Hyperuricemia in Starvation.* (29971)

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Recent epidemiologic studies have revealed a striking correlation between obesity and hyperuricemia(1,2). This propensity of the obese is accentuated by starvation(2). Previous reports implicate a decrease in renal clearance of uric acid, but the mechanism of this decline has not been clarified(3-5). We have investigated this phenomenon in more detail and have determined the ratio of uric acid clearance to creatinine clearance as well as the influence of supplemental urea and potassium on the renal handling of uric acid.

Materials and method. Eleven obese patients, 16 to 51 years of age, were selected from volunteers seeking assistance in weight reduction. Nine patients were female and 2 male. They were hospitalized throughout the study on the Metabolic Research Ward of the Bronx Municipal Hospital Center.

One male patient had clinically overt maturity onset diabetes previously requiring insulin therapy, but presently receiving tolbutamide, three grams daily. Although glycosuria persisted, therapy was withheld during hospitalization. A second patient had subclinical diabetes mellitus. Another patient had idiopathic hypoparathyroidism, adequately controlled by treatment with calcium gluconate and vit D. There was no evidence of other endocrinopathy, nor other intercurrent disease; no medications, other than daily multivitamin capsules and occasional sedatives were administered during the study.

Each patient fasted for 3 weeks during this time having free access to water. Three patients underwent simple fast for 3 weeks. Two patients were given 40 mEq potassium as K-triplex or KCl daily during the 3-week study; 2 patients received the same quantity of potassium plus 40 to 50 g of crystalline urea daily; and 4 patients received 40 to 50 g of urea daily.

All chemical analyses were carried out on the Technicon AutoAnalyzer (Technicon Instruments Corp., Chauncey, N. Y.). Uric acid was determined by a modification of the method of Henry, Sobel and Kim(6); creatinine was determined by a modification of the alkaline picrate method(7); sodium and potassium were measured by flame photometry (we would like to thank Dr. Eli Seifter for carrying out the chemical determinations).

Results. As can be seen in Table I, serum uric acid concentration in the basal state ranged from 4.8 to 9.4 mg% prior to starvation; 7 of 11 patients displayed values above 7.0, an abnormal value in this laboratory. The mean pre-fast serum uric acid level was 7.3 mg%.

Following one week of starvation, serum uric acid levels increased to a mean of 14.7 mg% with a range of 7.4 to 21.0 mg%. This increase in serum uric acid levels persisted throughout the second and third weeks of starvation. As can be seen in the accompanying Table, supplementation with urea and/or potassium had no apparent influence on serum uric acid levels. One patient (#5) had an acute attack of gouty arthritis, responding promptly to colchicine.

The clearance of creatinine declined throughout the study reaching an average of 70% of control values at one week, 47% at 2 weeks, and 47% in 3 weeks. This decline was similar in all patients, regardless of the nature of their supplementation. Uric acid clearance declined much more rapidly, reaching 31% of control levels in 7 days, in parallel with the course of elevation of serum uric acid. This decline in uric acid clearance preceded the decline in creatinine clearance. Demonstration that the uric acid clearance declined earlier and independently of the creatinine clearance can be seen in the changing "Cua"/"Ccr" ratio.

Also noteworthy is that one patient with maturity onset diabetes mellitus, having continuing glycosuria throughout the study, had

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TABLE I.

Patient	Supplement	Control	Serum uric acid			Uric acid clearance ("Cua") % of control period*			Creatinine clearance ("Ccr") % of control period†			"Cua"/"Ccr"‡		
			1st wk	2nd wk	3rd wk	1st wk	2nd wk	3rd wk	1st wk	2nd wk	3rd wk	1st wk	2nd wk	3rd wk
1	None	8.1		13.6	9.7				63		54			
2	"	7.5	21.0	17.0	16.8	10		21	94		49	.11		.43
3	"	9.0	16.8	16.0	13.8	57	57		84	50	45	.68	1.14	
4	Potassium	4.8	12.6	19.2	18.4	26		29	66			.40		
5	"	8.8	10.2	15.0	15.8	39		20	70	39	26	.56		.77
6	Urea	7.4	17.0	15.2			28			36			.78	
7	"	9.4	20.0	23.8		8	19		122	109	75	.07	.17	
8	"	5.6	11.4	8.8		38	37		102	35		.37	1.06	
9	"	6.4	7.4	4.4	9.0	77	92	17	11	10		7.00	9.20	
10	Urea and potassium	7.0	17.6	20.0	16.8	10	24	30	65	49	32	.15	.49	.94
11	*Idem*	6.6	13.4	15.4	13.0	19	23	17	26			.75		
	Mean	7.3	14.7	15.3	14.2	32	40	22	70	47	47			
	± S.E.	±.4	±1.4	±1.6	±1.2	±8	±10	±2	±10	±11	±7			
	p		<.005	<.005	<.005									

* Cua during control period was 7.1 ± 0.4 ml/min (mean ± standard error). † Cer during control period was 112 ± 14 ml/min (mean ± standard error). ‡ Control ratio is 1.0, by definition.

changes in serum uric acid, uric acid clearance, creatinine clearance, and "Cua"/"Ccr" of a magnitude consistent with those shown by other patients.

Patient #5, who had an acute attack of gout at a serum uric acid level of 14-15 mg%, was treated with probenecid with only a temporary increase in uric acid clearance and a temporary decline in serum uric acid levels. No further attacks of acute gout recurred although fast persisted. He was maintained on colchicine as well as the probenecid therapy.

Discussion. Our studies confirm a tendency toward hyperuricemia in the obese, intensified by starvation. This is independent of changes in creatinine clearance and not influenced by supplements of potassium or restitution of normal urinary solute (urea) load. The rise in serum uric acid concentration during starvation is not accounted for simply by the changes in renal glomerular filtration rate but must be at least in part a reflection of changes in the renal tubular handling of uric acid. In another recent preliminary report(2), a decrease in "Cua"/"Ccr" was noted in one patient.

Possible explanations for the decline in uric acid clearance noted in the fasting obese patient include the suggestion that decreasing competition by declining filtered glucose predisposes to greater tubular reabsorption of uric acid(5). Studies by Shapiro *et al*(2) suggest that keto acids, elevated in starvation, may play a significant role. This is presumably analogous to the hyperuricemia associated with ethanol administration(8) and disorders of intermediary metabolism which lead to lactic acidosis(9,10). Further studies of uric acid metabolism in the obese are necessary to define the molecular mechanism of hyperuricemia.

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Effect of Dietary Sodium Restriction on Adrenal Cortical Response to ACTH.* (29972)

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In dogs fed a commercial dog food providing a daily intake of about 40 mEq of sodium, the dose of ACTH required to increase aldosterone output is larger than the dose producing maximal glucocorticoid secretion (1,2). A low sodium diet stimulates aldosterone secretion, but does not increase glucocorticoid output(3,4), suggesting that ACTH plays no role in the adrenocortical response to sodium restriction. However, this conclusion assumes that the low sodium diet has no effect on the adrenocortical response to ACTH. The present studies demonstrate that although there is no change in the glucocorticoid response to ACTH, the aldosterone-stimulating activity of ACTH is increased in dogs fed a low sodium diet.

Materials and methods. Fourteen male mongrel dogs weighing 5.8 to 11.2 kg were subjected to left nephrectomy. They were then fed a diet providing less than 1 mEq of sodium and 20 mEq of potassium per day for 5 days (4 dogs), 14 days (6 dogs), or 2 months (4 dogs). The changes in aldosterone and 17-hydroxycorticoid secretion produced in these dogs by 2, 5, 10, 50 and 100 mU doses of ACTH were then measured. Each of the dogs was anesthetized with pentobarbital, the right kidney removed, the right lumboadrenal vein cannulated(5), and the dog hypophysectomized. One hour after hypophysectomy (2 hours in the case of dogs on the low sodium diet for 2 months), a control adrenal venous blood collection was made and the adrenocortical response to various doses of ACTH then tested. ACTH (Upjohn) was administered intravenously. Adrenal venous blood was collected from the 4th to 14th minute after injection. Thirty minutes after injection (60 minutes in the case of most of the 50 mU doses) another adrenal venous blood specimen was obtained, following which another dose of ACTH was injected. The 100 mU dose was injected last, and the animal sacrificed after the first adrenal venous blood collection following this dose. The samples were collected in centrifuge tubes containing 3 drops of heparin solution, centrifuged promptly, and the plasma frozen for subsequent determination of aldosterone content by the method of Kliman and Peterson(6), and 17-hydroxycorticoid content by the method of Silber and Porter(7). Output of these hormones was calculated by multiplying their concentration in the adrenal venous blood by the adrenal venous plasma flow per minute. Comparably prepared control dogs that had been fed a commercial diet providing about 40 mEq of sodium were injected with the same doses of ACTH; most of the results in these control dogs have been published previously(1).

In all dogs, blood pressure was monitored throughout the experiment using a Grass Model 5 polygraph and a Statham strain

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