CXXXI. THE BIOCHEMISTRY OF SILICIC ACID.

III. THE EXCRETION OF ADMINISTERED SILICA.

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It has already been shown [King, Stantial and Dolan, 1933] that the level of soluble silicates in the urine can be influenced by diet. On continuous injection by the intravenous route of dilute neutralised solutions of sodium silicate, a rapid elimination, continuous during the time of injection and lasting for some hours afterward, has always occurred. Introduction of a suspension of silica dust into the stomach has led to rather smaller increases in the urinary output of silica. Such increases have, however, been definitely significant and point either to a partial dissolution of the silica by the alkaline duodenal juice or possibly to actual passage through the intestinal wall of the finest of the particles.

In the several experiments which have been performed, and in which the urinary excretion of silica has been markedly increased, no significant variations in the blood-silica, other than small temporary increases, have been observed. These facts appear to indicate a very low renal threshold for silicate.

Experimental.

The analytical procedure described by King and Stantial [1933] was followed throughout. Samples of blood and urine were collected in bakelite-coated vessels.

Ingestion of particulate silica. Preliminary experiments with rabbits demonstrated that when small quantities of finely powdered quartz[1] were introduced into the stomach, a significant rise occurred in the level of silica in the urine. This was more marked in dogs where the normal amount of silica in the urine is much smaller and the relative rise therefore greater. When 1 g. of the pulverised quartz, suspended in 50 cc. of water, was given to a dog by stomach tube, the urinary excretion of silica promptly rose from 1 mg. (normal) to 3·9 mg. per 100 cc. at 1 hour and remained high for several hours (4·7 mg. at 8 hours), returning the next day to its original level. Larger amounts of silica dust placed in the stomach appeared to be absorbed to a considerable extent and to be promptly excreted in the urine (Table I).

[1] Kindly prepared for us by Prof. H. E. T. Haultain, of the Department of Mining Engineering of this University, by prolonged grinding of quartz crystals in a steel ball-mill.

Table I. *Excretion of silica in the urine after administration by stomach tube of 5 g. powdered quartz.*

Hours	SiO_2 per 100 cc. urine mg.	SiO_2 per 100 cc. blood mg.
0	2·7	0·8
4	14·3	—
7	14·7	0·7
16	4·8	—
24	3·3	0·7

Ingestion of soluble silica. Owing to the alkalinity of solutions of sodium silicate it was found impossible to administer silica in this way, as the dogs invariably vomited the material. If the solution was neutralised to phenolphthalein with dilute hydrochloric acid just prior to administration by stomach tube, however, it was found that the dogs tolerated it well.

Deposits of gelatinous silicic acid tended to form in 5 % sodium silicate solutions when neutralised with hydrochloric acid, and it is probable that a large part of the silicate administered in this way was precipitated as silicic acid before it had been long in the stomach. The alkaline nature of the juices in the small intestine doubtless caused a partial re-solution of some of the silicic acid, but the amount remaining out of solution was probably a large proportion of the whole. Such portions as were absorbed—and they were considerable, although not necessarily constituting a large percentage of the total administered—appeared to be eliminated very quickly in the urine without any pronounced rise of the level of silica in the blood (Tables II and III). Analyses of the organs of the several dogs which were killed after the conclusion of the experiments failed, moreover, to demonstrate any increased concentration of silica in the tissues.

Table II. *Silica content of the urine after administration of silicic acid by stomach tube.*

Hours	mg. SiO_2 per 100 cc. urine	Hours	mg. SiO_2 per 100 cc. urine
Dog 480: 10 cc. 5 % sodium silicate neutralised by hydrochloric acid		Dog 390: 25 cc. 5 % sodium silicate	
0	1·7	0	2·0
1	4·1	1	17·5
2	23·3	3	49·3
3	14·9	5	56·7
4	22·3	6	43·5
5	25·3		
6	23·8	Dog 495: 25 cc. 5 % sodium silicate	
25	4·8	0	0·7
		2	49·2
		4	22·3
		6	11·9
		22	4·0
		29	2·8
Dog 346: 10 cc. 5 % sodium silicate		Dog 340: 25 cc. 5 % sodium silicate	
0	1·9	0	—
3	72·5	3	55·5
5	57·7	5	43·2
7	45·2	7	45·2
9	21·2	9	32·2
72	1·6	24	12·2
		72	1·4

Table III. *Excretion of silica in the urine after ingestion of silicic acid.*

Hours	mg. SiO_2 per cc. urine	cc. of urine	Total mg. SiO_2 in urine	mg. SiO_2 per 100 cc. blood
Dog 480: 100 mg. SiO_2 as silicic acid introduced into stomach.				
0	0·015	—	—	0·8
3	0·480	13·5	6·47	—
5	0·367	5·0	1·86	1·5
7	0·357	11·0	3·93	—
9	0·227	6·0	1·36	0·8
13	0·112	6·5	0·73	—
25	0·060	22·4	1·34	—
72	0·026	—	—	—
		Total	15·69	
Dog 390: 250 mg. SiO_2 as silicic acid introduced into stomach.				
0	0·014	—	—	0·5
3	0·555	13·0	7·21	1·0
5	0·367	17·0	6·25	—
7	0·357	17·0	6·10	0·8
9	0·247	8·0	1·98	—
13	0·132	5·0	0·66	—
25	0·076	36·0	2·77	—
72	0·038	—	—	—
		Total	24·97	

Intravenous injection of silicic acid. Several attempts were made to inject silicic acid in fairly concentrated solution into the ear-veins of rabbits. The solution of 5 % sodium silicate containing the equivalent of 10 mg. of silica per cc., neutralised with hydrochloric acid or by bubbling carbon dioxide into it immediately before using, was injected in quantities of 1 to 5 cc. In almost every case the rabbit died immediately or within a few minutes of the time of administration. The same experience was met with dogs, and it was thought probable that floccules of gelatinous silicic acid forming in the blood-stream caused the animals to die of embolism.

Attention was turned, therefore, to the continuous intravenous injection of solutions containing not more than 1 mg. SiO_2 per cc. over a period of several hours. Fresh solutions were prepared before each experiment.

For the continuous intravenous injections an ordinary hypodermic needle was attached by a fine rubber tube to the nozzle of the barrel of a syringe into which was fitted a rubber stopper carrying a finely pointed glass tube. Rubber tubing connected the glass tube to the tip of a graduated burette and a screw-clamp served to adjust the rate of flow of the solution from the burette. The number of drops falling into the syringe per unit time served as a rough but convenient indication of the rate of flow of the solution. The bottle containing the silicate solution was attached by means of rubber and glass tubing through a two-hole rubber stopper (one hole being plugged with cotton-wool) to the top end of the burette. The solution was delivered into the burette when desired by means of a pinch-cock on the rubber tubing. Before each experiment the whole apparatus was heated in a steriliser and clamped in an upright position to an iron stand which could be placed on the operating table next to the animal.

Female dogs whose urethra was exposed (for catheterisation) by previous operation were employed exclusively for the continuous intravenous injections. The animals were anaesthetised with 0·5 g. of sodium amytal dissolved in a little water. The needle was inserted in the vein of one of the fore-legs and the silicate solution allowed to flow at the desired rate by adjustment of the screw-clamp. A catheter was inserted, tied in place and closed by a pinch-cock, so that the contents of the bladder could be withdrawn at intervals. After about 6 hours the animals usually began to show symptoms of recovering from the anaesthesia; a further 0·5 g. of amytal injected into the rubber tube delivering the silicate solution sufficed to retain them under anaesthesia for a further 6 or 8 hours.

In the several experiments conducted in this way quantities of silicic acid from 100 to 200 mg. were injected over periods of 5 or 6 hours. The response in urinary output of silica was prompt, rising from a small initial value to a high value within the first hour and reaching very high concentrations in the urine toward the end of the period of injection.

During this time the level of silica in the blood was considerably raised, although only to a very minor extent when compared with the rise in the urine. The excretion of silica did not keep pace, however, with its introduction into the blood-stream, only half of the total amount administered being recovered in the urine. It is possible that some of the silica was eliminated by way of the faeces, being excreted in a similar way to calcium in the gut, although it is not unlikely that a fairly large proportion was retained in the body. Analysis of the spleen of one of the animals killed after the experiment showed a silica content considerably higher than normal. The presence of albumin in some of the samples of urine was noted in these experiments.

Table IV. *Continuous intravenous injection of silicic acid.*

Hours	cc. of solution injected	mg. SiO_2 per 100 cc. urine	cc. of urine	mg. SiO_2 excreted	mg. SiO_2 per 100 cc. blood
Dog 481: neutralised sodium silicate solution; 1 mg. SiO_2 per cc.					
0	—	1·0	—	—	—
1	10	3·4	11	0·37	0·2
2	14	15·7	7	1·10	2·6
3	20	20·3	6	1·22	2·7
4	30	36·9	7	2·58	2·8
5	30	34·3	6	2·08	1·7
6	65	68·3	4	2·74	2·8
9	—	61·5	30	18·50	2·8
22 (night)		30·7	15	4·61	1·7
28		34·6	33	11·40	1·7
Night		35·8	45	16·10	—
46	Total SiO_2 in-	15·2	44	6·70	—
73	jected = 169 mg.	2·2	860	18·92	1·4
94		3·0	250	7·50	—
120		2·4	—	—	—
166		1·5	—	—	—
			Total	93·82	
Dog 390: neutralised sodium silicate solution; 0·5 mg. SiO_2 per cc.					
0	—	0·6	—	—	0·3
1	50	26·5	3	0·80	—
2	75	96·7	6	5·81	—
3	43	169·2	5	8·46	6·15
4	80	129·2	6	7·76	6·60
5	95	18·7	31	5·81	—
6	50	55·7	11	6·12	—
7	—	26·0	21	5·46	—
8	50 cc saline	3·7	8	0·29	—
9		26·0	78	20·28	—
10		20·2	8	1·62	—
11		7·0	113	7·91	—
26		17·5	152	26·60	—
31		8·0	23	1·84	—
49		3·5	150	5·25	—
55	Total SiO_2 in-	3·3	16	0·53	—
73	jected = 196 mg.	6·5	200	13·00	—
99		5·0	—	—	—
147		4·8	—	—	—
218		2·6	—	—	—
			Total	117·54	

Two typical experiments using continuous intravenous injection of neutralised dilute sodium silicate solutions are illustrated in Table IV. The dogs were anaesthetised early in the morning and the catheter left in the bladder until late in the evening, a second administration of anaesthetic being given in the afternoon. The dogs were left in metabolism cages overnight and the urine caught in a metal container. Samples of blood were analysed by both the ashing and deproteinising methods, very little difference being found in the results by the two procedures. The very high silica content of the urine made it appear probable that some precipitation due to the acidity of the urine may have occurred. This appeared to be the case in some of the samples, and an increase in the silica value was obtained on warming the sample of urine with sodium hydroxide on the water-bath. All results for urine given in the Table are for sodium hydroxide-treated samples.

Intravenous administration of particulate silica. The milky suspension obtained by shaking quartz powder with isotonic NaCl was decanted from the precipitate of coarser material and was analysed for silica. The results indicated a SiO_2 content of 0·8 mg. per cc., approximately that of the diluted solutions of silicic acid used for continuous intravenous injection. This suspension was injected as in the experiments described in the previous section, over a period of 3 hours. The urine at this time was very bloody and the injection was discontinued. After 6 hours the dog died with no urine in its bladder, despite the fact that 250 cc. of liquid had been given and only a few cc. recovered during the first 3 hours. The silica content of the urine did not rise very greatly, being considerably less than when powdered quartz was given by mouth. This fact appears to point to dissolution of ingested silica by the duodenal juice. It was thought that the complete stoppage of the kidney secretion was probably due to an accumulation of the particles of silica in the glomeruli, but this was not borne out by histological examination[1]. Analysis of the kidneys did not show an abnormal amount of silica. The total amount given was only 200 mg., and this spread over the several organs of the body could not lead to an appreciable rise in the percentage of silica present. The spleen had a slightly higher than normal content. Results for this experiment are contained in Table V.

Table V. *Intravenous injection of powdered quartz suspension.*

Hours	cc. of suspension	mg. SiO_2 per 100 cc. urine	cc. of urine	mg. SiO_2 per 100 cc. blood
0	—	2·1	—	—
1	100	3·3	14	0·3
3½	150	9·9	19	0·8
6	Total SiO_2 injected = 200 mg.	—	None	0·9

Intravenous administration of organic silicate. "Silistren," a glycol ester of silicic acid which is extensively used as a therapeutic agent in Germany, proved a convenient form of organically bound silica. It is a transparent viscous liquid, readily soluble in water, and contains by analysis 14·7 % SiO_2. When dissolved in water it gives a proportion of blue colour with the colorimetric reagents corresponding to a little less than 5 % SiO_2 on the weight of silistren used. Whether this is due to some uncombined silicic acid, to a partial hydrolysis

[1] Histological examination of the kidney showed generalised degeneration of tubular epithelium. Widespread cytoplasmic degeneration of liver cells may have been a *post mortem* development.

due to the acidity of the test solution (the colour increases at a rate faster than that of a sodium silicate standard) or to a mild action on the reagents by the glycol silicate itself is not clear.

Silistren rapidly yields silicic acid at the temperature of boiling water. At room temperature it breaks down very slowly in watery solution, more rapidly in acid solution and in alkaline solution (Fig. 1).

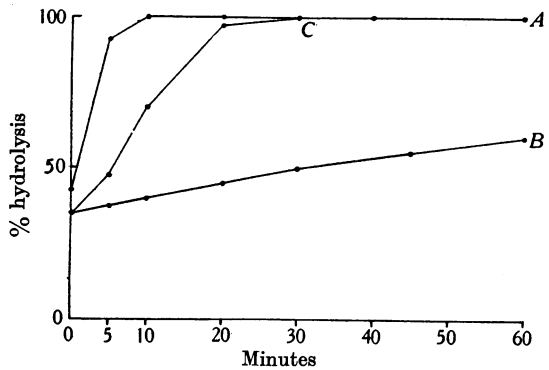

Fig. 1. Hydrolysis of glycol silicate in *A*, boiling water; *B*, *N*/10 H_2SO_4; *C*, *N*/10 NH_4OH.

Table VI. *Injection of organic silicate.*

	Dog 387				Dog 388			
	Urine		Blood		Urine		Blood	
Hours	mg. SiO_2 per 100 cc.	Total mg. SiO_2 in urine	mg. SiO_2 per 100 cc.	Total calculated mg. SiO_2 in blood	mg. SiO_2 per 100 cc.	Total mg. SiO_2 in urine	mg. SiO_2 per 100 cc.	Total calculated mg. SiO_2 in blood
0	0·7	—	2·2	22	1·06	—	2·3	27
¼	—	—	14·3	143	—	—	9·4	108
1	No urine		11·5	115	36·1	10·5	—	—
2	2·8	0·3	14·1	141	47·5	8·5	11·3	130
3	—	—	15·0	150	—	—	10·5	121
4	No urine		—	—	35·1	2·2	—	—
5	—	—	12·4	124	27·8	1·9	9·1	105
7	12·5	0·9	9·8	98	25·0	2·3	8·8	101
24	18·7	98·9 (night sample)	4·8	48	17·2	7·2 (night sample)	7·1	82
48	—	—	3·4	34	—	—	6·9	80
72	3·3	—	1·7	17	5·6	—	3·9	45
96	2·7	—	2·4	24	5·5	—	5·2	60
120	0·7	—	—	—	7·3	—	4·3	50

5·68 g. of silistren, corresponding to 0·836 g. of silica, were dissolved in 20 cc. of water in which a faintly opalescent solution was formed. An amount of the solution corresponding to 400 mg. silica was given to each of two dogs by injection into a vein of the fore-leg. Within an hour both dogs appeared ill, showed signs of nausea and later vomited. Samples of blood and urine were taken at regular intervals for analysis.

The urinary silica in one dog reached almost as high a level as that obtained when silicic acid was introduced into the stomach. The increases for the other

dog, which early in the experiment began to show bloody urine and developed anuria, were more moderate.

The blood-silica was raised and maintained at a higher level by using silistren than by any other means tried. It is possible that when present as an organic compound (*i.e.* glycol ester) silicic acid can remain at high concentration in the blood when it is incapable of remaining there as inorganic silicate. From the weight of the animals and the computed amount of blood present (1/13 body weight) it was estimated that at the highest level 150 mg. of silica were circulating in the blood-stream. As 400 mg. were injected and only a small part of the difference was accounted for by what appeared in the urine, it seems that other tissues than that of the kidneys were removing the silica from the blood, though whether as organic or inorganic silicate is, of course, not known. Both dogs died on the fifth day.

Administration of silicic acid by way of the lung. It was observed by Kraut [1931] that the silica level of the blood rose as a result of introducing a silicic acid solution into the lungs of human subjects by means of an ordinary throat spray. In order to determine if the urinary output of silica could be influenced by the animal breathing in silicic acid, two dogs were exposed to a fog of silicic acid solution. A large box with a tight-fitting cover, carrying a glass window, was used to confine the animals and a dilute solution of silicic acid was sprayed in from time to time as the fog appeared to settle. A slow current of air was blown into the box during the time of exposure so that the dogs might not suffer from lack of oxygen. After 2 hours the dogs were removed and catheter specimens of urine used for silica determinations then and at 6 and 24 hours. The results (Table VII) indicated considerable absorption of silica, but it is possible that the absorption took place by way of the intestine from such amounts of the solution as were licked by the dogs from their skin and fur or were expectorated from the trachea and swallowed.

Table VII. *Silicic acid administered by lung.*

2 hours' exposure to fog of neutralised 0·5 % sodium silicate solution.

Dog 340		Dog 390	
Hours	mg. SiO_2 per 100 cc. urine	Hours	mg. SiO_2 per 100 cc. urine
0	—	0	0·5
2	2·4	2	1·3
6	7·2	6	8·6
24	4·1	24	4·6

Table VIII. *Intra-bronchial administration of silicic acid.*

Dog 391: 7 cc. of neutralised 5 % sodium silicate sprayed into lung through bronchoscope.

Hours	mg. SiO_2 per 100 cc. urine
0	0·8
3	7·5
5	10·1
24	4·7
48	1·0
96	0·7

In Table VIII are shown the results obtained when the same silicic acid solution was introduced into the lungs by means of an atomiser used to blow the spray through the barrel of a bronchoscope introduced into the trachea

down to the bifurcation of the bronchus. A markedly increased output of silica was observed in the urine, but it is again not clear that this may not have been due, in part at least, to expectoration and swallowing of some of the solution.

SUMMARY.

Introduction of soluble or of particulate silica into the stomachs of animals leads to marked increases in the output of silicate in the urine without any corresponding increase in the blood.

Moderate increases in the concentration of silica in the blood and enormous increases in the urine were observed following the intravenous injection of silicic acid. Not all the silica injected could be accounted for by that recovered in the urine.

Intravenous injection of a suspension of finely particulate silica caused death of the animal within a few hours with moderate increases in the urinary silica.

The blood appears capable of maintaining a much higher concentration of organic than of inorganic silicate. Injection of a solution of the glycol ester of silicic acid resulted in considerable increases in the "total" silica content of the blood and moderate increases in the urine. The animals died several days subsequent to the administration of the organic silicate.

Spraying of silicic acid into the lungs led to increased urinary output, but it is not certain that this was due to absorption from the lungs.

It is suggested that animals possess a very low renal threshold for silicate.

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