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Renal handling of uric acid in normal and gouty subjects: evidence for a 4-component system

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SUMMARY Bidirectional renal urate transport was studied in both control and gouty subjects. 99·3% of filtered urate undergoes reabsorption as assessed by pyrazinamide suppression of urate secretion. The maximum uricosuric response to benzbromarone, equated with the minimum secretory rate, amounted to 50% of the filtered load in normal persons and was lower in gouty normoproducers. Since benzbromarone selectively inhibits reabsorption of secreted urate, the difference between secreted and excreted uric acid becomes a valid measure of urate reabsorption distal to the secretory site and amounts to 80% of the secreted load in both groups. These data conform to a 4-component model of renal urate handling in man.

In normal man about two-thirds of uric acid is excreted in the urine. Until quite recently the '3-component mechanism' proposed by Gutman and Yü (1961) has been widely accepted as a model for characterising the renal handling of urate. According to that formulation plasma urate is essentially completely filterable, at the glomerular membrane; virtually all the filtered urate is reabsorbed in the proximal tubule, and uric acid appearing in the final urine occurs almost entirely by a tubular secretory process.

Recently evidence has accumulated suggesting that the renal handing of uric acid is more complex than had been previously proposed. It has been postulated that a second reabsorptive site exists distal to the secretory site. Evidence for this comes in part from clinical studies of patients with Wilson's disease or Hodgkin's disease, who have increased renal clearance of uric acid. When these patients were given pyrazinamide (PZA), a drug known to suppress tubular secretion of uric acid, the urine became almost free of uric acid, indicating that their inappropriate renal clearance of urate did not result from a defect in proximal tubular reabsorption of filtered urate (Bennett *et al.*, 1972; Wilson and Goldstein, 1973). Furthermore, in pharmacological studies it has been observed that the response to uricosuric drugs is greatly diminished by pretreatment with PZA (Steele and Boner, 1973; Diamond and Paolina, 1973). These data could be interpreted to mean that uricosuria arising from either disease states or pharmacological manipulation is due to stimulation of tubular urate secretion or, alternatively and more likely, results from diminished reabsorption of secreted urate.

In this report we present data which conform to a 4-component system for renal handling of urate, namely: (1) plasma urate is completely filtered at the glomerulus; (2) filtered urate is subsequently reabsorbed, presumably in the proximal tubule; (3) tubular secretion of urate occurs further distally in quantities approximately 50% of the filtered load; and (4) reabsorption of about four-fifths of secreted urate occurs at a postsecretory site. In addition, by using pharmacological measures we are able to assess the site of inappropriate renal handling of urate in patients with primary gout who have abnormally low urinary uric acid secretion for their plasma urate values.

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Materials and methods

Binding of urate to plasma proteins was studied at different temperatures by equilibrium dialysis using dual-compartment Plexiglass cells with a capacity of 1 ml (Chemical Rubber Company, Cleveland, Ohio). Fresh heparinised plasma was separated from dialysate made up of Krebs-Ringer phosphate solution, pH 7·4, by a regenerated cellulose membrane (average pour diameter: 4·8). 3 μg of ^{14}C-uric acid (specific activity 0·15 mc/mmol) was added to either sample or diffusate side. In

some binding studies cold uric acid was added to the dialysate with the final uric acid concentration varying from 2·4 mg/dl (0·14 mmol/l) to 24 mg/dl (1·42 mmol/l). In studies using the highest concentration of uric acid Krebs-Ringer phosphate solution was replaced by 0·2 M Tris buffer, pH 7·4, in which urate remained soluble. After incubation for 12 hours aliquots were withdrawn from the sample and diffusate sides for assay of ^{14}C and enzymatic determination of urate.

The reabsorption of filtered urate was determined in 10 healthy subjects who had been given PZA to inhibit tubular secretion of uric acid. Urinary uric acid was determined in the 12 hour period between 3 and 15 hours after oral intake of 4 g of PZA. Reabsorbed uric acid was calculated as the difference between filtered and excreted uric acid.

Tubular secretory rate of urate was assessed in 8 healthy volunteers and in 12 patients with primary gout, all of whom had normal glomerular filtration rates. In the gouty group 3 patients were overproducers of uric acid, while 9 patients had normal production of urate but low urinary uric acid excretion relative to their plasma urate levels. Adequate diuresis was accomplished with tap water given at $\frac{1}{2}$-hour intervals. Urine specimens were obtained by voiding at hourly intervals.

After baseline values for plasma and urinary uric acid had been obtained 80 mg of micronised benzbromarone, a potent uricosuric drug, was given in a single oral dose (Sorensen and Levinson, 1976). Uric acid excretion was determined in each hourly fraction and expressed as μg/minute (μmol/min) divided by the creatinine clearance to correct for differences in nephron mass. Maximum uricosuria was usually obtained during the fourth hour after benzbromarone administration. Urate excretion during maximum uricosuria related to the mean plasma urate concentration for that collection period becomes a measure of minimum secretion at a particular plasma urate concentration. Uric acid determinations were performed by the enzymatic spectrophotometric method of Praetorius (1949), while creatinine in serum and urine was assayed on an SMA660 (Terrytown, NY) (Chasson, *et al.*, 1961). Medications were discontinued 14 days prior to all studies, which were conducted in the morning following an overnight fast. Informed consent was obtained from both normal volunteers and the gouty patients.

Results

FILTERED URATE LOAD

Plasma from 15 normal subjects and 20 patients with primary gout was evaluated for possible binding of urate to plasma proteins. The distribution of ^{14}C between plasma and dialysate is shown in Fig. 1. At 4°C about 15% of urate is bound to proteins, but as the temperature increases there is a marked reduction in binding of urate, such that at 37°C the mean concentration of ^{14}C in 22 plasma samples was 98·2% of the concentration in dialysate. Plasma from normal and gouty subjects had similar binding characteristics. A plot of the ratios of urate concentrations in plasma versus dialysate closely resembled the data for ^{14}C. All of the urate present in the 2 compartments of the cell at the onset of the dialysis study could be accounted for at the end of the incubation. Varying the concentration of uric acid in the dialysate from 2·4 mg/dl (0·14 mmol/l) to 24 mg/dl (1·42 mmol/l) did not alter the ratios of ^{14}C or urate between plasma and dialysate. The use of serum instead of plasma gave identical results.

The results of in-vitro protein binding studies at 37°C suggest that in-vivo binding of urate is likely to be nonexistent or of very low order and of no physiological consequence. To the extent that data obtained with semipermeable membranes in vitro can be extrapolated to the in-vivo situation in man, binding of urate to plasma proteins does not appear to be a factor affecting filtration of urate by the glomerulus. The filtered urate load can therefore be assessed from the plasma urate concentration and a measure of glomerular filtration rate such as the creatinine clearance. The mean filtered load for the 10 healthy subjects listed in Table 1 was 6·2 mg/minute (36·88 μmol/min) in the control period (not shown).

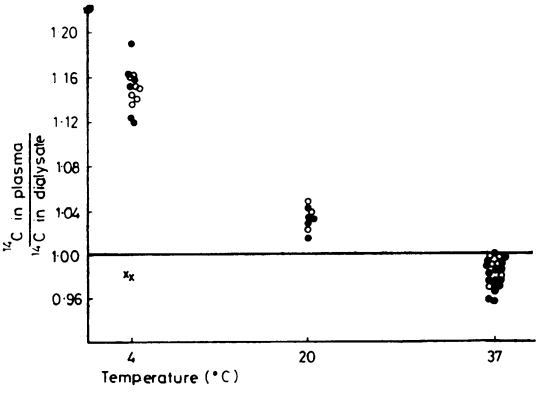

Fig. 1 *Effect of temperature on urate binding to plasma proteins. The concentration of uric acid in the dialysate ranged from 0·14 mmol/l to 1·48 mmol/l. Open circles, normal men; closed circles, gouty subjects; X indicates absence of binding of ^{14}C-labelled allantoin, the oxidation product of uric acid. No correction was made for Gibbs-Donnan effects.*

Table 1 *Tubular reabsorption of uric acid in 10 normal subjects following oral intake of 4 g pyrazinamide*

Sex	*Plasma urate at 9 h after PZA (mg/dl) (mmol/l)*	*Ccr (ml/min)*	*Uric acid filtered (μg/min) (μmol/min)*	*Uric acid excreted (μg/min) (μmol/min)*	*Reabsorption of filtered uric acid (per cent)*
M	6·97 (0·41)	121	8434 (50·16)	42 (0·25)	99·5
M	6·50 (0·38)	132	8580 (51·03)	76 (0·45)	99·1
M	6·28 (0·37)	116	7285 (43·33)	26 (0·15)	99·6
M	6·50 (0·38)	114	7410 (44·08)	48 (0·29)	99·4
M	5·48 (0·32)	80	4384 (26·08)	38 (0·23)	99·1
M	6·49 (0·38)	160	10 384 (61·77)	120 (0·71)	98·8
M	5·32 (0·31)	117	6224 (37·02)	67 (0·40)	98·9
M	6·50 (0·38)	129	8385 (49·88)	47 (0·28)	99·4
M	7·66 (0·45)	90	6894 (41·01)	25 (0·15)	99·6
F	3·90 (0·23)	100	3900 (23·20)	9 (0·05)	99·8
Mean	6·16 (0·36)	116	7188 (42·76)	50 (0·30)	99·3

TUBULAR REABSORPTION OF FILTERED URATE

The pronounced inhibition of tubular secretion caused by PZA is evident in Fig. 2. A single dose of 4 g is followed within a few hours by a striking reduction in excretion of uric acid, which lasts for almost 24 hours. Concomitantly plasma urate concentration rises. The difference between the quantities of filtered and excreted uric acid during maximum PZA suppression is a measure of the proportion of filtered urate that has been reabsorbed. Results of PZA studies in 10 healthy subjects are presented in Table 1. The mean excretion of uric acid in the 12-hour period from 3 to 15 hours after intake of 4 g of PZA was 50 μg/minute (0·30 μmol/min), representing less than 1% of the filtered load. Assuming complete suppression of tubular secretion of urate, a mean of 99·3% (range 98·8–99·8%) of the filtered load was reabsorbed. The tubular reabsorption may be even greater than determined from these studies, since tubular secretion of urate may not be completely inhibited by PZA.

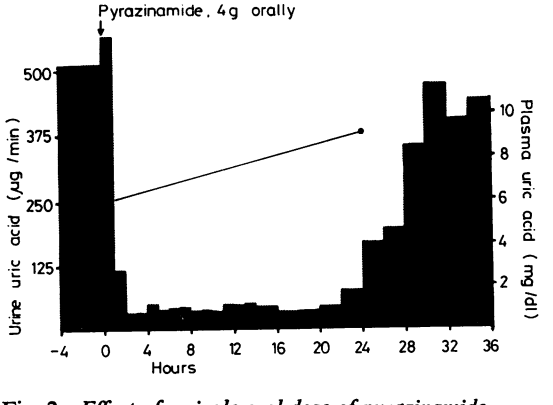

Fig. 2 *Effect of a single oral dose of pyrazinamide on renal urate excretion in a normal subject. SI conversion: plasma urate mmol/l = mg/dl × 0·0595.*

The capacity for reabsorption of filtered urate is evident from a study in which the filtered load was increased 4-fold by the administration of 16 g of RNA for several days (not shown). During the control period the filtered load of urate was 20 mg/minute (118·96 μmol/min). The fractional excretion of urate after PZA intake decreased to 0·5%; thus, a minimum of 99·5% of filtered urate had been reabsorbed.

The marked suppression of urinary uric acid after PZA administration implies that excreted uric acid is derived almost entirely, if not exclusively, from tubular secretion in normal man.

TUBULAR SECRETION OF URIC ACID

Reference has been made to a number of clinical and pharmacological observations that tubular secretion of urate greatly exceeds the quantity of uric acid that appears in the final urine, and furthermore that the difference between the two represents secreted urate that has been reabsorbed at a post-secretory site (Bennett *et al.*, 1972; Wilson and Goldstein, 1973). To clarify this relationship we first examined the effects of benzbromarone on uric acid excretion in individuals who had been pretreated with PZA to suppress tubular secretion of uric acid.

A representative study is shown in Fig. 3A. PZA causes a predictable fall in urinary urate excretion from a baseline value of 445 μg/minute (2·65 μmole/min) to a nadir of 31 μg/minute (0·18 μmol/min), equivalent to 0·5% of the filtered load. The typical uricosuric response which normally reaches a maximum 3 to 4 hours after oral intake of a single dose of 80 mg of benzbromarone (Fig. 3B) is completely abolished by pretreatment with PZA. At a time when the maximum uricosuric effect normally ensues, urinary uric acid was only 10% of the control excretion and plasma urate had increased paradoxically by 0·65 mg/dl (0·04 mmol/l), 3·4 hours after ingestion of benzbromarone. The results of 4 such studies in normal subjects are

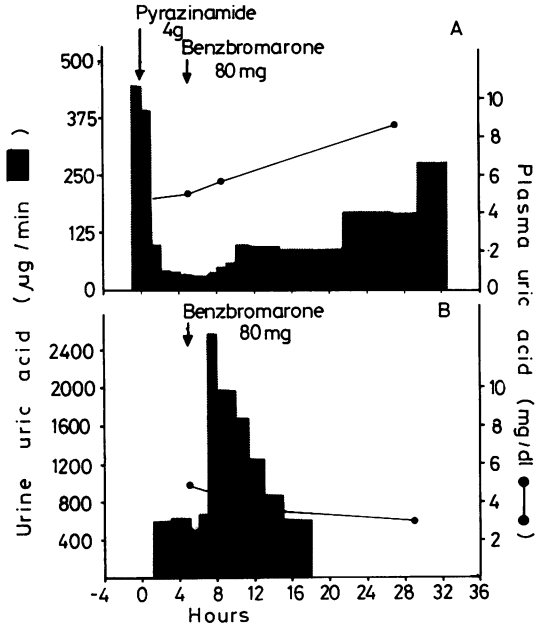

Fig. 3 A. *Inhibition of uricosuric response to benzbromarone by pretreatment with pyrazinamide.* B. *A representative study of the uricosuric response to benzbromarone. SI conversion: plasma urate mmol/l = mg/dl × 0·0595*

Table 2 *Eradication of uricosuric response to benzbromarone by pretreatment with pyrazinamide**

Time (min)	*Purate (mg/dl) (mmol/l)*	*UVurate (μg/min) (μmol/min)*
0–60	5·36±0·79 (0·32±0·05)	514±50 (3·06±0·30)
	Pyrazinamide 4 g given orally	
240–300	5·67±0·79 (0·33±0·05)	44±10 (0·26±0·06)
	Benzbromarone 80 mg given orally	
480–540	6·25±0·84 (0·37±0·05)	78±24 (0·46±0·14)
1560	7·91±0·52 (0·47±0·03)	

*Purate and UVurate are expressed as the mean±SD in 4 normal subjects.

summarised in Table 2. A uricosuric response to benzbromarone is lacking in all cases. A slight increase in urinary uric acid is noticeable after benzbromarone administration. Presumably the drug inhibits reabsorption of the minute quantities of urate that arrives at a distal reabsorptive site, either because trivial amounts of urate escape proximal reabsorption, or, more likely, because PZA fails to completely inhibit tubular secretion of urate.

These results suggest that uricosuric drugs act by inhibiting reabsorption of secreted urate at a post-secretory site. This means in turn that tubular secretion of urate can be determined by blocking distal reabsorption completely. To the extent that benzbromarone selectively inhibits postsecretory reabsorption of urate it is possible to assess tubular secretion of urate by measuring maximum uric acid excretion following administration of a suitable dose. In other words, the maximum uricosuric response can be equated to the minimum secretory rate.

The results of studies on tubular secretion in 8 healthy volunteers and 3 gouty subjects with overproduction of uric acid are shown in Table 3 and Fig. 4. Baseline urate excretion values during the control period and maximum uricosuric responses are plotted against plasma urate values over a range of 2·05 mg/dl (0·12 mmol/l) to 10·72 mg/dl (0·63 mmol/l). In this group of subjects a linear relationship is seen between tubular urate secretion and plasma urate concentrations ($r=0·956$; $P<0·0005$).

Since benzbromarone in the dose employed may only partially inhibit tubular urate reabsorption, it follows that the observed values represent minimum tubular secretory rates. The limited number of observations do not suggest that a Tm for tubular secretion has been reached within the range of plasma uric acid studied. The tubular secretion of uric acid is at least 5-fold greater than the quantity

Table 3 *Response to benzbromarone 80 mg in 8 normal subjects and 3 gouty patients with overproduction of uric acid*

	Pretreatment		*Uricosuric response**	
Subject	*Purate (mg/dl) (mmol/l)*	*UVurate/GFR (μg/cc) (mμmol/cc)*	*Purate (mg/dl) (mmol/l)*	*UVurate/GFR (μg/cc) (mμmol/cc)*
1	5·33 (0·31)	4·00 (23·79)	3·91 (0·23)	18·50 (110·04)
2	5·81 (0·34)	5·17 (30·75)	3·89 (0·23)	16·70 (99·33)
3	5·92 (0·35)	4·92 (29·26)	4·30 (0·25)	24·30 (144·54)
4	4·90 (0·29)	5·14 (30·57)	4·45 (0·26)	21·11 (125·57)
5	3·80 (0·22)	3·60 (21·41)	3·20 (0·19)	12·10 (71·97)
6	5·38 (0·32)	5·41 (32·18)	3·09 (0·18)	17·87 (106·29)
7	4·45 (0·26)	4·35 (25·87)	2·90 (0·17)	13·10 (77·92)
8	2·81 (0·17)	3·25 (19·33)	2·05 (0·12)	8·00 (47·59)
9†	10·72 (0·63)	9·59 (57·04)	8·27 (0·49)	37·43 (222·64)
10†	8·57 (0·51)	7·80 (46·40)	6·10 (0·36)	28·20 (167·73)
11†	9·35 (0·55)	8·68 (51·63)	6·45 (0·38)	25·60 (152·27)

*See text for details of methods. †Gouty overproducers.

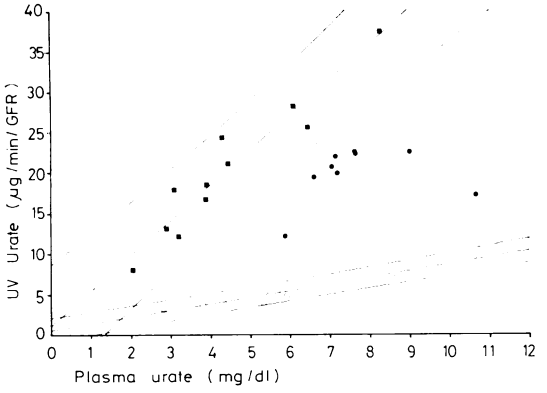

Fig. 4 *Regression lines and 95% prediction bands describing urate excretion as a function of plasma urate in 8 normal subjects and 3 gouty overproducers. Open squares depict control study ($r = 0{\cdot}971$; $P<0{\cdot}0005$), and closed squares depict maximum uricosuria after oral administration of benzbromarone; ($r = 0{\cdot}956$; $P<0{\cdot}0005$). Control data for 9 gouty subjects with normoproduction of uric acid are represented by open circles ($r = 0{\cdot}721$; $P<0{\cdot}025$), and during maximum uricosuria by closed circles; ($r = 0{\cdot}208$; P Not Significant). SI conversion: plasma urate mmol/l = mg/dl × 0·0595.*

of uric acid excreted in the urine. The difference between the regression lines depicting secretion and excretion represent uric acid that has been reabsorbed at the distal reabsorptive site.

In order to characterise the renal defect in primary gout more fully we studied the uricosuric responses to benzbromarone in 9 patients with normal production of uric acid. The mean urinary uric acid on a regular diet was 735 mg per 24 hours (4·34 mmol/24 h), and the ratio of urinary uric acid to urinary creatinine was 0·32 (Kaufman *et al.*, 1968). The data for this group are shown in Fig. 4 superimposed on the control values. Although urate excretion at varying concentrations of plasma urate is lower than normal in the gouty normoproducers, the slope of the regression line is not significantly different ($r=0{\cdot}721$; $P<0{\cdot}025$). Urate secretion in response to benzbromarone was distinctly lower in the gouty normoproducers when compared with control subjects and gouty overproducers of uric acid. Furthermore, over the limited plasma urate range studied, a linear relationship was not observed between these values and tubular urate secretion ($r=0{\cdot}208$; P=not significant). This observation is in sharp contrast with the values obtained in subjects with a normal tubular secretory apparatus.

Discussion

The data presented are consistent with a 4-component mechanism for urate transport in man. The model depicted in Fig. 5 involves: (1) complete filtration of plasma urate at the glomerular membrane; (2) virtually complete reabsorption of filtered urate; (3) subsequent secretion of urate at a rate at least 50% of the original filtered load; and (4) reabsorption of at least 80% of secreted urate at a second reabsorptive site which is sensitive to the action of uricosuric drugs.

Although the extent of urate filterability through the glomerular membrane has remained a controversial subject for years, current evidence suggest that plasma urate is completely filtered at the glomerulus. Protein binding of uric acid does occur at lower temperatures, but little or no binding is discernible at 37°C. We found that 15% of urate was bound to plasma proteins at 4°C, and similar observations have been published by others (Klinenberg and Kippen, 1970). Plasma from normal persons and gouty subjects had similar binding characteristics. On the assumption that absence of binding of urate occurs physiologically, the filtered urate load may be calculated from the concentration of plasma urate and the glomerular filtration rate.

We have used the 'pyrazinamide suppression test' to measure the minimum amount of filtered urate that is reabsorbed by the kidney. A basic assumption for the validity of this test is that PZA causes selective inhibition of tubular urate secretion. Studies in the chimpanzee have shown that pyrazinoic acid, a metabolite of PZA, at plasma concentrations of less than 100 μg/ml, which is obtained following an oral dose of 3 to 4 g of PZA, is strikingly antiuricosuric (Fanelli and Weiner, 1973). At higher plasma concentrations, pyrazinoic acid leads to

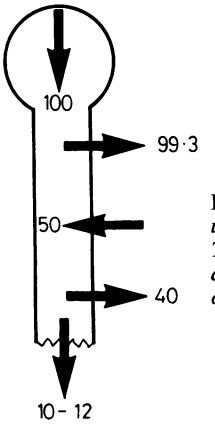

Fig. 5 *Schematic model of urate handling in the nephron. Tubular flux of urate is shown adjacent to each arrow in percent of filtered load.*

uricosuria, presumably because of inhibition of both tubular secretion, as well as reabsorption of urate. The finding that the fractional urate excretion amounts to only 0·7% after PZA administration indicates that urate undergoes virtually complete reabsorption at a site proximal to the tubular site of urate secretion. The capacity for reabsorption of filtered urate is extraordinary, as evidenced in studies in which the filtered urate load was increased by administration of yeast RNA for several days.

Rieselbach (1976) reported studies in 6 normal subjects whose mean filtered urate had been raised to 17·4 mg/minute (103·50 μmol/min). Their fractional urate excretion remained as low as 0·51%, indicating a mean reabsorption of 17·3 mg/min (102·90 μmol/min). In a single study we found that the fractional urate excretion was 0·5% after filtered urate had been increased to 20 mg/minute (118·96 μmol/min).

The pyrazinamide suppression test was originally advocated as a test for estimating urate secretory transport in man (Steele and Rieselbach, 1967). The validity of the test for this purpose was based on the premise that secretion of tubular urate occurs in segments of the nephron distal to all reabsorptive sites. With the finding that substantial quantities of secreted uric acid undergoes reabsorption further distally in the nephron, it is clear that the test grossly underestimates the magnitude of tubular secretion. However, it remains a valid test for quantifying reabsorption of filtered urate.

From the data obtained in studies with PZA it may be concluded that uric acid is derived almost entirely from tubular secretion in normal man. Several pieces of evidence make it clear that only a portion of secreted uric acid is excreted in the urine. The finding that the uricosuric response to benzbromarone is completely nullified in subjects pretreated with PZA can best be interpreted to mean that the uricosuric action of this compound is related to a direct inhibitory effect upon postsecretory reabsorption. Similarly, the uricosuric response to agents such as probenecid or intravenous chlorothiazide has been found to be greatly diminished in subjects pretreated with PZA (Steel and Boner, 1973; Diamond and Paolino, 1973). To the extent that it is possible to inhibit postsecretory reabsorption of urate, it is possible to study the secretory transport mechanism more directly. Benzbromarone is particularly suitable for this purpose, since it is not excreted by a renal tubular organic acid transport mechanism and therefore does not interfere with tubular secretion of uric acid (Podevin *et al.*, 1967). The paradoxical effect of urate retention seen when conventional uricosuric drugs are given in low dosage is not observed in the case of benzbromarone. The maximum urate excretion after benzbromarone administration becomes a measure of the tubular secretory rate for a given plasma urate level. Increased availability of urate to the secretory site results in a steep increase in the secretory rate. Obviously, the values observed in the present studies represent minimum secretory rates, since postsecretory reabsorption may have been only partially inhibited by benzbromarone in the dosage given.

Reabsorption of uric acid at the postsecretory site increases progressively with increasing availability of urate. Thus within the plasma urate range studied the magnitude of postsecretory reabsorption appears to be set at a constant percentage of the secreted load.

At least three-fourths of all patients with primary gout have normal urate production and require an elevated plasma urate concentration to obtain a normal level of uric acid excretion (Seegmiller *et al.*, 1961). The technique of measuring the uricosuric response to benzbromarone has allowed identification of a defect in the renal handling of urate in these patients which can be localised to the secretory site. Although gouty normoproducers can be characterised as having a subnormal response to benzbromarone, this drug, as is the case with other uricosuric agents, decrease postsecretory fractional reabsorption of uric acid, resulting in a lowering of plasma urate levels.

Recent reports of defects in urate reabsorption in man support the proposed scheme for renal handling of uric acid. One defect appears to involve diminished reabsorption of filtered urate in that urate excretion was not significantly reduced after PZA treatment (Greene *et al.*, 1972). Another defect exists in patients with urate clearances higher than the glomerular filtration rate, which would appear to involve markedly impaired reabsorption of both filtered and secreted urate transport throughout the nephron (Simkin *et al.*, 1973). We have reported a third defect confined solely to the postsecretory reabsorptive site (Sorensen and Levinson, 1980).

The exact mechanism and sites of tubular urate transport remain to be clarified. Recent micropuncture studies in the rat indicate substantial urate reabsorption in the loop of Henle (Greger *et al.*, 1974). Variation in urine flow exerts a moderate effect on urate excretion in man, suggesting a reabsorptive site also in the distal tubule or collecting ducts (Diamond *et al.*, 1972).

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