no effect on the surface or caused the appearance of a watery fluid, which could be drained off. Whether this fluid was a condensation of water molecules from the air or represented an actual secretion is not known. The mucous layer of control tissue had a glossy appearance, but was never watery.

5. *Effect on Ciliary Resistance to Mechanical Trauma.* It was noted that positive ions rendered the cilia peculiarly vulnerable to mechanical trauma. A single, very gentle stroke with a cotton-tipped swab dipped in Ringer's solution, which had no lasting effect on the control, completely stopped ciliary activity over all or most of the surface of the tissue receiving positive ions. This enhanced vulnerability completely disappeared when the tissue was exposed to negative ions. It also disappeared if the tissue was allowed to stand in the control chamber for an hour or more.

It is not at all obvious on *a priori* grounds that air ions should possess any capacity to influence biological systems. Nevertheless, evidence is collecting which establishes such activity in several areas. For example, positive ions reduce the succinoxidase content of the rat adrenal gland(4), and negative ions raise the CO_2 combining power of hamster blood plasma(7). During the past 2 years we studied the response of microorganisms suspended in very small drops of water when exposed to positive and negative air ions and have secured quantitatively reproducible alterations in survival curves(3).

While we have as yet developed no theory to account for the action of air ions on the rabbit trachea, it is possible that some of the changes we noted in the rate of water evaporation from droplets containing bacteria(3) may have significance here as well. A study of the inter-relationships and possible interdependence of the effects described in this series of experiments is currently in progress.

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Effect of Sodium Lactate Infusion on Urate Clearance in Man.* (23616)

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Gibson and Doisy(1) made the interesting observation, in normal human subjects, that ingestion of sodium lactate results in a striking if transitory decrease in the urinary excretion of uric acid, accompanied by a slight rise in plasma uric acid, suggesting "an elevated threshold in the kidney." Quick(2), Michael (3) and Nichols *et al.*(4) confirmed the decline in urinary uric acid excretion, a phenomenon which, in view of the physiological significance of lactic acid as a metabolic intermediate, may ultimately throw some light upon the still obscure nature of the renal tubular transport mechanisms for uric acid. The present study was designed to define this effect of lactate on renal excretion of uric acid more precisely by use of standard clearance technics.

Methods. Gouty subjects, in the intercriti-

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cal phase of the disorder, were employed in order to provide a wider range of urinary uric acid excretion levels. The 13 subjects studied were maintained on a low purine diet prior to study. Clearance measurements were made in the morning, with the patients in the post-absorptive state. Liberal fluid intake ensured adequate urine flow. Standard technics were employed(5). In all subjects glomerular filtration rate was measured by the inulin clearance, effective renal plasma flow by the para-aminohippurate clearance. Every experiment included three 15-minute control periods for determination of C_{inulin}, C_{PAH} and C_{urate}. The effect of lactate infusion on the maximal tubular excretory capacity was studied in one case by Tm_{PAH} estimations. The urine and blood pH was measured in a Cambridge pH meter immediately after procurement of the samples. Urate, inulin and PAH were determined by methods previously indicated(6).

Results. Effects of infusion of sodium r-lactate. Five experiments were performed: 2 with .17 M lactate, 2 with .5 M, 1 with .4 M. Representative results with each dosage are cited in Table I. C_{inulin} and C_{PAH} were not significantly altered(7). Tm_{PAH}, in the 1 case examined, transiently increased(7,8). A striking decline in urate excretion was consistently observed. This was uniformly apparent in the first 15-minute urine collection period and, when sufficient quantities of lactate were injected, became progressively more pronounced over the approximately 2-hour period of sustained infusion. In no instance, however, did C_{urate} decline to less than 1.0 ml/min. In the 5 experiments, the mean control UV_{urate} of 972 μg/min. fell to a mean minimum of 125 μg/min.; C_{urate} from 10.4 ml/min. to 1.4 ml/min.; and C_{urate}/C_{inulin} from 8.1% to 1.1%. An unequivocal rise in serum urate levels during the period of infusion was not demonstrated, presumably because of the brief duration of study. The urine pH invariably became alkaline, without any demonstrable change in blood pH.

Effect of sodium r-lactate on salicylate uricosuria. The uricosuria produced by injection of salicylate in appropriate dosage was found to be abolished, at least temporarily, by concomitant infusion of sodium lactate in adequate concentration. Thus in Case 4 (Table I) the mean control C_{urate}, increased from 11.8 ml/min. to a mean of 51.2 ml/min. during salicylate infusion, temporarily fell to 17.4 ml/min. after addition of .4 M sodium lactate to the continued salicylate infusion. Thereafter, C_{urate} gradually returned to the high levels observed with injection of salicylate alone, despite continued lactate infusion. Parallel changes occurred in C_{urate}/C_{inulin}. (It should be noted that the apparent wearing off of the suppressant effect of lactate on salicylate uricosuria may be due, in part, to enhancement of the uricosuric effect of salicylate when the urine is made alkaline by administration of sodium bicarbonate(9) or its equivalent.) Two analogous experiments in which .17 M instead of .4 M sodium lactate was employed failed to demonstrate any inhibition of salicylate uricosuria.

Effect of sodium r-lactate on probenecid uricosuria. In a parallel experiment with probenecid (Table I), the mean control C_{urate} of 9.1 ml/min. was increased to a maximum of 41.3 ml/min. by intravenous injection of .5 gm probenecid; upon addition to the probenecid infusion of sodium lactate in .4 M concentration, C_{urate} steadily decreased to a minimum of 4.6 ml/min., a decline which was sustained. C_{urate}/C_{inulin} rose and fell concomitantly. The effect of probenecid on the retention of urate caused by lactate was studied in two additional subjects by reversing the order of drug administration. The results shown in Fig. 1 are illustrative. The mean C_{urate}/C_{inulin} in the pre-medication period was 3.8%. After infusion of .17 M sodium lactate for 40 minutes at a rate of 14 ml/min., C_{urate}/C_{inulin} fell to 0.9%. At this point 1.5 g probenecid was given by mouth, the lactate infusion being continued for one hour. After 20 minutes C_{urate}/C_{inulin} began to rise, more rapidly when the lactate infusion was discontinued. The course of the $C_{urate}/C_{creatinine}$ thereafter reflected the usual probenecid uricosuria.

Effect of sodium r-lactate on urate retention caused by pyrazinamide. C_{urate} was reduced by administration of 1.0 g pyrazinamide(10) from the premedication 7.4 ml/min. to 4.3 ml/min. (Table I). Upon infusion of .4 M

sodium lactate, C_{urate} declined further to a minimum of 1.3 ml/min., in part doubtless due to the continued action of pyrazinamide. Since the final level of C_{urate} was not lower than ordinarily obtained with pyrazinamide or lactate alone, an additive or potentiating ef-

TABLE I. Effect of Sodium Lactate Infusion on Urate Clearance, Salicylate and Probenecid Uricosuria, and Urate Retention Caused by Pyrazinamide. (All infusions given intravenously at 8 ml/min.)

Age, B.S.A.	Period (min.)	C_{inulin} (ml/min.)	C_{PAH} (ml/min.)	UV_{urate} (μg/min.)	C_{urate} (ml/min.)	Urine pH
39, 2.04 M²	−58 to 0	106	410	672	7.4	5.4–5.6
		.17 M sodium lactate, 1000 ml				
	0– 25	92.7	367	300	3.3	6.0
	25– 45	104	415	160	1.8	6.8
	45– 86	106	413	170	1.9	7.3
	86–129	102	425	182	1.9	7.5
39, 2.27 M²	−45 to 0	145	681	935	9.5	5.5–5.7
		.4 M sodium lactate, 1000 ml				
	0– 15	176	860	675	6.9	6.1
	15– 30	143	715	141	1.4	6.6
	30– 60	130	612	115	1.2	7.1
	60– 90	136	637	115	1.2	7.6
	90–120	153	700	120	1.2	7.7
42, 2.07 M²	−115 to −85	124	459	688	7.1	6.8
	− 85 to 0	117	80.7*	838	9.0	5.9
		.5 M sodium lactate, 1000 ml				
	0– 22	120	82.6*	415	4.2	5.9
	22– 40	118	92.6*	148	1.5	6.6
	40– 80	120	81.2*	145	1.5	7.0
	80–121	120	—	113	1.1	7.5
39, 2.20 M²	−30 to 0	124	669	1085	11.8	—
		Sodium salicylate, 3.0 g, in 100 ml saline solution				
	0– 31	122	830	3302	41.3	6.5
	31– 42	145	770	3790	56.5	—
	42– 55	145	790	3727	55.7	6.9
		Sodium salicylate, 4 g, in .4 M sodium lactate, 1000 ml				
	55– 75	110	895	1165	17.4	6.8
	75– 95	133	917	2038	30.4	7.1
	95–136	108	872	3523	52.6	7.3
	136–165	110	830	3450	51.5	7.6
60, 1.58 M²	−30 to 0	89.3	311	919	9.1	6.2–6.4
		Probenecid, .5 g, in 100 ml saline solution				
	0– 15	71.7	260	2050	20.7	6.4
	15– 30	93.9	273	3230	35.9	6.6
	30– 45	86.8	280	3225	41.3	6.7
		Probenecid, .5 g, in .4 M sodium lactate, 1000 ml				
	45– 65	95.1	319	1828	22.0	6.9
	65– 87	93.2	291	653	7.5	7.3
	87–125	71.9	244	417	4.6	7.6
	125–165	71.0	296	448	4.7	7.6
37, 2.05 M²	−28 to 0	127	469	571	7.4	5.6
		1.0 g pyrazinamide orally				
	0– 22	117	483	530	6.9	5.7
	22– 41	120	503	482	6.3	5.9
	41– 61	130	475	330	4.3	5.8
		.4 M sodium lactate, 1000 ml				
	61– 86	132	505	197	2.6	6.2
	86–105	123	577	100	1.3	6.9
	105–125	123	571	100	1.3	7.5
	125–135	116	586	113	1.5	7.6

* Tm_{PAH} (mg/min.).

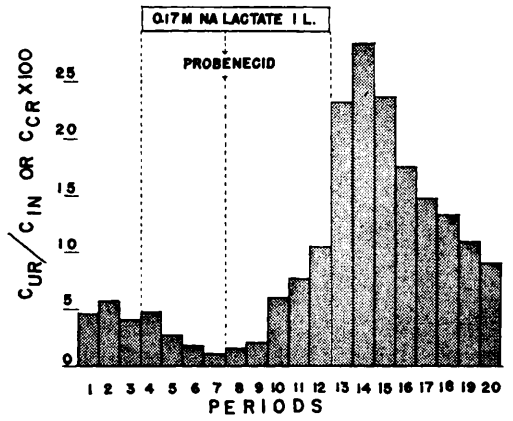

FIG. 1. Gouty subject. The first 3 clearance periods, each of 10 min duration, indicate C_{urate}/C_{inulin} before medication. In periods 4 through 12, a total of 1 liter of 0.17 M sodium lactate was infused at approximately 10 ml/min. At point indicated by arrow, 1.5 g probenecid was given by mouth. Initial reduction in C_{urate}/C_{inulin} produced by infusion of 0.17 M sodium lactate was gradually overcome by uricosuric action of the probenecid. Upon cessation of lactate infusion, however, the probenecid effect was much more pronounced (post-infusion periods each of 1-2 hours duration, endogenous creatinine clearance used as measure of filtration rate).

fect is not suggested.

In another experiment the initial C_{urate} of 6.8 ml/min. was first reduced by infusion of .4 M sodium lactate to 1.7 ml/min.; then, with continued lactate infusion, pyrazinamide, 1.0 g was given orally. The minimum C_{urate} resulting was 1.3 ml/min.

Discussion. The striking reduction in urinary uric acid excretion effected by lactate is of particular interest because no other natural metabolite has yet been demonstrated to share this property in such pronounced degree. High fat diets cause similar but apparently less marked uric acid retention(11-13), presumably through the action of some metabolic intermediate (acetoacetic acid?(2)). Pyruvate causes an increase in urinary uric acid excretion(1,2); but even though administration of lactate may result in a distinct rise in blood pyruvate (and α-ketoglutarate) levels(14), the predominant effect on uric acid excretion is that of lactate. Administration of citrate (as the potassium salt, 25 g by mouth over a period of 50 minutes) caused an increase in C_{urate}/C_{inulin} from 4.8 to 8.8% in one hour(15). Intravenous infusion of .4 M acetate likewise increased the urate clearance to about 2-fold; lesser concentrations of acetate had no measurable effect(15).

Alkalinization with .4 M sodium bicarbonate by sustained intravenous injection caused an equivocal rise in C_{urate}/C_{inulin}, from a mean of 8.0% to a mean of 9.7%(9). Alkalinization of the urine by means of Diamox slightly decreased C_{urate}/C_{inulin}, from a mean of 6.4% to a mean of 5.3%(9), in most cases associated with an approximately 10% reduction in glomerular filtration rate.

The possible physiological role of lactic acid in the regulation of renal excretion of uric acid has long been a subject of interest, notably in connection with the lacticacidemia and reduced urinary uric acid excretion of exercise (16). Nichols *et al.*(4), using clearance technics, found that the sharp decrease in urate clearance observed *during* exercise might be accounted for by the accompanying reduction in glomerular filtration rate, but persisted long after the filtration rate had returned to normal upon cessation of exercise; the increased plasma lactic acid levels also persisted. Moreover, there appears to be a significant relationship between the height of the plasma lactic acid level and the degree of uric acid retention(3,4). These observations would suggest that the metabolism of lactic acid may be a factor in the regulation of uric acid excretion, at least under the conditions of exercise.

The present study makes clear that infusion of sodium lactate causes no reduction in the filtered urate loads presented to the tubules and implies that excessive lactate in the glomerular filtrate and/or blood enhances tubular reabsorption or, possibly, decreases tubular excretion of urate. It is known that filtered lactate is completely reabsorbed by the tubules, at least until the Tm for lactate is approached, at blood lactate levels of 60-100 mg %(17,18); such high blood levels are attained with strenuous exercise but not by injection of lactate in the concentrations here employed.

Summary. Renal clearance studies are described which corroborate and extend earlier observations indicating that administration of sodium lactate in sufficient dosage results in

a profound fall in urinary excretion of uric acid. C_{urate} declined from a mean control level of 10.4 ml/min. to a mean minimum of 1.4 ml/min. The uricosuria produced by salicylate and probenecid was temporarily abolished by lactate. The significance of these findings is discussed.

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Quantitative Measurement of Inhibition of the Enzymatic Detoxification of Malathion by EPN (ethyl p-nitrophenyl thionobenzenephosphonate).* (23617)

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Frawley *et al.*(1) recently demonstrated that simultaneous administration of ethyl p - nitrophenyl thionobenzenephosphonate (EPN) and S-(1,2-dicarbethoxyethyl)-O, O-dimethyl phosphorodithioate (malathion) to rats and dogs causes marked potentiation of the acute and subacute toxicity of these insecticides. The widespread use of organic phosphorus-containing insecticides on food crops makes it possible for the diet of man and domestic animals to contain low quantities of several of these compounds. For an accurate evaluation of the health hazards which might result from potentiation of the action of cholinergic organic phosphates it was desirable to have a sensitive, direct method for measuring the biochemical event responsible for the effect which could be applied to the tissues of animals fed low levels of these insecticides. It has been observed by Cook *et al.*(2) that EPN inhibits the hydrolytic detoxification of malathion by rat liver homogenates *in vitro*. This observation provides a possible explanation for potentiation of the toxicity of malathion by EPN since the low mammalian toxicity of malathion is apparently highly dependent upon rapid and complete detoxification. The present communication describes a quantitative method for measuring inhibitory action of EPN on detoxification of malathion. Data are presented which show the applicability of this method for *in vitro* experiments and for measurements on tissues taken from animals given acutely toxic and low dietary levels of EPN. The tissue distribution of the esterase which catalyzes the hydrolytic detoxification of malathion was also studied.

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Methods and materials. Adult male and