THE CHEMICAL EVALUATION OF ANTACIDS

By Harry Brindle

From the Department of Pharmacy, Manchester University

Received July 15, 1953

To assess the value of an antacid for medicinal purposes the obvious method is to study the effect on the gastric secretion in the stomach of the human subject. This subject may be a normal person or one with hyperacidity or, if emphasis is placed on clinical use, one suffering from an ulcerous condition. It is very difficult however to secure reliable information by this method. There are very wide variations in the constitution of the gastric juice of the same individual even within a short space of time and according to Mutch[1] critical assessment of the relative healing or prophylactic virtues of antacids is impossible.

It may well be that the results of well designed chemical tests will supply more reliable information than *in vivo* experiments which might at the first sight appear to be more desirable. Such chemical tests, however, should approach as nearly as possible the normal conditions which might exist in the stomach of a patient who is taking an antacid to control hyperacidity. The acid absorption test for magnesium trisilicate of the British Pharmacopœia 1953 consists in adding to the antacid a considerable excess of 0·05N hydrochloric acid and stirring continuously at 20° C. for 4 hours and determining the amount of acid neutralised by titrating the excess with 0·05N alkali. The neutralising capacity test for aluminium hydroxide gel of the British Pharmaceutical Codex 1949, is similar but the reaction is carried out at 37° C. for one hour. These tests are of value for the purpose for which they were designed, i.e., to ensure that the medicinal substance has a certain minimum capacity to neutralise acid. No attempt is made to approach the conditions under which the antacid will be expected to act medicinally except that the British Pharmaceutical Codex directs that the test be carried out at about body temperature, 37° C. If the results of such tests are used as criteria for evaluating antacids it is possible that very erroneous conclusions may be reached. The conditions of these tests differ from those occurring in actual use in that there is (*a*) a considerable excess of acid at all times during the test and this may not be the case in the stomach, (*b*) the effect of buffers etc. present in the stomach is not allowed for, (*c*) in the stomach there is a continuous and variable secretion of acid and formation of other substances, and (*d*) there is continuous removal of the stomach contents to the duodenum.

These factors must have a considerable effect upon the *in vivo* action of antacids and must be considered when attempts are made to correlate the results of chemical tests with the probable action in the stomach. Hammarlund and Rising[2] added hydrochloric acid at intervals of 30 minutes to the antacid and recorded the *p*H every 5 minutes for 3 hours. Alstead[3] used human gastric juice for his tests and Mutch[1] also added hydrochloric

acid in small portions at intervals to an excess of antacid and determined the *p*H at frequent intervals. Mutch[4] measured the resulting *p*H when varying amounts of acid and antacid were left in contact for different periods.

The present writer is not here concerned with the clinical value of antacids in ulcerous conditions where such considerations as their influence on peptic digestion, laxative effect and protective action on the gastric mucosa would have to be taken into account; neither is he concerned with the properties of mixtures of antacids, nor in examining a large variety of antacids. The object of the work here described was to devise a comparatively simple chemical test which would enable some assessment to be made of the neutralising power of an antacid which would take into account, (*a*) the presence of buffers similar to those in gastric juice, (*b*) body temperature, (*c*) rate of neutralisation, (*d*) ultimate *p*H when antacid is in excess. These are important factors in the clinical use of antacids which do not enter into the official tests.

Experimental

After a number of trials of different concentrations of hydrochloric acid and different buffers it was finally decided that an artificial gastric juice which would be suitable for experimental use would be 0·05N hydrochloric acid containing 0·15 per cent. each of pepsin, peptone and sodium chloride. It was advisable to preserve it with about 0·5 per cent. v/v of chloroform by shaking with a slight excess of chloroform. This artificial gastric secretion had an average *p*H at 38° C. of 1·5. The *p*H of different batches varied between 1·45 and 1·55 probably due to some variation in the pepsin and peptone. Because of this variation in the initial *p*H of the fluid it was better to take account of the change of *p*H on addition of the antacid in preference to the actual *p*H readings. The general plan of the experimental work as finally decided after many trials of different conditions was to add a 20 per cent. excess of the antacid to 100 ml. of the artificial secretion at 38° C. and record the change of *p*H at frequent intervals keeping the liquid briskly stirred. It will be shown that it was possible to obtain a fairly accurate figure for the amount of acid neutralised in any given time.

Relationship of p*H change to amount of acid neutralised.* The correspondence between the recorded *p*H change and the amount of acid neutralised was determined by heating 100 ml. of the artificial juice to 38° C. and titrating with 0·5N sodium hydroxide added in small portions with constant stirring and recording the change in the *p*H of the fluid. It was realised that these were not conditions which would be directly comparable with those occuring during the actual test of the antacid. Sodium chloride was formed as the result of the neutralisation of the acid and the volume was increased eventually by 10 per cent. Neither of these circumstances might occur during the actual testing of an antacid but it was considered that the differences would be negligible for all practical purposes. In any case although a knowledge of the proportion of acid neutralised by the antacid might be useful information, the change of

*p*H produced is probably of greater significance. The result is shown graphically in Figure 1.

A number of titrations were carried out and satisfactorily concordant results were obtained. The degree of accuracy varied somewhat in different parts of the titration but the variation never exceeded ±5 per cent., the figures being much more consistent as neutrality was approached.

Comparison of artificial with human gastric secretion. Samples of human gastric secretion showed considerable variation of *p*H with alkali treatment even when there was not much difference in their "hydrochloric acid" acidity. In order to determine if the artificial secretion would behave roughly similarly to the natural, a number of samples of human gastric juice of about 0·05N acidity were selected and titrated with 0·5N sodium hydroxide under the same conditions as those just described for the artificial secretion. There was a considerable variation between individual samples but the average gave a result very similar to those for the artificial juice (see Fig. 1). It is evident from these curves that in testing an antacid it should be possible to determine with considerable accuracy the percentage of hydrochloric acid neutralised in any given time when the antacid is added to a definite amount, in these experiments 100 ml., of the artificial gastric secretion. Although no allowance has been made for the "emptying" of the stomach the information so gained should be very valuable when a comparison is made of the probable relative efficiencies of antacids.

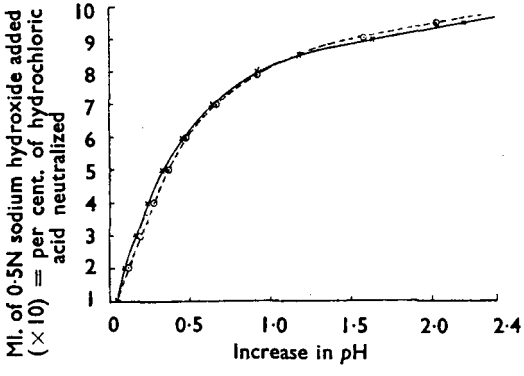

FIG. 1. Titration curves of sodium hydroxide against human and artificial gastric secretion.

——×——×— Artificial secretion.
– – ⊙ – – ⊙ – Human secretion.

As explained above, the object of the work here described was to devise a test for antacids for which the conditions could be standardised, which would supply information regarding the probable speed of action and ultimate *p*H in the stomach. For some clinical purposes rapid neutralisation of the stomach acid may be required, for others a steady, slow neutralisation may be desirable. Again in some conditions it may be that a final *p*H of about 2 to 2·5 or alternatively 5 to 6 is required and this *p*H attained either rapidly or slowly.

It is suggested that the test described below would supply most of the information required and should be of value in comparing the antacids now in use, and also for the evaluation of new antacids or mixtures.

Method of Testing

After a number of trials the following conditions and apparatus appeared to offer the most advantages and fewest disadvantages.

100 ml. of the artificial gastric secretion described above is placed in a 150-ml. beaker and immersed in a water bath at 38° C. to a depth equal to the level of the liquid inside the beaker. The liquid is kept constantly stirred and the electrodes of a *p*H meter immersed in it. The *p*H meter may be of the automatic recording type but this is not essential. When the *p*H and the temperature are constant, the latter at 38° C., the antacid is added and the *p*H read at frequent intervals. The amount of antacid to be added is arbitrary but for each experiment described below a 20 per cent. excess over the "neutralisation value" of the antacid was used. This neutralisation value was determined by adding a weighed amount of the antacid to 100 ml. of 0·05N hydrochloric acid at 38° C. taking care that there will be finally an excess of about 50 ml. of the acid. The temperature was kept at 38° C. by immersing the beaker in a water bath and the mixture was thoroughly stirred continuously. After four hours or when the reaction was complete the mixture was filtered, if necessary, and after washing the filter paper and residue, if any, the excess of acid titrated with standard sodium hydroxide using bromophenol blue as indicator. The term "neutralisation value" for the antacid as used in this paper was the weight of the antacid required to neutralise 100 ml. of 0·05N hydrochloric acid under these conditions. At the elevated temperature in the presence of a considerable excess of acid and absence of buffers it may be assumed that the figure obtained for the amount of acid neutralised is a maximum one. This often differed markedly from the result which would be obtained by the electrometric titration in the presence of buffers when a large excess of acid is not used, these being the conditions of the test.

Details and results of tests. A selection was made of a number of antacids which were obtained in the ordinary way either from the makers or through wholesale suppliers. The samples therefore are representative of those which would normally be used by patients. In each case the "neutralisation value" was determined by the method given above and 20 per cent. above this quantity added to 100 ml. of the artificial gastric secretion. The *p*H was read at frequent intervals, usually 1-minute intervals at the beginning of the experiment, but at wider intervals later when a small *p*H change does not represent as much acid neutralised.

The Tables give the increase of *p*H at intervals of 10 minutes for 30 minutes and then after the first hour. Since the initial *p*H of the liquid was about 1·5 the approximate actual *p*H can be calculated by adding 1·5 to the figure for the increase in *p*H.

Magnesium trisilicate. 3 samples of magnesium trisilicate were first tested and the results up to 1 hour are given in Table I and are expressed graphically in Figure 2. The experiments were usually carried out over a 3-hour period but the significant time was the first 60 or 90 minutes. Table I gives the results up to 60 minutes and the Figure 2 up to 90 minutes. The approximate actual *p*H at any stage can be calculated by adding 1·5 to the figure given for the increase in *p*H. The approximate percentage

of hydrochloric acid neutralised is obtained from the graph given in Figure 1.

It is interesting to note the variation between the 3 samples. Sample C was a specimen which had been stored for about 12 months but samples A and B were of recent manufacture. It is not suggested that there had

TABLE I

INCREASE IN *p*H VALUE AND PERCENTAGE OF HYDROCHLORIC ACID NEUTRALISED ON ADDING 20 PER CENT. EXCESS OF MAGNESIUM TRISILICATE TO ARTIFICIAL GASTRIC SECRETION AT 38° C.

Antacid	Neutralisation value	After 10 minutes		After 20 minutes		After 30 minutes		After 60 minutes		Final *p*H with 100 per cent. excess of antacid
		*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	
Magnesium trisilicate:										
A	0·4393 g.	0·30	47·5	0·58	67·5	0·86	78	2·00	95	7·5
B	0·4358 g.	0·50	62·5	1·02	82·5	1·52	90	3·36	100	
C	0·4586 g.	0·32	50·0	0·53	65·0	0·64	70	0·82	77	

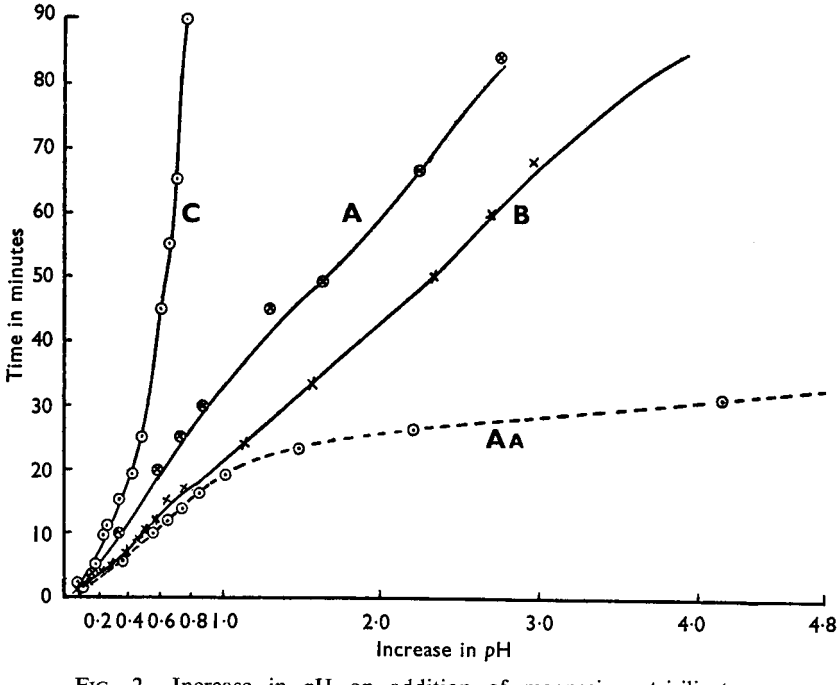

FIG. 2. Increase in *p*H on addition of magnesium trisilicate.

A. Sample A.
AA. Sample A without buffer.
B. Sample B.
C. Sample C.

been any deterioration in the case of C since no figures were available for its original behaviour. For all practical purposes samples A and B had neutralised all the acid in 1 hour but C had neutralised only 77 per cent. and the reaction was proceeding very slowly. The final *p*H in all the cases was about 7. Near the conclusion, sufficient magnesium trisilicate was added to give an excess of 100 per cent., but this had little effect upon the final *p*H value which was still 7·0 to 7·5. It will be noticed that when the increase in *p*H is plotted against the time the graph is practically a straight line until there is almost full neutralisation of the acid.

TABLE II

INCREASE IN *p*H VALUE AND APPROXIMATE PERCENTAGE OF HYDROCHLORIC ACID NEUTRALISED ON ADDING 20 PER CENT. EXCESS OF VARIOUS ANTACIDS TO ARTIFICIAL GASTRIC SECRETION AT 38° C.

Antacid	Neutralisation value	After 10 minutes		After 20 minutes		After 30 minutes		After 60 minutes		Final *p*H with 100 per cent. excess of antacid
		*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	
Aluminium phosphate suspension	18·85 g.	1·02	82	1·04	83	1·07	84	1·12	85	3·24
Dried aluminium hydroxide gel (A) ..	0·1829 g.	0·17	30	0·24	40	0·32	49	0·45	60	3·88
do. supplied as B.P.C. (B) ..	1·144 g.	0·98	81	1·76	91	1·93	93	1·98	94	3·82
Aluminium hydroxide gel	8·707 g.	1·40	88	2·14	95	2·32	96	2·40	98	4·76
Magnesium phosphate	0·511 g.	2·36	96	2·88	98	3·13	100	3·28	100	5·45
Bismuth carbonate ..	1·159 g. to 1·179 g.	0·0	0	0·0	0	0·0	0	0·0	0	1·53

Other antacids. Tests with the artificial gastric secretion were carried out on a few other slow-acting antacids. Sodium bicarbonate, calcium carbonate, magnesium hydroxide and others which act quickly were not tested at this stage because the results could be forecasted with considerable accuracy. It is intended to apply the test to all possible antacids including mixtures in the near future. The results of the antacids tested are given in Table II and graphically in Figures 3 and 4.

Many more readings were taken than are shown in Table II and in Figures 3 and 4, and tests were repeated to ensure that the results were reproducible.

Aluminium phosphate. A proprietary suspension stated to contain 7·5 per cent. of aluminium phosphate was used. It will be noted that the initial reaction was very rapid, the equivalent of about 78 per cent. of the

hydrochloric acid being neutralised in 3 minutes and 81 per cent. in 7 minutes. Thereafter, however, there was little further action. With about 100 per cent. excess of the suspension the final *p*H was 3·24.

Dried aluminium hydroxide gel. The neutralising capacity of sample B was much below the minimum standard of the British Pharmaceutical Codex. A sample of the minimum B.P.C. standard would have a "neutralising value" of 0·25 g. whereas of sample B 1·144 g. was required. It was therefore less than ¼ of the minimum "official" strength. As judged by the neutralisation curve it would appear to be efficient but a

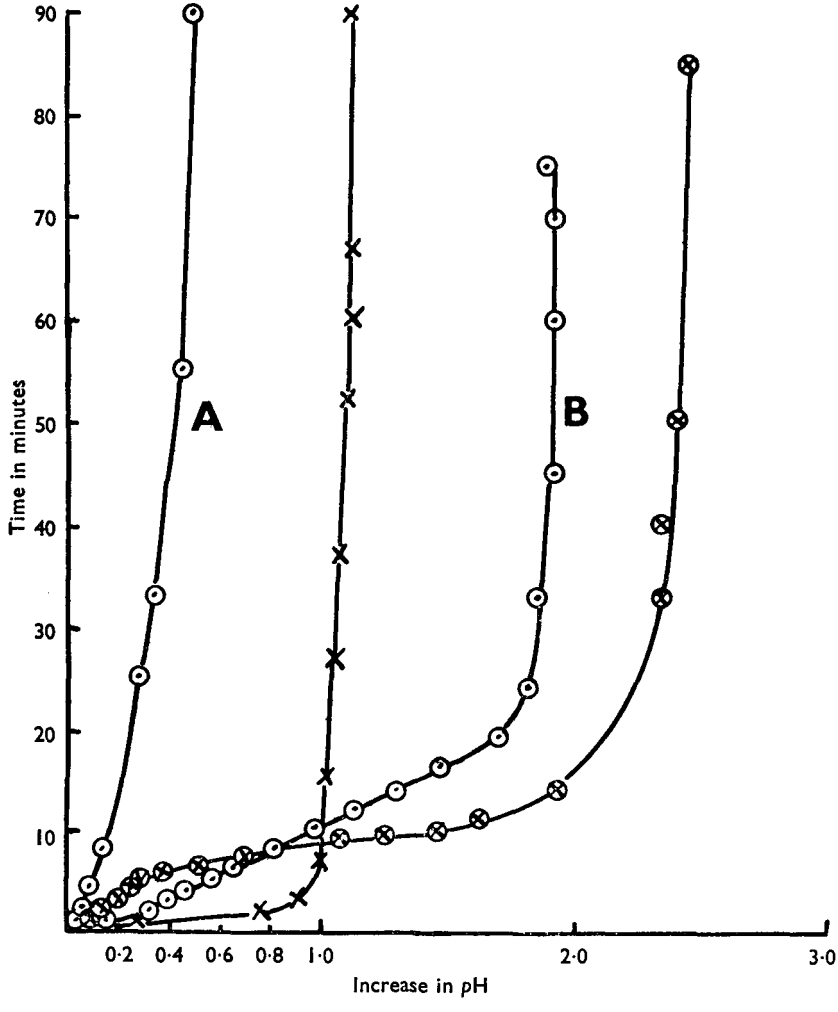

FIG. 3. Increase in *p*H on addition of antacids.

—×—× Aluminium phosphate.
—⊕—⊕ Aluminium hydroxide gel.
—⊙—⊙ Dried aluminium hydroxide gel, samples A. and B.

large dose would be required. The neutralisation "curves" for both samples show the usual straight line until practically all the acid had been neutralised.

Aluminium hydroxide gel; *supplied as B.P.C.* The neutralisation was more rapid than with the dried gel and a higher final *p*H was reached.

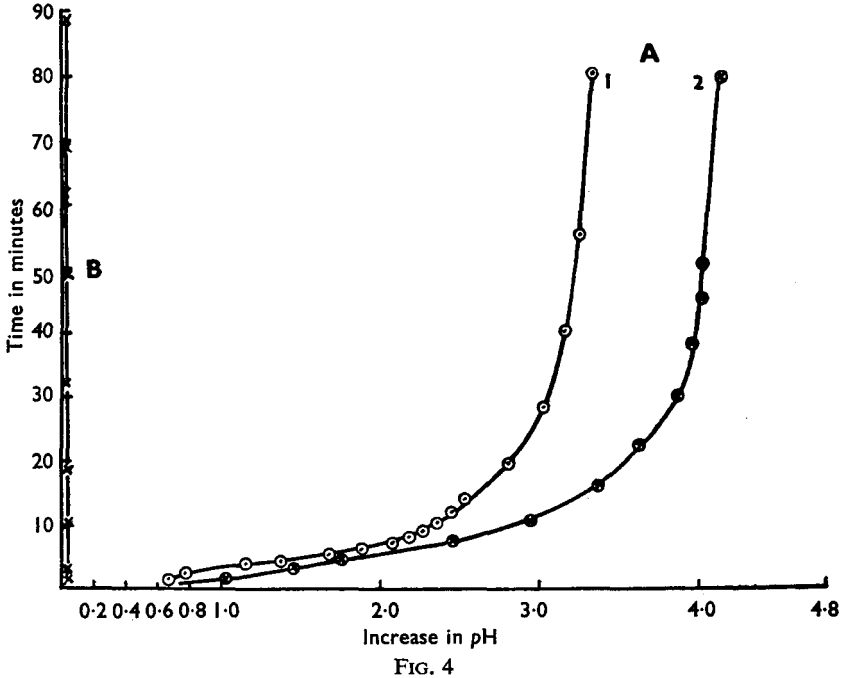

FIG. 4

A. Magnesium phosphate.
   1. Artificial secretion.
   2. Human gastric secretion.
B. Bismuth carbonate.

The minimum B.P.C. standard is equivalent to a neutralisation value of 2·5 g. This sample was well below the B.P.C. standard. Judging by these results it would appear that there are samples of aluminium hydroxide gel and dried aluminium hydroxide gel on the market which are not of a satisfactory standard.

Magnesium phosphate. This is the most rapid of the "slow acting" antacids which were tried. Neutralisation of the hydrochloric acid present was practically complete and a *p*H of 3·5 was reached in 5 minutes. For comparison human gastric secretion equivalent to 100 ml. of 0·05N hydrochloric acid was used and the result is given in Table III and graphically in Figure 4. This sample of human secretion was more acid than the artificial, 70·3 ml. being the equivalent of 100 ml. of 0·05N. It was to be expected therefore that the neutralisation of the more concentrated acid would be more rapid. It would appear possible from the graph that the human secretion in this case was not so well buffered as the artificial. Even with this sample of human secretion which was somewhat

unusual the general plan of the reaction was very similar to that occurring with the artificial secretion.

Bismuth carbonate. Several samples of the light and medium varieties were tried. Certain samples gave a very slight initial *p*H increase representing about 5 per cent. acid neutralisation but in most cases there was no appreciable effect upon the *p*H value. 5 g. of a sample which gave a slight initial rise in *p*H was boiled with successive quantities of 100 ml. of distilled water. The first 100 ml. of the washings had *p*H 8·65 and required 0·53 ml. of 0·1N hydrochloric acid to neutralise it to methyl orange. There was a gradual decrease in the volume of acid required for each washing portion, the second requiring 0·4 ml., the third 0·3 and the fourth 0·2 ml. It would appear probable, therefore, that the slight initial reaction of some samples was due to the presence of soluble alkali as an impurity in the bismuth carbonate. It was decided, therefore, that

TABLE III

NEUTRALISATION OF HYDROCHLORIC ACID IN ARTIFICIAL GASTRIC SECRETION AND HUMAN GASTRIC SECRETION

	After 2 minutes		After 3 minutes		After 5 minutes		After 10 minutes	
	*p*H increase	Hydrochloric acid neutralised per cent.	*p*H increase	Hydrochloric acid neutralised per cent.	*p*H increase	Hydrochloric acid neutralised per cent.	*p*H increase	Hydrochloric acid neutralised per cent.
Artificial gastric secretion ..	0·90	78	1·20	85	1·8	92	2·35	96
Human gastric secretion ..	1·4	88	1·60	90	2·1	95	2·95	100

under the conditions of this test pure bismuth carbonate had no neutralising action upon the artificial gastric secretion. 100 per cent. excess of bismuth carbonate had no effect upon the original *p*H after more than one hour's contact.

The result with bismuth carbonate is interesting as throwing into sharp relief the fact that the results of an "acid absorption" test such as that of the British Pharmacopœia for magnesium trisilicate or a "neutralising capacity" test as that of the British Pharmaceutical Codex for aluminium hydroxide gel may lead to very erroneous conclusions if considered as criteria for evaluating antacids. 1·159 g. to 1·179 g. of bismuth carbonate was capable of neutralising 100 ml. of 0·05N hydrochloric acid when tested by a method similar to these but double that amount (100 per cent. excess) had no appreciable neutralising effect after 2 hours when added to 100 ml. of artificial stomach secretion containing hydrochloric acid of 0·05N concentration at 38° C. thus approaching nearer to actual conditions in the stomach. This is not to say that bismuth carbonate is valueless in cases of gastric or duodenal ulcer but its efficiency as an antacid is obviously open to very grave doubt.

Comparison of the effect of magnesium trisilicate on unbuffered 0·05N hydrochloric acid and the artificial stomach secretion. A test was carried out under the same conditions as previously but using 100 ml. of

unbuffered 0·05N hydrochloric acid and the figures obtained for the *p*H change and percentage of hydrochloric acid neutralised compared with those given by 100 ml. of the artificial stomach secretion (buffered 0·05N hydrochloric acid) using the same weight of the same sample of magnesium trisilicate. The results are given in Table IV and Figure 2.

It will be noticed that neutralisation was much more rapid in the case of the unbuffered hydrochloric acid. This result emphasises the desirability of using buffered hydrochloric acid when evaluating antacids.

TABLE IV

COMPARISON OF THE ACTION OF MAGNESIUM TRISILICATE ON UNBUFFERED 0·05N HYDROCHLORIC ACID AND ON ARTIFICIAL STOMACH SECRETION (BUFFERED 0·05N HCL)

Antacid	Neutralisation value	After 10 minutes		After 20 minutes		After 30 minutes		After 60 minutes		Final *p*H with 100 per cent. excess of magnesium trisilicate
		*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	*p*H increase	Hydrochloric acid neutralised, approximately per cent.	
Magnesium trisilicate buffered 0·05N HCl	0·4393 g.	0·30	47·5	0·58	67·5	0·86	78	2·00	95	7·05
Magnesium trisilicate unbuffered 0·05N HCl	0·4393 g.	0·56	67	1·10	84	3·8	100			7·50

DISCUSSION

From the results obtained when various antacids are added to the artificial gastric secretion it is considered that the proposed fluid is a suitable medium for testing and comparing antacids. The actual conditions in the stomach are simulated as nearly as possible. No allowance is made for continued secretion of gastric fluid and the removal of the stomach contents. These vary enormously in the living body and could scarcely be reproduced in a test in which the conditions should be capable of standardisation. If it is desired an allowance could be made for these changes since the test gives information regarding the rate at which the acid is neutralised and the state of the liquid at any time is ascertainable. Pepsin and peptone may not be ideal buffers to use but they are probably the nearest readily available substances which can be regarded as imitating the buffers etc. in normal gastric secretion. Standard pepsin and peptone are unobtainable but variations within limits are not important if increase in *p*H on addition of the antacid is considered and not the actual *p*H.

The results with bismuth carbonate and the comparison of the artificial medium with unbuffered 0·05N hydrochloric acid indicate that some standard method of testing antacids is desirable.

In clinical practice there are considerable differences in the conditions which it is desired to bring about in the alimentary tract of patients. Sometimes, the object is to remove only the excess of acid as in simple hyperacidity. Here an antacid which reacts slowly and leaves a final

*p*H of perhaps 2 to 2·5 is required. Peptic action could still occur at this *p*H. Alternatively it may be desirable to prevent peptic action but not to alkalise the stomach contents, in which case a final *p*H of about 4 to 5 would be required and a slow-acting antacid suitable. In the case of actual pain a quick acting antacid to give rapid relief combined with a slow one to maintain the condition would probably be used. In general, modern practice is against the use of soluble alkalis as tending to produce the so-called acid rebound. It is suggested that valuable information is made available by a test such as the one given above. Further in the case of old and new antacids some information can be deduced as regards efficient dosage. Although the amount and rate of secretion of hydrochloric acid varies very much, an average figure may be taken to be the equivalent of about 3 ml. of 0·05N acid per minute during waking hours. Therefore, twice the "acid equivalent" mentioned above should be taken every hour if full neutralisation is required. If the doses are more widely spaced some idea of the conditions likely to occur can be obtained from a consideration of the dose used and the ascertained rate of neutralisation when 20 per cent. excess over the "acid equivalent" is used in the above described test.

SUMMARY

1. It is suggested that a standard test using buffered hydrochloric acid should be used for the evaluation of antacids.

2. The solution suggested for the test is an artificial gastric secretion consisting of 0·05N hydrochloric acid buffered with 0·15 per cent. each of pepsin, peptone and sodium chloride.

3. An "acid neutralisation value" of the antacid is obtained by subjecting it to the action of an excess of 0·05N hydrochloric acid at 38° for 4 hours. The acid neutralisation value is the weight of antacid which will neutralise 100 ml. of 0·05N hydrochloric acid.

4. An excess of 20 per cent. of the antacid is added to 100 ml. of the artificial stomach secretion at 38° C. and the change of *p*H noted at frequent intervals. Results are obtained for the rate of neutralisation of the acid.

5. The importance of using buffered hydrochloric acid is stressed and comparisons are made between the results with buffered and unbuffered acid and also with human gastric secretion.

6. A number of antacids are tested and results are given for the rate of neutralisation of the acid and for the final *p*H obtained.

I wish to thank Dr. R. W. Fairbrother, D.Sc., M.D., F.R.C.P., Director of the Department of Clinical Pathology and Mr. H. Varley, M.Sc., A.R.I.C., Chief Biochemist in the same Department, for procuring for me a number of samples of human gastric secretion.

REFERENCES

1. Mutch, *Lancet*, 1949, **256**, 859.
2. Hammerlund and Rising, *J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 295.
3. Alstead, *Lancet*, 1941, **240**, 420.
4. Mutch, *Brit. med. J.*, 1937, **2**, 735.

DISCUSSION

The three papers on antacids were discussed together.

The first paper was presented by MR. J. ARMSTRONG, the second by MR. D. N. GORE, and the third by PROFESSOR H. BRINDLE.

MR. N. L. ALLPORT (London) was surprised by the general agreement that bismuth carbonate had little antacid value. Having examined a number of aluminium hydroxide gel preparations, he had often been worried because frequently a certain amount of sodium carbonate was left in them; there did not seem to be any test in the B.P.C. for its presence. It would be interesting to know whether by application of the tests suggested by the authors, sodium carbonate could be detected in washed aluminium hydroxide gel.

DR. W. MITCHELL (London) said that making allowances for slight differences in the techniques of the authors, it was clear that various specimens of magnesium trisilicate behaved differently. Had the authors any information concerning the magnesium trisilicate used? At least two types of material were available, light and relatively dense, and although the B.P. suggested that magnesium trisilicate could be made by reacting magnesium sulphate with sodium silicate, it could also be made by reacting magnesia with silica gel. The latter was the more attractive method because it obviated the necessity of washing out soluble by-products. Both products complied with the B.P. tests including total acid absorption, but how they behaved *in vivo* was another matter.

MR. A. W. BULL (Nottingham) asked whether the low level of the curve for magnesium trisilicate in Figure 1 of Mr. Gore's paper was due to the fact that the experiment was carried out at room temperature whereas in the other two papers the temperature was 37° C. Further clarification of the influence of conditions of manufacture of aluminium hydroxide on its antacid properties was needed. Dried aluminium hydroxide gel was slower in attaining a satisfactory *p*H level than "liquid" gel but it was excellent for maintaining an effective *p*H level. It would be interesting to know whether superimposition of the curves for individual constituents of a compound antacid mixture, for example, of the curve for a quick acting antacid such as magnesia on the curve for aluminium hydroxide gel, would make it possible to predict the behaviour of the mixture. Theoretically one would expect the mixture to show quick attainment of a satisfactory *p*H level and prolonged activity.

DR. G. E. FOSTER (Dartford) drew attention to the wide range of the amounts of different antacids quoted in the National Formulary as being required to deal with the daily output of hydrochloric acid by the stomach. The figure for bismuth carbonate of 136 g., indicating its poor antacid value, appeared to be substantiated by the papers under discussion. It was somewhat surprising, if bismuth carbonate possessed such poor qualities, that it should have attained the reputation it had enjoyed for many years in the treatment of gastric complaints. Did the *in vitro* test bear any relationship to its clinical efficiency? In the course of his work he had made aluminium hydroxide gels for the purpose of absorbing

enzymes and other biological products, and he recalled some papers by Willstätter and co-workers published in 1923 in which conditions for the preparation of different types of aluminium hydroxide gel were described. He had found that the gels produced had remarkably different absorptive properties, and it would be interesting for their antacid properties to be tested in order to ascertain which method of preparation gave the most efficient product.

MR. J. H. OAKLEY (London) said that the B.P.C. gave no guidance as to how aluminium hydroxide gel should be made. Many different starting materials were allowed, and there was no indication of the concentrations of the solutions to be employed, the temperature at which these solutions should be mixed, nor of the order of mixing. Further, the process used in washing the gel could modify the physical texture of the product. It would be interesting to learn whether the authors had noticed any appreciable differences in the behaviour of different batches of the liquid gel such as those which had apparently been noticed in the case of the dried gel. Referring to mixture of magnesium hydroxide, he said he would expect, from the information contained in the papers, that its neutralising effect would be very small and transient, and he asked whether the authors could give any information on the type of curve one might expect for the product. It was a common practice to mix oils, such as liquid paraffin, with antacids, and he desired to know whether that would delay the onset of and prolong the antacid action.

MR. R. L. STEPHENS (Brighton) said that possibly the action of bismuth had been explained by Mr. Armstrong when he pointed out that the purpose of an antacid was to prevent the action of pepsin. If the *p*H were brought to the level at which pepsin was no longer active, no damage would occur to the stomach wall. He had recently found that Mist. Bismuth. Co. cum Pepsin., even when the *p*H was reduced to 2 or lower, would not digest white of egg. The pepsin appeared to be completely inactivated. That was a possible clue to the value which was attached to bismuth for many years. He suggested that sufferers from indigestion might find greater relief from something which would inactivate the pepsin and leave the hydrochloric acid relatively alone. A common example of a mixture of antacids was Mist. Mag. Trisil. Co. in which sodium bicarbonate and magnesium trisilicate appeared together. He had found that with some grades of magnesium trisilicate the mixture had a *p*H substantially that of sodium bicarbonate, namely 8·4, and others appeared to react, some excess of carbon dioxide was removed, and a solution of sodium carbonate resulted with a *p*H of about 10. It would be of interest to know whether the authors had encountered samples of magnesium trisilicate which gave a *p*H of 10 when mixed with sodium bicarbonate.

MR. C. J. EASTLAND (London) confirmed that the antacid power of dried aluminium hydroxide gel decreased with the prolonged application of heat more or less in proportion to the temperature to which it was exposed. One practical issue was the effect of storage at high temperatures, such as obtained in the tropics, on liquid preparations of aluminium

hydroxide gel. Even at 37° C. something like 25 per cent. of the potency of the preparation was lost after three months. The effect of heat might account for the great variation in the acid neutralising powers of different samples of dried gel. With regard to the question of acid rebound, a paper was recently published in the *Lancet* describing the introduction of sodium bicarbonate and magnesium trisilicate as test antacids into the fasting stomachs of patients. It was stated that no evidence was found of rebound secretion of acid within the period of the test which was admittedly short, namely, 2½ to 3 hours.

MR. G. R. WILKINSON (London) said that the percentage of alumina in the preparations under test, particularly the dried gel, varied. He had found that if it were dried to, say, 52 per cent. of Al_2O_3, the activity might fall to 10 per cent. of that of the same gel if it were dried to 48 per cent. of Al_2O_3. The powders which were used were very slow in their reaction rate. Using a similar test, he was obtaining a *p*H of 3 to 3·2 within 5 minutes of addition, rising to between 3·4 and 3·5 within 10 minutes, and it would be useful to have the authors' comments on that point. The sources from which the alumina was derived had a marked influence on its reaction rate, because in his view the gel, when dried, was not aluminium hydroxide. Other ions had an important part to play in its activity, and also later in its buffering action. Referring to testing for sodium in aluminium hydroxide gel, since saccharin and sodium benzoate were permitted as flavouring and preservative, there might be something of the order of 0·3 per cent. of sodium ions present which was considerably greater than the amount of sodium which was left behind after washing. It would be interesting to know why *p*H 1·5 was used as a basis for the test set out in Mr. Armstrong's paper. In his opinion *p*H 1 was more convenient. On the question of storage in the tropics, he had found that if the storage conditions and containers were satisfactory, the material would retain its activity over a period of years. With the liquid preparation, if the temperature exceeded 40° C. gelling took place, but there did not appear to be any serious diminution in its acid neutralising capacity.

MR. C. E. WATERHOUSE (Southport) stated that of the two grades of magnesium trisilicate on the market, one had a bulk density in the region of 2 and the other in the region of 5. He had previously pointed out that although the two types of material might have similar acid absorption per g. they were often administered on a volume dose basis. It would be interesting to know whether the samples examined by Professor Brindle comprised each of these types of material or whether they were of one particular type only. If they were not of the same type, he desired to know whether the method used with the light or heavy variety showed any difference in acid absorption. The methods put forward were very elegant, but control of the material was vitiated if the actual dose consumed by the patient could vary to such an extent.

MR. D. N. GORE, commenting on Mr. Armstrong's paper, pointed out that in explaining the difference between the reactivity of aluminium hydroxide and dihydroxy aluminium aminoacetate, the author had made

the point that the greater speed of action of the latter was due to salt formation on the amino group. Whilst that was true, depending upon the *p*H of the solution, the aluminium moiety in that compound—if it were a compound—was more reactive than an equivalent weight of quite good quality dried aluminium hydroxide gel. He referred to the suggestion that pre-wetting of the dried gel increased its reactivity to acid. When determining curves for mixtures containing sodium carbonate and dried gel, in spite of the fact that the gel was wetted for some 30 to 40 minutes whilst acid was removed selectively by the sodium carbonate, it appeared to behave in a similar manner to freshly wetted gel in its reaction as soon as the carbonate was neutralised and excess of acid became available. This suggested that the presence and strength of acid was a positive factor related to the apparent reactivity of the gel.

PROFESSOR H. BRINDLE remarked that although the suggested methods differed somewhat, they were more or less on the same lines. In his own view a buffer should be present. It was not safe to judge antacid power in the absence of a buffer, and the temperature should be approximately body temperature, otherwise there would be considerable variation in the range of neutralisation when one antacid was compared with another. The end-point in the official test using an indicator was very uncertain for an antacid which had a buffer action. Very often there were 2 to 3 ml. differences in the determinations which he carried out even with considerable care being taken in trying to keep to the same *p*H. In his opinion something should be done officially in view of the difficulty in carrying out the test, subject as it was to personal variation in the choice of end-point.

MR. S. G. E. STEVENS (London) drew attention to Mr. Gore's reference to aluminium glycinate, and asked whether the N.N.R. specification of 14·5 per cent. of water was the optimum which should be aimed at, because he had found that if an attempt were made to dry very much below that, the antacid value was reduced. The purity of the aluminium glycinate used was not defined. It would seem that unless one was sure of the basic chemical nature of the compound under investigation, difficulties could be encountered. For instance, Mr. Gore stipulated that results should be read at 10-minute intervals, and it would be interesting to know the magnitude of variation to be found if the measurement were taken at, say, 9 minutes with a material which might vary by as much as 10 per cent.

MR. J. ARMSTRONG, in reply, said that the presence of sodium carbonate would not be demonstrated by their *in vitro* test. Chemical testing would be required. Some difference was shown in reactivity between heavy and light magnesium trisilicate. The heavy material gave a higher *p*H, but the general pattern was similar. Aluminium hydroxide preparations prepared by different methods gave different responses in their *in vitro* test and it was possible to prepare dried aluminium hydroxide preparations which had no antacid effect. It was agreed that the method of precipitation, conditions of reaction and washing affected the antacid properties. The results in the paper were based on commercially available

preparations of aluminium hydroxide both "liquid" and dried. It was known that aluminium compounds inactivated pepsin by forming complexes. It might be that bismuth compounds behaved similarly. It was possible to heat dried aluminium hydroxide gel with water and obtain greater reactivity. Overheating, for example at 90° C. for 5 minutes, destroyed antacid activity, while heating at 70° C. for 5 minutes gave better results than the same sample which had not been heated. All samples of dried gel were commercial samples, of B.P.C. quality, with an Al_2O_3 content of 52 to 54 per cent. Since overheating or prolonged drying could cause loss of reactivity, it was possible for a preparation dried to an Al_2O_3 content of 48 per cent. to have a higher antacid activity than a preparation further dried to contain 52 per cent. The *p*H of 1·5 was chosen as being representative of the acidity of average gastric contents. If stronger acid were used—for example *p*H 1—erroneous results might be obtained, as established by Professor Brindle's paper. The recent paper in the *Lancet* dealing with acid rebound might well cause a different approach to that problem, but further experimental evidence was necessary.

MR. D. N. GORE, in reply, said he and his co-authors had given little direct attention to methods for determining the presence of alkali in aluminium hydroxide gels. A few samples of the dried gel had shown something of the order of 1 per cent. The carbon dioxide contents were of the order of 5 to 10 per cent., which suggested the presence of basic aluminium carbonates. He agreed that the preparative history of aluminium gels to a large extent determined their properties.

The low reactivities for magnesium trisilicate were not a function of temperature. Determinations at 37° C. gave a quicker response for the sample, but the final *p*H values were the same, irrespective of temperature. He agreed that the effect of ions in aluminium hydroxide gel might have a profound effect on antacid properties. The samples of magnesium trisilicate used in the work appeared to be all of the denser type. None of the very light material had been tested. The moisture content of the aluminium glycinates typified in the paper was of the order of 5 per cent. This was determined by an infra-red moisture meter, as distinct from the prolonged heating at high temperatures described in the N.N.R. monograph. Referring to the emphasis placed by the authors of the other papers on the need for the tests to be carried out at body temperature and in the presence of buffers, he made the point that in his and his collaborators' opinion the same conclusions were reached by either method and the presence of buffer substances when testing a substance for buffer activity tended to mask the results and was of debatable value.

PROFESSOR H. BRINDLE, in reply, referring to the figures quoted from the N.F., said that an acute controversy arose with regard to the figure for bismuth carbonate, and in a weak moment he had agreed to try to settle it. He considered that one would get a good idea as to the rate of neutralisation by mixtures from consideration of the superimposed curves obtained from the constituents of the mixture. It was difficult

to see the force of the suggestion that the *p*H should be 1 rather than 1·5, for it was just as easy to obtain 1·5 as 1. In any case *p*H 1 was much lower than the average for the gastric secretion. Having examined a large number of gastric samples he had found only one to be in the neighbourhood of *p*H 1. In his view one should keep to natural acidity in testing antacids.