Preliminary Observations on a New Approach to Treatment of Peptic Ulcer and Digestive Disorders

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THIS article presents the rationale and a clinical experience with a medication which embodies a different approach to the treatment and possible prevention of peptic ulcer and digestive disorders. Previous medications have been designed to interfere with or stop the secretion of hydrochloric acid or to neutralize stomach contents.

The medication to be discussed in this report is intended to rehabilitate and enhance normal mucosal homeostasis and thereby increase the vitality and the resistance of the mucosa to acid attack. It is assumed that these objectives contribute to normal digestion and establish conditions which are conducive to the relief of symptoms and healing of the mucosa.

Normal mucosal homeostasis includes a complementary interaction of enzyme systems which maintains healthy neutral acid-base equilibrium of the mucosa despite the fact that the gastric mucosa secretes acid and forms an equivalent quantity of the intramucosal alkali, and the duodenal mucosa secretes alkali and forms an equivalent quantity of intramucosal acid.

Conway[1] said, "The high acidity of the parietal secretion is associated with an alkalinization within the secreting cells. . . . Likewise the non-parietal cells, chiefly it would seem those secreting mucus, require protection from acidity. Two intracellular enzymes have been shown to catalyze neutralizing reactions. These are the carbonic anhydrase and urease (enzyme systems)".

HYPOTHESIS

Carbamine,* carbamide (synthetic urea) with citric acid and sodium bicarbonate, is a medication which provides optimum substrates and a medium for the carbonic anhydrase and urease enzyme systems, and rehabilitates the healthy functional status and resistance to acid attack of the gastroduodenal mucosa. This establishes conditions which are conducive to relief of symptoms, normal digestion, and healing of the mucosa.

BASIS OF HYPOTHESIS

Goodfriend, Vanderkleed and Goodfriend[2] said, "We believe that the natural mechanism whereby the gastric and duodenal mucosae resist ulceration include the interaction of the urease and carbonic-anhydrase enzyme systems. These enzyme systems are histochemically closely associated in large quantities in the gastroduodenal mucosae. Their products neutralize acid and alkali, respectively,

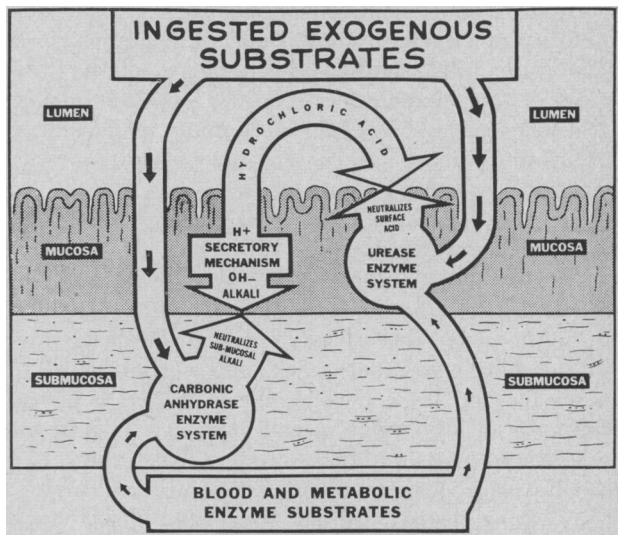

Fig. 1.—The theoretical action of Carbamine in maintaining acid-base equilibrium and enhancing resistance of the mucosa (Goodfriend, Vanderkleed, Goodfriend).

and the two systems can potentially interact to maintain acid-base balance in the mucosae." (Fig. 1.)

Davenport[3] showed that the carbonic anhydrase enzyme system functions to neutralize submucosal alkali and thus contributes to the acid-base equilibrium of the gastric mucosa.

Davies and Longmuir[4] showed that excessive secretion of hydrochloric acid and the accompanying formation of excessive submucosal alkali resulted in ulceration of isolated frog stomachs, and that outside sources of the substrate of the carbonic anhydrase prevented this ulceration. They said, "In active mucosa, the rate of acid secretion rose above the rate of oxygen uptake or metabolic carbon dioxide output so that *external supplies** of carbon dioxide, were required. In the absence of external supplies of carbon dioxide, mucosae with high rates of acid secretion were ulcerated or perforated. This damage was apparently associated with a disturbance of the acid-base balance within the cell so that unneutralized alkali accumulated and disorganized the oxyntic cells. Such damage never occurred when adequate (external) supplies of carbon dioxide were available to these cells." They assumed that the action in the duodenum is opposite to that in the stomach, in that the alkali is secreted into the lumen and acid remains in the submucosal region. Excessive acid secretion by the stomach is associated with excessive alkali secretion by the duodenum and the formation of excessive acid in the duodenal submucosa.

*Carbamine, made available by Key Pharmaceuticals, Miami, Florida, U.S.A.

*The italics are the author's.

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Fitzgerald and Murphy[5] showed that the urease enzyme action neutralized acid and that the ingestion of a favourable concentration of carbamide (synthetic urea) significantly increased the urease activity and acid-neutralizing capacity of the gastric and duodenal mucosae of experimental animals.

Monod[6] and Spiegelman[7] showed that the quantity of enzyme which a cell may synthesize is favourably influenced by the presence of the substrate of that enzyme in a medium which is favourable to its action. Howell and Sumner[8] and Sumner and Somers[9] have shown that the most favourable substrate concentration and medium for urease action is 2½% carbamide at pH 6.7 with a citrate buffer and carbon dioxide.

The foregoing data validate the theoretical mechanism of action of Carbamine in the treatment of peptic ulcer disease and certain digestive disorders. The ingredients, urea and carbon dioxide, of Carbamine have been extensively tested in the treatment of inflammation and ulceration of mucous membranes and epithelial surfaces by Robinson,[10] Gurshot and McCawley,[11] Goodfriend[12] and others. They showed that similar urea solutions relieve pain, debride ulcers and wounds, eliminate odour, aid healing and stop bleeding while being completely harmless to healthy tissues. While these studies were not concerned with peptic ulcer or gastrointestinal diseases, it is obvious that these properties are desirable in a drug for digestive symptoms and peptic ulcer disease.

After preliminary clinical tests, Jordan[13] said, "A recent approach to ulcer therapy by the use of enzyme substrates has definite theoretical possibilities and merits further clinical investigation." Winkelstein[14] said, "Carbamine [is] another form of ulcer therapy recently introduced. The basic idea is to supply the enzyme urease of the surface epithelium of the stomach with a large amount of its substrate (carbamide), and the enzyme carbonic anhydrase in the parietal cells with a large amount of its substrate, carbonic acid. I have treated 60 cases with this effervescent mixture. A level teaspoonful in one half glass of water four times a day between meals is the usual dosage. The symptomatic results have been very good in these 60 cases . . ."

Thus, the theory of Carbamine was validated by published biochemical and enzymatical data, and its therapeutic effectiveness was indicated by preliminary clinical studies.

PROCEDURE

The therapeutic effectiveness of Carbamine was tested in the treatment of over 200 patients with various types and degrees of severity of gastroduodenal ulcer and other digestive disorders. The latter included hiatus hernia, gastritis, duodenitis, esophagitis, hypermotility, and duodenal diverticulitis. All patients were seen during the private practice of internal medicine at a 13-bed private hospital. All diagnoses were based upon physical and psychological studies, gastric acid, blood and urine tests, and gastrointestinal roentgenography. Follow-up radiographs were made in most cases.

Protocols were maintained during a five-year period on 106 patients. These are summarized in Table I. Subsequent treatment of approximately 100 patients showed similar results. No placebo, double-blind, or paired-alternative controls were employed.

TABLE I.—RESULTS OF CARBAMINE TREATMENT IN 106 PATIENTS
(61 Males; 45 Females—Ages 24 to 82)

Disease	*No. of cases*	*Relief of symptoms*			*Side effects*	*Recurrence*
		Good	*Fair*	*Poor*		
Ulcer: gastric....	4	4	—	—	None	2
Ulcer: duodenal..	71	54	9	8	None	19
Esophagitis.....	2	2	—	—	None	—
Gastritis.....	8	8	—	—	None	1
Duodenitis.....	7	7	—	—	None	3
Hiatus hernia...	7	5	—	2	None	2
Duodenal diverticulitis...	7	5	2	—	None	1
Totals.....	106	85	11	11	0	28

Percentages: good to fair 91%. No recurrences: 73%.

Carbamine was administered in place of antacids and antispasmodic and anticholinergic drugs in this therapeutic regimen. The basic therapy was a heaping teaspoonful in one-third glass of water four times daily (one hour after meals and before retiring) for six weeks. Prophylactic dosage once or twice daily, especially before retiring, was continued thereafter. Additional doses of this agent, as often as every two hours, were administered to control symptoms in severe cases, including those with frank hemorrhage. The treatment of obstructed cases included drainage of the stomach by means of a Miller-Abbott tube and intravenous feeding. Carbamine was administered through the tube until the obstruction was relieved, then the tube was removed and the drug was administered orally. All cases complicated by bleeding received transfusions of whole blood. Patients with acute, active disease were confined to bed with a Sippy diet and Carbamine for 13 days. Ambulation with restricted diet and four daily doses was continued for the next 13 days, then unrestricted diet with four doses daily was prescribed for 13 days. Thereafter, patients were continued on an unrestricted diet and one or two doses of Carbamine per day. Patients with duodenitis, gastritis, esophagitis, hiatus hernia and duodenal diverticulitis were usually ambulatory. During acute symptoms they received at least four doses of the medication daily, but their activity and diet were not restricted. This regimen was continued as one dose before retiring. Aside from the supportive measures mentioned, Carbamine was the only peptic ulcer–digestive medication administered to the patients reported in this study.

RESULTS

Carbamine promptly relieved the symptoms of pain, heartburn, belching, nausea, vomiting, food intolerance, etc. in 91% of patients (Table I).

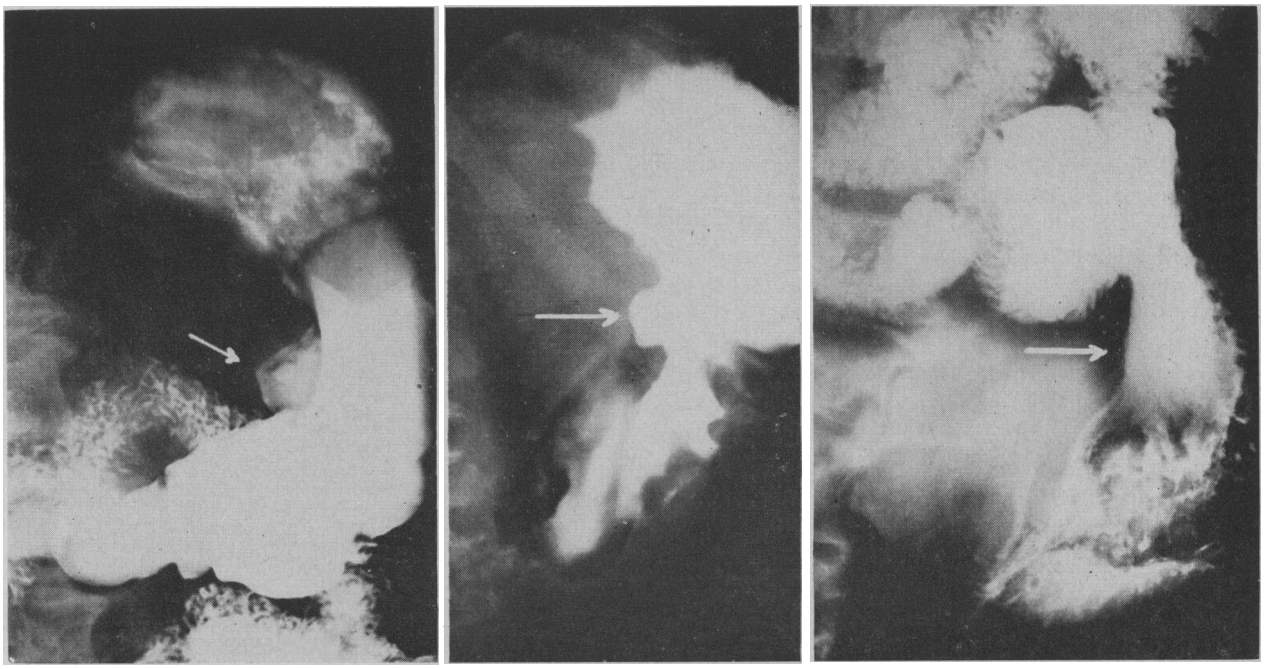

Fig. 2a. Fig. 2b. Fig. 2c.

Fig. 2a.—Large gastric ulcer before Carbamine medication. Fig. 2b.—Partially healed ulcer with complete relief of symptoms after two weeks of Carbamine medication. Fig. 2c.—Complete healing and disappearance of ulcer niche after two months of Carbamine medication.

Four cases of gastric ulcer had excellent results; three showed complete healing and disappearance of niches on subsequent roentgenographs. This is illustrated by Fig. 2a-2c which depicts the roentgenographs of a male, aged 68. His symptoms started with pain at first relieved by food, but then becoming constant during the week prior to admission. He had lost 20 lb. in weight and had diminished appetite. The patient was hospitalized and placed on a restricted diet with Carbamine, administered one hour after meals and upon retiring. Symptoms were completely relieved in one week, at which time he was discharged from the hospital. He continued on a modified diet and four doses of Carbamine daily for three months, during the last two of which he had resumed unrestricted diet and employment. The roentgenograph illustrated by Fig. 2c showed complete healing of the ulcer with disappearance of the niche. He was instructed to continue with a prophylactic single dose of the agent before retiring and to resume four daily doses in the event of any recurrence of digestive disorder. Follow-up visits showed that this regimen has prevented recurrence of the ulcer for a period up to eight years.

Of 71 patients with radiologically verified duodenal ulcer, 54 had excellent to good relief from Carbamine medication. Nine had fair relief and eight had poor to no relief. Subsequent roentgenographic studies showed disappearance of ulcer niches in 58 of 71 cases. There were no recurrences in 50 cases. Nineteen had recurrences within periods up to eight years, and no data were available for the other two cases.

In four cases of obstructing duodenal ulcer, the combination of drainage by means of the Miller-Abbott tube, intravenous alimentation, and administration of Carbamine resulted in the control of pain and reduction of obstruction within 10 days. Two of these patients have had no recurrence on continued prophylactic single dosage of Carbamine upon retiring, for periods of seven to eight years. The other two have had severe recurrences which required operation. These were the only two patients who required surgery of the over 200 patients treated with this agent during the present study.

Nine cases of gastroduodenal ulcer with frank bleeding were treated with Carbamine in this study. In all of these cases, transfusion was also required. None of the patients required surgical intervention to control bleeding. While it is difficult to determine the rapidity of the control of the hemorrhage, it is my opinion that Carbamine significantly aided the control of hemorrhage and prevented recurrent hemorrhages, especially in those patients who continued prophylactic daily dosage before retiring.

Carbamine produced rapid relief of symptoms in two cases of esophagitis, eight cases of gastritis, seven cases of duodenitis, five of seven cases of hiatal hernia, and five of seven cases of duodenal diverticulitis. There was no recurrence of symptoms in 23 of the foregoing 27 successfully treated cases during periods of up to eight years. It did not reduce the acid secretion in patients with hyperacidity or restore acid secretion in achlorhydric cases. It is assumed that the effectiveness of this agent in relieving the symptoms was the result of the restoration of the homeostasis of the gastroduodenal mucosal membrane and of normal digestion in accord with the hypothesis.

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Carbamine was found to be helpful in the diagnosis and treatment of other diseases which were masked by digestive symptoms. Its administration in these situations relieved epigastric and abdominal distress, pain, nausea and vomiting which may result in inadequate diagnoses and interference with effective treatment of other diseases. This is illustrated by the case of a man, aged 65, whose chief complaint was chronic pain and heartburn with episodes of violent vomiting for 24 hours, occurring every three months for nine years. Previous studies had yielded conflicting results. The medication was administered every two hours for the first day and then four times daily with bland diet. This stopped the vomiting and relieved pain and heartburn. Further studies then showed a coincident diabetes and myocardial infarction with cardiac decompensation. Carbamine in prophylactic dosage was continued during the establishment of effective control of the diabetes and heart failure. There have been no recurrences of pain, heartburn, nausea or vomiting.

The administration of Carbamine resulted in satisfactory relief of symptoms in 80%, fair relief in 10% and no relief in 10% of patients. The duration of relief extended from one to eight years (the period of observation of this report). The duration of relief of symptoms and prevention of recurrences appeared to be directly related to acceptance by the patient of indicated psychotherapy and co-operation in the prophylactic administration of the medication. The results with this agent were more favourable than those with previous antacids, antispasmodics and anticholinergics. The symptomatic relief obtained was more rapid, more complete and of longer duration. This may have been attributed to the effect of Carbamine in restoring the mucosal homeostasis and the absence of side effects that permitted continued prophylactic administration.

An outstanding characteristic of this medication as compared to all previous medication is its absence of toxicity and side effects. No patient showed any evidence of increased blood urea nitrogen, constipation or diarrhea. None complained of side effects and all found it a pleasant-tasting, effervescent medication.

DISCUSSION

Carbamine is presented as a new approach to peptic ulcer therapy, and clinical examples are used to demonstrate the ease and flexibility of administration, and the freedom from side effects. It is the author's opinion that the use of this agent in place of all other ulcer medications constituted a distinct improvement over therapies previously prescribed for the same patients.

While Carbamine is assumed to restore the mucosal homeostatic enzyme systems, its effectiveness in neutralizing gastric acidity may be an important factor in its therapeutic effectiveness. This

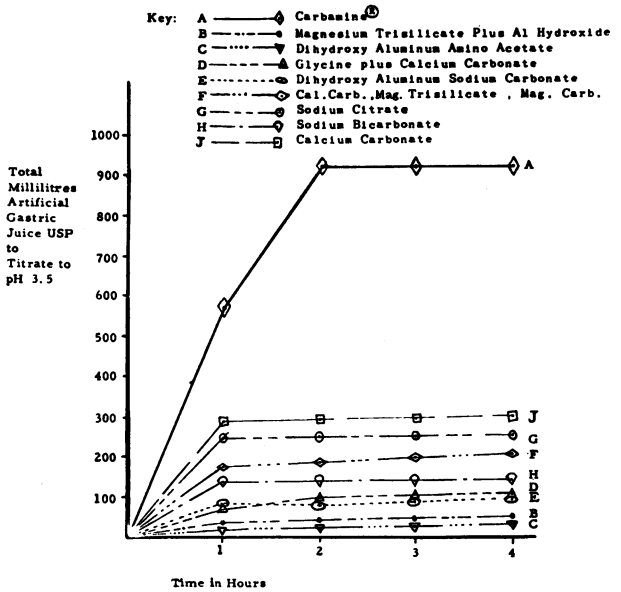

Fig. 3.—Comparative stomach acid-neutralizing effectiveness of Carbamine and available antacids.

is illustrated by Fig. 3, which shows that it is much more effective than available antacids in neutralizing the acidity of gastric juices. While the relief of symptoms by antacids may be the basis for the therapeutic effectiveness of Carbamine, the role of its ingredient, carbonic acid, appears to be of equal importance. Bálint[15] said, "The results of this work suggest that the primary factor in the formation of gastric ulcer may be alkali, not acid, when the alkali is not neutralized in the oxyntic cell by carbonic acid supplies through the carbonic anhydrase enzyme system. In the duodenum the reverse process may occur; sodium bicarbonate is secreted into the lumen and hydrochloric acid into the blood." Experiments reported by Cummins, Grossman and Ivy[16] confirmed Bálint's observations.

The evaluation of drugs for gastrointestinal disorders and peptic ulcer disease involves holistic considerations. The pathogenesis of these diseases usually includes a vicious cycle of psychosomatic and somatopsychic factors. Drugs which cause side effects, interfere with acid secretion and digestion, and require restricted diet, altered environment and modified habits may contribute to the cycle of chronicity and recurrences. Carbamine causes no side effects and supports digestion of unrestricted diets under usual environment and living activities.

Recurrences in susceptible patients were usually prevented by continuation of one dose of Carbamine before retiring. If dietary abuses or environmental crises could be foreseen, four doses daily were resumed in anticipation. If they occurred unforeseen, it was necessary to continue the four doses daily for a week or two. Since the active ingredients of Carbamine, urea and carbon dioxide, are non-toxic and are normally present in the blood and tissues, prophylactic dosages were continued indefinitely with complete safety. In many

instances, patients learned to regulate dosage to their needs.

The author is fully aware of the significance of psychotherapy in the treatment of these patients. Patients previous to and during this study had received supportive psychotherapy. It was evident that, during this study, the effectiveness of psychotherapy was aided by relief of symptoms, the total absence of side effects and the elevation of patient morale as the result of the early resumption of unrestricted diet and living activities.

SUMMARY

This article presents a different approach to the treatment of peptic ulcer and digestive disorders. The objectives of this approach, embodied in a new medication, are to restore mucosal homeostasis, acid-base equilibrium, resistance to acid and digestive functions.

The medication, Carbamine, was administered to over 200 patients with various types and degrees of severity of gastroduodenal ulcer, hiatus hernia, esophagitis, gastritis, duodenitis, duodenal diverticulitis and cholecystitis, for periods up to eight years.

It relieved pain, heartburn, belching, nausea, vomiting, food intolerance, etc. in 91% of patients. Seventy-three per cent of patients had no recurrences on prophylactic daily dosage before retiring, with resumption of usual living habits, occupation and diet.

There were no side effects in any patients treated with Carbamine.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

OBSERVATIONS FROM BOER-LAND

In such diseases as pneumonia and pleurisy it is usual to paint the affected side of the chest with varnish or some substance that will afford an impermeable covering. Many, in addition, apply outside this a sheet of oilcloth or thick paper and make it adhere to the body. The object of this practice obviously is to imprison the heat in the affected part. The custom of completely covering the body with green paint was commented upon in England at one time, but I have never seen it here, and have heard of its occurrence in one camp only, where three children were the innocent objects. Needless to say all died.

Early in my connexion with the department, one of the best educated men in the camp at Balmoral in consulting me about his child, who was dying of dysentery, asked my opinion of an odd custom. This was to kill a goat, immediately to slit up the abdomen, and remove the entrails. The child was then to be wrapped in the still warm body-cavity until the skin cooled. This, as I afterwards found out, is a common custom in any case of severe illness. Some, in desperate cases, resort to the opening of a large vessel in the neck of a dog. Collecting the blood in a suitable receptacle, they immediately serve it up to the patient, who is forced to take as much as he can swallow. The idea is that the nourishing and vitalizing powers of the fresh blood will carry a doubtful case through a crisis.

Every household endeavours to have its supply of sulphur. Diluted freely with powdered sugar it is a favourite remedy for the common cold. It is used, too, in any chronic cough or throat trouble, and besides its immediate curative effect it is supposed to grant a more or less lasting immunity from such diseases.

In almost every Dutch homestead may be found a small box containing an assortment of medicines in condensed solutions—a development of the pre-tabloid days. This is called the "huis apotheck" or house apothecary. In it there is some remedy that is supposed to antagonize almost every disease, and the confidence placed in them is absolute. They are in reality cheap and unstable compounds on which the manufacturers make enormous profits. In several there is opium, and it is not unknown for a child to be given so much of this that death results.—R. E. McConnell, *Canad. Med. Ass. J.*, 2: 20, 1912.