MAGNESIUM TRISILICATE*

BY

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Since the publication of my original papers (Mutch, 1936, 1936a, 1936b) on this substance last year a number of alleged trisilicates of magnesium have been placed on the market and a certain amount of analytical work on siliceous magnesian precipitates has been published by N. Glass (1936). The results of the manufacturers' efforts have on the whole been disappointing. Many of the products offered for sale are either grossly contaminated or incorrectly described, being of compositions which in no way approximate to that demanded by the theoretical formula, and Glass's studies are deprived of their scientific interest by his use of inaccurate methods of analysis (Ragg, 1936). If any ultimate judgement is to be made of the clinical value of a new therapeutic substance it is essential that the true substance itself shall be employed uniformly.

Identity

Much advance has been made in recent years in our knowledge of the molecular structure of the silicates. Chemical methods failed to distinguish adequately between different silicates bearing a common group constitutional formula. Physical analysis, particularly the diffraction radiograph, has supplied the need and is steadily evolving order out of chaos. For example, three hydrated silicates of aluminium possess the same formula $H_4Al_2Si_2O_9$. Their diffraction radiographs, however, are dissimilar and provide a basis for the classification of substances of this

Medicinal magnesium trisilicate can therefore be defined as a laboratory-prepared substance with a composition represented by the formula $H_4Mg_2Si_3O_{10}$ and yielding a pure diffraction radiograph of sepiolite No. 1 or of sepiolite No. 2. The artificial magnesium trisilicate which I originally described and have continued to use is such a substance. Radiographically it is identical with sepiolite No. 1. It is not, as is erroneously implied in Martindale's *Extra Pharmacopoeia* (1936), to be confused with "precipitated magnesium silicate." Such precipitates are vague and variable siliceous gels containing a certain amount of magnesium. "Synthetic" magnesium trisilicate is a chemical entity built up from its component parts, which, after association in colloidal form, are subjected to a process of maturation at 15° C.

I am indebted to Dr. D. F. Claringbull and Dr. M. M. Hey of the Mineral Department of the British Museum (Natural History) for the radiological identification of the product. The diffraction radiograph exhibited well-defined first order lines at 1.32, 1.54, 1.72, 2.62, 3.41, and 4.46 Angström units, whilst the line expected at 11.35 was outside the limits of the radiograph. The radiograph agrees accurately with the most recently published data (Migeon, 1935) and with radiographs of natural sepiolite No. 1 taken at the same time for purposes of comparison. The intrinsic particles were shown to be of finely colloidal dimensions with a crystalline basis. In size they were much smaller than those of kaolinite or of the most refined varieties of medicinal kaolin available.

Analytical Survey

Chemical analyses of a number of the products put forward by various manufacturers as magnesium trisilicate are given in Table I.

TABLE I.—Analysis of Various Brands offered as "Magnesium Trisilicate"

No.	Manufacturer	Sample	(1) MgO	(2) SiO ₂	(3) Loss on Igni- tion	(4) Fe ₂ O ₃ Al ₂ O ₃ & CaO	(5) Ratio MgO : SiO ₂ (Theore- tical, 1 : 2.24) (gravimetric)	(6) Contami- nation with Silica (SiO ₂ in excess of true formula)	(7) Antacid Value (N/20 HCl neutralized by 1 gramme, Ignited Wt., in 4 hours at 37° C.)	(8) Adsorption (Methylene- blue ad- sorbed per gramme, Ig- nited Wt., in 14 days at saturation)
1 2 3	A	1 2 3	% 22.43 22.34 21.71	% 50.19 50.01 48.92	% 23.17 24.70 27.40	% 1.39 2.50 1.54	1 : 2.24 1 : 2.24 1 : 2.25	% Nil Nil + 0.44	c.cm. 300.8 300.7 303	mg. 271 281 282
4	B		20.99	46.72	29.22	2.15	1 : 2.22	— 0.89	308	240
5 6 7	C	1 2 3	20.12 20.77 21.12	44.19 45.05 44.93	32.94 32.31 31.67	0.92 0.87 1.19	1 : 2.20 1 : 2.17 1 : 2.13	— 1.7 — 3.1 — 4.9	308 315 300	282 272 250
8 9	D	1 2	19.97 21.04	47.68 51.99	30.29 25.86	1.41 1.53	1 : 2.39 1 : 2.47	+ 6.69 + 10.2	288 242	276 256
10 11	E	1 2	17.29 16.16	52.71 53.70	26.91 25.86	1.28 2.07	1 : 3.05 1 : 3.32	+ 36.7 + 48.2	205 242	256 234
12	F		15.94	52.94	36.90	1.25	1 : 3.32	+ 48.2	236	264
13	G		13.61	59.73	23.74	1.04	1 : 4.39	+ 95.9	173	180

chemical composition into three distinct groups—dickite, kaolinite, and nacrite (Ross and Kerr, 1931). Hydrated trisilicate of magnesium occurs in two forms (Longchambon, 1935): sepiolite No. 1 or meerschaum and sepiolite No. 2. The composition of each is represented by the formula $H_4Mg_2Si_3O_{10}$, often written as $2MgO \cdot 3SiO_2 \cdot 2H_2O$. Structurally they are distinct, and each gives its own characteristic diffraction radiograph.

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METHODS

The analytical methods described by J. W. Mellor (1913) were carried out with meticulous care. Refinements were introduced to ensure full precipitation of the silica (Mellor, 1913; Scott, 1925; Groves, 1936) and the recovery of all traces of iron and alumina (Mellor, 1913a) carried down with it. The moiety of magnesium (Mellor, 1913b) which incorporates itself with the calcium precipitate was also dealt with by the standard approved technique.

Loss on ignition was measured by heating over a Meker burner to a constant weight.

Antacid values were determined by adding a known excess (100 c.cm.) N/20 HCl to an accurately weighed amount of the sample (about 0.2 gramme) and incubating at body temperature for four hours, in which circumstances decomposition is almost complete. The unused excess of acid was estimated by backward titration with N/20 NaOH. These values as well as those for the adsorption of methylene-blue have been calculated on the basis of the ignited weight. The actual clinical values are influenced by the amount of water (Table I, column 3), and consequently are lower.

Adsorption.—Exactly 0.2 gramme of the sample was washed into a 50-c.cm. test-tube and the volume made up to 20 c.cm. with distilled water; 25 c.cm. of aqueous methylene-blue solution 0.2 per cent. were added. The corked tube was kept at room temperature and shaken several times a day. At the end of fourteen days the unadsorbed excess of methylene-blue was estimated colorimetrically. Adsorption continues for many days and is not complete before the end of two weeks. The strengths and proportions were arranged to give saturation figures falling on the horizontal portion of the graph (Mutch, 1936): methylene-blue concentration in adsorbate against concentration in supernatant fluid, at equilibrium.

FINDINGS

Water Content.—The loss in weight on ignition represents all the free water and most of that combined. When sepiolite is heated it loses water without decomposition up to about 600° C., when the diffraction radiograph indicates a change to enstatite (Migeon, 1935). Further losses occur continuously up to 1,000° C., when they cease and the radiograph changes to that of cristobalite, the molecular structure having been broken down completely and every trace of moisture having been driven off. It will be seen that all samples contained water far in excess of that demanded by the theoretical formula. The antacid and adsorption values have been calculated on the basis of ignited weight. As already pointed out, in actual practice the powder received by the patient would contain a certain amount of water (Table I, column 3) and be proportionately less effective. Any value above 30 per cent. for water content must be regarded as needlessly high. The adsorptive and antacid qualities of true sepiolite No. 1 are in no way impaired by careful drying down to a water content of 25 per cent. or even less. Undesirable dilution is particularly noticeable in sample 12.

Magnesia : Silica Ratio.—In pure sepiolite the gravimetric ratio between the MgO content and that of SiO₂ is 1:2.24. Any increase in this ratio represents contamination with free silica or the presence of one of the higher silicates. A decrease in the ratio represents admixture with free magnesia or the presence of some silicate with a higher magnesium content such as french chalk. The ratios observed are given in Table I, column 5. The discrepancy between each sample and true magnesium trisilicate is indicated by the data in column 6. In certain instances the product conforms closely in general composition to the demands of the theoretical formula. Other products depart widely from these primary requirements. Clearly much material contaminated with large amounts of free silica, sometimes in almost equimolecular proportion, has been supplied when magnesium trisilicate has been prescribed.

Antacid Value.—The antacid properties are affected adversely by the presence of an excess of silica. For example, the crudely siliceous sample 13 was little more than half as potent as the correctly proportioned sample 1. Two drachms of sample 13 must therefore be prescribed to secure the same neutralizing effect as one drachm of the standard material. Conversely the antacid action is increased by adulteration with magnesium oxide. In such an event, however, the adsorption potency suffers and the valuable property of lag in the rate of neutralization is partly lost. Sample 7 illustrates the falling off in adsorptive power which occurs when magnesium is present in excess of the theoretical requirements.

Adsorptive Value.—This is dependent upon a number of factors many of which are still obscure. In the series of siliceous magnesias surveyed the action is greatest in those products which conform most closely in chemical composition to the formula 2MgO.3SiO₂.nH₂O. Contamination with an excess of either constituent is associated with a falling off in adsorptive power—for example, sample 13, with its almost incredibly high silica content, possesses the feeblest adsorptive value of all.

Clinical Utility

All clinical observations carried out at Guy's Hospital during the last two years (1935 and 1936) have been made with true artificial sepiolite No. 1 (brand magsorbent), which conforms accurately to the dictates of the theoretical formula and yields the pure diffraction radiograph of the natural mineral. It is completely insoluble in water and its intrinsic particle size is of a fine colloidal order. Its applied pharmacological properties include:

1. The combination of a useful total antacid potency with a slowness in the rate of interaction with hydrochloric acid of gastric strength.
2. The provision for strong adsorption effects externally or in the stomach and intestine through the medium of (a) any unneutralized excess of sepiolite; (b) colloidal silica produced during interaction with gastric acid in accordance with the equation

Continuous Control of Gastric Acidity.—It is estimated that the daily secretion of gastric juice corresponds to 1½ to 3 litres of 0.3 per cent. HCl. The average 2¼ litres can be neutralized in the laboratory by about 2¼ litres of milk or 230 grains of dried sodium bicarbonate. In the stomach the problem is complicated by varying rates of secretion and constant loss through the pylorus. Kark and Davis (1936) found that even 50 per cent. more milk than that theoretically needed, given hourly as 5-oz. feeds, failed to control gastric acidity. Free HCl at times rose to 0.1 per cent. and the total acidity to the equivalent of 0.2 per cent. HCl. W. N. Mann (1937), also working at Guy's Hospital, confirmed this inadequacy of simple neutralization with milk. He then administered true artificial sepiolite hourly and found a complete absence of free HCl over a period of eight hours. The gastric tube was kept in place continuously throughout this period and the stomach contents were sampled every thirty minutes.

These observations confirm and amplify the earlier observations on fractional test-meal graphs (Mutch, 1936b). Two factors make possible this exercise of complete and continuous acid control on a spaced scheme of dosage. First, the slowness of the interaction between

sepiolite and acids. At body temperature and with N/20 hydrochloric acid a substantial secondary neutralization continues for more than an hour after the quick initial interaction has occurred (Mutch, 1936, 1936a, 1936b). Secondly, the non-poisonous nature of the sepiolite, which enables adequate doses to be given to compensate for the continuous loss through the pylorus. Animal experiments have failed to reveal any deleterious cumulative effect (Mutch, 1936a), and clinically it has been found that artificial sepiolite does not induce alkalosis.

Alkalosis.—The hourly administration of milk equivalent in all to about $3\frac{1}{2}$ pints of 0.3 per cent. hydrochloric acid daily does not abolish the acidity of the gastric juice. Chemically this volume of milk is equivalent to about 345 grains of dried sodium bicarbonate. The danger of clinical alkalosis probably begins when the daily intake of sodium bicarbonate exceeds 300 grains. Much larger quantities of sepiolite No. 1 can, however, be given with impunity. Alkalosis is caused by simple absorption of a soluble alkali when the dose administered exceeds the demands of the acid actually in the stomach at the time. It is caused also in part by the loss of that portion of the gastric acid which is neutralized by the medicament, unless (1) the basic substance administered is eventually metabolized—for example, ammonium or protein—or (2) the base is reprecipitated in insoluble form in the small intestine.

In the case of sepiolite, soluble magnesium chloride is produced as the gastric juice is neutralized. In an alkaline medium the base, magnesium, is readily reprecipitated as magnesium hydroxide and so prevented from interfering with the internal balance between bases and acids. Sepiolite itself is neutral and insoluble, so that the unutilized excess cannot add to the body's alkali reserves.

The validity of these deductions has been borne out in practice. Magnesium trisilicate has been used extensively without provoking symptoms of alkalosis (A. F. Hurst, 1936; T. Hunt, 1937; T. L. Hardy, 1937). Biochemical

FIG. 1.—Fractional Test-meal Curve of a Case serving as a Basis for Biochemical Observations on Possible Alkalosis. (Note the hyperchlorhydria.)

analyses of the blood and urine confirm these findings. I am indebted to Dr. J. H. Ryffel for the following analyses carried out on a patient recently under my care in Guy's Hospital for duodenal ulcer. The man, aged 35, had suffered from bouts of epigastric pain in late relation to meals since 1929. Dr. Lindsay Locke's radiographs showed marked deformity of the duodenal bulb. The faeces contained occult blood and gave a spectrum of haematoporphyrin. The fractional test-meal curve was that of hyperchlorhydria with slight delay (Fig. 1). The

plasma bicarbonate was estimated and various urinary analyses made, as recorded in Table II. It will be seen that in spite of the taking of $3\frac{1}{2}$ ounces of true artificial sepiolite daily for three weeks his urine remained acid, there was no fall in the ammonia N/total N ratio, and no

TABLE II.—Alkali Reserve with Large Doses of Sepiolite. (Note: No alkalosis)

	Day of Treatment	URINE						Occult Blood in Faeces	
		Volume	pH	Total Acidity N/10	Ammonia	Urea	Ratio Ammonia Nitrogen to Total Nitrogen		Plasma Bicarbonate Molar
Before Treatment } <i>Treatment : Hourly 2-drachm doses of sepiolite No. 1 (magsorbent) (3½ oz. daily)</i>		c.cm. 1,100	5.6	34/100	0.024	2.0	2.4	0.030	+
<i>Diet : 5 oz. milk basis feeds</i>									
During Treatment }	1	1,300	6.0	10/100	0.021	1.45	2.9	+	
	2	1,400	5.8	21/100	0.029	1.89	3.1		
	3	1,200	6.0	10/100	0.015	1.51	2.1		
	5	1,350	6.8	2/100	0.011	0.94	2.4	—	
	6	1,900	6.8		0.020	1.16	3.4		
	7	1,600	6.8		0.022	1.29	3.4		
	8	2,000	6.2	11/100	0.018	1.10	3.3	—	
	9	2,200	7.0		0.032	1.29	5.0		
	16	1,750	7.0		0.020	1.32	3.0		
	17	1,950	6.9	0.022	1.27	3.5	—		
	18	1,600	7.4	0.024	1.10	4.3			
	21	2,103	6.9	10/100	0.014	0.97	3.0	—	
	22	970	6.6		0.030	2.08	2.8		

sensible increase in the plasma bicarbonate. There was thus no chemical evidence of established or commencing alkalosis.

Laxative Action.—Artificial sepiolite sometimes produces a laxative effect. The action is not apparent in laboratory animals and is usually inappreciable in man. On occasions, however, it proves troublesome. Magnesium chloride released in the stomach operates osmotically in the bowel as a saline aperient. The varying response of different individuals can be attributed to several factors. Personal susceptibility doubtless plays a part. The amount of magnesium chloride produced depends not only on the dose of silicate given but on the acidity and volume of the gastric contents and the rate of outflow through the pylorus. The proportion remaining in solution is determined by the extent to which precipitation of insoluble magnesium hydroxide and carbonate is effected by the alkaline pancreatic juice. The final amount available in solution in the lower part of the bowel is again influenced by the reaction of the ileum and colon. If their contents are acid, hydroxide and carbonate will pass once more into solution and act osmotically as an evacuant. There is clearly the fullest opportunity for the display of wide individual variations in response. The effect is easily controlled when necessary by the simultaneous administration of a suitable amount of some constipating adsorbent such as kaolin or charcoal or of a constipating antacid such as chalk.

Dosage

HYPERCHLORHYDRIA AND CHRONIC PEPTIC ULCERATION

When sepiolite is added to a chemically equivalent amount of dilute hydrochloric acid the interaction not only takes place relatively slowly but is incomplete. For example, with N/20 HCl the mixture remains strongly

acid after fourteen days' contact when the pH is still as low as 3.5. Fig. 2, showing the acidity day by day, indicates that an indefinitely long period would be required to secure much diminution in acidity below pH 3.6. Neutrality can only be achieved by adding more sepiolite. With N/20 HCl a 10 per cent. excess of sepiolite is required to approach this end. Fig. 3, giving the seven-day pH reading of mixtures containing N/20 HCl and graduated excesses of sepiolite, demonstrates that even with a 50 per cent. excess of sepiolite a slight acidity persists at the end of a week. Other factors which influence dosage are the volume and strength of the gastric juice, the rate of loss through the pylorus, the degree of duodenal regurgitation, and the completeness of the result

FIG. 2.—Acidity of Mixture containing Equivalent Weights of Artificial Sepiolite (Magsorbent) and N/20 HCl. (Note: (1) substantial lag in neutralization; (2) that final balance does not approach the neutral point.)

FIG. 3.—Influence of an Excess of Artificial Sepiolite (Magsorbent) on the Final Acidity of Mixtures with N/20 HCl (pH measured after seven days at room temperature).

desired. Fortunately the substance is non-toxic and non-cumulative and does not cause alkalosis, so that if absolute anacidity is sought for doses can be increased without stint. W. N. Mann found in his case of gastric ulcer that one drachm hourly was sufficient to abolish all free HCl from the stomach for a period of eight hours. Such complete neutralization is widely recognized as advantageous in the treatment of chronic peptic ulceration, but is rarely required in other cases. If kept up long enough it would inevitably be detrimental. Mann's data can,

however, be taken as a basis on which to estimate the probable requirements of other patients. Another observation which must influence selection of the dose for particular cases is that the rate of interaction and the completeness of neutralization both fall off rapidly as the strength of the acid diminishes. For example, using a substantial and constant excess of acid of various strengths (100 c.cm. N/20 HCl or its equivalent and 0.15 gramme

FIG. 4.—Neutralization Lag at Various Acidities. Sample 1, using 1 Gramme Sepiolite 1 (Magsorbent), Ignited Weight, plus Marked Excess of Acid.

FIG. 5.—Neutralization at Various Acidities. Sample 2, using 1 Gramme Sepiolite 1 (Magsorbent), Ignited Weight, plus Marked Excess of Acid.

sepiolite, ignited weight) and estimating the residual acid at various intervals by backward titration, it was found that after one hour N/20 HCl had used up about 75 per cent. of the sepiolite, N/50 HCl had used 60 per cent., N/100 HCl had used 47 per cent., whilst the N/200 acid had interacted with only 33 per cent., so that at the lowest acidity two-thirds of the dose remained unutilized after one hour and about one-half was still undecomposed at the end of four hours. Automatic adjustment to the conditions in the stomach must clearly occur. Full details

are given in Table III and Figs. 4 and 5 for two different samples of material. Even at N/100 HCl and with a dosage far below the theoretical requirements most of the sepiolite will pass into the duodenum unchanged provided the pylorus is patent.

TABLE III.—*Neutralization Lag at Various Acidities. (Note conspicuous slowness of interaction at low dilutions)*

Sample	Time	Volume of HCl (expressed as N/20) neutralized by 1 gramme (Ignited Weight) of Sepiolite (Magsorbent)			
		Using N/20	Using N/50	Using N/100	Using N/200
1	Hours				
	1	180	140	106	68
	2	243	168	134	98
	3		216	163	119
	4	290	252	168	131
2					
	1	184	152	92	70
	2	220	192	152	
	3		240	197	117
	4	294	266	212	129

HYPOCHLORHYDRIC GASTRITIS

Within certain limits of dosage advantage can be taken of the general adsorbent action of sepiolite in the treatment of gastritis of the subacid type. It has just been shown (Figs. 4 and 5) that at low degrees of acidity the neutralizing effect of sepiolite is greatly enfeebled. It can be demonstrated also that the reaction as measured by the pH value remains on the acid side of the neutral point on a properly balanced system. The final pH attained by mixtures of acid of various concentrations with equivalent weights of sepiolite was: N/10, < 2.8; N/20, 3.3; N/50, 6.0; N/200, 6.3. (Readjusted for dilution the value for N/20 HCl becomes 5.1 instead of 3.3.)

Fig. 6 gives daily observations on N/200 HCl mixed with its equivalent of sepiolite. By the end of twenty-four hours the pH was only 4.7, and the general trend of the curve indicates that several weeks would have elapsed before neutrality could have been approached. Experi-

FIG. 6.—Acidity of Mixture containing Equivalent Weights of Artificial Sepiolite (Magsorbent) and N/200 HCl.

menting with the effect of an excess of sepiolite on the ultimate acidity it was found that N/200 HCl mixed with 23 per cent. excess of sepiolite still remained slightly acid (pH 6.7) at the end of a week. Pepsin remains active at the neutral point and is not destroyed until an alkalinity of pH 7.25 is reached. Such pepsin therefore as remains free, together with the portion adsorbed by the colloidal silica released from the sepiolite, would in the above circumstances still be available for protein digestion.

As a general approximation the total daily dose which could probably be taken by patients with hypochlorhydria without abolishing peptic digestion would be considerably greater than the chemical equivalent of two litres of gastric juice at the maximum free HCl strength of the fractional test meal + 50 per cent. for pyloric loss + 25 per cent. for permissible excess of sepiolite over acid—for example, maximum free HCl = 0.05 per cent. (approximately N/70). The daily dose of sepiolite on these assumptions would be 2½ grammes, or 39 grains, of the substance as prescribed (25 per cent. moisture)—that is, a 7-grain tablet five or six times a day.

Summary

1. Medicinal magnesium trisilicate is defined as a "compound represented by the formula $H_4Mg_2Si_3O_{10}$ and giving the pure diffraction radiograph of the natural mineral sepiolite No. 1." The ratio $MgO:SiO_2 = 1:2.24$ (gravimetric).

2. It is shown that many of the marketed brands fail entirely to conform to these basal requirements.

3. The following therapeutic applications are discussed: (a) the continuous control of gastric acidity in hyperacid states; (b) the production of gastric anacidity without systemic alkalosis; (c) the utilization of the general adsorbent properties of the silicate in hypo-acid conditions.

4. It is demonstrated that: (a) Artificial sepiolite No. 1 does not cause alkalosis. (b) The extent and speed of interaction with acids diminish rapidly at hypochlorhydric strengths. Within certain limits of dosage the neutralizing effect is automatically adjusted to the demands of the gastric juice. (c) Within a certain range a useful amount of the silicate can be given in hypochlorhydric states without its neutralizing the gastric contents to such an extent as to destroy peptic activity.

5. An explanation of the variability of its mildly laxative action is put forward.

6. Schemes of dosage appropriate to hyperchlorhydric and hypochlorhydric conditions respectively are discussed.

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The French Society of Dermatology and Syphilology announces that an anonymous donor has offered a prize of 5,000 francs for the best work on dermatology or syphilology, to be awarded every two years. The first award will be in May, 1939, the subject being the processes of sensitization and immunization in the epidermomycoses. Both French and foreign authors whose work has been written in French or translated into that language are eligible for the prize. The articles should be sent to the general secretary, Dr. P. Fernet, 11, Rue de Sontay, Paris, 16e, before March 30, 1938.