml/min*		*mg/min*		*mg/min*		*mg/min*			
R.H.	496	1,072	4.8	9.1	9.14	4.95	6.4	7.4	116	104	5.51	9.46	0.30	0.68	5.21	8.78	0.055	0.071
P.D.		857	4.9	7.5	12.31	13.66	6.4	6.8	109	97	5.34	7.28	0.32	0.52	5.02	6.76	0.059	0.070
M.G.	545	1,203	5.1	8.6	11.18	12.59	9.7	14.9	130	137	6.63	11.78	0.49	1.27	6.14	10.51	0.074	0.109
D.H.	445	809	4.7	9.0	9.73	12.59	7.6	12.2	121	122	5.70	10.98	0.36	1.10	5.34	9.88	0.063	0.100
D.S.	505	1,154	4.2	7.5	11.57	11.26	9.6	14.8	99	117	4.15	8.76	0.40	1.10	3.75	7.66	0.097	0.126
F.F.	447	980	4.5	9.2	16.16	12.20	10.0	12.0	155	135	6.94	12.42	0.45	1.11	6.49	11.31	0.065	0.089
F.C.	376	840	4.1	6.4	12.18	14.85	8.9	12.4	115	115	4.72	7.36	0.36	0.79	4.36	6.57	0.077	0.108
Mean																	0.070	0.096
±SD																	±0.016	±0.021

* Each clearance represents the mean of three clearance periods. All clearances are corrected to a standard body surface of 1.73 m².

TABLE II

Renal clearance of inulin and urate in gouty subjects *

Subject	Urinary uric acid	Mean plasma uric acid	Urine flow rate	$C_{uric\ acid}$	C_{inulin}	Filtered uric acid	Urine uric acid UV	Uric acid reabsorbed	$\frac{C_{urate}}{C_{inulin}}$
	mg/24 hr	*mg/100 ml*	*ml/min*	*ml/min*	*ml/min*	*mg/min*	*mg/min*	*mg/min*	
Gout with uric acid production in normal range									
R.L.	321	6.0	5.41	3.3	61	3.68	0.20	3.48	0.054
M.C.	455	7.1	8.06	6.1	111	7.88	0.43	7.45	0.055
R.McJ.	513	8.1	8.55	4.3	96	7.80	0.35	7.45	0.045
O.N.	334	6.7	6.08	5.8	86	5.76	0.39	5.37	0.067
E.H.	525	7.3	6.58	3.7	69	5.04	0.27	4.77	0.054
Mean									0.055
± SD									±0.009
Moderate overproduction of uric acid									
M.W.	470	7.8	6.02	6.4	92	7.22	0.50	6.72	0.070
J.McG.	634	8.8	10.12	4.5	76	6.70	0.40	6.30	0.059
W.O.	624	7.0	8.85	7.4	96	6.72	0.52	6.20	0.077
G.P.	587	7.2	6.38	5.5	80	5.78	0.39	5.39	0.069
R.W.	438	6.2	9.03	4.2	129	8.00	0.26	7.74	0.033
Mean									0.062
± SD									±0.017
Excessive production of uric acid									
C.P.	756	7.0	8.36	10.5	83	5.81	0.74	5.07	0.127
R.J.	1,131	11.3	7.02	6.9	88	9.94	0.78	9.16	0.078
T.J.	1,178	8.4	6.25	12.5	119	10.04	1.06	8.98	0.105
T.J.[repeat]		8.7	12.48	12.0	111	9.68	1.05	8.63	0.108
F.J.	1,186	11.2	10.66	8.6	92	10.34	0.97	9.37	0.093
G.S.	529	9.8	7.12	3.6	85	8.33	0.35	7.98	0.042
T.B.	1,112	8.8	6.63	9.5	125	10.99	0.83	10.16	0.076
Mean									0.087
± SD									±0.027

* See footnote to Table I.

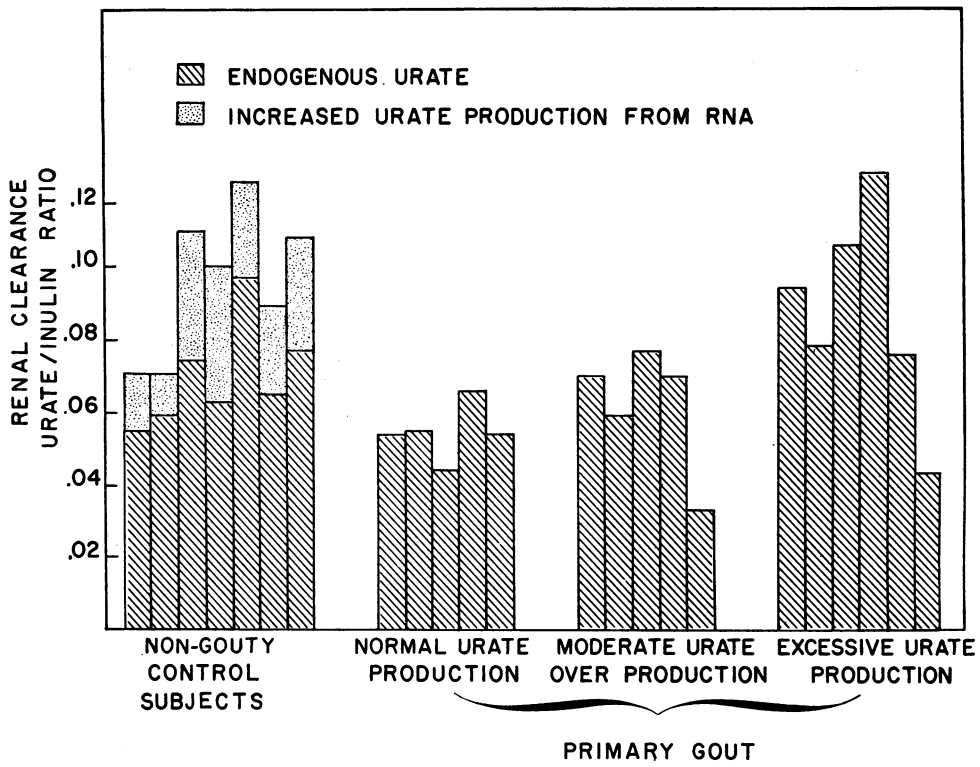

FIG. 1. URATE/INULIN CLEARANCE RATIO IN NONGOUTY CONTROL SUBJECTS BEFORE AND AFTER RNA, AND IN GOUTY SUBJECTS.

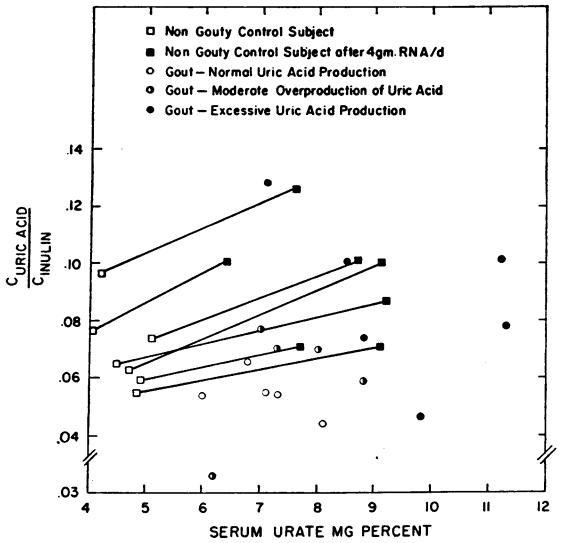

FIG. 2. THE URATE/INULIN CLEARANCE RATIO OF GOUTY AND NONGOUTY SUBJECTS IN RELATION TO THE SERUM URATE LEVELS.

production of uric acid, the mean C_{urate}/C_{inulin} ratio of 0.062 ± 0.017 is also substantially less than that found in normal subjects who were made hyperuricemic. By contrast, the gouty subjects who produced excessive amounts of uric acid (mean C_{urate}/C_{inulin} ratio of 0.087 ± 0.027) included a substantial number in whom the ratio was indistinguishable from that of nongouty subjects in whom a comparable excessive production of uric acid had been produced by RNA ingestion. A graphic comparison of the groups is presented in Figure 1, and the relationship of C_{urate}/C_{inulin} ratio to filtered urate load is revealed in Figure 2.

DISCUSSION

Gouty patients appear to be a heterogeneous group not only in regard to the extent of their uric acid production (1, 9) but also in their ability to excrete uric acid. These two factors tend to operate in a complementary fashion. In general, the group of patients who produced excessive amounts of uric acid showed a renal handling of filtered urate comparable with that of normal subjects given a similar filtered load. At the other extreme were the gouty patients with a normal uric acid production who exhibited an impairment of renal excretion of urate to account for their hyperuricemia. These findings differ from those of Nugent and Tyler (5) in showing that a substantial number of gouty patients, particularly among those who overproduce uric acid, have C_{urate}/C_{inulin} ratios indistinguishable from those of normal control subjects (see Figure 2). All six of the gouty patients studied by Nugent and Tyler showed a diminished renal handling of uric acid even in some patients who produced excessive amounts of uric acid in the daily urine. We also have examples of patients (G.S. and R.W.) in whom both a renal retention of uric acid and an overproduction of uric acid are present. The etiological relationship, if any, of these two processes is not clear at the present time.

The efficiency by which uric acid is removed from the body by the kidney is reflected in the uric acid clearance values ($C_{uric\ acid}$) in Tables I and II. In general, the values for the gouty patients are lower than those for control subjects, which is a result, in part, of the somewhat lower glomerular filtration rate found among the gouty subjects. The ratio value obtained for the C_{urate}/C_{inulin} obviously corrects for differences in inulin clearance and reflects the ability of the kidney to excrete the load of uric acid that is filtered at the glomerulus.

The possibility that metabolic defects quite unrelated to purine metabolism might be responsible for the renal retention of uric acid in some patients is suggested by the hyperuricemia accompanying the glycogen storage disease characterized by a glucose-6-phosphatase defect (10). Indeed, clinical gouty arthritis has been reported in a child exhibiting such a metabolic defect (11). On the other hand, clinical gouty arthritis is not an inevitable consequence of elevated serum urate levels. Among 261 hyperuricemic relatives of gouty patients studied recently (12) only 15 per cent had clinical gout. Furthermore, the hyperuricemia resulting from chronic renal disease is only rarely associated with clinical gout. Such observations lend further support to the view that hyperuricemia is a necessary, but not a sufficient, condition for the development of acute gouty arthritis.

SUMMARY

Urate/inulin clearance ratios have been determined in 7 nongouty males before and after pro-

duction of an increased urate load and in 16 gouty patients who were classified by the extent of their uric acid production. In all 5 gouty subjects who showed a normal production of uric acid there was a diminished urate/inulin clearance ratio. Among the patients who produced excessive amounts of uric acid there were individuals in whom the urate/inulin clearance ratios were identical with those of normal control subjects in whom an excessive uric acid production was induced by dietary means. Other gouty patients were found in whom some degree of both overproduction and diminished renal excretion coexisted.

The heterogeneous causes for hyperuricemia among gouty patients suggest a corresponding variety of basic metabolic defects to account for these manifestations.

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REFERENCES

1. Seegmiller, J. E., Grayzel, A. I., Laster, L., and Liddle, L. Uric acid production in gout. J. clin. Invest. 1961, **40**, 1304.
2. Coombs, F. S., Pecora, L. J., Thorogood, E., Consolazio, W. V., and Talbott, J. H. Renal function in patients with gout. J. clin. Invest. 1940, **19**, 525.
3. Smith, H. W. The Kidney, Structure and Function in Health and Disease. New York, Oxford Univ. Press, 1951.
4. 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.
5. 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.
6. McCarthy, D. D., and Ogryzlo, M. A. Effect of fasting on uric acid excretion by the kidney (abstract). Arth. Rheum. 1960, **3**, 280.
7. Walser, M., Davidson, D. G., and Orloff, J. The renal clearance of alkali-stable inulin. J. clin. Invest. 1955, **34**, 1520.
8. Liddle, L., Seegmiller, J. E., and Laster, L. The enzymatic spectrophotometric method for determination of uric acid. J. Lab clin. Med. 1959, **54**, 903.
9. Wyngaarden, J. B. On the dual etiology of hyperuricemia in primary gout. Arth. Rheum. 1960, **3**, 414.
10. Howell, R. R., Ashton, D., and Wyngaarden, J. B. Glucose-6-phosphatase deficiency glycogen storage disease. Pediatrics 1962, **29**, 553.
11. Jeune, M., Charrat, A., and Bertrand, J. Polycorie hépatique, hyperuricémie et goutte. Arch. franç. Pédiat. 1957, **14**, 897.
12. Hauge, M., and Harvald, B. Heredity in gout and hyperuricemia. Acta med. scand. 1955, **152**, 247.