inadequacies in the mathematical model employed in the theoretical analysis, especially if the medians of the distributions of secretion rates greatly exceed the respective means reported in the literature, would result in the calculation of a falsely low antacid dose.

DISCUSSION AND CONCLUSIONS

All the parameters needed to calculate the adequate dose of antacid will probably never be known in most cases of peptic ulcer before treatment; some of the techniques, such as the measurement of emptying rate and starting index, are moderately time-consuming procedures (Hunt and Spurrell, 1951). The basal secretion, however, is known in many, if not most patients, and with knowledge of its value and the observations of other workers on emptying rates and starting indices, an approximation of the antacid dosage can be obtained (Fig. 1). If no information at all is available an approximate dose can be determined based on statistical data as in Table II. The calculated doses listed in both the Figure and Table II are those required to neutralize basal secretion and do not take into consideration the secretory response to frequent meals that further increase gastric secretion and consequently the required dose of antacid. It is obvious from Table V that doses of antacid must be given at least hourly if any effect is to be produced by commonly used doses.

It is emphasized that while the adequacy of the mathematical model here employed to describe the secretion into and emptying from the stomach is well established in the literature, there is wide variation in the values of the different parameters

in various reports (Table I), and thus the calculated doses of antacid are approximate only. The independence of the half-time of gastric emptying and the starting index, assumed in some calculations above, may not be strictly true and would also affect the calculated antacid dosage. Inadequate mixing of antacid is a further unpredictable factor influencing the required dose of antacid. Any rhythmic gastric actions would introduce further uncertainties, since for given average basal secretion and emptying rates the dose required would vary according as the time of administration was related to the commencement of the cyclic periods. Notwithstanding these uncertainties, the general agreement in antacid requirement between the study of Price and Sander-son (1956) *in vivo* and this mathematical study using data from the literature confirms the general validity of the conclusions.

It is emphasized that the dosage determined in the above calculations is minimum dosage. The stimulation of gastric secretion by meals would necessitate increased antacid dosage, and it is possible that gastric secretion and emptying may not be independent variables, and those patients with high secretion rates may have rapid emptying rates, thereby increasing dosage of antacid.

We believe that the minimum antacid doses are as follows: If no information is available on the patient's gastric function, then a dose of 50 mEq. once hourly is adequate for duodenal ulcer in a man, 26 mEq. for duodenal ulcer in a woman or gastric ulcer in a man. If the patient's basal secretion rate is known, a dose of neutralizing capacity eight times the secretion rate should suffice in most cases, if given hourly.

Part II An evaluation of antacids *in vitro*

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In this part of the paper we assess the neutralizing capacity *in vitro* of a series of antacids and determine the approximate dose of each required in the treatment of peptic ulcer.

METHOD

The method used differed from that of previous studies (Johnson and Duncan, 1945; Hammarlund and Rising, 1949; Dale and Booth, 1955) in that a known amount of antacid preparation was added to 25.0 ml. of distilled

water and titrated to pH 4.5 with N_{10} HCl solution at room temperature. For these determinations an autotitrator (Radiometer) was used; the autotitrator was regulated to a delay in shut-off of five seconds (which meant the reaction mixture had to retain the desired pH (4.5) for at least five seconds). When powders were used 40 mg. was mixed in 25 ml. of distilled water, when a liquid preparation was used 4 ml. was made up to 25 ml. in distilled water, and when a tablet preparation was assessed the whole tablet was placed in 25 ml. of distilled water; when tablets were investigated the neutralizing

capacity of a crushed tablet was compared later with that of the whole uncrushed tablet. Titration was performed to pH 4.5 as soon as possible after the antacid preparation was mixed in the 25 ml. of distilled water and was repeated at the end of five minutes, 10 minutes, 30 minutes, and two hours, and the results expressed in terms of millilitres of N_{10}/HCl required to produce a pH of 4.5 in the reaction mixture at the above intervals of time. Constant mixing was maintained with a magnetic stirrer.

To determine the reproducibility of the above method, a rapidly acting antacid, a slowly reacting antacid, and a tablet were assessed on separate days and the results compared. As most other studies of similar nature were done at 37°C., the effect of temperature on the above reaction was determined at 10°C., 40°C., and 80°C. in a series of antacid preparations. Also, as the pH end-point to which antacids have been titrated in the past has varied, the effect of titration to different pH levels was determined in a series of antacids.

RESULTS

NEUTRALIZING CAPACITY OF ANTACID PREPARATIONS AT ZERO, FIVE, 10 AND 30 MINUTES, AND AT TWO HOURS These results are shown in Table VII, the neutralizing capacity being expressed in terms of the volume of N_{10}/HCl required to produce a pH of 4.5 for at least five seconds. Though 40 mg. of antacid was actually titrated, the results in Table VII are expressed in terms of 1 g. of antacid. To make the results comparable, all preparations have been expressed in terms of the neutralizing capacity of 1 g. dry weight of the active constituents. In the case of liquid preparations, the volume containing this amount of antacid is stated after each preparation.

MINIMAL EFFECTIVE DOSE OF ANTACID PREPARATION It has been shown mathematically that assuming

hourly dosage, the secretion rates of Bruce, Card, Marks, and Sircus (1959) and of Sun and Shay (1957) and the emptying rates of Hunt (1959), and assuming secretion rate and emptying rate are independent variables, the antacid dosage must have a neutralizing capacity of 50 mEq. to be adequate in 90% of male duodenal patients (Myhill and Piper, Part I). Approximately half this dose is required to treat 90% of female duodenal ulcer patients and of male gastric ulcer patients. Consequently it is of some interest to know the dosage of antacid required to produce this neutralizing capacity. In Table VIII the amount of each antacid required to produce a neutralizing capacity of 50 mEq. is given; from this the approximate dose necessary can be determined, as indicated in gastric and duodenal ulcer patients in both sexes in the observations of Myhill and Piper. As antacids are commonly given in drachm doses, Table VIII also shows the number of drachm doses required to produce this neutralizing capacity.¹ For the purpose of the above calculations, the neutralizing capacity of each antacid at 10 minutes was considered.

EFFECT OF TITRATION END-POINT OF ANTACIDS ON NEUTRALIZING CAPACITY OF ANTACID The mEq. of HCl required to titrate 1 g. of antacid preparation or 1 ml. of solution to pH 6, 4.5, and 3 is given in Table IX. It is seen that certain antacids have considerable buffering capacity; in the case of aluminium hydroxide gel, the neutralizing capacity if titrated to pH 3 is 19 times as great as the value obtained if titrated to pH 6.

¹For the purpose of these calculations 1 drachm of a solution was considered to be 3.5 ml. and 1 drachm of a solid 3.9 g. The latter is only an approximation owing to the varying specific gravity of the different antacids.

TABLE VII
NEUTRALIZING CAPACITY OF A SERIES OF ANTACIDS AT ZERO, FIVE, 10, AND 30 MINUTES
AND TWO HOURS MIXING

Antacid (1g.)	Neutralizing Capacity (ml.N/10HCl) (time after mixing in min.)					Neutralizing Capacity (ml.N/10HCl) (time after mixing in min.)					
	0	5	10	30	120	0	5	10	30	120	
Powders						Tablets (1g.)					
Na ₂ CO ₃	165	165	167	170	172	Gastrogel	1	2	5	7	20
NaHCO ₃	115	115	115	115	117	Gastrobrom	5	10	15	20	28
CaCO ₃	50	77	110	137	162	Glysinal	0	0	2	2	5
MgO	15	30	87	187	305	Actal	7	7	7	7	7
Mag. trisilicate	5	7	10	12	15	Amphotab	1	2	2	2	5
MgCO ₃	5	5	7	7	17	Gelusil	1	2	2	2	7
BiCO ₃	5	5	5	5	5	Nulacin	2	5	10	15	22
						Kolantyl wafer	1	5	5	7	12
Solutions						Sebella					
Al(OH) ₃ gel (18.5 ml.)	10	10	12	12	17		1	2	2	5	7
Titralac (7.2 ml.)	167	170	175	177	180	Titralac	2	22	42	62	100
D.A.S.C. (10.0 ml.)	15	25	25	27	32	Rabro	2	25	32	45	55
Aludrox (19.5 ml.)	17	27	32	42	62	Almacarb	1	2	3	4	6
Oxaine (19.5 ml.)	45	45	47	50	62	Dijex	3	4	5	6	7
Mucaine (19.5 ml.)	30	30	32	35	50						
Kolantyl gel (16.7 ml.)	57	57	60	62	67						
Milk of magnesia (12.0 ml.)	325	332	332	332	332						

TABLE VIII
AMOUNT OF VARIOUS ANTACIDS REQUIRED TO NEUTRALIZE 50 meq. HCl.

Antacid	Neutralizing Capacity of 1g. or 1 ml.		Dose Required to Neutralize 50 mEq. HCl.	Dose Required in Terms of Drachm Doses	
	ml. N/10 HCl	mEq. HCl.			
Powders					
NaHCO ₃	115	11.5	4.4 g.	1.1	
MgO	85	8.5	5.9 g.	1.5	
CaCO ₃	110	11.0	4.5 g.	1.2	
Mag. trisilicate	10	1.0	50 g.	12.9	
MgCO ₃	8	0.8	63 g.	16	
Solutions					
Al(OH) ₃ gel	0.7	0.07	715 ml.	201.1	
D.A.S.C.	2.6	0.26	192 ml.	54.1	
Milk of magnesia	27.7	2.8	17.8 ml.	5.0	
Titralac	24	2.4	20.6 ml.	5.9	
Aludrox	1.7	0.17	294 ml.	82.8	
Oxaine	2.4	0.24	208 ml.	58.6	
Mucaine	1.7	0.17	294 ml.	82.8	
Kolantyl gel	3.4	0.34	147 ml.	41.4	
				<i>Weight of Tablet</i>	<i>No. of Tablets</i>
Tablets					
Gastrogel	5.0	0.5	100 g.	1.08	93
Gastrobrom	15.0	1.5	33.3 g.	1.48	23
Glycinal	2.5	0.25	200 g.	0.72	278
Actal	7.7	0.77	65 g.	0.60	109
Amphotab	2.5	0.25	200 g.	1.04	192
Gelusil	2.5	0.25	200 g.	1.36	147
Nulacin	10.0	1.0	50 g.	3.12	17
Kolantyl wafer	5.0	0.5	100 g.	1.64	61
Sebella	2.5	0.25	200 g.	0.53	379
Titralac	42.5	4.25	11.8 g.	0.65	18
Rabro	32.5	3.25	15.4 g.	1.54	10
Almacarb	3.0	0.3	167 g.	1.28	130
Dijex	4.6	0.46	109 g.	1.65	66

TABLE IX

EFFECT OF pH END-POINT TO WHICH ACID IS TITRATED ON THE NEUTRALIZING CAPACITY OF ANTACIDS

	pH 6	pH 4.5	pH 3
	mEq. HCl	mEq. HCl	mEq. HCl
NaHCO ₃ (1 g.)	7.0	10.8	11.8
CaCO ₃ (1 g.)	2.0	10.8	18.5
Amphogel (1 ml.)	0.01	0.06	0.19

EFFECT OF TEMPERATURE OF REACTION MIXTURE ON NEUTRALIZING CAPACITY OF ANTACIDS Three antacids (NaHCO₃, Amphogel, Glycinal) were assessed at 0°C., 20°C., and 37°C. The variation due to temperature was less than 10%.

REPRODUCIBILITY OF RESULTS The titration reading at 10 minutes was determined for three antacids (NaHCO₃, Amphogel, and Amphotabs) on three separate days. The correlation was good; the variation around the mean for each of the three antacids did not exceed 10%.

DISCUSSION

Methods of assessing the potency of antacids in the past have consisted of two general classes: those that

involve the periodic removal of a small volume of reaction mixture and the subsequent addition of an equal volume of acid solution (Johnson and Duncan, 1945; Hefferren, Schrotenboer, and Wolman, 1956) and those that involve only the addition of fresh hydrochloric acid (Hammarlund and Rising, 1949; Dale and Booth, 1955). In these methods, the pH of the reaction mixture was determined every few minutes for intervals of three hours (Hammarlund and Rising 1949) or until the pH reached 1.8; the results are commonly expressed in terms of the pH changes produced. These methods have been investigated in detail by Hefferren *et al.* (1956) who found the method of Hammarlund and Rising (1949) gave in six of seven preparations tested a pH of 3 to 4 at the end of the test period of three hours, indicating little differentiation of antacids at this time. They also found that the method of Dale and Booth (1955) gave results similar to the method of Johnson and Duncan (1945).

These workers have obviously tried, in varying degree, to reproduce conditions existing in the stomach, namely, continual addition of acid and the continual loss of the reaction mixtures through the pylorus. This is an impossible ideal owing to the great variation in the emptying rate of the stomach and in the rates of gastric acid secretion.

Accordingly, we feel that there is no simple method of assessment *in vitro* that will determine with any degree of accuracy the amount of antacid required to produce effective neutralization of the gastric contents. The dose required is determined by at least three variables, gastric secretion, gastric emptying, and the neutralizing capacity of the antacid. If the former two variables are known, the approximate dose can be calculated from the mathematical data of Myhill and Piper (Part I); if these results are not known the only alternative is to administer a dose that statistically should be adequate based on the mathematical data of the above authors and the studies *in vivo* of Price and Sanderson (1956). The most readily determined index of dose is the neutralizing capacity of the antacid and the present study shows the great variation that exists among commonly used antacids.

Elevation of the pH of the gastric contents above the level at which peptic digestion is possible is only one of the methods by which antacids inhibit the peptic activity of gastric juice. Many compounds have been known to have adsorbent powers and this property has been used in biochemistry for many years; the therapeutic implications of this action were first noted in 1941 by Schiffrin and Komarov. In a previous study, we found many of the commonly used antacids also had an adsorbent action on pepsin, and, in the case of aluminium hydroxide gel, the adsorbent action was much more important than its pH effect when the gel was used to inhibit peptic activity (Piper and Fenton, 1961). This marked adsorbent action was present when the gel had been titrated to a pH of 1.5, *i.e.*, when its neutralizing action had already been exerted; the adsorbent action was much reduced at low pH levels, so this study underestimated the peptic inhibitory action of aluminium hydroxide gel by virtue of its adsorbent action. Most preparations have little or no adsorbent action and consequently when dosage is assessed their acid neutralizing capacity is the property to be considered.

Long-acting antacids have little advantage over rapidly acting preparations because of the rapid emptying rate of the stomach. Hunt and Spurrell (1951) have shown that the half-life of gastric contents varies from nine to 30 minutes with a mean of 21.8 minutes. Consequently a preparation that has a markedly greater neutralizing capacity at two hours than at 15 to 20 minutes has little real advantage because at two hours less than 2% of the initial dose remains in the stomach of the average patient. Also, the duration of action of a rapidly acting preparation can be prolonged by an excess dose.

The ideal antacid should possess several character-

istics. 1 It should act rapidly. 2 It should be palatable. 3 It should not be absorbed or cause constipation or diarrhoea. 4 Its cost should be low. 5 Ideally, it should be equally active in liquid, powder, or tablet form. 6 No other medicament such as anticholinergic drugs or sedatives should be contained in the same preparation, as its activity may determine the maximal dosage possible and so prevent an effective dose of the antacid component.

It is seen from the present study that the three most potent antacids are sodium bicarbonate, magnesium oxide or hydroxide, and calcium carbonate. The magnesium salts tend to cause diarrhoea, though this can be combatted by the simultaneous administration of an antacid that tends to cause constipation, such as aluminium hydroxide gel or calcium carbonate. Acid rebound as a complication of antacid therapy has been refuted by recent work (Pereira-Lima and Hollander, 1959; Gillespie, 1959). The readily absorbed sodium bicarbonate may, however, cause systemic alkalosis, especially in patients with decreased renal function (Kirsner, 1951). The relative rarity of this complication even when large doses of sodium bicarbonate have been administered has, however, been emphasized (Kirsner 1951; Price and Sanderson, 1956).

Calcium carbonate is an insoluble salt but in the presence of hydrochloric acid would be converted to calcium chloride which is soluble and readily absorbable. The tendency of antacids containing calcium salts and sodium bicarbonate to cause hypercalcaemia, alkalosis, and azotaemia has been recognized for some years (Burnett, Commons, Albright, and Howard, 1949). Wenger, Kirsner, and Palmer (1957) studied the incidence of the latter syndrome in a series of 3,300 duodenal ulcer patients on antacid therapy in the decade 1947-56. The patients were given hourly doses of calcium carbonate of 2 to 4 g. throughout the day; the daily dose of calcium carbonate was usually at least 20 g. but in several instances it was 40 to 50 g.; all patients except one received 90 ml. of milk and cream at hourly intervals. Slightly more than 1% (40 patients) developed a hypercalcaemic syndrome. Myerson, Snape, and Sall (1957) postulated, on the basis of metabolic studies, that another commonly used antacid, aluminium hydroxide gel, may, by inhibiting phosphate reabsorption, prevent the development of phosphate calculi and the milk-alkali syndrome in patients being treated for peptic ulcer.

It is obvious from the above study that a standard dose of antacid does not exist. When each preparation is prescribed, one must be aware of the minimal effective dose based on knowledge of the patient's basal secretory rate or the statistical data given in Table II (Part I of this paper). With many

preparations, such as aluminium hydroxide gel, the necessary dose may indicate a dose that is enormous by comparison with the dose commonly advised. It is seen too that the more potent antacids are prone to produce systemic or local side-effects such as metabolic alkalosis, hypercalcaemia, and diarrhoea. Remembering that antacid therapy is often taken for years, often too with minimal supervision, it is likely that effective neutralization can only be obtained in the majority of cases in the absence of side-effects by a combination of antacids, either together or perhaps preferably in a routine by the patient, the maximum dose of each being given that will not, or statistically should not, produce complications. Thereby the side-effects of different antacids which often act antagonistically can be overcome and an effective dose of antacid administered.

The dose of antacid required, as indicated in the calculations of Myhill and Piper (in Part I), makes effective neutralization of the gastric contents difficult, if not almost impossible, in the case of the marked hypersecretor if antacids alone are used. Consequently, we consider that in those with high basal secretory rates all efforts should be made to reduce gastric secretion by other means such as the use of anticholinergic drugs. The latter group of drugs, if administered alone, have little effect on the pH of gastric juice yet reduce markedly the gastric secretory rate (Piper and Stiel, 1961). Consequently, the concurrent administration of antacids would with this aid more readily effectively neutralize gastric juice, whereas either alone may not in many cases sufficiently elevate the pH of the gastric contents to inhibit peptic digestion.

The less effective neutralizing effect of tablet antacids shown in the present study agrees with the observations of Lehman and Pollack (1955) and of Rossett and Rice (1954). This appears to be partly due to failure of the tablet to disintegrate rapidly with the consequent reduction of the surface area of the antacid tablet with which the acid can react. As their neutralizing capacity is increased by crushing the tablet, the patient should be advised to chew the tablet or else suck it if maximum therapeutic effect is to be obtained.

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