Organic acid excretion patterns in gout

HERBERT J. KRAMER, ESTHER LU, AND HARVEY C. GONICK

From the Department of Medicine, UCLA School of Medicine, Los Angeles, California

The hyperuricaemia associated with gout is believed to be due to overproduction of uric acid, to impaired renal excretion of uric acid, or to alterations in both mechanisms (Seegmiller, 1966). In all likelihood, gout encompasses a heterogeneity of biochemical disorders, the metabolic or enzymatic bases of which with one exception, have not yet been completely delineated. The Lesch-Nyhan syndrome, a familial disorder with overproduction of uric acid, has been shown to be due to deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (Seegmiller, Rosenbloom, and Kelley, 1967).

In most instances, it has been shown that overproduction of uric acid, as measured by incorporation of labelled glycine, is accompanied by increased excretion of uric acid (Seegmiller, Grayzel, Laster, and Liddle, 1961). In a series of 300 patients examined by Gutman and Yü (1957), 67 per cent. were found to be normoexcretors (24-hr urinary urate excretion within the normal range of 418 ± 70 mg.), 28.7 per cent. were found to be hyperexcretors, and 4.3 per cent. hypoexcretors. On recalculating these data, Wyngaarden (1960) found that both normoexcretors and hyperexcretors with a normal glomerular filtration rate (GFR) had a reduced urate clearance when compared to normal subjects, implying that some hyperexcretor patients might also have a renal abnormality. It is now assumed that about one-third of gouty patients are overproducers, one-third have impaired renal tubular transport of urate, and one-third have a combined defect (Seegmiller and others, 1961). Rieselbach, Sorensen, Shelp, and Steele (1967) have presented preliminary data indicating that the decreased urate clearance in some gouty patients is due to impaired tubular secretion. Since it has also been previously shown that certain organic acids interfere with urate excretion, presumably by competing with urate for tubular secretion (Gibson and Doisy, 1923; Michael, 1944; Yü, Sirota, Berger, Halpern, and Gutman, 1957; Möller, 1962; Goldfinger, Klinenberg, and Seegmiller, 1965), we were interested in examining the organic acid excretion patterns in gouty patients with both reduced and normal urate clearance.

Fractional excretion values for urate in normal

control subjects have been calculated by Wyngaarden (1960) as 7.6 ± 2.4 per cent. of the filtered load. Since our gouty patients with normal renal function had a mean GFR of 98 ml./min., we have arbitrarily designated a value of 5.2 ml./min. (i.e. one S.D. below the normal mean) as the dividing line between reduced and normal urate clearance. Patients with reduced GFR were examined separately because of evidence that renal tubular transport of urate is altered in uraemia (Gutman and Yü, 1957).

Materials and methods

The study population consisted of 32 males, aged 32 to 79 years, with well-documented primary gout. All subjects were studied as outpatients on an *ad libitum* diet without therapy for at least 3 weeks. Fifteen of these patients were found to have normal urate clearance (>5.2 ml./min.) on multiple occasions. Seventeen patients had reduced urate clearance. These two groups were again subdivided into subjects with normal GFR (creatinine clearance >80 ml./min.) (Table I) and those with reduced GFR (creatinine clearance <80 ml./min.) (Table II). P.S.P. excretion and maximum concentrating ability after infusion of Pitressin® (Kleeman, Adams, and Maxwell, 1961) were used as additional parameters of renal function. Blood pH and PCO_2 were determined by the Astrup technique (Siggaard Andersen, Engel, Jørgensen, and Astrup, 1960).

Serum and urinary urate concentrations were measured by the colorimetric method of Caraway (1963). Creatinine concentration was determined by the standard picric acid method (Folin and Wu, 1919). Total urinary organic acid concentration was determined by a modification of the technique of Van Slyke and Palmer (1932) described in a previous communication (Goldberg, Paul, and Gonick, 1966). Normal values for 24-hr excretion of total organic acids and the fluctuation of total organic acid excretion on a non-standardized diet were reported in this earlier communication (Goldberg and others, 1966).

In five normal control subjects (laboratory personnel, aged 19 to 40 years), eight patients of the group with reduced urate clearance, and four patients of the group with normal urate clearance, 24-hr excretion of the following individual organic acids were determined: lactate, pyruvate, oxalate, citrate, cis-aconitate, α -ketoglutarate, succinate, fumarate, and L-malate.

A gas chromatographic method, modified from that described by Alcock (1965), was established for continuous

quantitative analysis of citrate, cis-aconitate, α -keto-glutarate, succinate, fumarate, and L-malate. 10 ml. urine were applied to an ion exchange column, consisting of Dowex 2-X8, 50 to 100 mesh, at a flow rate of 1 ml./min. The column was prepared according to the method of Nordmann, Nordmann, du Ruisseau, and Gauchery (1956), except that the column height was increased to 20 cm. After washing with 50 ml. doubly distilled water, the organic acids were eluted with 30 ml. 12 N formic acid. The eluate was flash evaporated to dryness at 37°C. The residue was dissolved in 6 ml. BF₃-methanol reagent and transferred to a glass-stoppered test tube for steam esterification (Metcalf and Schmitz, 1961).

The esterified organic acids were then transferred to a separatory funnel containing an equal volume of doubly distilled water. Samples were extracted first with 1 ml. chloroform, and then three times with 0.4 ml. chloroform, and the volume was made up to 2 ml. Separation of the single organic acids was performed by gas liquid chromatography on a Barber Coleman 10 Gas Chromatography Apparatus with a Model 34 temperature programmer and a column of 5 per cent diethyleneglycol-adipate on Chromasorb W. The temperature was programmed to increase at a rate of 15°C./min., and the samples were injected at a column temperature of 75°C. The flame detector consisted of hydrogen at 20 lb./sq. in. with the flame heater at 225°C. The Argon carrier flow was set at 60 ml./min. the flash heater at 225°C. Recordings were taken with a Wheelco 8000 series multipoint recorder. Combined values for fumarate and succinate are reported because of the overlapping of their peaks. Quantitative analysis was done by comparing the areas of single peaks

with those obtained after extraction and separation of a mixture of standard organic acids in an identical manner.

Since lactate and pyruvate concentrations could not be accurately measured by this technique because of the temperature programming, urinary pyruvate was determined according to the method of Friedemann and Haugen (1943) and urinary lactate by the method of Barker and Summerson (1941). Urinary oxalate concentration was measured by the method of Riggs and Bricker (1966).

Results

I. URINARY EXCRETION AND CLEARANCE OF URATE

Values for 24-hr urinary excretion and clearance of urate in both groups of gouty patients with normal and reduced GFR are summarized in Tables I and II. A mean urinary excretion of 477 ± 145 (S.D.) mg./24 hrs was noted in the patients with reduced urate clearance. The average urate excretion in the patients with normal urate clearance was 919 ± 400 mg./24 hrs. Both groups had comparable glomerular filtration rates and mean plasma urate concentrations.

Both groups of gouty patients with reduced GFR had urate clearance values similar to those of patients in the groups with normal GFR. However, a significant increase in fractional excretion of urate was observed.

Table I *Urinary urate excretion, urate clearance and urinary excretion of total organic acid in gouty patients with normal GFR*

Urate clearance	Patient no.	GFR (ml./min.)	Serum urate (mg./100 ml.)	24-hr urate excretion (mg./24 hrs)	Urate clearance (ml./min.)	Fractional excretion of urate (%)	24-hr total organic acid excretion (mEq/24 hrs)
Reduced (7)	1	104	6.7	220	2.3	2.2	33.9
	2	98	12.7	716	3.9	4.0	58.3
	3	96	11.3	513	3.1	3.2	65.2
	4	91	9.4	483	3.6	4.0	34.7
	5	100	11.2	455	2.8	2.8	43.5
	6	103	6.6	502	5.2	5.1	62.0
	7	90	6.8	450	4.6	5.1	68.7
	Mean	97 ± 5	9.2 ± 2.6	477 ± 145	3.6 ± 1.0	3.8 ± 1.1	52.3 ± 14.7
	S.D.						
Normal (12)	8	97	8.6	663	5.3	5.5	67.9
	9	93	7.4	580	5.5	5.9	61.8
	10	111	14.8	1415	6.7	6.0	72.7
	11	102	8.6	932	7.5	7.3	58.9
	12	106	6.3	600	6.6	6.2	62.8
	13	83	16.4	1944	8.3	10.0	64.0
	14	93	8.1	650	5.6	6.0	62.6
	15	103	9.7	1040	7.4	7.2	55.1
	16	90	8.2	810	6.8	7.6	45.6
	17	100	8.7	774	6.2	6.2	68.5
	18	125	8.2	941	8.0	6.4	73.9
	19	80	7.7	673	5.6	7.0	49.1
	Mean	99 ± 12	9.4 ± 3.0	919 ± 400	6.6 ± 1.0	6.8 ± 1.2	61.9 ± 8.7
	S.D.						

Table II Urinary urate excretion, urate clearance, and urinary excretion of total organic acid in gouty patients with reduced GFR

Urate clearance	Patient no.	GFR (ml./min.)	Serum urate (mg./100 ml.)	24-hr urate excretion (mg./24 hrs)	Urate clearance (ml./min.)	Fractional excretion of urate (per cent)	24-hr total organic acid excretion (mEq/24 hrs)
Reduced (10)	20	28	9.9	230	1.6	5.7	18.5
	21	35	12.4	360	2.0	5.7	31.7
	22	49	11.9	420	2.5	5.1	48.1
	23	51	8.6	627	5.1	10.0	65.5
	24	52	11.5	378	2.3	4.4	128.1
	25	64	10.2	210	1.4	2.2	33.2
	26	70	7.0	509	5.1	7.3	38.3
	27	71	10.7	550	3.1	4.4	40.6
	28	72	9.1	630	4.8	6.7	73.1
	29	74	8.3	364	3.1	4.2	39.4
Mean S.D.		57 ± 16	10.0 ± 1.7	428 ± 149	3.1 ± 1.4	5.6 ± 2.1	51.7 ± 31.3
Normal (3)	30	62	5.8	494	5.9	9.5	49.0
	31	63	10.6	1120	7.3	11.6	49.7
	32	74	7.8	949	8.4	11.3	35.1
Mean S.D.		66 ± 7	8.1 ± 2.4	854 ± 324	7.2 ± 1.3	10.8 ± 1.1	44.6 ± 8.2

II. URINARY EXCRETION OF TOTAL ORGANIC ACID

Values for 24-hr urinary excretion of total organic acid in gouty individuals in each group are also summarized in Tables I and II.

24-hr urinary excretion of total organic acid in normal subjects on a non-standardized diet had previously been found to be 55.1 ± 18.7 mEq (Goldberg and others, 1966). 24-hr urinary excretion of total organic acid in both groups of gouty patients with normal GFR was not significantly different from that in controls. Similar values were obtained in the gouty patients with reduced GFR. The only exception was patient 24, with reduced GFR (see Table II), who had a markedly elevated total organic acid excretion (128.1 mEq/24 hrs).

III. URINARY EXCRETION OF SINGLE ORGANIC ACIDS IN NORMAL SUBJECTS

Mean values for 24-hr urinary excretion of single organic acids in control subjects are summarized in Table III and compared with values reported previously.

Highest 24-hr urinary excretion was observed for citrate, followed by lactate, L-malate, oxalate, cis-aconitate, and α -ketoglutarate. Lowest excretion rates were found for pyruvate and succinate-fumarate.

A typical gas-chromatographic elution pattern of organic acids from the urine of a normal subject is shown in Fig. 1 (overleaf).

IV. URINARY EXCRETION OF SINGLE ORGANIC ACIDS IN GOUTY PATIENTS

Values for 24-hr urinary excretion of single organic

Table III Daily excretion of various organic acids in five control subjects (mg./24 hrs)

Organic acid	Mean ± S.D.	Values reported in literature
Lactate	171 ± 64	188–250 (24)
Pyruvate	10.9 ± 1.6	8.16 ± 1.55 (25) 2.4 ± 4.9 (26)
Oxalate	75.1 ± 25.1	15–50 (27) 21–49 (28)
Citrate	462.8 ± 122.1	190–940 (26) 200–1000 (29) 210–1400 (30)
Cis-aconitate	58.6 ± 22.9	trace (31)
α -ketoglutarate	38.4 ± 6.8	14.13 ± 3.20 (25) 10.2–40.8 (26)
Succinate	13.5 ± 20.4*	2–12 (32)
L-malate	121.6 ± 51.8	—

* Including fumarate

acids in gouty patients are summarized in Table IV (overleaf).

Gouty patients with reduced urate clearance and normal GFR revealed a decreased average 24-hour urinary excretion of citrate, cis-aconitate, α -ketoglutarate, and L-malate (e.g. Case 4; Fig. 2, overleaf). Two patients (Cases 3 and 6) showed a significantly elevated lactate excretion.

One of the three patients in the group with reduced GFR (Case 24) also showed markedly elevated excretion of lactate, but in addition increased excretion of oxalate, cis-aconitate, and succinate-fumarate. L-malate excretion was found to be slightly elevated (Fig. 3, overleaf). Patient 30 also revealed a significantly increased excretion of succinate-fumarate. All patients in this group had markedly reduced excretion of citrate.

Table IV *Excretion of individual organic acids in gouty patients (mg./24 hrs)*

Urate clearance	GFR	Patient no.	Lactate	Pyruvate	Oxalate	Citrate	Cis-aconitate	α -keto-glutarate	Succinate-fumarate	L-malate
Reduced	Normal	1	180	17.1	19.4	28.6	40.8	8.2	20.5	53.0
		3	999	13.5	84.4	14.4	11.7	11.4	25.9	41.8
		4	157	6.7	42.8	161.5	42.0	14.6	7.8	25.4
		5	193	13.3	74.2	125.2	28.4	23.4	13.1	46.7
		6	342	11.1	42.8	113.5	67.3	22.4	16.5	18.3
		Mean S.D.	374 ± 357	12.3 ± 3.8	52.7 ± 26.3	88.6 ± 64.0	38.0 ± 20.4	16.0 ± 6.7	16.8 ± 6.9	37.0 ± 14.6
Normal	Normal	8	259	17.9	91.2	424.0	10.2	28.6	<0.1	48.1
		10	470	17.6	70.1	125.0	15.3	30.5	65.0	65.5
		13	312	12.6	134.0	294.0	42.0	37.8	22.1	42.0
		16	129	9.3	41.4	221.0	9.8	18.1	6.3	67.6
		Mean S.D.	293 ± 141	14.4 ± 4.2	84.2 ± 39.0	266.0 ± 126.0	19.3 ± 15.3	28.8 ± 8.1	23.4 ± 29.3	55.8 ± 12.7
		24	1092	14.6	164.9	60.6	124.7	32.0	227.5	197.0
Reduced	Reduced	30	160	7.9	52.6	189.8	21.9	13.2	77.9	104.0
Normal		27	123	10.4	35.6	65.0	24.7	10.3	36.2	51.3
Reduced		Mean S.D.	458 ± 549	11.0 ± 3.4	84.4 ± 70.3	105.1 ± 73.4	57.1 ± 58.6	18.5 ± 11.8	113.9 ± 100.6	117.4 ± 73.8

FIG. 1 Gas chromatographic elution patterns of individual urinary organic acids in a normal subject. 3 μ l. of a 15-fold concentrated chloroform extract of urine were applied to the column.
The organic acids are identified as follows: (1) fumarate, (2) succinate, (3) L-malate, (4) α -ketoglutarate, (5) cis-aconitate (6) citrate

FIG. 2 Gas chromatographic elution patterns of individual urinary organic acids in a gouty normoexcretor with normal GFR (Case 4). 3 μ l. of a 2-fold concentrated chloroform extract of urine were applied to the column. Numbers refer to compounds identified in Fig. 1

FIG 3 Gas chromatographic elution patterns of individual urinary organic acids in a gouty normoexcretor with reduced GFR (Case 24). 3 μ l. of a 20-fold concentrated chloroform extract of urine were applied to the column. Numbers refer to compounds identified in Fig. 1

Gouty patients with normal urate clearance and normal GFR showed a moderately reduced average 24-hr excretion of citrate and cis-aconitate. One patient (Case 10) had also an increased excretion of lactate and of succinate-fumarate.

V. RELATIONSHIP OF RENAL FUNCTION PARAMETERS AND ACID-BASE STATUS TO INDIVIDUAL ORGANIC ACID EXCRETION PATTERNS

Table V summarizes the renal functional and acid-base parameters in the patients in whom individual

urinary organic acids were measured. Neither the decreased citrate excretion nor elevated lactate excretion could be correlated with GFR, PSP excretion, maximum urinary concentration, or acid-base status (plasma CO_2 and pH). Case 24, with elevated excretion of several organic acids, was moderately acidotic (blood pH 7.33), but Case 27, who was much more severely acidotic (blood pH 7.25), showed no increase in urinary organic acid excretion.

Discussion

Renal excretion of urate in man is determined by glomerular filtration, tubular reabsorption, and tubular secretion (Gutman and Yü, 1961). Approximately 5 to 10 per cent. of the filtered urate appears in the urine. It has been estimated that 98 to 99 per cent. of filtered urate is reabsorbed by the proximal tubule and that approximately 80 to 90 per cent. of urinary urate is excreted *via* tubular secretion (Gutman, Yü, and Berger, 1969). Tubular transport of urate is thought to be an active energy-requiring process, probably related to active secretion of PAH and other organic acids by a common 'organic anion pump' (Weiner and Mudge, 1964). Urate and sodium reabsorption also appear to be interrelated under circumstances of extracellular volume expansion and contraction (Steele, 1969). Both reabsorption and secretion of urate in the mongrel dog (Zins and Weiner, 1968), and presumably in man, occur in the proximal tubule, while secretion also occurs in the distal nephron (Yü, Berger, Kupfer, and Gutman, 1960).

Hyperuricaemia associated with gout may be due to overproduction of uric acid, impaired renal excretion of uric acid or to alterations in both mechanisms (Seegmiller, 1966). Studies concerned with the role of the kidney in the pathogenesis of hyperuricaemia in gout, however, have yielded equivocal results

Table V Renal function parameters and acid-base status in patients with individual urinary organic acid determinations in gouty patients

Urate clearance	GFR	Patient no.	GFR (ml./min.)	PSP excretion (per cent after 2 hrs)	Maximum urine concentration (mOsm/L)	Plasma CO_2 (mM/L)	Blood pH
Reduced	Normal	1	104	57	905	20	7.37
		3	96	62	518	18	7.43
		4	91	26	501	29	7.42
		5	100	64	673	23	7.37
		6	103	47	601	22	7.37
Normal	Normal	8	97	73	690	21	7.37
		10	111	36	613	20	7.39
		13	83	25	452	26	7.40
		16	90	32	766	18	7.37
Reduced	Reduced	24	52	35	639	18	7.33
Normal		30	62	75	792	23	7.38
Reduced		27	71	78	545	12	7.25

(Gutman and others, 1969; Nugent and Tyler, 1959). Wyngaarden (1960) calculated from the data of Gutman and Yü (1957) a mean normal fractional excretion of urate of 7.6 ± 2.4 per cent. Gouty hyperexcretors with normal GFR (>100 ml./min.) revealed a fractional excretion of urate of 6.6 ± 2.0 per cent, whereas gouty normoexcretors showed a value of 5.9 ± 1.7 per cent. Thus, both groups of gouty patients showed reduced fractional excretion of urate, suggesting a renal contribution to the hyperuricaemia. On the other hand, Gutman and others (1969), after an investigation of tubular reabsorption and secretion of urate in ten unselected patients, concluded that 'in view of the similarities in renal regulation of uric acid excretion in normal and gouty man, it does not seem necessary to postulate a specific renal defect in excretion of uric acid in primary gout'.

In the present study we have divided the gouty subjects with normal GFR into the two groups of patients with normal urate clearance and patients with reduced urate clearance. This latter group would appear to have impaired renal transport of urate as a major contributory cause of hyperuricaemia. Gouty patients with reduced GFR were found to have higher fractional excretion of urate than gouty patients with normal GFR. This finding is in accord with previous studies of the renal handling of urate in non-gouty azotaemic patients (Steele and Rieselbach, 1967).

Normal control values for 24-hr urinary excretion of certain of the individual organic acids, *i.e.* pyruvate, oxalate, citrate, and succinate-fumarate, were in agreement with those reported previously (Zelnicek, 1959; Evans, MacIntyre, MacPherson and Milne, 1957; Dempsey, Forbes, Melick and Henneman, 1960; Hockaday, Frederick, Clayton and Smith, 1965; Östberg, 1931; Taussky, 1949; Weitzel, 1947). Excretion of α -ketoglutarate was slightly higher and of cis-aconitate markedly higher than reported by others (Zelnicek, 1959; Evans and others, 1957; Halpern, 1960). The 24-hr excretion of lactate was found to be in a similar range to the values reported by Gambigliani-Zoccoli, Giaccherio, Zambelli, and Reschia (1939), who used the titrimetric method of Friedemann and Graeser (1933).

The 24-hr urinary excretion of total organic acid in our gouty patients on a non-standardized diet was found to be in the range of values previously observed in normal subjects (Goldberg and others, 1966). Only one patient (Case 24) in the group of gouty patients with reduced urate clearance and reduced GFR was found to have markedly raised total organic acid excretion. This was due to increased excretion of lactate, oxalate, cis-aconitate, succinate-fumarate, and L-malate, suggesting a possible deficiency of the enzyme malate dehydrogenase, which catalyses the transformation of malate to oxaloacetate. Since we

have no direct evidence concerning uric acid production, the genesis of this patient's gouty diathesis must remain speculative. However, it is of interest that succinate has been shown to act as a substrate for purine synthesis *via* the succinate-glycine- δ -aminolevulinic acid cycle (Nemeth, Russell, and Shemin, 1957), and therefore accumulation of succinate could lead to increased production of urate. Alternatively, any of the accumulated organic acids could compete with urate for tubular secretion.

Although in the remaining patients total organic acid excretion was normal, all showed a *decreased* excretion of citrate, which was more prominent in the group with reduced urate clearance. This decrease in citrate excretion could not be related to systemic acidosis, as has been shown in patients with renal tubular acidosis (Morrissey, Ochoa, Lotspeich and Waterhouse, 1963) and in uraemic patients with acidosis (Gonick and Drinkard, 1969). Lactate excretion was found to be *increased* in three out of seven patients with reduced urate clearance and in two out of five patients with normal urate clearance. In addition to Case 24 (discussed above), two other patients also showed increased excretion of succinate-fumarate: Case 30, a patient with reduced GFR, and Case 10, a patient with normal urate clearance and normal GFR.

Previous studies have shown that both lactate and citrate can influence the renal handling of urate. Administration of lactate has been shown to depress urate excretion in the dog (Reem and Vanamer, 1964), the rabbit (Moeller, 1962), and man (Gibson and Doisy, 1923; Michael, 1944; Yü and others, 1957); this was attributed in the rabbit to inhibition of urate secretion (Moeller, 1962). In man, it has also been found that the hyperuricaemia following physical exercise (Nichols, Miller, and Hiatt, 1951) and over-indulgence in alcohol (Lieber, Jones, Losowsky, and Davidson, 1962), and associated with glycogen storage disease (Howell, Ashton, and Wyngaarden, 1962), was related to elevated plasma levels of lactate. An inverse correlation between plasma lactate levels and urate clearance has been demonstrated (Michael, 1944; Yü and others, 1957; Handler, 1960). The administration of citrate, on the other hand, increases urate excretion, presumably by providing a source of energy for tubular transport of urate through increased delivery of substrate to the Krebs cycle (Yü and others, 1957).

Other organic acids have also been shown to affect urate excretion. Pyruvate administration appears to increase excretion (Gibson and Doisy, 1923), probably by mechanisms similar to citrate, whereas β -hydroxybutyrate decreases urate clearance (Goldfinger and others, 1965).

The observations in the present paper must be regarded as only a preliminary survey of the possible pathogenetic role of organic acids in gout. Because

of technical difficulties, organic acid measurements were confined to the urine and we can therefore reach no definitive conclusion regarding the overall metabolism of these acids in hyperuricaemic subjects. It is equally plausible that the increased lactate excretion and decreased citrate excretion in several of the gouty patients may be due to a primary metabolic defect in synthesis or degradation of these organic acids or may simply reflect renal ischaemia secondary to the medullary damage and renal vascular changes which are almost invariably seen in gout (Gonick, Rubini, Gleason, and Sommers, 1965). However, the possibility remains that either increased lactate or decreased citrate levels interfere with the tubular transport of urate, leading to decreased urate clearance in some gouty patients. In an equally speculative vein, the increased succinate (-fumarate) excretion observed in three patients may reflect another metabolic derangement which leads to hyperuricaemia. Further definition of this derangement is not possible since we have no information on urate production in these patients and the effect of

succinate (-fumarate) on tubular handling of urate has not been studied in detail.

Summary

The 24-hr urinary excretion of total organic acids were measured in 32 gouty patients with both reduced and normal urate clearance and individual Krebs cycle organic acids were assayed in 12 of these patients. With one exception all gouty patients showed normal total urinary organic acid. However, 5 patients revealed an increased excretion of lactate and all 12 showed a decreased excretion of citrate, more pronounced in individuals with reduced urate clearance. An increase in succinate-fumarate excretion was observed in an additional 3 patients. The pathogenetic significance of these changes in organic acid excretion remains to be further defined.

The authors gratefully acknowledge the assistance of Mrs. Jean Mayfield, R.N., who supervised the gout clinic, and the secretarial assistance of Arda Burton and Audrey Malmgren.

References

- ALCOCK, N. W. (1965) *Analyt. Biochem.*, **11**, 335 (A simple procedure for the extraction and esterification of some organic acids)
- BARKER, S. B., AND SUMMERSON, W. H. (1941) *J. biol. Chem.*, **138**, 535 (Colorimetric determination of lactic acid in biological material)
- CARAWAY, W. T. (1963) 'Uric Acid' in 'Standard Methods of Clinical Chemistry', ed. D. Seligson, vol. 4, p. 239. Academic Press, New York
- DEMPSEY, E. F., FORBES, A. P., MELICK, R. A., AND HENNEMAN, P. H. (1960) *Metabolism*, **9**, 52 (Urinary oxalate excretion)
- EVANS, B. M., MACINTYRE, I., MACPHERSON, C. R., AND MILNE, M. D. (1957) *Clin. Sci.*, **16**, 53 (Alkalosis in sodium and potassium depletion (with especial reference to organic acid excretion))
- FOLIN, O., AND WU, H. (1919) *J. biol. Chem.*, **38**, 81 (A system of blood analysis)
- FRIEDEMANN, T. E., AND GRAESER, J. B. (1933) *Ibid.*, **100**, 291 (The determination of lactic acid)
- , AND HAUGEN, G. E. (1943) *Ibid.*, **147**, 415 (Pyruvic acid. II. The determination of keto acids in blood and urine)
- GAMBIGLIANI-ZOCCOLI, A., GIACCHERO, R., ZAMBELLI, E., AND RESCHIA, C. (1939) *Z. klin. Med.*, **135**, 457 (Milchsäure und Kreislaufinsuffizienz)
- GIBSON, H. V., AND DOISY, E. A. (1923) *J. biol. Chem.*, **55**, 605 (A note on the effect of some organic acids upon the uric acid excretion of man)
- GOLDBERG, G., PAUL, W., AND GONICK, H. (1966) *Clin. Chem.*, **12**, 830 (A titrimetric method for determining organic acids and bases in urine)
- GOLDFINGER, S., KLINENBERG, J. R., AND SEEGMILLER, J. E. (1965) *New Engl. J. Med.*, **272**, 351 (Renal retention of uric acid induced by infusion of beta-hydroxybutyrate and acetoacetate)
- GONICK, H. C., AND DRINKARD, J. P. (1969) *Clin. Res.*, **17**, 430 (Effects of alkalization and vitamin D on net mineral acid balance in uremics)
- , RUBINI, M. E., GLEASON, I. O., AND SOMMERS, S. C. (1965) *Ann. intern. Med.*, **62**, 667 (The renal lesion in gout)
- GUTMAN, A. B., AND YÜ, T. F. (1957) *Amer. J. Med.*, **23**, 600 (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)
- , —, (1961) *Trans. Acad. Amer. Phscns*, **74**, 353 (A three-component system for regulation of renal excretion or uric acid in man)
- , —, AND BERGER, L. (1969) *Amer. J. Med.*, **47**, 575, (Renal function in gout. III. Estimation of tubular secretion and reabsorption of uric acid by use of pyrazinamide (pyrazinoic acid))
- HALPERN, M. J. (1960) *Clin. chim. Acta*, **5**, 264 (Les acides organiques de l'urine dans quelques cas normaux et pathologiques)
- HANDLER, J. S. (1960) *J. clin. Invest.*, **39**, 1526 (The role of lactic acid in the reduced excretion of uric acid in toxemia of pregnancy)

- HOCKADAY, T. D. R., FREDERICK, E. W., CLAYTON, J. E., AND SMITH, L. H. (1965) *J. Lab. clin. Med.*, **65**, 677 (Studies on primary hyperoxaluria. II. Urinary oxalate, glycolate, and glyoxylate measurement by isotope dilution methods)
- HOWELL, R. R., ASHTON, D. M., AND WYNGAARDEN, J. B. (1962) *Pediatrics*, **29**, 553 (Glucose-6-phosphatase deficiency glycogen storage disease. Studies on the interrelationship of carbohydrate, lipid, and purine abnormalities)
- KLEEMAN, C. R., ADAMS, D. A., AND MAXWELL, M. H. (1961) *J. Lab. clin. Med.*, **58**, 169 (An evaluation of maximal water diuresis in chronic renal disease. I. Normal solute intake)
- LIEBER, C. S., JONES, D. P., LOSOWSKY, M. S., AND DAVIDSON, C. S. (1962) *J. clin. Invest.*, **41**, 1863 (Interrelation of uric acid and ethanol metabolism in man)
- METCALFE, L. D., AND SCHMITZ, A. A. (1961) *Analyt. Chem.*, **33**, 363 (The rapid preparation of fatty acid esters for gas chromatographic analysis)
- MICHAEL, S. T., (1944) *Amer. J. Physiol.*, **141**, 71 (The relation of uric acid excretion to blood lactic acid in man)
- MÖLLER, J. V. (1962) *Acta physiol. scand.*, **54**, 30 (The effects of D- and L-lactate and osmotic diuretics on uric acid clearance in the rabbit)
- MORRISSEY, J. F., OCHOA, M., JR., LOTSPEICH, W. D., AND WATERHOUSE, C. (1963) *Ann. intern. Med.*, **58**, 159 (Citrate excretion in renal tubular acidosis)
- NEMETH, A. M., RUSSELL, C. S., AND SHEMA, D. (1957) *J. biol. Chem.*, **229**, 415 (The succinate-glycine cycle. II. Metabolism of δ -aminolevulinic acid)
- NICHOLS, J., MILLER, A. T., JR., AND HIATT, E. P. (1951) *J. appl. Physiol.*, **3**, 501 (Influence of muscular exercise on uric acid excretion in man)
- NORDMANN, J., NORDMANN, R., RUISSEAU, J. P. DU, AND GAUCHERY, O. (1956) *Rev. franç. Ét. clin. Biol.*, **1**, 67 (Études sur le cycle tricarboxylique chez l'homme au moyen de la chromatographie sur papier des acides organiques)
- NUGENT, C. A., AND TYLER, F. H. (1959) *J. clin. Invest.*, **38**, 1890 (The renal excretion of uric acid in patients with gout and in nongouty subjects)
- ÖSTBERG, O. (1931) *Skand. Arch. Physiol.*, **62**, 81 (Studien über die Zitronensäureausscheidung der Menschenniere in normalen und pathologischen Zuständen)
- REEM, G. H., AND VANAMEE, P. (1964) *Amer. J. Physiol.*, **207**, 113 (Effect of sodium lactate on urate clearance in the Dalmatian and in the mongrel)
- RIESELBACH, R. E., SORESEN, L. B., SHELPE, W. D., AND STEELE, T. H. (1967) *J. clin. Invest.*, **46**, 1108 (Tubular secretion of urate per unit GFR in gout) (Abstract)
- RIGGS, W. M., AND BRICKER, C. E. (1966) *Analyt. Chem.*, **38**, 897 (Photochemical determination of oxalate)
- SEEGMILLER, J. E. (1966) *Proc. roy. Soc. Med.*, **59**, 292 (The study of human intermediary purine metabolism and its regulation)
- , GRAYZEL, A. J., LASTER, L., AND LIDDLE, L. (1961) *J. clin. Invest.*, **40**, 1304 (Uric acid production in gout)
- , ROSENBLUM, F. M., AND KELLEY, W. N. (1967) *Science*, **155**, 1682 (Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis)
- SIGGAARD ANDERSEN, O., ENGEL, K., JØRGENSEN, K., AND ASTRUP, P. (1960) *Scand. J. clin. Invest.*, **12**, 172 (A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood)
- STEELE, T. H. (1969) *J. Lab. clin. Med.*, **74**, 288 (Evidence for altered renal urate reabsorption during changes in volume of the extracellular fluid)
- AND RIESELBACH, R. E. (1967) *Amer. J. Med.*, **43**, 876 (The contribution of residual nephrons within the chronically diseased kidney to urate homeostasis in man)
- TAUSSKY, H. H. (1949) *J. biol. Chem.*, **181**, 195 (A microcolorimetric method for the determination of citric acid. II. A note on the substitution of ferrous sulfate for hydrazine sulfate as the reducing agent)
- YÜ, T. F., BERGER, L., KUPFER, S., AND GUTMAN, A. B. (1960) *Amer. J. Physiol.*, **199**, 1199, (Tubular secretion of urate in the dog)
- , SIROTA, J. H., BERGER, L., HALPERN, M., AND GUTMAN, A. B. (1957) *Proc. Soc. exp. Biol. (N. Y.)*, **96**, 809 (Effect of sodium lactate infusion on urate clearance in man)
- VAN SLYKE, D. D., AND PALMER, W. W. (1932) 'Total organic acids. Titration of total organic acids in urine', in 'Quantitative Clinical Chemistry', ed. J. P. Peters and D. D. Van Slyke, vol. 2 "Methods", p. 647. Williams and Wilkins, Baltimore
- WEINER, I. M., AND MUDGE, G. H. (1964) *Amer. J. Med.*, **36**, 743 (Renal tubular mechanisms for excretion of organic acids and bases)
- WEITZEL, G. (1947) *Hoppe-Seyler's Z. physiol. Chem.*, **282**, 174 (Über das regelmässige Vorkommen der Bernsteinsäure im menschlichen Harn)
- WYNGAARDEN, J. B. (1960) In 'Gout, The Metabolic Basis of Inherited Disease', ed. J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson. McGraw-Hill, New York.
- ZELNICEK, E. (1959) *Nature (Lond.)*, **184**, 727 (α -Ketoglutaric acid and pyruvic acid in blood, cerebrospinal fluid and urine)
- ZINS, G. R., AND WEINER, J. M. (1968) *Amer. J. Physiol.*, **215**, 411 (Bidirectional urate transport limited to the proximal tubule in dogs)