HYDRATED MAGNESIUM TRISILICATE IN PEPTIC ULCERATION

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Synthetic magnesium trisilicate ($\text{Mg}_2\text{Si}_2\text{O}_5 \cdot n\text{H}_2\text{O}$) is a tasteless white insoluble powder, possessing adsorbent and antacid properties of particular value in the treatment of gastric hyperacidity and chronic peptic ulceration of the stomach, duodenum, and jejunum. As an adsorbent it far transcends bismuth salts, magnesia, aluminium hydroxide, prepared chalk, and other medicaments in common use in these conditions. In Table I are given

TABLE I.—*Adsorption Powers of Common Antacid Substances*

Adsorbent	Potency (Weight of Methylene-blue Removed per gram of Substance Tested the Saturation Poi
Magnesium trisilicate (synthetic sepiolite Type 11)	176
Ditto (allowing for loss on ignition)	244
Aluminium hydroxide (B.P.C.)	Less than 1
„ „ („alocol”)	2
Bismuth oxycarbonate (B.P.)	Less than 1
Calcium phosphate (tribasic, B.P.)	0
Chalk (prepared, B.P.)	3
Kaolin suspended in aluminium hydroxide („kaldrox”)	1½
Kaolin suspended in aluminium hydroxide („kaomagma”)	2
An amount of „kaldrox” containing 1 gram of kaolin	8
An amount of „kaomagma” containing 1 gram of kaolin	10
Kaolin (B.P.)	12
„ (purified „colloidal”)	14
„ Maclean's powder” (B.P.C.)	0
„ „ (proprietary)	0
Magnesia (proprietary tablets)	0
Magnesium hydroxide (B.P.C.)	Less than 1
„ oxide (heavy, B.P.)	0
„ „ (light, B.P.)	Less than 1
Talc (purified, B.P.C.)	3

the relative adsorbent powers of such compounds, expressed as milligrams of methylene-blue removed by 1 gram of each substance.

Adsorption of Histamine

As described in a previous paper,* the range of its adsorptive affinities covers all basic dyes and in less degree many acidic ones also. It includes certain proteins, proteoses, food poisons, bacterial toxins, putrefactive amines, and alkaloids. Among the many interesting substances adsorbed is histamine; 1 gram of magnesium trisilicate removed 9 mg. of the acid phosphate at the clearance point in three hours from an aqueous solution. The diazo-reaction and the response of the virgin guinea-pig's uterus were used as tests for the completeness of the adsorption. More detailed study with dyes indicates that at the saturation point a much greater quantity would be taken up; if the time lag about to be discussed is taken into account, the weight of histamine removable per gram should probably be doubled again.

Histamine is a product of protein putrefaction, and in certain states of intestinal stasis can be produced from its parent substance histidine by the bacteria of the small

* The first of this series of three articles appeared on January 25th, p. 143, and the second on February 1st, p. 205

intestine. When injected subcutaneously, it causes a flow of acid gastric juice—a phenomenon which is the basis of the histamine test meal, and may have an important bearing on the causation of hyperchlorhydria. Although substantial adsorption from aqueous solution commences as soon as the trisilicate is added, an even greater secondary adsorption follows and continues for a week or more.

Delayed Adsorption

This latency is of practical importance. It permits a continuous adsorption therapy on a scheme of inter-

TABLE II.—*Illustrating Delayed Adsorption*

Sample	Methylene-blue (mg.) adsorbed per gram of the Magnesium Trisilicate	
	After 3 hours	After 7 days
1	40	100
2	50	172
3	60	169
4	108	167
5	113	218
6	121	160
7	124	208

mittent dosage, the substances adsorbed during the first three hours following ingestion being insufficient to satisfy even one-half of the total adsorptive affinities of the trisilicate. This is illustrated by the data in Table II, which relate to a variety of dye concentrations in the supernatant fluid.

Experiments with powders of different grades indicated that the lag was not determined by the size of the particles, provided that the whole would pass a 200-mesh sieve. It was still observable in magnesium trisilicate which had been allowed to stand under water for a week ;

FIG. 1.

therefore it cannot be explained as due to progressive hydration of the silicate. One gram (ignited weight) removed 244 mg. of methylene-blue in seven days (saturation point determination). A similar amount of trisilicate was left under distilled water at room temperature for the same period; methylene-blue was then added to secure a concentration and total equal to that of the dye in the control tubes. During the next three hours only 126 mg. of dye were removed, but a week later the amount adsorbed was 242 mg., a close approach to the control figure

Antacid Value

As an antacid, 1 gram (ignited weight) of the trisilicate neutralizes 310 c.cm. of N/20 HCl, the approximate equivalent of normal gastric juice. The ultimate interaction is a chemical one, producing magnesium chloride and an insoluble residuum of hydrated silica. Neutralization proceeds with a lag analogous to that observed during the adsorption of methylene-blue. A rapid initial neutralization uses up 75 to 80 per cent. of the available magnesium during the first hour. A slower secondary neutralization utilizes the remaining 20 to 25 per cent. of magnesium at a steadily diminishing rate. The process is substantially complete in three or four hours, but a trace amounting to 0.5 per cent. of magnesium remains undissolved even after a week.

The magnitude of this lag is shown clearly in Fig. 1, where neutralization curves are given for several different batches of material individually prepared. The quick primary neutralization and the progressive secondary one make it possible to secure a continuous antacid effect throughout the whole normal period of gastric digestion by the administration of a single dose. The validity of this deduction was tested by gastric analysis.

An ordinary stomach tube was passed, and the resting juice was sampled (acidity = 0.13 per cent. HCl). Three grams of the trisilicate suspended in 4 oz. of water were then introduced through the tube. One hour later the stomach was evacuated as completely as possible, and its contents were quickly filtered (acidity of filtrate = 0.11 per cent. HCl). The washed residue (0.19 gram) contained only a small portion of the remains of the trisilicate administered, but on standing in contact with an excess of N/20 HCl for a week it neutralized 12.4 c.cm. of the acid. The residue recovered from another individual with similar acidity controls neutralized 9.6 c.cm. N/20 HCl.

Clearly magnesium trisilicate after remaining in the stomach for an hour still retains antacid potentialities,

even when there is a positive acidity in the gastric juice before the introduction of the trisilicate and at the time of its removal. The effect of a small dose of the trisilicate on the standard test meal curve is demonstrated in Figs. 2, 3, and 4.

Further details from a series of cases appear in Table III. Reduction in acidity is apparent throughout the whole three-hour period in each instance, but is most marked during the first one and a half hours. With the dosage used (35 grains, ignited weight basis) acidity was

kept down to a sub-normal figure whenever the maximum acidity in the control test meal was not greater than 0.28 per cent. With higher degrees of hyperchlorhydria up to 0.33 per cent. the trisilicate kept the acidity down below normal for one and a half hours, but some rise occurred later. At extreme figures even up to an acidity of 0.41 per cent. the antacid action was perceptible throughout the whole three-hour period, but the dose used was insufficient to prevent some degree of hyperacidity in the earlier phases as well as in the later ones. It seems probable, therefore, that the dosage for full control should be 35 grains three-hourly for acidities up to 0.3 per cent., a similar dose two-hourly for acidities between 0.3 per cent. and 0.35 per cent., and a higher dose for extreme cases.

Clinical Potentialities

The presumptive suitability of this substance for the treatment of chronic peptic ulceration in

the stomach, duodenum, and jejunum depends on a particular combination of properties:

1. Its antacid power is sustained for hours even in the presence of an excess of acid. Not only does this facilitate the continuous control of hyperchlorhydria in the gastric contents as a whole, but it furnishes a basis for a local antacid therapy in the floor of the ulcer itself. In the presence of acid the trisilicate acquires a gelatinous consistency, and if any of the mass lodges in the ulcer crater it will progressively neutralize the acid which diffuses through it. It should not be impossible, there-

FIG. 2.

FIG. 3.

FIG. 4.

fore, to secure a local hypochlorhydria at the ulcer site, even when the acidity in the main gastric contents is high.

2. Its adsorbent power is sustained, and cannot be exhausted in a few hours or even in a few days. For

TABLE III.—*Effect of Synthetic Magnesium Trisilicate on the Fractional Test Meal Curve*

Case	Resting Juice % HCl	Maximum Acidity (% HCl Test Meal)			
		1st Period (0 to 1½ hours)		2nd Period (1½ to 3 hours)	
		Control	Using Trisilicate	Control	Using Trisilicate
Normal	0.08	0.17		0.15	
1	0.01	0.10	0.04	0.01	0.00
2	0.08	0.22	0.04	0.19	0.02
3	0.19	0.28	0.09	0.25	0.15
4	0.33	0.30	0.11	0.33	0.22
5	0.25	0.32	0.14	0.32	0.26
6	0.27	0.36	0.28	0.36	0.32
7	0.31	0.41	0.30	0.38	0.37

this reason it cannot be saturated with foodstuffs adsorbed from the gastric contents. A great reserve will always be left for the removal of soluble necrotic products at the ulcer site and of toxic substances in general.

3. It has strong antipeptic powers available for the protection of the ulcer base from destructive digestion. Since its adsorptive action is sustained, and cannot quickly be used up, trisilicate arrested in the crater should establish a local pepsin-free zone even when peptic digestion is proceeding freely in other parts of the stomach.

4. As its antacid power is utilized, hydrated silica is liberated in a form possessing strong adsorptive affinities for pepsin, food poisons, and other substances.* This activity of the end-product intensifies the adsorbent effect of the parent substance, magnesium trisilicate.

5. It can be given in large doses without disturbing the general motility of the digestive tract. It does not cause either constipation or diarrhoea.

6. No matter how great a quantity may be given it cannot reduce the gastric reaction materially below the neutral point.

7. Being completely insoluble in water any unused excess is voided in the stools. It cannot be absorbed, and so produce direct alkali poisoning.

Illustrative Cases

Fifteen patients in whom the existence of chronic peptic ulceration in stomach, duodenum, or jejunum had been established by clinical examination, x-ray visualization, and by the association of hyperchlorhydria, with evidence of high alimentary bleeding, were treated with synthetic magnesium trisilicate. No other antacid preparation was employed, either in the form of buffer salts or of alkalis. The patients were kept in bed on two-hourly feeds. As soon as pain was under control, and tests for occult blood in the stool were negative, a three-hourly regimen was substituted. Feeds at first consisted of milk prepared with Irish moss, custard, junket, cream, milk jelly, egg beaten in milk and proprietary milk foods with the addition of a little orange juice, grape fruit juice, vegetable purée, and marmite as soon as all pain had disappeared.

The dosage of magnesium trisilicate was kept low in the hope that a sufficient acid-free and pepsin-free zone might be established locally in the ulcer crater, as already discussed, without there being any necessity to neutralize the gastric contents as a whole. The clinical results encourage one to believe that such actually was the case. The preparation of magnesium trisilicate used was mag-sorbent, which on drying lost 10 per cent. of moisture, and on ignition an additional 15 per cent. of more closely combined water. It was given in doses ranging from 7 to 28 grains midway between each feed, so that the patients received only 5 to 21 grains of the anhydrous substance at a time. These are relatively small doses when compared with the data in Table III for the control of the acid response to a standard test meal. Nevertheless they were adequate to secure satisfactory clinical results.

In only one instance did any persistent difficulty arise. The patient was a man aged 38, with recurrent deep duodenal ulceration confirmed radiographically and with an exceptionally severe hyperchlorhydria, the total acidity rising above 0.4 per cent. The full 21 grain dose was required to control his pain symptomatically, and seven weeks' treatment was needed to rid him of his pain permanently and of traces of "occult" blood from the stool.

In every other case the desired result was obtained with doses not exceeding 16 grains (anhydrous weight), but with very high acid figures it would appear advisable to use a higher scheme of dosage. Half an hour before each feed one to four teaspoonfuls were given (dose determined by bowel action) of an emulsion of paraffin in a watery dispersion of colloidal kaolin, in order to eliminate attrition at the ulcer site and impedance at the pylorus and duodeno-jejunal flexure. Regular bowel action was maintained carefully, colon lavage being used as a rule in preference to purgatives.

Three brief case histories will suffice to indicate the type of patient treated.

CASE I.—Duodenal Ulcer

C. H., aged 24, with five years' history of attacks of pain one to one and a half hours after meals, relieved by food. Occasional vomiting. An x-ray photograph in May, 1934, showed deformity of duodenal bulb. Another in September, 1934, confirmed it. The test meal revealed a moderate hyperchlorhydria, no gastric delay.

Date	Occult Blood Test (Faeces)		Pain	X-Ray
	Guaic	Haemato-porphyrin		
October 15	2+	2+	+	Duodenal defect
" 18	2+	2+	+	
Magnesium trisilicate commenced				
October 25	2+	2+	—	
" 29	+	2+	—	Normal
" 30	+	+	—	
November 2	—	+	—	
" 7	—	—	—	
" 12	—	—	—	
" 14 (discharged)	—	—	—	

CASE II.—Gastric Ulcer

W. E., aged 28, had recurrent attacks of epigastric pain half an hour after meals. There had been severe haematemesis and a secondary anaemia. There was well-marked hyperchlorhydria, but no gastric delay.

* *British Medical Journal*, February 1st, p. 205.

Date	Occult Blood Test (Faeces)		Haemoglobin (Blood) Per Cent.
	Guaiaac	Haemato-porphyrin	
September 23—haematemesis			(No iron or trans-fusion given)
October 9	2+	2+	38
.. 13	2+	2+	39
.. 15	+	+	38
.. 16	+	+	36
.. 19 magnesium trisilicate commenced	+	+	38
.. 20	—	+	45
.. 21	—	—	55
.. 24	—	—	56
.. 26	—	—	55
.. 31	—	—	60
November 5	—	—	70
.. 9	—	—	75

CASE III.—*Jejunal Ulcer*

J. B. B., aged 48, had suffered from dyspepsia since 1925. In 1927 appendicectomy was performed. In 1930 an investigation revealed hyperchlorhydria and gastric bleeding. In 1931 he had posterior gastro-jejunostomy for a chronic prepyloric ulcer. In 1933 the ulcer was still active, and a partial gastrectomy was undertaken. In 1934 there were daily bouts of left epigastric pain, not closely related to meals. The patient had severe constipation, general exhaustion, and loss in weight. An x-ray examination showed the deep crater of a jejunal ulcer. There was much occult blood in the faeces.

On the routine treatment previously outlined, and a dose of 5 grains (anhydrous weight) of the trisilicate between every feed, the pain quickly disappeared and the general condition improved. Although the pain had recurred daily for more than six months, he was able to start convalescence with a pain-free abdomen and a radiologically normal jejunum after sixteen days of treatment.

The clinical results were equally satisfactory in the remaining cases, and further detailed descriptions would be wearisome. Synthetic hydrated trisilicate of magnesium quite clearly supplied an effective medicinal control for all. The special features of its employment are: (1) The combination of three therapeutic actions in a single substance—namely, antacid, antipeptic, and antitoxic, each of which fulfils a useful role in the stomach and duodenal bulb. (2) A sustained action whereby hydrochloric acid, destructive ferments, and toxins can be removed continuously for several hours after the administration of a single dose. (3) The possibility of a local therapy at the ulcer base independently of changes occurring in the gastric contents as a whole. (4) Freedom from the risk of inducing toxic alkalosis.

Summary

1. Synthetic hydrated magnesium trisilicate possesses antacid and general adsorbent properties, readily applicable to the treatment of chronic peptic ulceration and hyperchlorhydric dyspepsia (discussed more fully in the two preceding papers).

2. It differs from all other antacids in clinical use in the vigour of its adsorbent action, as measured by the methylene-blue method (Table I).

3. Its neutralizing action continues for several hours even in the presence of an excess of acid, and exerts a sustained control over gastric hyperacidity (test meal analyses, Table II, and curves).

4. This prolonged neutralizing action enables a minimum amount of mineral base to control hyperchlorhydria

continuously. The quantity required is far below that which has been known to produce toxic symptoms of alkalosis. The trisilicate itself is insoluble in water and weak alkalis, so that any unused excess remains unabsorbed.

5. The possible local therapeutic action in the ulcer crater is discussed.

6. A series of successfully treated cases of chronic peptic ulceration is quoted in which the only antacid substance administered was synthetic hydrated trisilicate of magnesium.

OESTROGENIC ACTION OF COMPOUNDS OF THE ANDROSTERONE-TESTOSTERONE SERIES

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It has been known for some years that extracts of testis and male urine may show oestrogenic activity,¹ but this has usually been ascribed to the presence in the extracts of oestrogenic substances, probably of the oestrone group, in addition to male hormone. The fact that large amounts of oestrone can be isolated from stallion urine by mild chemical treatment is, of course, strong evidence in favour of this view,² but a purely oestrogenic substance has never actually been isolated from other male mammals. It is now recognized that substances of a more or less similar chemical nature to oestrone may have some degree of oestrogenic power, even if their primary biological activity is of quite a different nature.³ Further, it has been found possible to hydrogenate oestrone, which itself shows no male hormone activity, to a substance having male hormone activity but no oestrogenic power.⁴ It is not unlikely, therefore, that substances having both male hormone and oestrogenic properties may occur naturally. The first male hormone obtained, androsterone, isolated from male urine by Butenandt⁵ and prepared artificially from cholesterol by Ruzicka and his co-workers,⁶ was found to be non-oestrogenic by the vaginal cornification test⁷ and by a plumage test.⁸ Butenandt and Kudzus,⁹ however, have recently reported that *trans*-dehydroandrosterone, androstenedione, and testosterone cause opening of the vagina in the intact immature rat. The first of these substances is present in human male urine and has some male hormone activity (Butenandt and Dannenbaum).¹⁰ Testosterone, however, isolated from testes by Laqueur and his co-workers,¹¹ is the most active male hormone so far described.

Saturated and Unsaturated Compounds

Butenandt's work provided the first evidence that naturally occurring compounds might show the activities of both ovarian and male hormones. The three compounds found to be oestrogenic by Butenandt are all unsaturated, and therefore more similar to oestrone than is androsterone, but certain saturated compounds of the series, including androstanediol (the dihydroxy derivative of androsterone), are also oestrogenic on the intact immature rat.¹² Moreover, androstanediol increases the size of the uterus and vagina of the adult ovariectomized rat.¹³