SYNTHETIC MAGNESIUM TRISILICATE

ITS ACTION IN THE ALIMENTARY TRACT

BY

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It has been shown in an earlier paper* that hydrated silicates of magnesium possess antacid and adsorbent properties reaching a maximum in the trisilicates and becoming negligible in the tetrasilicates or talc series. A synthetic trisilicate approximating in composition to the idealized formula of sepiolite or meerschaum was found to be far more active in these respects than any other silicate examined. Its adsorptive range for toxic and other substances was described. The present research relates to its behaviour in the alimentary tract.

Interaction with the Acid of the Gastric Juice

Normal gastric juice corresponds approximately in strength to N/20 hydrochloric acid. Hydrated trisilicate of magnesium reacts with such acid in accordance with the equation

a proportion of the $(n+2)\text{H}_2\text{O}$ being linked more closely with the SiO_2 than is here represented.

The process appears to be a complex balanced interaction between two hydrated colloids and two electrolytes. Magnesium trisilicate is insoluble in water. If left in contact with distilled water for a week and shaken repeatedly the subsequent filtrate does not give any of the usual reactions for magnesium and only a feeble coloration with magneson reagent (nitrobenzene-azo-resorcinol), which is sensitive to magnesium down to dilutions of 1 in 1,000,000.

The silica resulting from the action is insoluble also, and the weight of silica recoverable by filtration after interaction with an excess of acid for a week is equal to that in the original magnesium silicate.

In the experiment 2.166 grams (ignited weight) of unheated magnesium trisilicate was treated thus. The ignited weight of the residue collected by filtration was 1.432 grams, and contained 0.5 per cent. only of magnesium and 1.425 grams of SiO_2 . Analysis of the original trisilicate disclosed 66.3 per cent. of SiO_2 (ignited weight basis). The amount used, therefore (2.166 grams), should contain 1.436 grams of SiO_2 , a figure agreeing reasonably well with the weight of the residue actually measured. A reaction in which one of the end-products (SiO_2) is thrown out of solution should proceed to completion. The conditions, however, are not so simple. Magnesium trisilicate and silica in the form evolved are active hydrated colloids, and the former, in the presence of acid, assumes the state of a colloidal gel, which hinders diffusion. With low dilutions of hydrochloric acid, com-

pletion is not achieved even in a week. Analysis of the solid residue at various stages gave the results in Table I:

TABLE I.—Composition of Residue (Washed and Ignited) after Treatment of Synthetic Magnesium Trisilicate with Excess of N/20 HCl

Time	Composition of Residue	
	Magnesium (Mg)	Silica (SiO_2)
	per cent.	per cent.
0 hours	17.5	66.3
3 "	3.6	89.3
24 "	1.1	96.6
1 week	0.5	96.8

At body temperature, and with hydrochloric acid of a strength comparable to that of gastric juice, 0.5 per cent. of magnesium remains in the solid phase, fixed either chemically or by adsorption. An appreciable time is required for the attainment of final equilibrium, but, as Fig. 1 shows, the reaction is substantially over in three or four hours.

Subject to a small correction, the total antacid effect can be calculated as equivalent to the magnesium content of the silicate. From the clinical view-point it is the slowness of the reaction which is of the greater interest. The duration of useful antacid action is approximately

equal to that required for gastric digestion and to the usual interval between successive meals. The trisilicate thus offers the possibility of a sustained antacid therapy on a reasonably spaced system of dosage. The practical importance of the lag in neutralization made it desirable to obtain confirmatory evidence and measurement.

Equal volumes of N/20 hydrochloric acid were added to equal weights of the trisilicate, shaken repeatedly, and the residual acidity

FIG. 1.—Progressive neutralization of N/20 HCl by synthetic hydrated magnesium trisilicate.

was estimated at intervals. Fig. 1 shows the successive amounts of acid removed by the silicate. A rapid initial neutralization accounted for about one-half of the magnesium, whilst most of the remaining half was used up in a slow secondary neutralization during the next few hours.

Interaction with Pepsin

Pepsin disappears quickly from solution after the addition of magnesium trisilicate. Various amounts of the silicate, ranging from 0.75 gram to 3 grams, were added to a series of tubes containing 10 c.cm. of 0.1 per cent. pepsin in N/20 HCl and filtered. Acid was added to 3 c.cm. of each filtrate until a darkening could be obtained with Congo red, and the volume of each was made up to 6 c.cm. by the addition of N/20 HCl. Fibrin was added to each and to control tubes of N/20 HCl and of the original pepsin solution proportionately diluted. After incubation and filtration the control with the original pepsin solution gave a strong biuret reaction, but the reaction was completely negative in every other instance.

* See *British Medical Journal*, January 25th, 1936, p. 143. The third and final article of the series will appear next week.

Distilled water in contact with synthetic magnesium trisilicate acquires a slightly alkaline reaction, pH 8.5. Pepsin is destroyed by even lower degrees of alkalinity, the critical pH being 7.25. It is unlikely, however, that such degrees of alkalinity could ever be induced in the stomach by the administration of reasonable amounts of the silicate to normal individuals, or to subjects with hyperchlorhydria. The following experiment was therefore carried out to ascertain whether pepsin is removed from solution by the silicate, even when a clinical degree of acidity is maintained in the suspending fluid.

To 100 c.cm. of 0.1 per cent. pepsin in N/10 HCl was added 2.3 grams of the silicate, and the mixture was tested with Congo red paper every few minutes. Whenever the neutral point was approaching through the interaction of the silicate and acid 1 c.cm. of N/1 HCl was added. This was required five times during one hour. After filtration the residual acid was estimated, and the mixture was made up to N/10 by further additions of N/1 HCl. A sample of the original pepsin solution was diluted with N/10 HCl to match the dilution undergone by that treated with silicate, and the pepsin potency of each was compared by the edestin method. It was found that pepsin had been removed equivalent to 27 mg. per gram of silicate (ignited weight basis).

Since the fluid contained active pepsin at the end of the experiment, and had never been allowed to become neutral, whilst its acidity had never been higher than N/10 HCl, the pepsin could not have been destroyed by any change in reaction, but must have been removed by the silicate. Pepsin removed by the silicate is not released when the silicate is decomposed with acid. Thus 2 grams of silicate were treated with a strong solution of pepsin, and filtered. After washing with distilled water the pepsinized silicate was suspended in N/10 HCl, and acidity to Congo red was maintained by the periodic addition of a little N/1 HCl for three-quarters of an hour. The filtrate from this was tested for pepsin with edestin against suitable control solutions with completely negative results. Possibly the pepsin does not pass into solution, because it is still adsorbed by the silica produced by the action of the acid on the silicate. From considerations of hydron concentration it would seem probable, however, that the pepsin after removal is destroyed in the surface layer of the silicate.

Interaction in the Small Intestine

After the ingestion of magnesium trisilicate the small intestine should receive a magma of hydrated silica in a gel condition (formed during the interaction of the silicate and the hydrochloric acid of the gastric juice), mixed with a significant proportion of magnesium trisilicate which has escaped decomposition in the stomach by reason of the neutralization lag already discussed. Unsplit magnesium trisilicate, even after admixture with an excess of adsorbable material, retains useful adsorbent properties, because, as in the case of neutralization, the process of adsorption is affected by a considerable lag. The relative proportion of the trisilicate saturated in three hours varies with the concentration of the adsorbate in the surrounding fluid.

In Table II a representative series of estimations is given of the amount of dye taken up from aqueous

TABLE II

Dye Solution	Weight of Dye (mg.) Adsorbed by 1 gram of Synthetic Magnesium Trisilicate	
	After 3 Hours	After 1 Week
No. 1	51	129
No. 2	75	209
No. 3	110	244

solutions of methylene-blue at three different concentrations after contact with the silicate for various lengths of time. In these instances more than 50 per cent. of the adsorption potentialities of the substance remained unsatisfied after three hours, from which it is reasonable to infer that, with suitable dosage, adsorption by magnesium trisilicate continues throughout the length of the small intestine.

TABLE III

Original Dye Solution Methylene-blue	Concentration of Dye (after 7 days) in Residual Supernatant Fluid		Weight of Dye Adsorbed (mg.) per gram of Synthetic Magnesium Trisilicate	
	Distilled Water	0.3 % NaHCO ₃	Distilled Water	0.3 % NaHCO ₃
per cent.	mg. per litre	mg. per litre	mg.	mg.
0.1	0	0	100	100
0.2	280	200	172	180
0.3	560	510	244	249

The alkaline reaction of the upper jejunal contents may possibly affect the range of substances taken up, but in the case of methylene-blue it does not sensibly alter the amount of dye adsorbed. In Table III are given comparable figures for adsorption of methylene-blue in distilled water and in a 0.3 per cent. aqueous solution of sodium bicarbonate respectively at various concentrations of dye.

Hydrated Silica

This substance enters the duodenum in the form of a gel, and, as shown in an earlier paragraph, the dried weight of silica produced by the action of weak acid on magnesium trisilicate corresponds with that of the silica present in the original unsplit molecule. Silica-gel has no antacid properties, but, as formed by the decomposition of magnesium trisilicate, it possesses great adsorbent power for application in the small intestine. Its behaviour has been studied in relation to a typical food poison, a dye, and a digestive ferment.

TABLE IV

Adsorbent	Weight of Methylene-blue Adsorbed at Saturation Point by 1 gram of Adsorbent (Ignited Weight)
Hydrated silica from interaction of acid and magnesium trisilicate:	mg.
Specimen 1	87
Specimen 2	90
Flowers of silica-gel (commercial) ...	46
Purified kaolin	14
Magnesium trisilicate (synthetic) ...	244

The substance was prepared by leaving synthetic magnesium trisilicate in contact with an excess of N/20 HCl for a week. The residue was washed and dried. It contained less than 0.5 per cent. magnesium. In this form it readily removed methylene-blue from aqueous solution. The details are given in Table IV, with comparable estimations for commercially prepared silica-gel, purified kaolin, and the original magnesium trisilicate respectively.

When left in contact with distilled water it does not affect the pH of the water perceptibly, so that pepsin adsorption tests can be carried out without fear of destruction of the ferment by alkalinity. Thus 2 grams were added to 50 c.cm. 0.1 per cent. pepsin in N/20 HCl. The fluid was still acid to Congo red at the end of one hour, when it was filtered, and the pepsin remaining in the filtrate was estimated by the edestin method. It was found that 1 gram (ignited weight) of the silica had removed 44 mg. of pepsin (B.P.)

Silica residue after treatment with pepsin in this way becomes activated and capable of digesting proteins. Such a sample was washed with N/20 HCl until the washings ceased to show any peptic activity. The washed pepsinized silica residue was incubated with fibrin in 20 c.cm. of N/20 HCl. Sufficient fibrin was digested in three-quarters of an hour to give a biuret reaction. A control flask of untreated silica residue suspended in 20 c.cm. N/20 HCl, which had been used as the final washing fluid for the pepsinized silica residue, failed to give any biuret reaction after similar incubation. The pepsin, therefore, is not destroyed by the silica residue, but is removed from solution in an active condition. After adsorption it is still available for the digestion of foodstuffs.

Müller's mussel poison was selected for experiments on the adsorption of food poisons by the silica residue. A solution of poison obtained from the liver of the Californian salt-water mussel was used. Its minimum lethal dose for intraperitoneal injection in a 20-gram white mouse was 0.04 c.cm. Of this solution 10 c.cm. was shaken with 2.5 grams (ignited weight) of silica residue for one hour, and filtered through paper. The filtrate was injected two hours later into 20-gram white mice.

0.2 c.cm.: No effect.

0.5 c.cm.: A little transient malaise after half an hour.

1.0 c.cm.: Death in twenty minutes.

0.04 c.cm. control solution caused death in three minutes.

From these figures it can be calculated that 1 gram of the silica residue removes about 100 minimum lethal doses (mouse) from an aqueous solution in one hour at the clearance point.

From these observations it must be concluded that, when magnesium trisilicate is given by mouth, the contents of the small intestine come under the influence of two potent adsorbents—namely, a proportion of unsplit magnesium trisilicate, together with hydrated silica as a freshly formed gel. Both substances remove toxic substances from solution, including well-recognized food

FIG. 2.—Rats, second generation. (From Rat 6, first generation.) Magnesium-trisilicate-fed half litter.

poisons. The insoluble residue is eventually voided from the colon, and can be recovered from the faeces.

Faeces were collected from two different individuals. Soluble salts were removed by lixiviation, filtration, and washing. The residue was reduced to ash, and the silica was estimated, with the results shown in Table V.

Freedom from Toxic Action

Preliminary doses were given to cats, rabbits, guinea-pigs, rats, and mice in amounts ranging from 1 to 10 grams (ignited weight) per kilo of body weight. The

TABLE V

	Daily Dose of Trisilicate (Ignited Weight)	Diet	SiO ₂ (Faecal Ash)
			per cent.
Volunteer 1...	30 grains	Mixed	2nd day ... 32.0 4th day ... 22.0 6th day ... 12.2 (Control ... 6.6)
Volunteer 2...	120 "	Milk	2nd day ... 17.3 4th day ... 29.7 6th day ... 31.1 (Control ... 0.8)

powder was mixed with the food and water, and the animals took it readily without suffering any apparent harm or inconvenience.

Six young adult white rats were then given daily doses of 0.6 gram of the silicate (0.45 gram ignited weight) for six months. During this time they remained in perfect

TABLE VI.—Rats: First Generation
[Daily dose of magnesium trisilicate = 0.45 gram (ignited weight)]

Rat	Original Weight	Monthly Gain in Weight						Final Weight Sept.	Total Gain
		March	April	May	June	July	Aug.		
	grams	grams	grams	grams	grams	grams	grams	grams	grams
1	101	16	13	3	6	16	20	197	96
2	98	13	23	11	17	36	24	215	117
3	100	14	17	13	18	36	22	238	138
4	106	11	16	16	20	29	21	224	118
5	78	9	8	6	5	19	17	142	64
6	104	13	41	21	23	28	19	210	106
			Litter born						

health and gained weight systematically (Table VI). Rat No. 6 gave birth to a litter after a little over two months of silicate feeding. This litter of twelve was divided into two groups, one-half being kept as controls,

FIG. 3.—Rats, second generation. (From Rat 6, first generation.) Control half litter.

and the others being fed with silicate from the moment of weaning onwards. (Their parents had been similarly fed with silicate before conception, throughout pregnancy, and during lactation.) Each member of the second generation was given a level dose of 0.45 gram (ignited weight) daily. In the early weeks this corresponded to the enormous dose of 18 grams (ignited weight) per kilo, or about 25 grams of the parent substance—equivalent to a daily dose of between 3 and 4 lb. to an average man. Without exception they continued to grow normally (see growth charts, Figs. 2 and 3), and with every appearance

of complete health. Some months later two of this generation produced healthy litters, and the feeding experiments are being continued with the third generation. There was no disturbance of bowel action at any stage, in the direction of either constipation or diarrhoea. There was no hardening of the stools or pitting of the surface of the faeces, as noted by other observers in the case of animals fed with other bulky insoluble powders.

Three animals of the first generation were killed after seven months' feeding, during which time each had consumed an amount of trisilicate approximately equal to its own original body weight—equivalent to considerably more than a hundredweight for an average man. Two animals of the second generation were killed after four months' continuous trisilicate feeding. The intestinal tracts, their contents, and the various viscera were carefully examined, and sections were cut of the stomach, small intestine, colon, liver, pancreas, spleen, kidney, lung, thyroid, thymus, suprarenal, and heart muscle, but there was no evidence of morbid change in any part.

Many other post-mortem examinations were carried out on other species with similar results. In every case the trisilicate was found to be distributed evenly along the alimentary tract and mixed intimately with the contents. There was no evidence of sedimentation, the formation of concretions, or other localized accumulations in any area.

Other systematic feeding experiments were carried out on young adult white mice. The daily dose per animal was 0.23 gram (ignited weight), corresponding to about 10 grams per kilo, or 14 grams of the parent substance. The animals grew normally, and had every appearance of health (see Table VII), producing litters after a few months

TABLE VII.—Mice

[Daily dose of magnesium trisilicate = 0.3 gram (0.23 gram ignited weight)]

Mouse	Original Weight	Monthly Average of Weekly Weighings					Final Weight Sept.	Total Gain
		April	May	June	July	Aug.		
	grams	grams	grams	grams	grams	grams	grams	grams
1	22	23	24	25	25	25	27	5
2	24	24	25	25	27	30	31	7
3	23	24	25	25	25	24	25	2
4	22	21	20	21	19	21	23	1
5	26	26	28	29	30	30	30	4
6	17	19	21	21	20	21	20	3

of feeding. At the end of five months of trisilicate feeding they were all killed, and naked-eye and histological examinations were performed exactly as in the case of rats. Again it was impossible to detect any morbid change in the digestive tract or viscera.

Human Dosage

Single doses varying from 1 drachm to 1 ounce of the parent powder were given to twelve volunteers without the production of any kind of symptom. Daily doses were then given over a period of a month as follows: four received 1 drachm daily; four received 2 drachms daily; and four received 3 drachms daily in divided doses for three consecutive weeks. There was no modification of appetite, digestion, bowel action, or of the consistency of the stools. There were no objective signs of disturbance, and no malaise or other subjective symptoms of ill-health.

Summary

1. Hydrated magnesium trisilicate, as prepared for these experiments, is completely innocuous when taken by mouth even in relatively enormous doses, and does not disturb the normal action of the bowel.

2. In the stomach it exerts a prolonged neutralizing action, which continues for several hours. Its general adsorbent action is similarly continuous. Hydrated silica is produced by its interaction with the gastric juice, and is itself a powerful adsorbent for many substances, including shell-fish poison and pepsin. The pepsin so adsorbed is still available for the purposes of digestion.

3. In the small intestine the contents are subjected to the combined adsorptive action of hydrated silica and a proportion of unsplit magnesium trisilicate. The adsorptive affinities of the latter cannot be exhausted quickly, and should therefore be available throughout the whole of the intestinal tract.

4. In the faeces a rise in the percentage of silica occurs.

ALUM-PRECIPITATED TOXOID IN DIPHTHERIA IMMUNIZATION

BY

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The procedure at present recommended by most authorities for active immunization with A.P.T. against diphtheria is to give a single dose of 0.5 c.cm. or 1 c.cm. to children under 8 years (as up to that age reactions are rare), and in children over 8 years to use the Moloney test as a detector of hypersensitive individuals, giving the single dose to Moloney-negative subjects and employing T.A.F. in three doses in those individuals who are Moloney-positive.

Two-shot Immunization with A.P.T.

The published results of this one-shot method indicate that a fairly high Schick conversion rate can be obtained by the use of a single dose of 1 c.cm., but the rate obtained is not high enough to warrant the omission of a Schick test after immunization to detect those children who have failed to develop immunity. Further, the work of Volk¹ suggests that the Schick reversion rate may be too high to be ignored: in a group of 170 children who were Schick-negative four to six weeks after receiving one injection of A.P.T. on retesting after six months 9.5 per cent. were found to have reverted to the Schick-positive state. An additional disadvantage in so-called one-shot immunization is the advisability of the use of the Moloney test in children over 8 years. This in actual practice amounts to a two-shot procedure. It is suggested that these disadvantages may be eliminated and routine immunization procedure considerably simplified by using A.P.T. in two small doses. About a year ago, in a private communication, Dr. R. A. O'Brien indicated that in laboratory experiments by Mr. A. T. Glenny A.P.T. in two small doses of 0.1 c.cm., at a three-weeks interval had given a higher and more rapid immunity than a single dose of 0.1 c.cm., and suggested that in children one would expect a similar result.

In 1934 I² found that in children aged 8 to 14 years formol toxoid could be safely employed without the inconvenience of a preliminary Moloney test if an initial dose of 0.1 c.cm. of the toxoid were given subcutaneously, this small dose serving both as a primary antigenic stimulus and as a "detector" of hypersensitive children, the use of the formol toxoid being discontinued and toxoid-antitoxin floccules being substituted in the few cases which showed any material degree of reaction to the initial (0.1 c.cm.) dose of toxoid. Similarly, in using a small initial dose of A.P.T. one would get warning of hypersensitiveness without the risk of the marked reaction and induration which in sensitive persons results from a dose of 1 c.cm., the initial dose of 0.1 c.cm. acting as a detector dose and obviating the use of the Moloney test.