SILICOSIS AND THE METABOLISM OF SILICA

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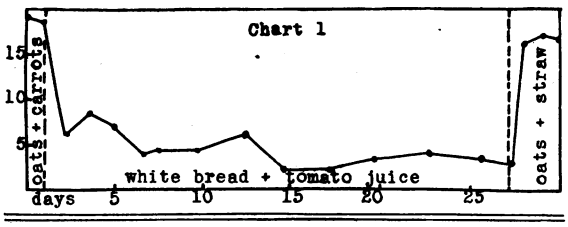
SILICOSIS is an industrial disease arising from the entrance of finely particulate silica into the lungs of workers in dusty trades. The presence of large amounts of silica in the lungs leads to the production of extensive nodular fibrosis. It is the purpose of this communication to present the results of a study of the metabolism of silica when introduced into the body in a variety of ways, and the means which the body has at its disposal for the elimination of silica.

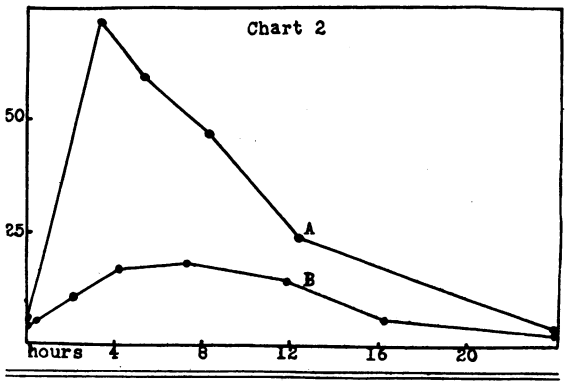
In previous studies from this laboratory[1, 2] attention was drawn to the fact that all body tissues and fluids, whether fetal or adult, showed the presence of significant amounts of silica when examined by a delicate colorimetric method of analysis. Whether or not silicon should be considered an essential constituent of animal protoplasm cannot at present be decided. Its universal presence appears reasonable, however, when one remembers that it is always a constituent of the environment of the developing egg, whether that environment be the water of the ocean or the blood of a mammalian mother.

The paths of entry for silica into the body are, of course, the digestive tract and the lungs. The most of that entering the gut is eliminated in the fæces, but a fairly large amount must be absorbed into the blood, as is shown by the constant excretion of silica in the urine, particularly in the case of herbivorous animals which are ingesting large amounts in their food. All foods of vegetable origin contain silicon, the hulls of grains, hay and straw being particularly rich in this element.[3] That there is little retention of this absorbed silica in the body is indicated by the relatively low silica content of the liver, spleen and kidneys of these animals.

That the silica content of the urine may be influenced at will by the diet was shown by an experiment in which four rabbits, which had been kept on whole oats and carrots, and which showed a high silica content in the urine, were placed for four weeks on a white bread and tomato juice diet; the urinary silica values began to drop immediately the change of diet was made, and continued low until the animals were put back on oats and hay, when the amounts excreted in the urine rose very markedly (Chart 1).

The administration of pure silica into the





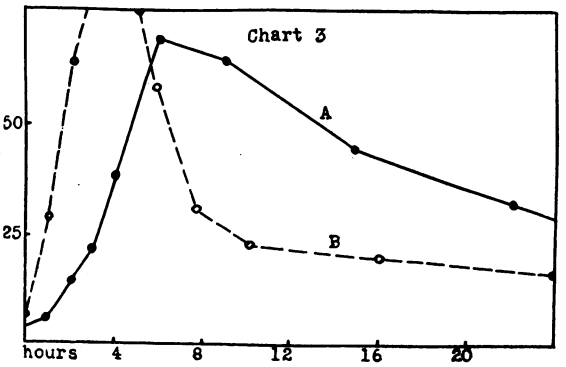


CHART 1.—Influence of diet on the urinary excretion of silica in rabbits.

CHART 2.—Effect of administration into the dog's stomach (A) of silicic acid, and (B) of powdered quartz, on the excretion of silica in the urine.

CHART 3.—Effect of silicic acid injected into the blood stream on the excretion of silica in the urine. (A) 150 mg. injected during 6 hours; (B) 200 mg. injected during 5 hours.

The figures on the left represent mg. SiO_2 per 100 c.c. of urine.

stomach, whether as silicic acid or as powdered quartz, was also followed by a prompt increase of the content of silica in the urine (Chart 2). The increases were, naturally, more marked when the soluble silica was used (silicic acid) than when the insoluble form was given. It would appear that whatever silica enters the blood by way of the intestine passes rapidly into the urine, there building up to high concentration without any demonstrable increase in the silica concentration of the blood.

Several experiments were conducted in which soluble silica was introduced into the blood stream by continuous intravenous injection over periods of several hours (Chart 3). The urinary excretion of silica promptly rose from small initial amounts to high values within the first hour, and very high concentrations of silica were found in the urine toward the end of the period of injection. The level of silica in the blood was raised during this time to only a very minor extent when compared with the increases in the urine. These experiments appeared to indicate that the body possesses a very efficient mechanism for the disposal of silica, once it has entered the blood stream in the soluble form. The existence of a low kidney threshold for silicate was thus demonstrated.

The entrance of silica into the lungs is brought about by the inhalation of finely particulate silica dust. Miners, sand-blasters, and many other workers in dusty trades are subject to the presence of large quantities of silica in the air they breathe; even in normal individuals seldom exposed to dusty conditions a considerable amount of particulate silica must enter the lungs.

Of the silica dust inhaled, the majority of the particles are wafted up by the cilia of the bronchial epithelium and are either expectorated or swallowed, but the finest of the particles find their way into the alveolar spaces, and once they have lodged in the parenchyma there is no ready means of exit. Some particles which are engulfed by phagocytic cells which have passed into the air spaces are expectorated with their enveloping cells; other ingested particles are drawn into the lung parenchyma, and the migration of the phagocytes carries them varying distances in the lymph channels. That many particles reach the lymph nodes, and even the spleen by way of the blood stream, is attested by the high silica content of these glands.[1] The finest of the particles may, however, be slowly dissolved by the mildly alkaline body fluid constantly bathing them, to be carried away in solution and excreted in the urine.

Former experiments by the authors,[2] and by Kraut[4] showed an increase in the urinary output of silica following the spraying of neutralized sodium silicate solutions into the lungs, but the increases noted may have been due to expectoration and swallowing of the solution followed by absorption into the blood from the gut. Experiments have now been completed, however, which demonstrate absorption from the lung with no possibility of the silica reaching the blood by way of the intestine. Under amytal anæsthesia the œsophagus of a dog was exposed and was clamped off by means of artery forceps, the prongs of which had been bent so as to exert only a gentle pressure. A bronchoscope was inserted through the trachea into the left bronchus, and the dog was then raised into a vertical position. Fifty c.c. of silica-containing solution (soluble or particulate) were now allowed to run slowly down into the lung through a narrow tube passed down the bronchoscope. Thorotrast was mixed with the silica solution,

TABLE I.

URINARY EXCRETION OF SILICA WHEN ADMINISTERED INTO THE LUNG.

Amytal anæsthesia; œsophagus clamped off with artery forceps.

Dog 27: silicic acid solution (60 mg. SiO_2) introduced into the left lung.

Hours	*Mg. SiO_2 per 100 c.c. urine*	*c.c. urine*	*Total SiO_2 excreted in the urine*
0	1.8	–	–
2	44.2	20	8.8
4	47.4	14	6.6
7	29.4	17	5.1
Night	28.1	66	18.6
25	28.0	1	0.3
Total SiO_2 recovered =			39.4 mg.

Dog 29: 50 c.c. of quartz suspension (0.5 g. SiO_2) introduced into the left lung.

Hours	*Mg. SiO_2 per 100 c.c. urine*	*c.c. urine*	*Total SiO_2 excreted in the urine*
0	1.1	–	–
3/4	5.4	19	1.0
3	12.0	14	1.7
5	8.6	8	0.7
7	11.2	16	1.8
Night	6.9	40	2.8
25	5.4	4	0.2
Total SiO_2 recovered =			8.2 mg.

and an x-ray photograph taken as soon after administration as possible, to determine into which areas of the lung the solution had penetrated. Catheter specimens of urine were taken immediately before the administration and at intervals afterwards. These samples were measured as to volume and to silica content by the colorimetric procedure described in the protocols.

The results of two experiments are given in Table I. In the first (where soluble silica was used) a very marked increase from 1 to nearly 50 mg. per cent of silica in the urine took place. In the time during which the urinary silica was followed a total of 40 mg. was excreted. If it be assumed that this silica came entirely from the silicic acid placed in the lung, then 66 per cent of that administered was recovered in the urine. Lesser increases were observed in the second case where a very finely particulate suspension of quartz dust (made by water sedimentation of powdered quartz) was employed. As might be expected, there was not so great a rise in the output of silica in the urine as in the case where soluble silica was administered. During the twenty-four hours the dog was kept under the anæsthetic a urinary silica level of about ten times the original was maintained. A total of 8 mg. was recovered, which is a little less than 2 per cent of the half gram of silica administered. This 2 per cent probably represents the very finest of the particles in the sample given. It is believed that these increases indicate a capacity on the part of the body fluids circulating in the lung to dissolve silica even when it is present in the form of the highly insoluble crystalline fragments of quartz. The rate of solution is, of course, a function of the size of the particles with which the dissolving fluid is in contact, and in this experiment the finest particles obtainable from a quartz dust, prepared by sedimentation after prolonged grinding in a ball-mill,* were used. The majority of the particles were under three microns in size.

In the case of human beings it is probable that large numbers of extremely fine particles, smaller even than the very fine particles observable under the microscope in the lungs of individuals exposed to a dusty atmosphere, are constantly finding their way into the lung. In contact with the fluid in the lung these smallest of particles may suffer fairly rapid solution, the larger particles slower and only partial solution. In this way there may be a constant drainage of silica from the lung, the dissolved silica being carried away by the blood to be excreted in the urine.

Having gained some knowledge of the metabolism of silica from animal experimentation, it was considered advisable to test the urine of a group of miners exposed to silica dust. Through the courtesy of Dr. W. D. Robson, the authors were allowed to collect 58 specimens of urine from underground workers in a mine at Schumacher. The men came direct to the mine dispensary from the changing-room, and were each asked to void a specimen of urine in a Bakelite test tube fitted with a rubber stopper. Analysis of the samples was made a few days later in the laboratory at Toronto. The results are set forth in Table II. It will be seen that the values in milligrams per 100 c.c. of urine vary all the way from less than 1 to nearly 6.

TABLE II.

SILICA CONTENT OF THE URINE OF GOLD MINERS

No.	*Specific gravity*	*Mg. SiO_2 per 100 c.c. urine*	*No.*	*Specific gravity*	*Mg. SiO_2 per 100 c.c. urine*
531	1.018	1.6	134	1.023	1.7
363	–	5.6	M.	1.007	1.1
309	1.023	3.0	61	1.027	3.4
178	–	3.5	301	1.014	1.6
762	1.010	1.8	101	1.029	1.9
99	–	4.0	540	1.024	1.8
155	–	1.3	1558	–	2.9
208	1.028	1.2	65	1.028	2.8
197	1.025	–	75	1.021	1.7
226	1.026	2.0	754	–	3.0
483	1.028	1.7	331	–	1.4
148	–	1.0	185	–	2.4
763	1.029	3.6	A.	–	2.7
407	1.026	1.4	1562	–	3.8
635	1.027	1.9	22	–	4.9
603	1.028	3.3	681	1.030	2.5
59	1.029	0.9	602	1.025	2.4
198	1.023	1.8	153	1.027	5.6
45	1.028	1.8	152	1.028	1.6
K.	1.027	1.7	A.	1.022	1.7
29	1.023	2.0	793	1.026	1.4
94	1.022	0.7	796	1.028	1.7
460	1.024	1.7	787	1.026	1.7
113	1.022	1.3	593	1.023	1.9
291	1.023	5.5	177	1.023	1.6
149	1.024	1.2	253	1.027	1.5
74	1.023	2.4	790	1.024	1.9
409	1.024	1.3	2152	1.028	2.6
57	1.019	0.8			
			Average of 40 medical students and laboratory workers –		1.0

* Kindly prepared for us by Prof. H. E. T. Haultain, of the Department of Mining Engineering of this University.

On inquiry as to where the men had been working prior to coming off shift, it was found that in many instances those showing high silica values had been in the dustiest parts of the mine. The variations did not always correspond, however, to the amounts of dust to which the men had been exposed. The average of the mining group was about two and one-half times the urinary output of silica in a large group of students in Toronto.

In view of the fact that the ingestion of silica so markedly increases the output of silica in the urine, too much emphasis cannot be placed on the values found. Moreover, diet is an important factor in influencing the excretion of silica and it was found impossible to gain a knowledge of the diet of these mine workers. In order to rule out the possibility of high silica values being related to concentrated urines, specific gravity determinations were made on most of the specimens. It will be seen from Table II that the silica content of the urines is quite independent of the specific gravity.

The twenty-four hour output of silica was studied in a group of six miners on seven different occasions during periods when they were not exposed to the dust. Drs. N. R. Russell, H. H. Moore and W. D. Robson kindly cooperated in securing the specimens. Despite wide variations, the results appeared to indicate that miners away from their work and not exposed to dust continue to excrete silica in amounts

TABLE III.

URINARY SILICA OF NORMAL PERSONS EXPOSED TO QUARTZ DUST.

	Mg. SiO_2 per 100 c.c.	*c.c. of urine*	*24 hr. output of SiO_2 (mg.)*
F.	1.70	1,600	27
H.	3.20	2,010	64
K.	3.23	1,580	51
Twenty-four hour specimens taken in the same containers 1 week after exposure.			
F.	0.97	1,660	16
H.	0.75	2,000	15
K.	0:40	1,750	7

well above that of the non-mining population. The normal daily excretion of silica for people without exposure to dust is about 10 to 15 mg., and the output among these men ranged from normal to nearly 50 mg. for the twenty-four hour periods.

During the course of some experiments in this laboratory with finely ground quartz dust, three normal, healthy laboratory workers were subjected during the course of most of one day to an atmosphere containing large amounts of finely particulate silica. It was thought worth while to collect the urine during the following twenty-four hours from each of these persons for analysis. The results showed in each case an output of silica which was definitely higher than normal (as judged by the excretion of silica one week later), the second and third case being considerably higher than the first.

It seemed worth while to attempt to determine whether the amounts of silica dissolved and excreted in the urine of men with silica deposits in their lungs could be influenced experimentally. If silica in the lung is dissolved by the action of the mildly alkaline tissue fluid, it might be possible to accelerate the rate of solution by increasing the alkali reserve of the blood plasma. Although there would be no appreciable change in the actual pH of the blood, the extra available alkali bicarbonate might bring about the solution of more silica. The results of the administration of alkali to silicotic patients, and to dogs who had received intratracheal administration of powdered quartz, were, however, indecisive. Although some increases were observed, the results were too erratic for any conclusion to be drawn. It had been hoped to follow the excretion of silica on twenty-four hour samples, but it was found impossible to do so. No significant increases were observed in the percentages of silica in the urine samples, but since the total daily output was not known, it cannot be said whether or not there was an increased excretion of silica.

It has been suggested that some phagocyted particles may find their way from the alveoli up the bronchial tree into the trachea and may be either swallowed or expectorated in the sputum. Irwin[5] has brought forward evidence in this connection by the demonstration that cells of the reticulo-endothelial system which have ingested particles of thorium dioxide migrate through the lung until they are found in the upper respiratory tract and finally in the trachea. In the sputa of persons exposed to siliceous dust, then, it might be expected that considerable amounts of silica would occur. No sputa from such cases have been available, but several samples were obtained for us by Dr. C. B. Ross from sanitarium patients in Graven-

hurst. In most of these cases, both silicotic and control, there was destructive tuberculosis, and, as might be expected, those patients with silica deposits in their lungs excreted siliceous material in the sputa. Since the sputa were all extremely viscous and difficult to handle, the analyses were carried out on samples of the sputum transferred directly from the Bakelite test tubes to platinum crucibles, and weighed without drying. The results are complicated, therefore, by the presence of varying amounts of moisture in the specimens. Among the silicotic group the case RB gave definitely the highest value found.* (See Table IV). RB had ". . . extensive silicosis coupled with a destructive tuberculosis and the sort of sputum one would expect with such a lesion." The lower values were associated with the presence of less destructive tuberculous lesions in the lungs. Su, for instance, ". . . had a prolonged exposure to mine dust. . . his general condition is good; the lung changes are essentially fibrotic with no evidence of exudative or destructive changes. What little sputum he has is probably catarrhal with post-nasal elements."

TABLE IV.
THE SILICA CONTENT OF SPUTUM

Non-Silicotic Group			*Silicotic Group*		
Case	*Mg. SiO_2 per 100 g. sputum (wet weight)*		*Case*	*Mg. SiO_2 per 100 g. sputum (wet weight)*	
	Mar. 24 (1933)	Apr. 28		Mar. 24	Apr. 28
Br.	0.17	–	RB	1.49	1.97
Du.	0.55	–	Lu.	0.48	–
Do.	–	0.21	Le.	–	0.50
Ki.	0.80	–	Oi.	0.41	–
La.	0.14	–	Su.	0.24	–
MG	–	0.33	So.	–	1.25
Pr.	–	0.22	Tr.	–	0.74
Sm.	0.23	–	Yu.	–	0.45
			Coal miner (Scotland)		4.03

"As regards the controls, I note that Ki's estimation is at least twice as high as the average of all cases, excluding RB's. In checking Ki's history I find that he is a painter and decorator by trade. He has had to handle considerable mica-finished wall paper, and in the handling and brushing of it he has been troubled with dust. He has followed this trade for years. He is suffering from a moderately advanced tuberculosis, the lesion being moderately exudative and destructive. Du, whose estimation was 0.55, gives a history of having worked for more than two years in Scotch coal mines."*

The silica content of the blood was determined in several cases. The blood was collected by Dr. Ross at the sanitarium, and was analyzed by the method for total silica in blood as described elsewhere.[1] All the patients examined were tuberculous, some of whom had a history of exposure to silica.

TABLE V.
MG. OF SILICA PER 100 C.C. OF BLOOD.

Non-silicotic		*Silicotic*	
Br.	0.92	Rb	0.96
Du.	0.80	Br.	0.54
Ki.	0.86	Lu.	0.66
La.	0.68	Su.	0.95
Sm.	0.76	Oi.	0.67

There appears to be no significant difference between the level in the blood of the non-silicotics and of the silicotics. This is in agreement with the findings for animals which were injected with silica and in which no appreciable increase of the blood silica was found, despite the fact that the urinary silica rose to high levels. Because of the low kidney threshold for silica, a silicotic person dissolving any significant amount from his lungs would probably excrete it almost immediately in the urine.

SUMMARY

Silica in small amounts appears to be a natural constituent of all animal tissue.

Silica which reaches the blood stream, either by absorption from the gut or by solution in the lung, is rapidly excreted in the urine. Soluble silica injected into the blood is quickly eliminated in the urine. There appears to be a low kidney threshold for silica.

The urinary excretion of silica is at a higher level in persons exposed to silica dust than in normal persons.

Attempts to influence the absorption of silica from the lungs by administration of alkali gave inconclusive results.

The elimination of silica by way of the sputum from patients having deposits of silica in their lungs appears to be higher than in those having no history of exposure to dust.

* Since these samples were analyzed, Dr. W. P. Warner has supplied us with the sputum of a former coal miner who had an exposure over several years to carbon and silica dust. His sputum was dark grey in colour, indicating the presence of carbon, and ocntained a large amount of silica (4.03 mg. per cent).

* Communications from Dr. Ross.

Only small amounts of silica are present in the blood. No significant differences were found between its level in the blood of normal and silicotic persons.

Our thanks are due to Dr. F. G. Banting for suggesting this research to us, and for his help and advice during the course of the experiments.

THE COLORIMETRIC DETERMINATION OF SILICA IN URINE

The colorimetric procedure for the determination of silica in the urine consists in the production of a silicomolybdic acid complex which is reduced to give a blue colour, the depth of colour being proportional to the amount of silica present. For the determination a phosphate-free filtrate must be obtained. This may be accomplished by the use of NH_4OH and $CaCl_2$ (King and Stantial, 1933). In this procedure the precipitation of phosphate is carried out at an alkaline reaction, and as a result glass vessels cannot be used. To avoid the alkaline precipitation the method described by Jacobs (1929) for the precipitation of phosphate, iron and protein from blood has been adapted for urine analysis. As the mixture is at no time alkaline, the whole procedure may be carried out in glass. The method described removes phosphates as ferric phosphate, excess iron as basic ferric acetate, any proteins, fat and debris, and a portion of the urinary pigment. The amount of urine used will depend on the silica content. One c.c. of the urine of rabbits or other herbivora which have a high output of silica, and 5 c.c. of human urine are usually appropriate amounts to give a convenient depth of blue colour in the test solutions.

Reagents.—All chemicals must be silica-free and blanks should be run frequently to ascertain that no contamination of the reagents has occurred.

N H_2SO_4.

Twenty-seven decimal eight c.c. of concentrated sulphuric acid made to 1 litre with water.

Ferric chloride solution.

Ten per cent ferric chloride ($FeCl_3 . 6H_2O$) dissolved in 0.2 N HCl. Twenty c.c. of this stock solution are diluted to 200 c.c. for use in analysis.

N NaOH.

To obtain a silica-free sodium hydroxide solution, 2.3 g. of metallic sodium are dropped in small pieces into water in a nickel crucible packed in ice. The solution is made up to 100 c.c. and stored in a wax bottle.

Sodium acetate solution.

Three decimal seven five g. of crystalline sodium acetate ($NaC_2H_3O_2 . 3H_2O$) are dissolved in water, 7 c.c. N NaOH added, and the solution made to 250 c.c. This solution is kept in a wax bottle.

Pipettes should be brought into these alkaline solutions for only the briefest time.

Molybdate sulphuric reagent.

Ten g. ammonium molybdate are dissolved in 200 c.c. of N H_2SO_4 with shaking.

Aminonaphtholsulphonic acid solution.

Thirty g. sodium bisulphite, 6 g. sodium sulphite, 0.5 g. 1, 2, 4-aminonaphtholsulphonic acid, are dissolved and made up to 250 c.c. The main part of this solution is preserved in the ice-box and a small amount kept in a brown glass bottle on the bench for use.

Standard silica solution.

Crystals of sodium silicate ($Na_2SiO_3 . 9H_2O$) may be used in the preparation of the standard solution, but owing to variation of the water content it requires very careful standardization against picric acid (King and Lucas, 1928) and consequent adjustment each time it is made. It has been found more satisfactory to use pure fused lumps of anhydrous potassium silicate (K_2SiO_3). As this substance is very hygroscopic, the sample should be ground in a mortar as quickly as possible on a dry day and stored in a weighing bottle in a dessicator. Twenty-five decimal seven mg. of this dry salt dissolved in water and made up to 1 litre gives a solution 10 c.c. of which contains 0.1 mg. SiO_2. This solution will keep for 3 or 4 weeks, but as routine practice a fresh supply is made each week. In weighing, a small amount is transferred to a covered weighing bottle with as little exposure to air as possible, weighed, and made up to the required volume. If the K_2SiO_3 has been kept dry, and the weighing carried out carefully and quickly, no further adjustment will be necessary.

METHOD

One to 5 c.c. of the urine to be tested is placed in a 250 c.c. Erlenmeyer flask, and made just acid to methyl orange with acetic acid. Equal quantities of the ferric chloride and sodium acetate reagents are added and water to 25 c.c. The solution is brought quickly to the boil, with constant shaking, the precipitate allowed to coagulate for a minute and then filtered while still hot through a No. 32 Whatman filter paper. The quantity of precipitating agents added must be determined by trial, as different urines require different amounts. Five c.c. of normal human urine is usually cleared of phosphate by 5 c.c. of each of the reagents, while 10 c.c. of the reagents is sometimes not sufficient for 2 c.c. of dog urine. The filtrate should be clear and practically colourless. If the urinary pigment is not removed 0.5 g. of finely powdered charcoal or active carbon (silica-free) is added and a blank determination carried through. If any colour is obtained on the addition of the reagents the value is subtracted from the test to give the true silica content of the urine.

One c.c. of the filtrate is tested for phosphate in a small test tube by the addition of 2 c.c. N H_2SO_4, 4 drops ammonium molybdate in N H_2SO_4 and 2 drops of the aminonaphtholsulphonic reagent. The development of any blue colour indicates the presence of phosphate and the precipitation must be repeated, using more of the iron and acetate reagents.

A second 1 c.c. portion is tested for iron by adding 2 or 3 drops of a potassium ferrocyanide solution and a drop of dilute acetic acid. When iron is present in the filtrate as shown by the formation of a green colour, the development of the blue colour in the silica determination will be retarded. A slight alteration of the pH of the urine will usually result in the filtrate being iron-free.

If the filtrate is iron- and phosphate-free the silica is determined colorimetrically as follows. An aliquot portion of the filtrate (*e.g.*, 15 c.c.) and 2, 5 and 10 c.c. of silicate standard (0.02, 0.05 and 0.1 mg. SiO_2) are pipetted into 25 c.c. flasks and the volumes made to about 20 c.c. Two c.c. of the 5 per cent ammonium molybdate in N H_2SO_4 are added, and the solutions allowed to stand 5 minutes. One-half c.c. of aminonaphtholsulphonic acid is then added, the volumes made up to 25 c.c. and the solutions mixed. The blue colours are compared after 5 minutes in a Duboscq colorimeter.

Calculation:

$$\frac{\text{Reading of Standard}}{\text{Reading of Test}} \times \text{conc. of Standard} \times \frac{25}{\text{c.c filtrate used}} \times \frac{100}{\text{c.c. urine used}} = \text{mg. } SiO_2 \text{ per } 100 \text{ c.c. urine}$$

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