THE FATE OF CREATINE WHEN ADMINISTERED TO MAN.

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The fate of creatine in the organism has been the subject of many investigations. A recent review of the literature on this subject discloses conflicting ideas concerning creatine-creatinine metabolism. The apparent inconsistencies may be ascribed to several factors, the most outstanding being the varying quantities of creatine administered, usually quite small, together with the fact that administration of the substance was not continued over a sufficiently long period. In most cases the difficulty and expense of isolating pure creatine limited the amount which could be used for experimentation.

It is possible to omit much of the literature since one may refer to the excellent review on this subject by Hunter (1). In his classic paper Folin (2) concluded that creatine and creatinine were independent of one another in metabolism, and that the former was utilized as a food. However, the results of later investigations, particularly those of Rose and Dimmitt (3) and Benedict and Osterberg (4), have shown that ingestion of creatine may lead to an increased output of creatinine in the urine. This evidence coupled with the fact that the creatinine found in muscular tissue is apparently derived from the "creatine complex" by the action of enzymes, leads one to believe that urinary creatinine must depend upon creatine as its precursor.

The possibility of creatine acting as an anabolite has been shown by Benedict and Osterberg (4). Dogs that were fed on a basal diet to which creatine was added not only gained weight but showed a marked positive nitrogen balance. The evidence obtained in these experiments seems to indicate that creatine may serve as a food, which would confirm the idea advanced by Folin (2) in 1906.

In this investigation, we carried out feeding experiments with creatine on man. The results obtained show definitely that creatine and creatinine are not independent of one another in the body. Furthermore, these experiments demonstrate that a major portion of the creatine retained by the tissues may be converted to creatinine. Proof is given that creatine may spare protein.

EXPERIMENTAL PROCEDURE.

The writers served as the subjects for the present experiments, subsisting upon a creatine-free diet for 6 and 8 weeks respectively. The diet, consisting of shredded wheat, bananas, bread, butter, strawberry preserves, sugar, and milk, represented an intake of approximately 3400 calories. The diet was adhered to strictly with respect to its composition. During the experiment, daily exercise was part of the regular routine. The type of exercise indulged in was not strenuous and varied from day to day.

It was found that the nausea induced by the bitter taste of the creatine could best be avoided by dissolving it in hot weak tea. The creatine was taken about 2 hours after the noon meal. By recrystallizing commercial creatine twice, the resulting product was found to be pure upon analysis.

The urines collected at the end of 24 hours were diluted to the same volume each day with a few exceptions. Total nitrogen was estimated by the macro Kjeldahl-Gunning method and creatinine by the Folin method. Creatine was determined by the autoclave method of Folin. Creatinine zinc chloride was used as a standard for the creatine and creatinine determinations. Ammonia nitrogen was estimated by the procedure of Van Slyke and Cullen.

In order to be certain that the body was in nitrogen equilibrium the experimental diet was begun 2 weeks before the first sample of urine was collected. After a satisfactory control period during which the urinary constituents studied were fairly constant, the administration of creatine was begun.

The detailed results of the experiments are recorded in Tables I and II. The experimental periods lasted 29 and 44 days during which time 250 and 340 gm. of creatine, respectively, were ingested. The analyses for July 12 cannot be considered because

of a mistake made in taking unknown quantities of creatine on the previous day. These data have been omitted from the averages obtained for this period.

Results.

During the first few days of creatine feeding its retention by the body is striking. A gradual decrease in retention may be noted, however, as the experiment proceeds. On the other hand, the extra creatinine eliminated rises slowly towards a maximum level. It is interesting to note that the smallest creatine and extra creatinine output during the entire experiment is obtained after the 1st day of creatine feeding. If creatinine is to be considered as the end-product of creatine metabolism we must assume that creatine may be stored without any appreciable breakdown.

Apparently the ability of the tissues to store creatine should reach its maximum after the daily ingestion of 10 gm. of creatine over a period lasting more than a week. At this point Subject A. C. (Table I) doubled the daily dose of creatine fed. The figures for the extra creatinine eliminated and the creatine retained both show marked increases. In fact the output of extra creatinine on the 2nd day of this period shows an increase of about 160 per cent over the control period. We believe this figure represents the largest percentage creatinine output due to creatine feeding recorded in the literature. The unexpected increased retention of creatine indicates that the creatine reservoir may be larger than has been hitherto thought possible. As the period progresses the amount of creatine retained becomes smaller.

At the end of an 8 day period during which time 160 gm. of creatine were taken, the daily dose was dropped back to 10 gm. Although this period lasted but 2 days evidence regarding creatine storage in the body is given. The excretion of creatine was greater than the intake on the 1st day.

Subject L. P. G. continued to consume 10 gm. of creatine daily over a period of 34 days. In Table II it is seen that the creatine and creatinine excretion rose slowly until a fairly even level was reached at about the end of the first period. Although the

TABLE I.

Experiment 1. Fate of Ingested Creatine.

Subject A. C.

The figures for creatine are expressed as creatinine.

Date.	Volume of urine.	Total N.	NH_3	Total creatinine.	Preformed creatinine.	Creatine.	Creatine retained.	Extra creatinine eliminated.	Percentage of retained creatine eliminated as creatinine.	Weight.	
1925	*cc.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*per cent*	*kg.*	
June 20										70.4	
" 29										72.0	
July 1	840	7.80	0.327	1.49	1.49						Preliminary period of 7 days.
" 2	850	7.77	0.271	1.52	1.52						No creatine given.
" 3	1,020	7.82	0.339	1.54	1.54						
" 4	730	7.41	0.315	1.55	1.55						
" 5	590	7.53	0.347	1.46	1.46						
" 6	685	7.66	0.241	1.49	1.49					72.0	
" 7	470	7.42	0.336	1.53	1.53						
		7.62	0.311	1.51	1.51						Average daily output.
July 8	690	9.04	0.378	4.44	1.73	2.71	5.91	0.22			
" 9	595	8.60	0.436	5.26	1.96	3.30	5.32	0.45			
" 10	1,090	9.57	0.554	6.12	2.14	3.98	4.64	0.63			First period of creatine administration.
" 11	970	9.70	0.571	6.53	1.90	4.63	3.99	0.39			10 gm. of creatine (8.62 gm. creatinine)
" 12*	740	8.32	0.549	2.96	1.73	1.23					ingested daily.

July 13	715	8.82	0.420	5.84	2.22	3.62	5.00	0.71		
" 14	610	9.13	0.431	6.15	2.17	3.98	4.64	0.66		
" 15	735	9.02	0.532	6.16	2.26	3.90	4.72	0.75		
" 16	710	8.96	0.473	7.14	2.32	4.82	3.80	0.81		
" 17	650	9.46	0.448	8.11	2.32	5.79	2.83	0.81		
		9.14	0.471	6.19	2.10	4.08	4.54	0.60	13	Average daily output.
July 18	1,200	12.56	0.445	16.38	3.59	12.79	4.45	2.08		
" 19	1,240	12.56	0.445	15.54	4.05	11.49	5.75	2.54		Second period of creatine administration.
" 20	780	12.12	0.420	16.12	3.88	12.24	5.00	2.37	74.0	20 gm. of creatine (17.24 gm. creatinine)
" 21	990	12.37	0.414	17.24	3.66	13.58	3.66	2.15		ingested daily.
" 22	860	11.80	0.381	15.87	3.46	12.41	4.83	1.95		
" 23	930	12.37	0.398	16.00	2.74	13.26	3 98	1.23		
" 24	960	12.88	0.386	16.00	2.70	13.30	3.94	1.19		
" 25	1,275	12.31	0.487	18.45	3.42	15.03	2.21	1.91		
		12.37	0.422	16.45	3.44	13.01	4.23	1.93	45	Average daily output.
July 26	940	9.99	0.429	11.69	2.32	9.32	−0.70	0.81		Third period of creatine administration.
" 27	670	9.48	0.429	11.17	3.02	8.15	0.47	1.51		10 gm. creatine (8.62 gm. creatinine) ingested daily.
		9.73	0.429	11.43	2.67	8.73	−0.12	1.16		Average daily output.
July 28	490	7.14	0.420	4.62	2.20	2.42		0.69	75.2	Fourth period. No creatine ingested.
" 29	620	8.03	0.408	2.80	2.12	0.68		0.61		
		7.58	0.414	3.71	2.16	1.55		0.65		Average daily output.

* Figures for day not averaged.

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