NEW DEVELOPMENTS IN THE PATHOPHYSIOLOGY AND TREATMENT OF DUODENAL ULCER INCLUDING HISTAMINE H_2 RECEPTOR ANTAGONISTS

M E D I C A L G R A N D R O U N D S

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THE PROBLEM

1) Duodenal ulcer is a chronic and recurrent disease.[1] Effective therapy should decrease or prevent the number of recurrences and complications, as well as hasten healing of an acute ulcer.

2) Asymptomatic patients may have the sudden onset of severe complications such as a bleeding episode or perforation without warning.

3) During asymptomatic periods it is difficult for patients to continue medical therapy.

4) The highly variable course in different patients makes evaluation of therapy difficult even in controlled trials.

5) Anxiety and depression, if present, decrease the effectiveness of medical therapy, and in many cases, anxiety and depression are difficult to treat.[2] (See Table 1, next page.)

6) Gastric hypersecretion in many duodenal ulcer patients is difficult to control. (See Table 2 and Figures 2-6.) Currently available drugs are either impractical or inadequate for this purpose in many patients.

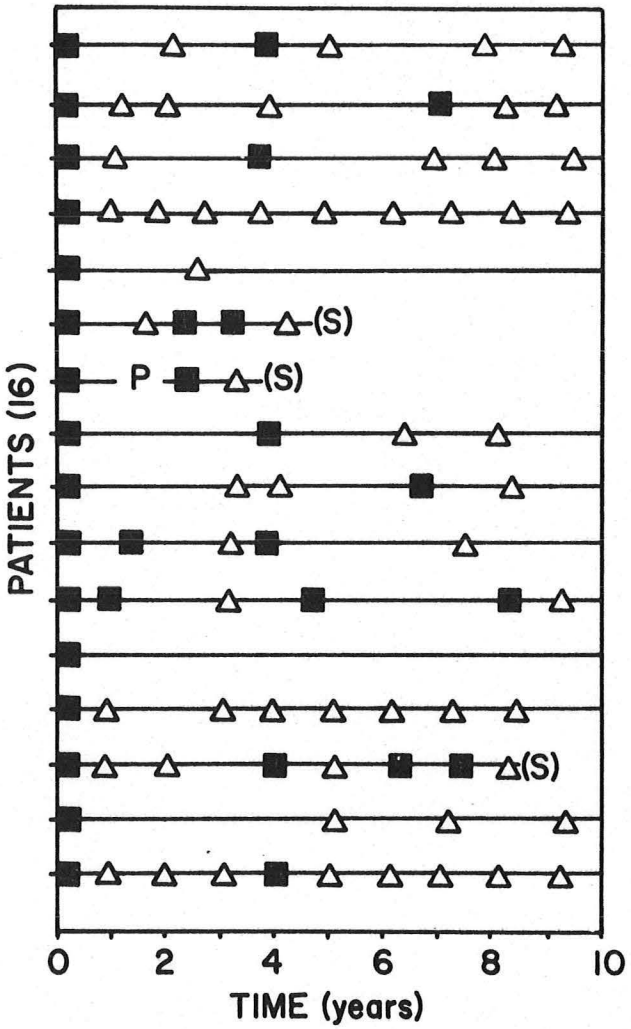

Fig. 1. Chronicity and periodicity of duodenal ulcer in 16 patients. (Redrawn from Malmros, H., and Hiertonn, T.: Acta Med. Scand. 133:229, 1949.)

TABLE I

Prospective Analysis in Peptic Ulcer Patients
by Rutter
(J. Psychosomatic Research, 7:45, 1963)

Anxiety at Initial Interview	Follow-Up 6 Months Later	
	Continued Pain	Unable to work
None N = 35	10%	11%
Moderate to Severe N = 28	62%	40%
P Value	.01	.02

GASTRIC ACIDITY IN DUODENAL ULCER PATIENTS IS DIFFICULT TO CONTROL FOR THE FOLLOWING REASONS:

1) Many patients with a duodenal ulcer have a large secretory capacity--that is, a higher than normal parietal cell mass (See Table 2) [3,4]

2) Some patients have a very high basal and nocturnal secretory rate (See Table 2). [5,6]

TABLE 2

BASAL ACID OUTPUT, PEAK ACID OUTPUT, BASAL/PEAK,
SERUM GASTRIN, AND CLINICAL COURSE IN 3 DUODENAL ULCER PATIENTS

PATIENT	BASAL mEq/hr	PEAK* mEq/hr	BASAL/ PEAK	SERUM GASTRIN (pg/ml.)	CLINICAL COURSE
M.C.	34.9	72.8	0.48	43	Recurrent episodes of pain for 6 years. Three UGI bleeds all occurring when not taking antacids.
C.S.	7.2	41.2	0.18	69	Epigastric pain for several years. Finally becoming intractable → surgery.
P.G.	3.0	26.0	0.11	82	Very easily managed on antacids.

*Histamine

3) There is increased parietal cell responsiveness to gastrin and possibly to histamine in patients with duodenal ulcer. [7,8]

4) Duodenal ulcer patients have a higher net acid secretory rate in response to a meal than do normal subjects.[9] (See Fig. 2)

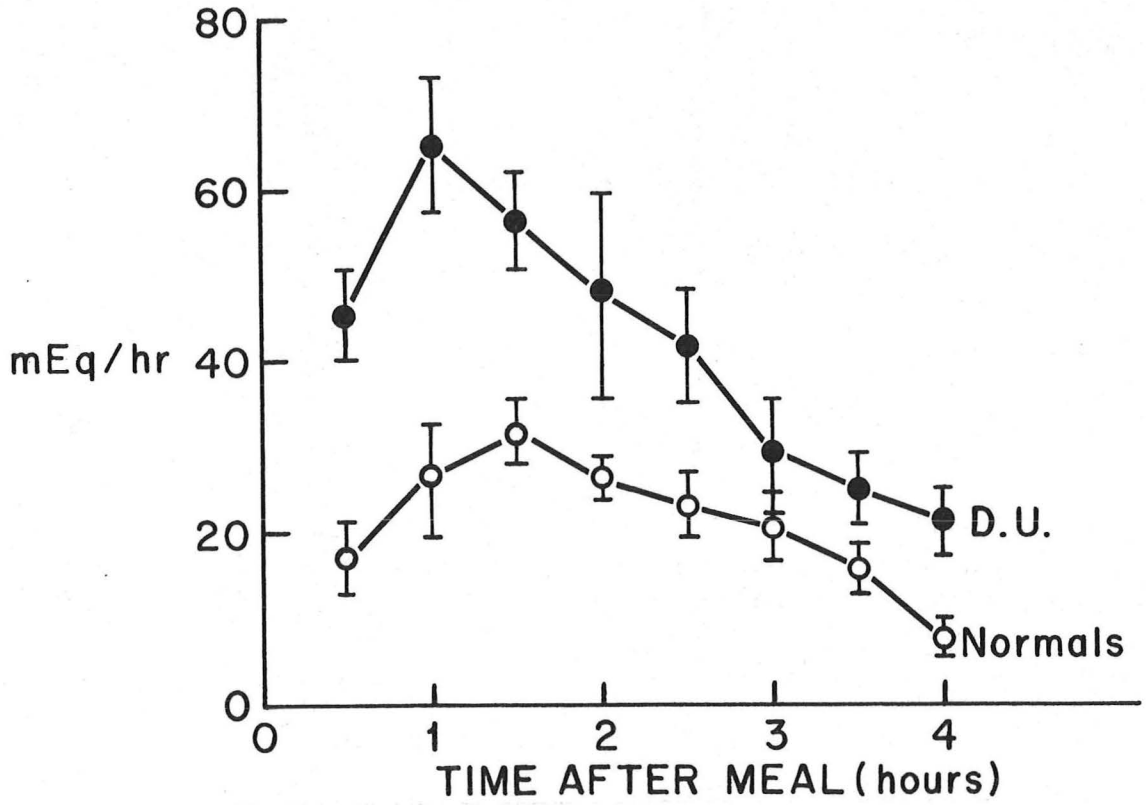

Fig. 2. Rate of acid secretion after eating in 6 normal subjects and in 7 patients with D.U. (from Fordtran, J.S. and Walsh, J.H. JCI. 52:645, 1973).

5) Duodenal ulcer patients not only have a greater than normal net secretory response to food, but they secrete a higher than normal fraction of their peak secretory capacity.[9] (See Table III)

TABLE III

Acid secretion in response to a meal as percent of peak histamine response in 6 normals and 7 D.U. patients (JCI 52:645, 1973).

ACID SECRETION

	BASAL mEq/hr	PEAK HISTAMINE mEq/hr	PEAK MEAL	$\frac{\text{PEAK MEAL}}{\text{PEAK HISTAMINE}} \times 100$
NORMAL	1.4	34.5	30	86
D.U.	7.5	58.2	64	115

6) Normal auto-regulation of acid secretion is impaired in patients with duodenal ulcer--that is, acid secretion is not reduced as gastric acidity increases. This is at least in part due to a failure of antral acidification to normally inhibit antral gastrin release.[10] (See Fig. 3&4)

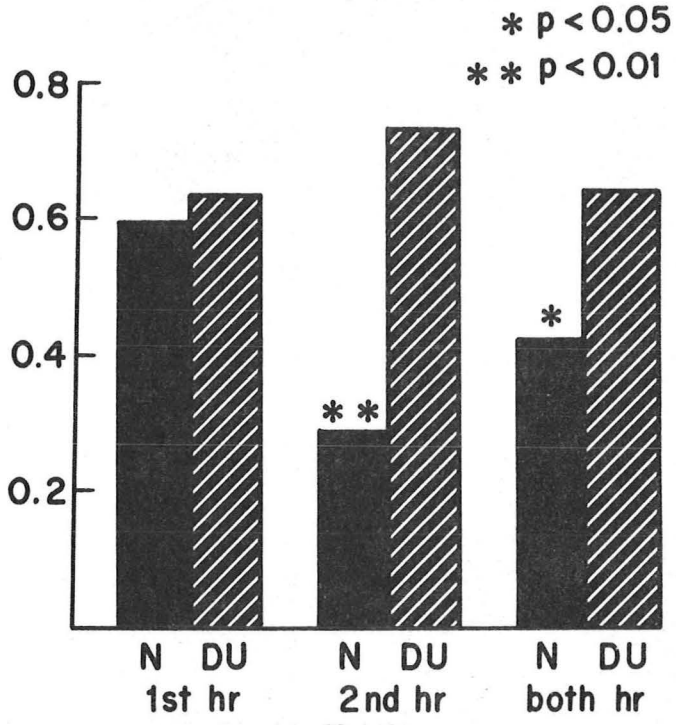

Fig. 3. Meal-stimulated acid secretion at pH 2.5 as a percent of that secreted at 5.5 in 7 normal subjects and 6 duodenal ulcer patients (from Walsh, J.H., Richardson, C.T. and Fordtran, J.S. Studies of pH Dependence of Gastrin Release and Acid Secretion in normal subjects and duodenal ulcer patients. Submitted for publication).

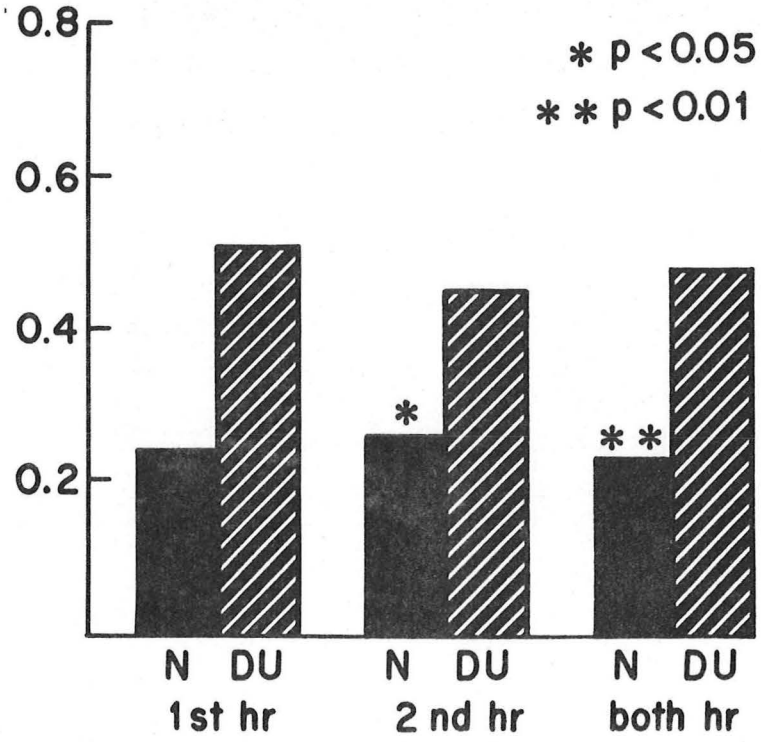

Fig. 4. Serum gastrin concentration at pH 2.5 as a percent of that at 5.5 in 7 normal subjects and 6 duodenal ulcer patients (from Walsh, J.H., Richardson, C.T. and Fordtran, J.S. Studies of pH Dependence of Gastrin Release and Acid Secretion in normal subjects and duodenal ulcer patients. Submitted for publication).

7) There is more rapid emptying of the buffer content of a meal and possibly antacids from the stomachs of patients with duodenal ulcer.[9] (See Fig. 5)

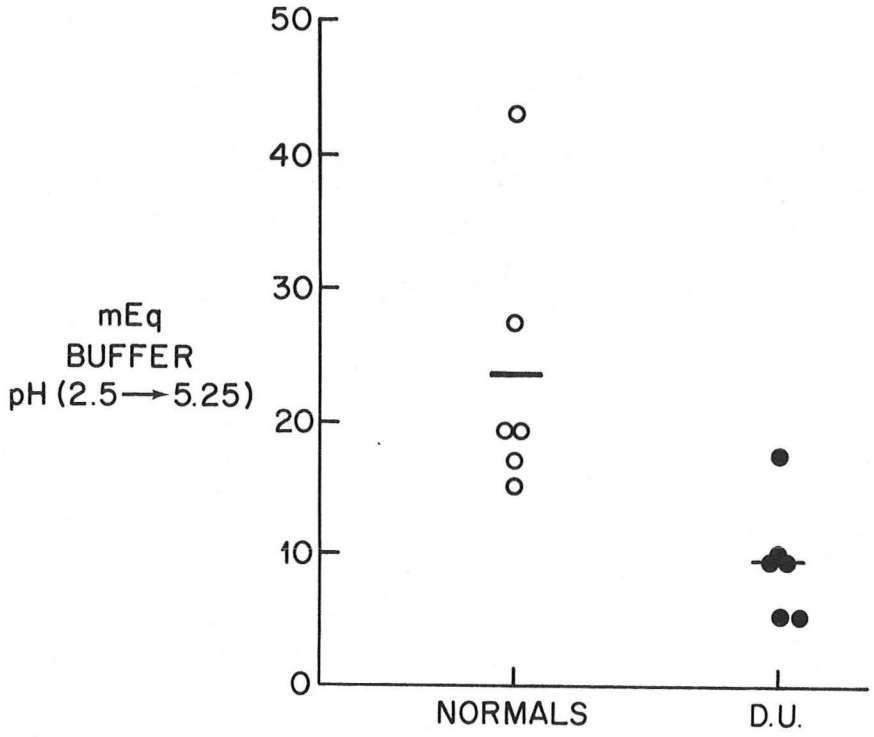

Fig. 5. Buffer content of the stomach at 2 hrs. after beginning the meal in 6 normal subjects and in 6 patients with duodenal ulcer, (JCI. 52:645, 1973).

All of the above factors lead to an increase in gastric acidity in patients with duodenal ulcer, (See Fig. 6).

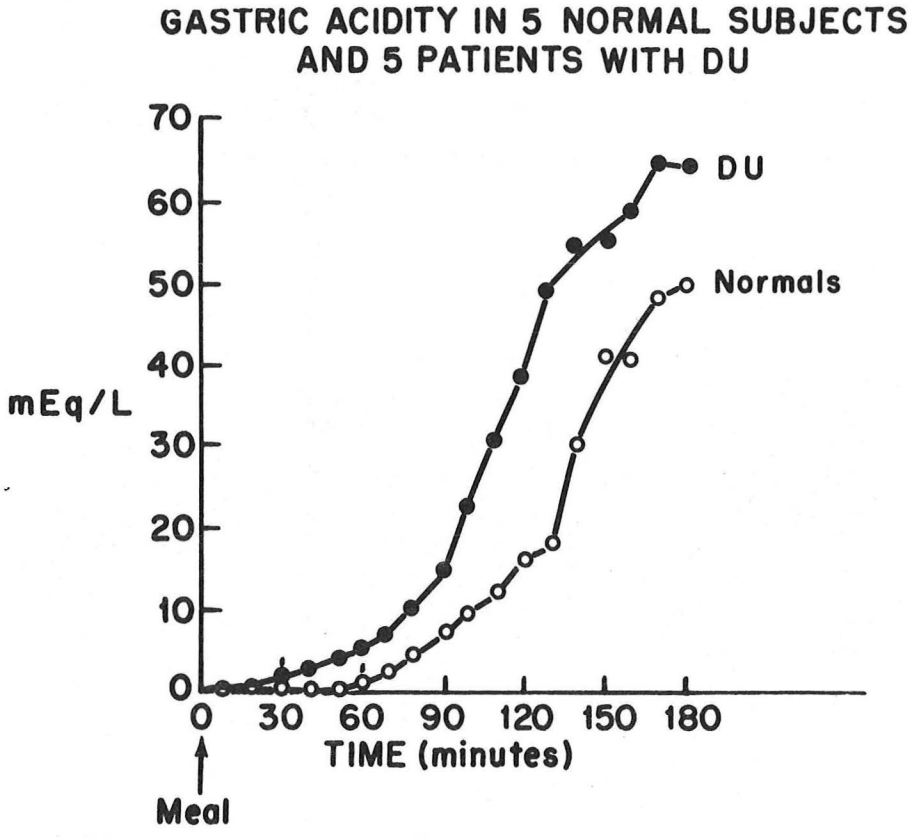

Fig. 6. Gastric acidity in 5 normal subjects and 5 patients with duodenal ulcer.

THE RATIONALE OF CURRENT MEDICAL THERAPY:

1. It must be assumed that the duodenal mucosa becomes ulcerated whenever acid-pepsin concentrations become too high for too long a period of time for the natural resistance of the mucosa and that reduction in gastric acidity will aid in healing even though acid is not completely eliminated or even decreased to the degree necessary to reduce "peptic activity".

This assumption is supported by the following facts:

a) Duodenal ulcer does not develop in the absence of gastric acid.

b) There is a threshold level of peak stimulated acid output (about 12-14 mEq./hr.) below which patients do not develop a duodenal ulcer.

c) In experimentally induced peptic esophagitis in cats, reduction of acid concentration from 50 to 5 mEq. per liter (pH 1.3 to pH 2.3) completely eliminates esophagitis even though pepsin concentrations and "peptic activity" with hemoglobin as a substrate were equal at both concentrations of acid.[11] (See Fig. 7)

2. It also must be assumed that reduction of anxiety will hasten healing, decrease symptoms, and improve prognosis.

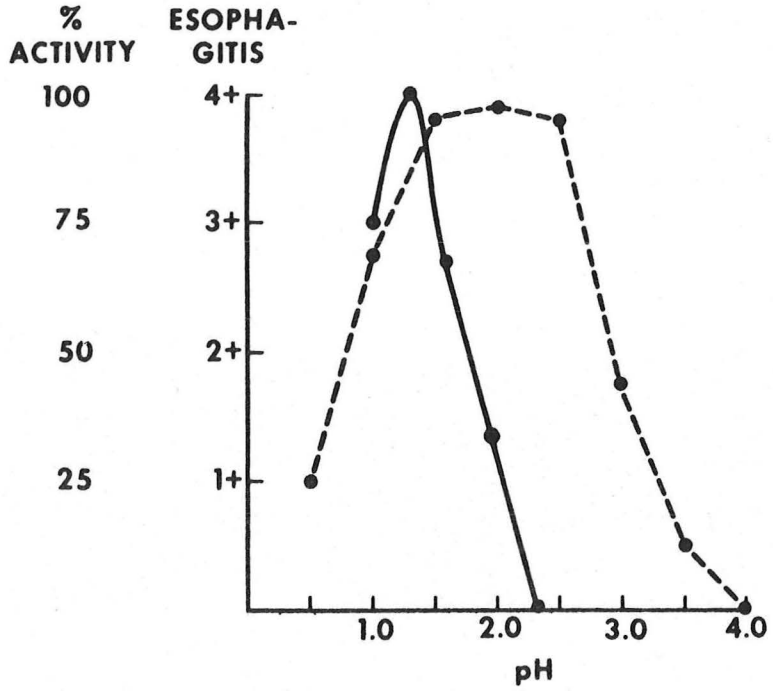

Fig. 7. In vivo pH-pepsin activity curve, with cat esophagus as substrate (•——•) as compared with an in vitro pH-pepsin assay using hemoglobin as a substrate (•----•), (from Goldberg et al. Gastro. 56:224, 1969).

METHODS TO REDUCE GASTRIC ACIDITY:

DIET THERAPY:

1) Bland diets and/or hourly milk therapy do not reduce gastric acidity. [12-14]

2) Four controlled studies have shown no benefit of a bland diet on the clinical course of peptic ulcer. [15-18]

3) There is no convincing evidence for restricting citrous juices, spices, or "rough" foods from the diet of duodenal ulcer patients.

4) The value of small frequent feedings as opposed to 3 larger meals a day has not been adequately studied. The theoretic advantage of small meals is that volume stimulus is reduced whereas the theoretic disadvantage is that duodenal ulcer patients may have an exaggerated response to a meal -- perhaps even small meals. (See Fig. 2 and Table III)

ANTACID THERAPY:

1) IN THE BASAL STATE:

   a) Antacids are effective for only 20-40 minutes in the basal state because of rapid emptying and must, therefore, be taken hourly to maintain a substantial reduction in gastric acidity in duodenal ulcer patients.

   b) Doubling the antacid dose does not significantly enhance the duration of neutralization, since rate of emptying determines duration of action.

2) AFTER A MEAL:

   a) Antacids in large doses reduce acidity for at least 3 hours. This relatively prolonged effect is due to delayed emptying of the antacid (because of the meal) and also because of reconstitution of acidified meal protein as a buffer. (See Fig. II)

   b) Different antacids vary markedly in potency, and this should be taken into account when antacids are prescribed. (See Table IV) Therefore, it is preferable to judge antacid dosage according to milliequivalents of neutralizing capacity rather than volume or number of tablets of different antacids. Fortunately, in vivo antacid potency is easily estimated by a relatively simple in vitro assay.[19] (See Table V)

   c) Calcium-containing antacids are currently not used by our group because of concern about an elevation of serum calcium and creatinine in patients treated with large amounts of calcium carbonate and because of calcium-induced gastric hypersecretion.[20] (See Fig. 8 and 9.)

TABLE IV

IN VIVO COMPARISON OF FOUR ANTACIDS IN 11 PATIENTS WITH DUODENAL ULCER.*

TEST SUBSTANCE	MEAN [H]+SE
Water	68.8 ± 8
Phosphaljel	58.8 ± 9
Gelusil	29.4 ± 10
Maalox	7.6 ± 3
Camalox	3.8 ± 4

*60 ml of antacid given 1 hr. after a meal; gastric acidity was measured 3 hr. after the meal. When analyzed by paired analysis, each value is significantly different from the preceding value ($p<0.02$). (from Fordtran, J.S., Morawski, S.G., and Richardson, C.T.,New Eng. J. Med. 288:923, 1973.)

TABLE V

TABLE 57-1. TITRATION TO *p*H 3.0 OF 1 ML OF ANTACID WITH 0.1 N HCl, 60 RPM, 37°C

		0 Time		10 Min		30 Min		60 Min		120 Min*
Antacid	Contents	*ml*	%†	*ml*	%†	*ml*	%†	*ml*	%†	*ml*
Ducon	Al and Mg hydroxides, Ca carbonate	20.2	29	29.9	43	45.7	65	58.3	83	70.4
Mylanta II	Mg and Al hydroxides, simethicone	4.3	10	8.2	20	17.3	42	27.9	67	41.4
Titralac	Glycine, Ca carbonate	32.9	85	36.0	93	37.4	97	37.9	98	38.7
Camalox	Al and Mg hydroxides, Ca carbonate	12.7	49	20.6	80	32.5	91	35.6	99	35.9
Aludrox	Al hydroxide gel, Mg hydroxide	6.4	23	12.3	44	24.8	88	27.9	99	28.1
Maalox	Mg and Al hydroxide gel	5.5	21	10.8	42	19.9	77	24.5	95	25.8
Creamalin	Hexitol stabilized Al hydroxide gel, magnesium hydroxide	11.1	43	17.8	69	25.6	99	25.7	100	25.7
Di-Gel	Al and Mg hydroxides, simethicone	5.6	23	12.4	50	22.8	93	24.1	98	24.5
Mylanta	Mg and Al hydroxides, simethicone	4.1	17	7.2	30	15.8	66	21.4	90	23.8
Silain-Gel	Mg and Al hydroxides, simethicone	3.3	14	6.6	29	14.0	61	20.1	87	23.1
Marblen	Mg and Ca carbonates, Al hydroxide, Mg phosphate, Mg trisilicate	17.2	75	19.5	86	20.6	91	21.7	95	22.8
WinGel	Al and Mg hydroxides, hexitol stabilized	8.4	37	13.1	58	19.6	87	20.5	91	22.5
Gelusil M	Mg trisilicate, Al hydroxide, Mg hydroxide	11.1	49	17.9	80	20.0	89	20.9	94	22.3
Riopan	Mg and Al hydroxides	3.5	16	6.2	28	12.6	57	18.0	81	22.1
Amphojel	Al hydroxide gel	3.9	20	9.3	48	16.4	85	18.5	96	19.3
A-M-T	Mg trisilicate, Al hydroxide gel	6.5	36	10.4	58	13.3	74	15.2	85	17.9
Kolantyl Gel	Bentyl, Al hydroxide, Mg hydroxide, methylcellulose	5.7	34	9.7	57	14.6	86	15.3	90	16.9
Trisogel	Mg trisilicate, Al hydroxide gel	7.2	43	10.9	66	13.7	83	16.0	97	16.5
Malcogel	Mg trisilicate, Al hydroxide gel	3.9	25	8.0	50	10.7	67	12.8	81	15.9
Gelusil	Mg trisilicate, Al hydroxide	4.1	31	7.2	54	10.5	79	11.0	83	13.3
Robalate	Dihydroxyaluminum aminoacetate	3.4	30	7.7	68	10.4	92	10.8	95	11.3
Phosphaljel	Al phosphate gel	2.5	59	2.9	68	3.8	90	3.9	93	4.2

*The value in this column, divided by 10, is a measure of buffer capacity of the antacid in milliequivalents per milliliter after 120 minutes. This applies to the special circumstances of this in vitro test.

†Percentage of final volume added at 120 minutes. These data are reproduced from reference 24, slightly modified.

(Adapted from New Eng. J. Med. 288:923, 1973.)

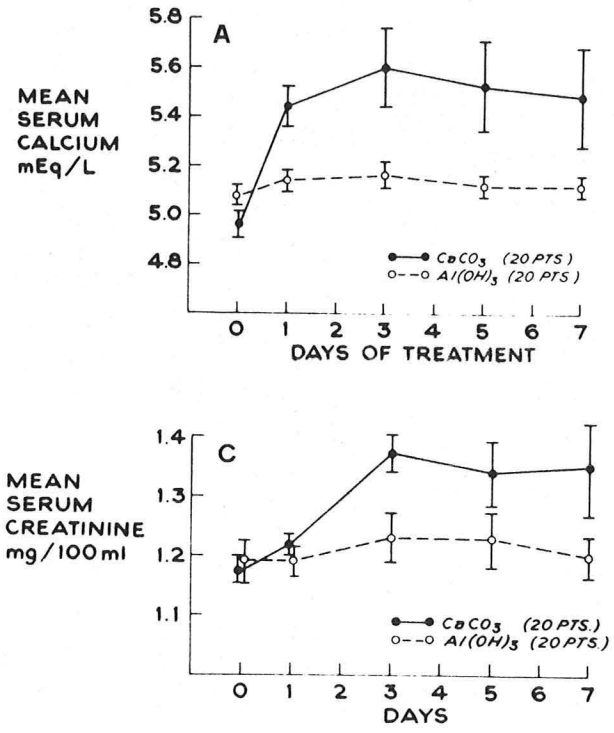

Fig. 8. Effect of calcium carbonate and aluminum hydroxide, ingested every two hours, on serum calcium and creatinine. On alternate hours both groups of ulcer patients received milk. (from McMillan, D.E. and Freeman, R.B. Medicine 44:485, 1965.)

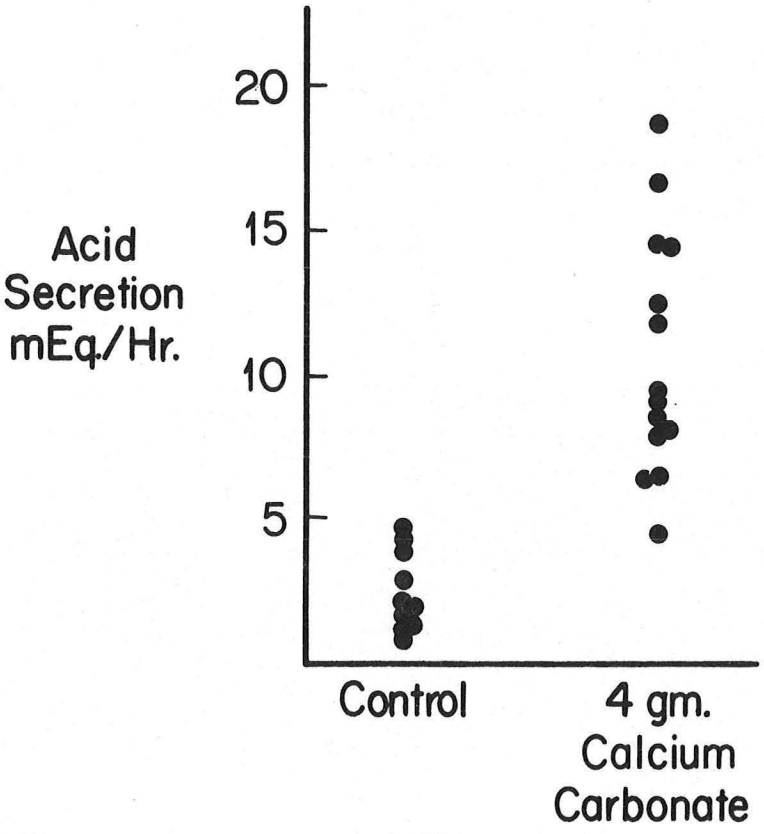

Fig. 9. Acid secretion 3-4 hours after 4 gm of calcium carbonate as compared to water or noncalcium antacid control in one D.U. patient. (from Fordtran, J.S. Acid Rebound. New Eng. J. Med. 279:900, 1968.)

d) The response of patients to antacids varies widely and to some extent is dependent on the acid secretory rate, (See Fig. 10). The response, however, of an individual patient to antacid therapy cannot be predicted from measurement of his gastric acid secretion.[19]

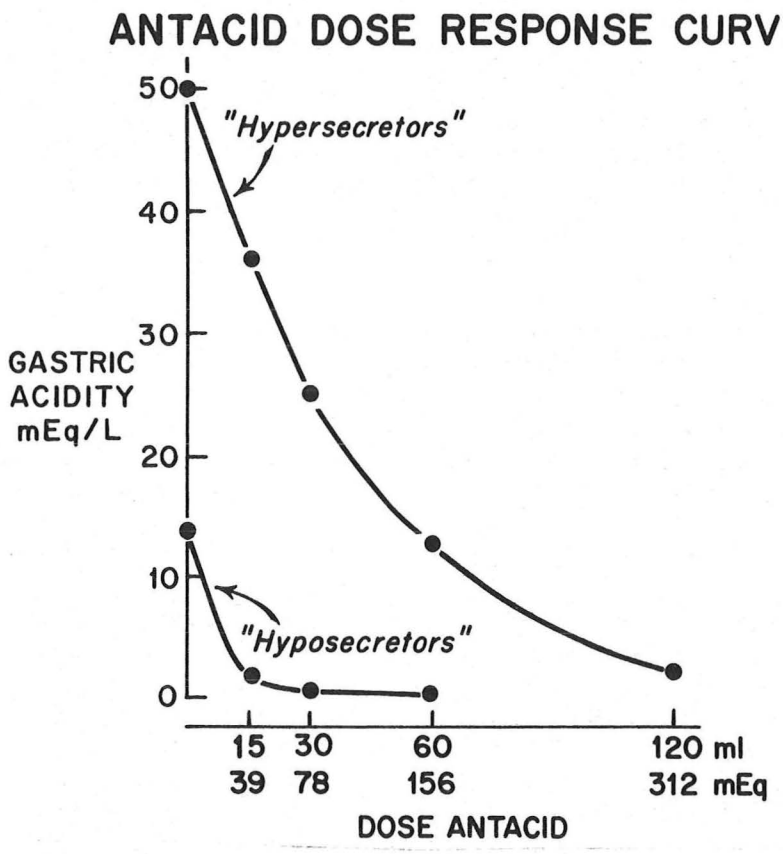

Fig. 10. Average antacid dose response (Maalox) in a group of patients whose peak histamine response was greater than 25 mEq./hour ("hypersecretors") and in a group of patients whose peak histamine response was less than 17 mEq./hour ("hyposecretors"). A steak meal was fed and one hour later from 0 to 120 ml. of Maalox was ingested. Gastric acidity was measured 2 hours later (i.e. 3 hours after the meal). (from New Eng. J. Med. 288:923, 1973.)

e) Commonly recommended doses of antacids for treatment of duodenal ulcer are much too low. For example, a 5-fold reduction in acidity for 2 hours in an average patient with duodenal ulcer would require 156 mEq. of antacid. (See Fig. 11) This is equivalent to from 371 to 22 ml of liquid antacid, depending on the brand selected. Most physicians use 15 ml regardless of the commercial preparation.

3) EFFECT ON GASTRIC ACIDITY:

When used in large doses, antacids do reduce gastric acidity.[21] (See Fig. 11)

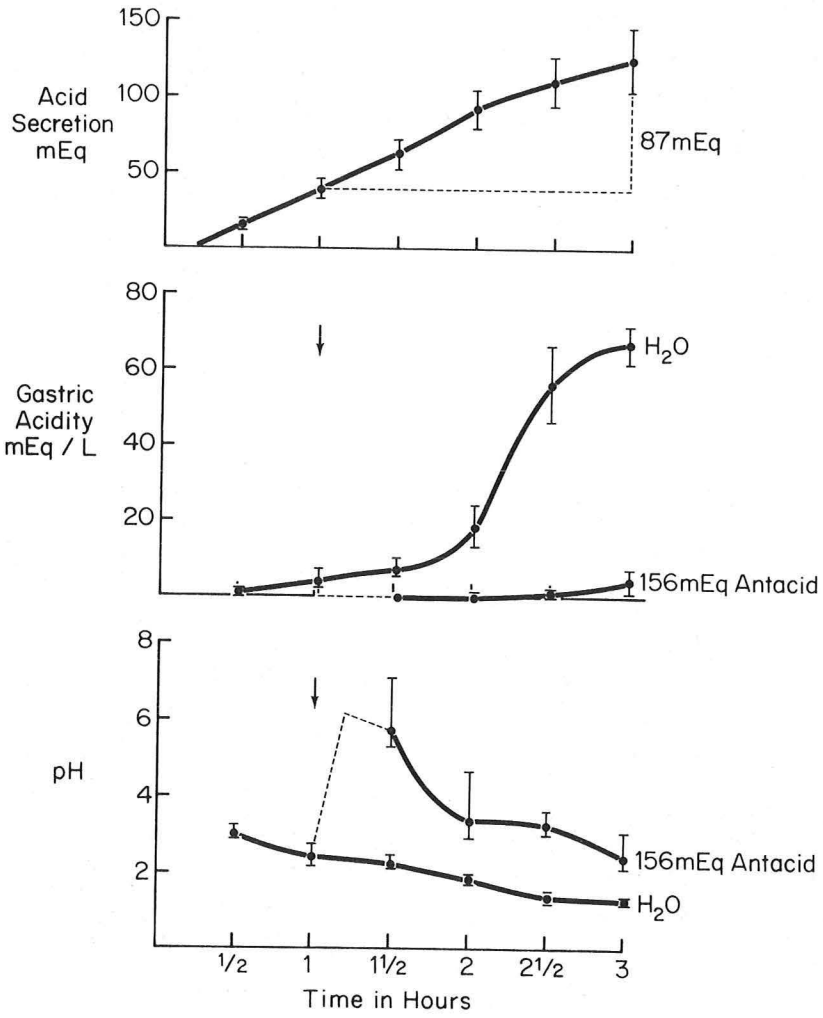

Fig. 11. Cumulative acid secretion (top) in 7 patients with D.U. after a steak meal; gastric acidity (middle) after a steak meal in the same patients in response to either 156 mEq. antacid (Maalox, 60 ml.) or water, 60 ml. given 1 hr. after the meal; and pH measurement (bottom) in the same studies. The meal was ingested at 0 time and the arrow indicates ingestion of antacid or water. Results are means ± S.E. (from New Eng. J. Med. 288:923, 1973.)

Even though antacids reduce gastric acidity quite well, they are actually very inefficient since it requires 156 mEq. of antacid (60 ml. Maalox) to effectively neutralize 87 mEq. of acid secreted in response to a steak meal. (See Fig. 11) Another group of 6

D.U. patients recently studied in our laboratory secreted an average of 103 mEq. of acid during the 3-hour period after a meal. In this group of patients it would have required more than 60 ml. of Maalox to effectively neutralize the acid secreted in response to the meal.

PROBLEMS WITH ANTACID THERAPY:

When antacids are given in quantities sufficient to significantly reduce gastric acidity at least two problems may occur.

1) Most potent antacids contain magnesium hydroxide, and therefore, cause diarrhea. Morrissey and Barreras have recently reviewed the subject of antacid therapy and have suggested that post-antacid therapy diarrhea is a major problem.[22] They have recommended using only 10-15 ml. of a magnesium-aluminum hydroxide compound (Maalox or Mylanta) alternating with a product free of magnesium hydroxide (Gelusil or Amphojel). Their regimine may well decrease or prevent the incidence of diarrhea, but based on the data shown in Fig. 11, it is doubtful that such doses effectively reduce gastric acidity.

2) Patients will not take antacids as prescribed for a variety of reasons including taste fatigue, cost, difficulty in remembering or arranging schedules so that antacids can be taken at work or school, etc.

CONCLUSIONS:

Even though antacids are ineffective in neutralizing gastric acidity unless given in large doses, we recommend that until more efficient therapy is clinically available, antacids be used in doses sufficient to at least reduce gastric acidity. We suggest the following compromise.

1) 80 mEq. of antacid (2 tbls. Maalox, 2 tbls. Mylanta, or 3 tbls. Amphogel, etc.) every hour while the patient is awake for 1-2 weeks of initial therapy. If diarrhea develops, alternate Maalox, Mylanta, or other magnesium hydroxide containing compounds with Amphogel or Gelusil.

2) After the initial 1-2 weeks, therapy can be modified so that 80 mEq. of antacid is given 1 hour after a meal since this is the time that post-cibal acid secretion is the highest (See Fig. 2) and since the meal adequately buffers acid during the first hour (See Fig. 11). 80 mEq. antacid should also be given 3 hours after a meal since studies in our laboratory have shown that gastric acidity can be suppressed for a total of 4 hours after a meal if a dose of antacid is given at 1 and 3 hours after the meal. We also suggest an 80 mEq. dose of antacid at bedtime.

3) Maintenance therapy should include antacid 1 hour after a meal and at bedtime in the hope of preventing a recurrence.

ANTICHOLINGERGIC THERAPY:

1) These drugs competitively inhibit the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine. Thus, they antagonize the muscarinic action of acetylcholine.

2) When given orally in an amount just below the dose which produces side effects ("optimum therapeutic dose")*,anticholinergic drugs reduce basal nocturnal acid secretion by 50-60%, (See Fig. 12) and histamine-stimulated secretion (.04 mg/kg) by about 40% of the control rate of secretion. The reduction in histamine (or gastrin) stimulated secretion is presumably due to diminished sensitivity of the parietal cells since even toxic amounts of atropine do not reduce secretion in response to doses of histamine or gastrin which elicit a maximal response.[23]

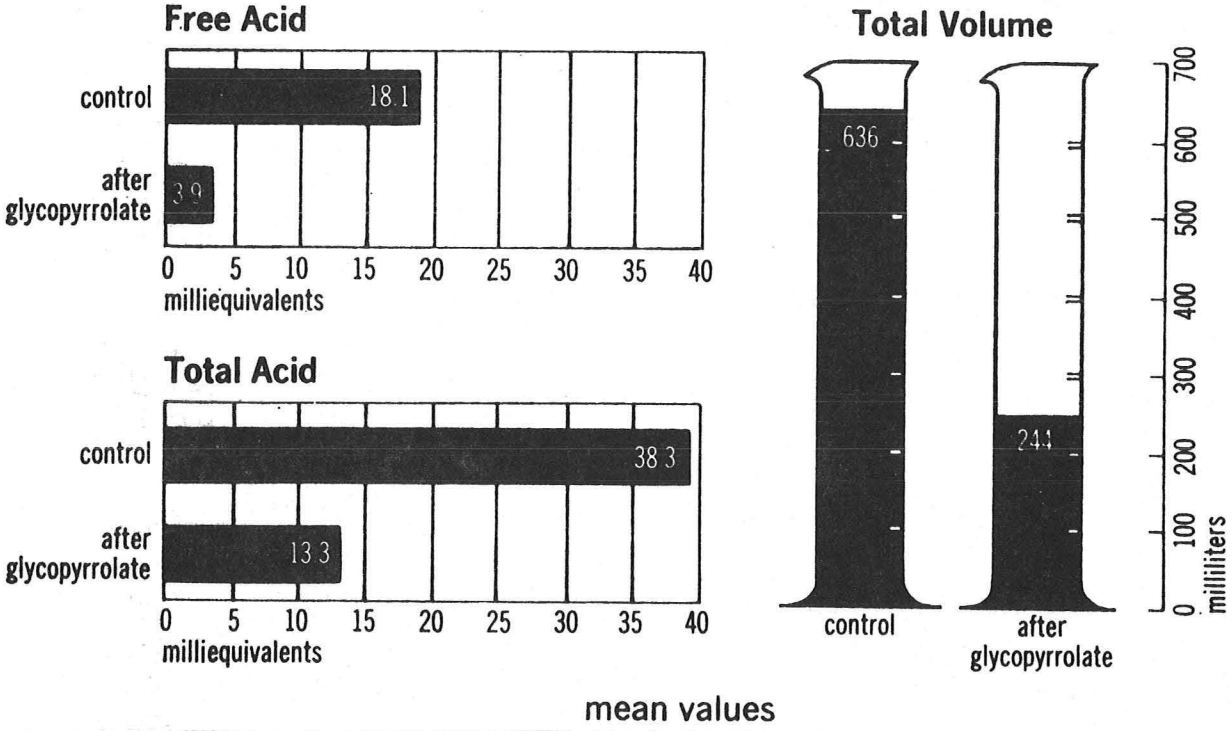

Fig. 12. Effect of glycopyrrolate on nocturnal gastric secretion in peptic ulcer patients. (from Barman, M.L., and Larson, R.K.: Amer. J. Med. Sci. 246:325, 1963.)

3) An optimum therapeutic dose (OTD)* of Isopropamide (Darbid®) given 2 hours before the meal inhibits steak stimulated acid secretion by approximately 25-35 percent (See Fig. 13).[24]

* Optimum therapeutic dose (OTD) is defined as the oral dose which produces definite but tolerable side effects. The absolute amount of drug varies in different subjects and is determined by slowly increasing the dose over a period of 1 to 2 weeks.

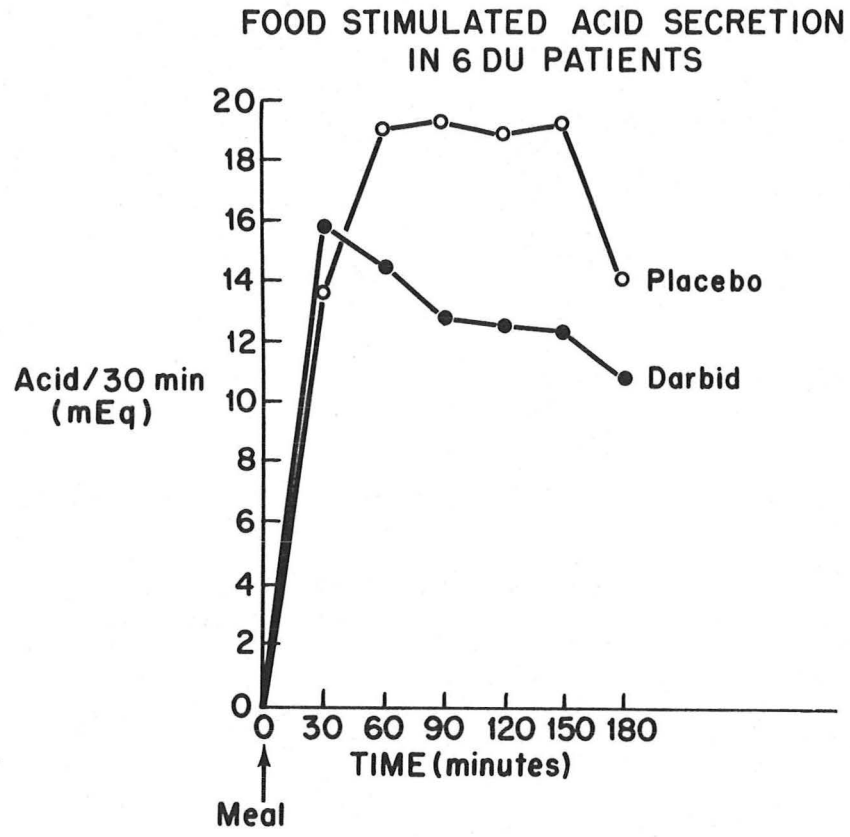

Fig. 13. Food stimulated acid secretion per 30 min. in 6 D.U. patients after a placebo and after an optimum therapeutic dose of Darbid.

4) An optimum therapeutic dose of anticholinergic drug will reduce gastric acidity after a standard meal.[24]

5) Anticholinergic drugs in optimum therapeutic doses have little if any inhibitory effect on gastric emptying of food or PEG (non-absorable marker) from the stomach. [24,25] (See Table VI and Fig. 14)

6) The duration of action is variable. The effect of Nacton and Darbid persists for 8-9 hours whereas atropine action is considerably shorter.

TABLE VI

Effect of Poldine on Volume and Buffer Capacity of the Stomach 90 Minutes After a Steak Meal

	CONTROL	POLDINE
Gastric Volume (ml)	368 ± 43	370 ± 96
Buffer Capacity	20.6 ± 2.7	20.7 ± 4.6

(From Bieberdorf, F.A. et al. submitted for publication.)

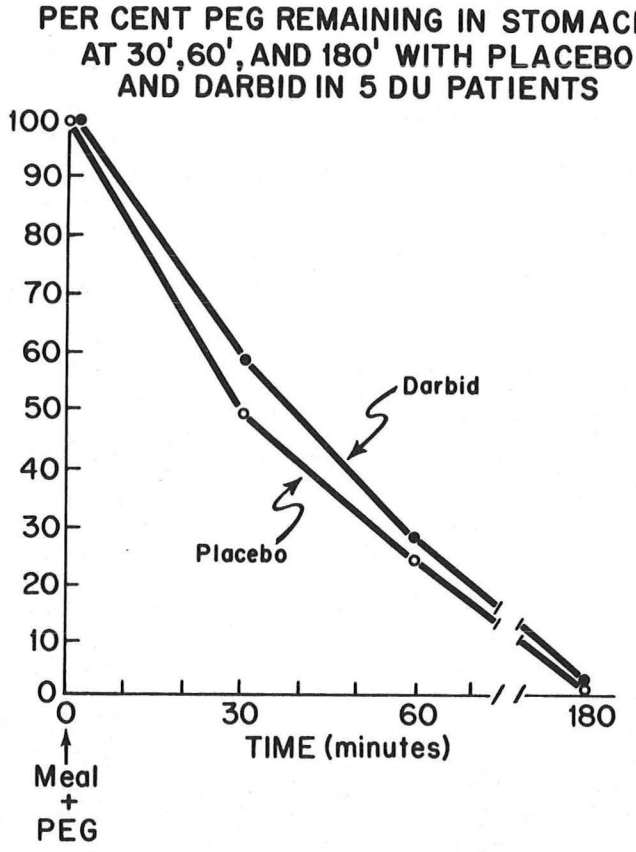

Fig. 14. Gastric emptying as measured by the serial dilution technique and reported as percent PEG remaining in the stomach.

7) Anticholinergic therapy for 12-18 months does not reduce the parietal cell mass as measured by peak histamine secretion rate.[26]

8) Clinical trials are especially difficult because side effects tend to identify patients on active drugs. Results of controlled trials have given conflicting results and it is not possible to say whether or not anticholinergic drugs are beneficial in the long-term management of duodenal ulcer.

PROBLEMS WITH ANTICHOLINERGIC THERAPY:

1) Even when an optimum therapeutic dose of anticholinergic is carefully prescribed for each patient, side effects may still occur. Mild dryness of the mouth, blurred vision, and photophobia are not considered complications of therapy but are an indication for a slight reduction in dosage. Constipation may occur and may be treated with small amounts of laxative providing there are no other signs of toxicity.

   Urinary hesitancy is an indication to decrease the dose of anticholinergic, and if it is severe, the drug should be discontinued. Anticholinergics should not be used in any patient with prostatic hypertrophy.

2) CNS symptoms may develop especially in elderly patients and include nervousness, dizziness, insomnia, headache, loss of taste, nausea, and vomiting.[27] If any of these symptoms occur the drug should be discontinued.

3) Acute glaucoma, impotence, and pulmonary complications caused by dry bronchial secretions are rare but serious complications are an immediate indication for discontinuing therapy.

4) Anticholinergics should not be given to patients suspected of having gastric retention.

CONCLUSIONS:

We suggest using an optimum therapeutic dose of an anticholinergic at bedtime to suppress nocturnal acid secretion. If antacids are given every hour while the patient is awake, then anticholinergics during the day are not prescribed. If, however, antacids are only given one hour after meals or one and three hours after meals, then an anticholinergic should be given 30 minutes before each meal and at bedtime.

It is not known whether or not certain anticholinergic drugs have some selective action in inhibiting gastric secretion as compared to the inhibition of other functions. At present it would seem best to prescribe those anticholinergics which have been demonstrated to effectively inhibit both nocturnal (basal) and meal stimulated gastric acid secretion. Robinul, Nacton, and Darbid have been most extensively studied in regard to this.

NEW ADVANCES IN MEDICAL THERAPY:

1. SECRETIN:

In 1966 Grossman[28] suggested that secretin might be useful in the treatment of duodenal ulcer. This suggestion was based primarily on the findings 1) that secretin inhibited gastric acid secretion stimulated by gastrin and histamine in dogs[29] and 2) that after secretin infusion the pH of the duodenal contents both in the bulb and post-bulbar region was elevated significantly over control values in human subjects suggesting that the secretin stimulated pancreatic bicarbonate secretion as well as the decreased gastric acid secretion contributed to the elevated duodenal pH.[30]

The first suggestion that secretin might play a role in the inhibition of acid secretion was made by Greenlee et al. in 1957.[31] Johnson and Grossman[32] found in dogs that a secretin infusion, which more closely simulates endogenous release of secretin and which was submaximal for pancreatic secretion, caused a 90% inhibition of gastric acid secretion stimulated by gastrin. Although secretin is a potent inhibitor of gastrin stimulated acid secretion, it is a very weak inhibitor of histamine stimulated acid secretion.[32-35] Secretin does not inhibit acid secretion stimulated by indirect vagal stimulation produced by insulin hypoglycemia or 2-deoxy-glucose.[36]

Konturek[37] has reported the first study on the effect of secretin on food - stimulated acid secretion in duodenal ulcer patients. (See Fig. 15)

At the point of peak inhibition 45 minutes after the beginning of the infusion, acid secretion was inhibited by 80 percent of the control value. Serum gastrin concentration (See Fig. 16) was also decreased by secretin infusion suggesting that secretin might suppress the release of gastrin in man. It is unlikely, however, that this is a major factor in secretin mediated gastric acid inhibition since secretin inhibits food stimulated acid secretion to a very similar degree as pentagastrin stimulated acid secretion.

Clinical trials are now in progress using intramuscular secretin as a therapeutic agent

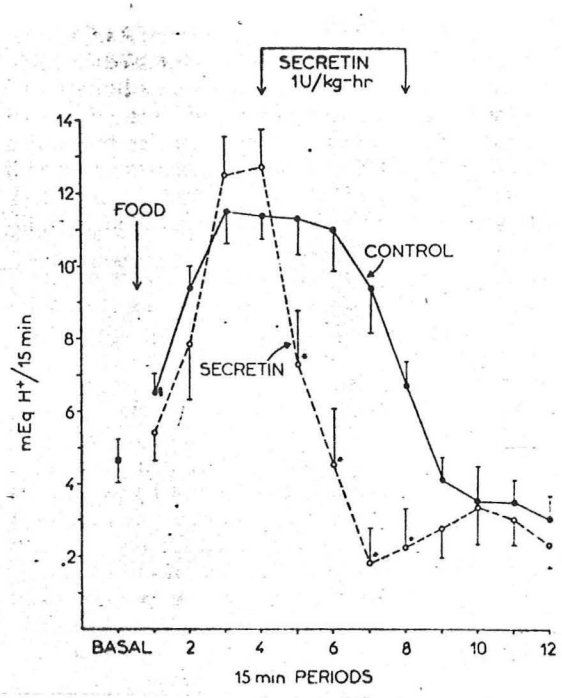

Fig. 15. Gastric acid secretion in response to food in D.U. patients with and without secretin infusion. (from Konturek, et al. GUT 14:842, 1973.)

In the treatment of duodenal ulcer. Although it appears to be a potent inhibitor of food stimulated acid secretion in patients with duodenal ulcer, the mode of administration will probably limit its usefulness.

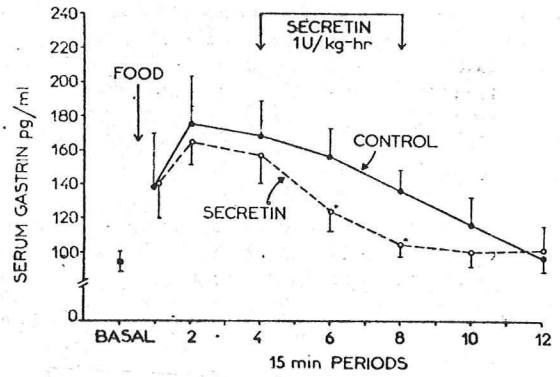

Fig. 16. Serum gastrin concentration (pg./ml) in response to food in D.U. patients with and without secretin infusion. (from Konturek, et al. GUT. 14:842, 1973.)

2. METIAMIDE:

In 1920, Popielski discovered an important action of histamine--stimulation of gastric acid secretion.[38] Soon after the classic anti-histaminics became available, it was realized that they did not block the action of histamine on gastric acid secretion. It was not, however, until 1966 that Ash and Schild proposed that there were two histamine receptors.[39] They described the so-called H_1 receptors which are present in the smooth muscle of the bronchi and the gut and are blocked by the classic antihistamines, such as, Diphenhydramine (Benadryl®). (See Table VII)

Black and his co-workers, using the analogy of catecholamine β receptor antagonists and working with the structure of histamine, began in 1964 synthesizing various analogues of histamine in an attempt to find an antagonist for the histamine receptors not blocked by classic antihistaminics. In 1972, Black et al. described the first drug, Burimamide, (See Fig. 17) that competitively antagonized the effect of histamine on the gastric parietal cell, guinea-pig atria, and rat uterus.[40] The histamine receptors in these tissues were labeled H_2 receptors. (See Table VII)

TABLE VII

HISTAMINE RECEPTOR	TISSUE	ANTAGONIST
H_1	Smooth muscle of gut and bronchi.	Classic antihistamines
H_2	Gastric parietal cell Guinea-pig atria Rat uterus	Burimamide, Metiamide

Further drug refinement led to the development of metiamide, a more active analogue of Burimamide. (See Fig. 17) Metiamide is more readily absorbed from the gastrointestinal tract. In animal studies metiamide has been shown to inhibit acid secretion stimulated by histamine, pentagastrin, 2-deoxyglucose, and a test meal.[41] The fact that this drug has such a broad effect in inhibiting acid secretion in animals suggests that metiamide will block acid secretion to any stimulus whether the stimulus is vagally mediated as in the sight or smell of food or other psychological factors; or from the release of gastrin both by distention of the stomach by food or the chemical action of food on the antral gastrin cells.

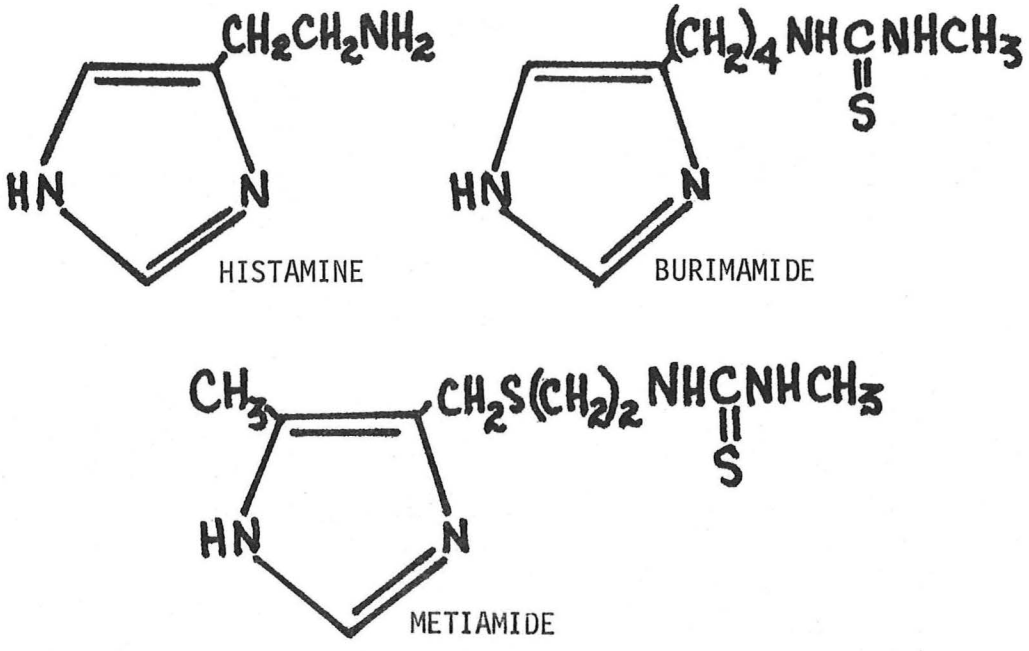

Fig. 17. Chemical structure of Histamine, Burimamide, and Metiamide.

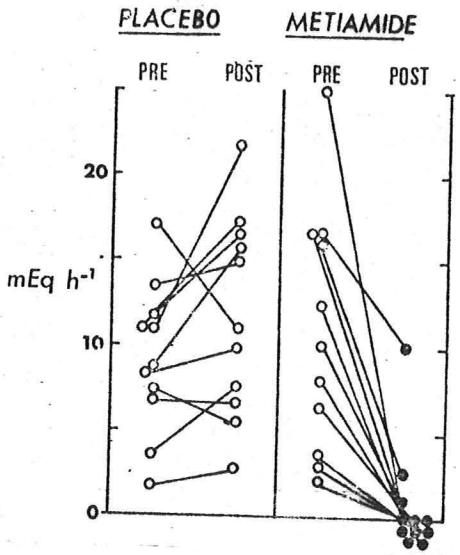

Fig. 18. Acid outputs of individual patients during a basal hour (pre) and for the second hour (post) after ingestion of either a placebo or 400 mg. of metiamide. (from Milton-Thompson, et al. Lancet. 1:693, 1974.)

Two recent studies in duodenal ulcer patients suggest that metiamide suppresses basal and nocturnal acid secretion quite effectively. Isenberg and his co-workers have demonstrated that metiamide suppresses basal acid secretion by 85 percent.[42] Milton-Thompson and his co-workers have also demonstrated that metiamide effectively suppresses basal (nocturnal) acid secretion.[43] (See Fig. 18)

In our laboratory we have studied the effect of metiamide on food stimulated acid secretion, and have found that the drug inhibits acid secretion in response to food in duodenal ulcer patients by 65-70 percent.[44] Since food is the major physiologic stimulus to acid secretion, the fact that metiamide significantly inhibits food stimulated acid secretion suggests that it might be very useful in the future treatment of duodenal ulcer.

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