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RENAL REGULATION OF URIC ACID EXCRETION IN NORMAL AND GOUTY MAN: MODIFICATION BY URICOSURIC AGENTS*

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THERE has been a recent resurgence of interest in the mechanisms of renal regulation of uric acid excretion in man, and the effects thereon of drugs, notably of uricosuric agents. The present study is an attempt to summarize the salient points brought out by investigations in this area during the past several years.

Current concepts of the renal regulation of uric acid excretion in normal man. The prevailing view[1], briefly stated, is that in normal

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man the plasma urate is wholly filtrable at the glomerulus[2]; the filtered urate is reabsorbed (presumably in the proximal convolution) to the extent of 90-95 per cent of the load presented to the tubules; and the urate excreted in the urine represents that 5-10 per cent of the filtered load which has escaped reabsorption. In quantitative terms, at a glomerular filtration rate of 120 ml/min., with a mean plasma urate of 5.6 per cent for normal adult males, and assuming complete filtrability of the plasma urate at the glomerulus, urate would be delivered to the glomerular filtrate at a rate of 6.7 mg./min. In normal adult males, UV_{urate} approximates a mean of 0.5 mg./min. There is, then, a mean deficit of 6.2 mg./min. or 92.5 per cent of the filtered urate, which is attributed to tubular reabsorption.

The work of Berliner and associates[3] indicates that reabsorption of urate in the tubules is an "active", presumably enzymatic, process of limited capacity, with a Tm of the order of 15 mg. urate/min. The nature of this transport mechanism has not been further defined. Nor has the nature of the proximate mechanism regulating renal excretion of urate been clarified, since, for reasons that are quite obscure, urate is excreted in the urine at filtered urate loads far below the tubular capacity for reabsorption of urate.

Current concepts of the renal regulation of uric acid excretion in gouty man. So far as has been determined, the plasma urate in the hyperuricemia of gout also is completely filtrable[2] and the renal regulation of uric acid excretion in gouty subjects does not differ in any essential from that of normal man. The quantitative relationships, however, are different, as indicated by the results of clearance studies, using standard techniques, made in 150 gouty subjects[4].

In gouty subjects, the glomerular filtration rate, as measured by the inulin clearance, usually is below the commonly accepted mean normal figure for men of 125 ml/min/1.73 sq. m. body surface[1, 4]. When compared with non-gouty subjects of equivalent age[5], however, the differences in distribution are not statistically significant[4]. The decline in filtration rate would thus appear to be ascribable for the most part not to gout per se but to vascular changes related to aging. Our data[4] do indicate a statistically significant reduction in renal plasma flow, as measured by the clearance of para-aminohippurate, when compared with non-gouty subjects of comparable age[5].

Since the filtration rate is relatively well maintained in relation to

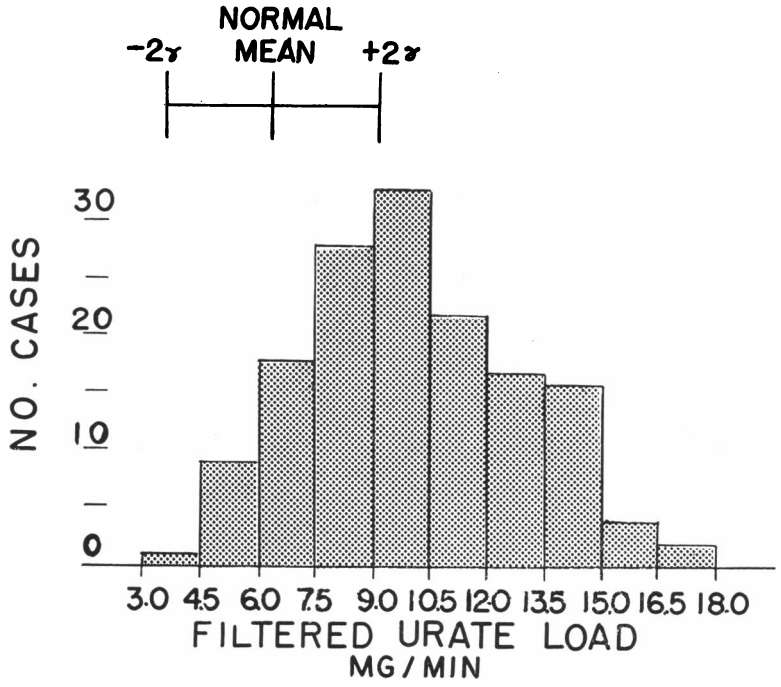

Fig. 1.—Distribution of filtered urate loads (C_{inulin} x P_{urate}) in 150 gouty subjects. The normal mean ± 2 sigmas is indicated.

age in most patients with gout, and the plasma urate is distinctly elevated (mean, 9.0 ± 1.4 mg. per cent in the 150 patients in question), it follows that the filtered urate load, calculated as the product of these two quantities, should be abnormally large. Figure 1, showing the distribution of the estimated filtered urate loads in 150 gouty subjects, fulfills this expectation. The mean was found to be 10.1 mg./min., about 50 per cent above the normal mean; and in some cases the filtered urate was more than twice the normal mean. For reasons indicated elsewhere[4], this increase is taken to be a reflection of over-production of uric acid in the gouty subjects in question.

The increase in filtered urate load occurring in most gouty subjects has interesting consequences in relation to the magnitude of the urate reabsorbed by the tubules, as calculated by the difference between the filtered and excreted urate. These alterations are best understood in the light of experiments by Berliner and associates[3], in which the filtered urate load in normal man was artificially increased by sustained

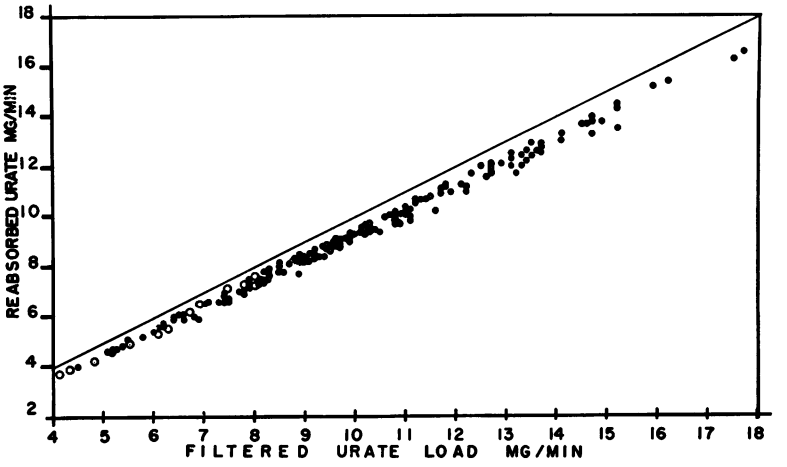

Fig. 2.—Relation of reabsorbed urate, mg/min., to filtered urate load in 12 non-gouty subjects (open circles) and 150 gouty patients (heavy circles). The diagonal line represents 100 per cent tubular reabsorption. Reabsorbed urate was calculated as the differences between filtered urate and UVurate, assuming no tubular excretion of urate. From Gutman and Yü, in the American Journal of Medicine 23:600-22, Oct. 1957. (Reprinted by permission.)

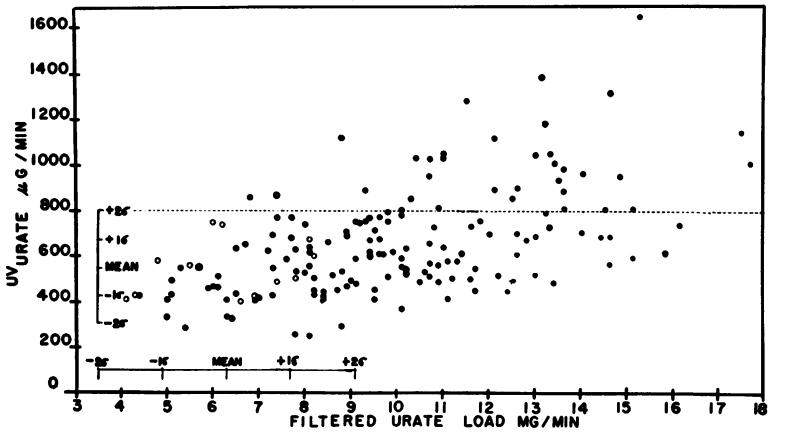

Fig. 3.—Relation of UV_{urate} to filtered urate load in 12 non-gouty subjects (open circles) and 150 gouty patients (solid dots). The normal means ± 2 sigmas are indicated. The broken line at 800 μg/min. indicates the normal mean UV_{urate} +2 standard deviations of distribution. From Gutman and Yü, in the American Journal of Medicine 23:600-22, Oct. 1957. (Reprinted by permission.)

TABLE I.—RELATION OF C_{INULIN} TO UV_{URATE} IN 150 GOUTY SUBJECTS

		UV*urate* (*μg/min.*)								
Cinulin* (ml/min.)	No. Cases	245— 349	350— 499	500— 649	650— 799	800— 949	950— 1099	1100— 1249	1250— 1399	1400— 1657
50- 69	5		3	2						
70- 89	31	5	8	10	7			1		
90-109	32	2	8	8	8	1	4		1	
110-129	41		10	14	7	4	2	1	2	1
130-149	27		1	6	10	4	5	1		
150-179	14		1	5	4	2	1	1		
Total	150	7	31	45	36	11	12	4	3	1

* Not corrected to standard body surface area.

intravenous injection of uric acid. Under these circumstances the quantity of urate reabsorbed by the tubules steadily increased until the tubular capacity for urate reabsorption was saturated. This phenomenon is observed also in gouty subjects[4], the magnitude of reabsorbed urate increasing with the filtered urate load without, however, reaching a manifest Tm in the cases studied (Fig. 2). It is of interest that no (statistically) significant difference between gouty and normal subjects was noted in the percentage of filtered urate which was reabsorbed. Our data fail to give any indication of an intrinsic tubular defect in the kidneys of gouty subjects—excessive tubular reabsorption of urate beyond that of a normal response to increased filtered urate loads—which can be construed to be the primary cause of the hyperuricemia of gout.

In contrast to the regular relationship of reabsorbed urate to the filtered urate load, the quantity of urate excreted in the urine of gouty subjects is quite independent of the rate at which urate is filtered at the glomerulus (Fig. 3). The data indicate that an abnormally high UV_{urate} occurs much more frequently in association with abnormally large filtered urate loads but this seems to be a function of the elevation in plasma urate level rather than of the rate of glomerular filtration. In patients with well preserved filtration rates (C_{inulin} greater than 100 ml./min.) UV_{urate} unpredictably may be excessive, within the normal range, or occasionally less than the normal (Table I).

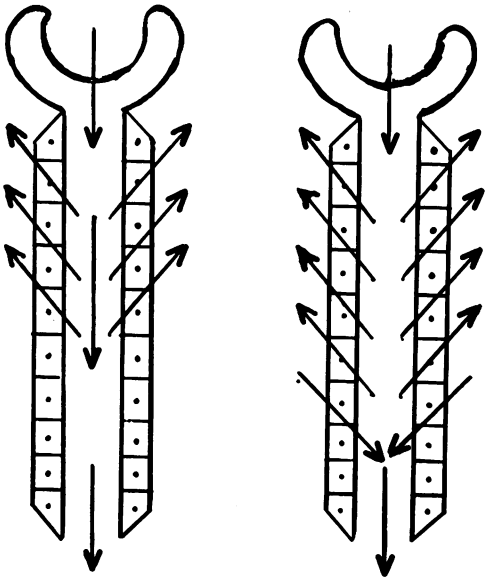

Fig. 4.—Schematic representation of two postulations of renal regulation of uric acid excretion in man. On the left, the plasma urate is pictured as virtually wholly filtrable at the glomerulus, the filtered urate is largely but not completely reabsorbed in passage through the tubules, and the excreted 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 excreted by the tubules.

The question of tubular excretion of urate in man. This striking dissociation of the rate of urinary urate excretion from the other parameters of renal function, over the wide range of variation observed in patients with gout and/or intrinsic renal disease, was apparent to Garrod[6] and many subsequent investigators. An independent mechanism for renal excretion of urate in man, a tubular excretory system, has been proposed at various times. At first this was postulated on the general grounds of the Heidenhain theory of tubular excretion; Brøchner-Mortensen[7] has commented upon the insufficiency of evidence on this point. Later, when the disparity between the glomerular filtration rate and uric acid clearance in man became evident, it was postulated that the plasma urate was largely or wholly non-filtrable at the glomerulus[8-10] because of presumed protein-binding or occurrence as macromolecular uric acid polymers. These assumptions appear not to be tenable[2]. However, the available data seem to be consistent with an alternative hypo-

thesis[4], that the plasma urate is completely filtrable at the glomerulus, the filtered urate is wholly, or virtually wholly, reabsorbed by the tubules, and the urate excreted in the urine is derived, under ordinary circumstances, entirely or in very large part by tubular secretion (Fig. 4). (The renal regulation of urate excretion would thus be analogous, in principle to that of potassium; the postulation of tubular excretion of potassium has been supported by substantial evidence[11, 12].) Under certain circumstances, a substantial proportion of the excreted urate would include filtered urate which has escaped reabsorption; for example, when tubular reabsorption of urate is deficient because of inborn or acquired tubular defects or as a result of suppression by uricosuric drugs. This would occur also should the filtered urate loads exceed the capacity of the normal tubules fully to absorb them.

Tubular excretion of urate occurs in birds and reptiles (evidence reviewed by Smith[1]). In the mammalia, tubular excretion of urate has been demonstrated in the rabbit after infusion of uric acid[13] and in the Dalmatian coach hound[14] which has a genetically transmitted renal tubular defect in urate reabsorption. Tubular secretion of urate has been reported to occur in an apparently normal young man with defective tubular reabsorptive mechanisms of unknown nature[15].

Effect of drugs on tubular reabsorption (and tubular excretion?) of urate. It has been known for many years that salicylate in large dosage (5 gm.) is uricosuric whereas smaller doses of one or two grams cause retention of uric acid. A similar dual action has been noted with phenylbutazone and other uricosuric agents[16]. These paradoxical effects occur without any change in the filtration rate or filtrability of the plasma urate. It is conceivable that these drugs first enhance, then suppress one or more mechanisms for tubular reabsorption of urate; it is also possible, however, that in low dosage they inhibit tubular excretion of urate and in larger dosage also inhibit the tubular transport system responsible for reabsorption of urate. A similar multiple system explanation might be advanced for the puzzling fact that relatively small doses of salicylate can largely counteract the uricosuric properties of probenecid[17].

Pyrazinoic acid, as the free acid or amide, profoundly reduces the elimination of uric acid by the kidneys, to 5 or 10 per cent of the premedication figure, without lowering the inulin clearance[18]. Here again it is not known whether urate is retained because of suppressed tubular

excretion or enhanced tubular reabsorption; if the former, the degree of urate retention would make it necessary to postulate virtually complete tubular reabsorption of urate and tubular secretion of all or almost all the excreted urate. Administration of large doses of sodium lactate likewise results in striking urate retention, without decline in the inulin clearance[19]; the significance of this long known phenomenon also remains to be clarified.

The enhancement of urinary uric acid excretion produced by uricosuric drugs in appropriate dosage is attributable, it is generally agreed, to suppression of tubular reabsorption of urate. This has been shown for cinchophen[20], salicylate[21], probenecid[22], phenylbutazone[23] and the phenylbutazone analogs G-25671[24] and its sulfoxide metabolite, G-28315[25].

Application of uricosuric agents to the prevention and treatment of tophaceous deposits in gout. By protracted use of suitable uricosuric agents in gouty subjects it is possible to maintain the rate of urinary excretion of urate at levels greater than the rate of urate production (i.e., negative urate balance). By this device the urate of the extracellular fluid can be sustained at concentrations low enough to reverse the flow of urate into the tissues, with reduction of the body pool of urate, including solid deposits. Thus it was shown in 1951[26] that tophaceous deposits can be mobilized, and the further deposition of uric acid prevented. Since our report in 1951, 82 patients with tophaceous gout have been treated with uricosuric drugs—probenecid, G-25671, G-28315, salicylate—over periods from 6 months to 7 years[27, 28]. Once the uricosuric regimen was established, no new tophi appeared. Of the tophi present, in 36 cases (44 per cent) they disappeared completely or were markedly reduced in size; in 31 cases (38 per cent) the reduction was only moderate or slight; in 15 cases (18 per cent), for the most part under treatment for less than one year, there has been no apparent change in the size of the tophaceous deposits.

Chronic gouty arthritis, with impaired function of one or more joints, was present in 52 of these patients. In 37 cases (71 per cent) it was possible to achieve complete restoration of joint motion, in 12 (23 per cent) improvement was moderate to marked. Of 52 patients with chronic joint pain, 47 (90 per cent) were completely relieved, 3 (6 per cent) were somewhat improved.

In some cases failure was due to insufficient uricosuric response

because of impaired renal function, inadequate drug dosage (intolerance, renal colic) or immoderation in diet. In a few instances a satisfactory uricosuric response was obtained and some tophi disappeared but others proved to be refractory; evidently some tophaceous deposits (as it happens, the minority) are not accessible to humoral agents.

SUMMARY

According to the prevailing view, the plasma urate in normal and gouty man is virtually wholly filtrable at the glomerulus; some 90-95 per cent of the filtered urate is reabsorbed in the tubules; and the urate excreted in the urine represents that 5-10 per cent of the filtered urate load which has escaped tubular reabsorption.

An alternative possibility is suggested, that the completely filtrable urate is wholly or virtually wholly reabsorbed by the tubules, and that the urate excreted in the urine in normal and gouty man ordinarily is derived entirely or in large part by tubular secretion.

Clearance techniques fail to disclose any primary, intrinsic anomaly of the kidneys in gouty subjects. The major abnormality appears to be "pre-renal", since the filtered urate load is apt to be excessive. The consequent increase in tubular reabsorption of filtered urate does not appear to exceed the normal response to increased filtered urate loads.

If the tubular reabsorption of urate is inhibited by uricosuric drugs, the urinary excretion of uric acid is enhanced and a state of negative urate balance supervenes. The beneficial results of such therapy in patients with tophaceous gout are described.

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