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PEPTIC ULCER THERAPY: THE ROLE OF BANTHINE

BY

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A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of
DOCTOR OF MEDICINE
of the
UNIVERSITY OF WISCONSIN

1951

"An ulcer is a circumscribed defect which extends through the muscularis mucosae: (a) An acute ulcer is characterized by a margin and floor in which little or no connective tissue is present. (b) A chronic ulcer is characterized by an abundance of fibrous tissue in its margin and floor. A local eosinophilia is usually evident. A peptic ulcer is a benign, nonspecific ulcer located in those portions of the alimentary tract bathed by gastric juice."[1] Ivy thus defined peptic ulcer for basis of discussion in his text, "Peptic Ulcer".

As regards etiology, the theories of ulcer genesis are set down by Ivy under two main headings, "Intragastric or Intraduodenal" and "Extragastric or Extraduodenal". Under these main headings there are ten subheadings and forty-two divisions under these, all theory.[2] In summary he says, "acute gastric or duodenal ulcer arises from (a) mechanical or chemical trauma, or (b) a vascular disturbance secondary to some toxic substance, as in burns, or (c) a vasoneurotic, infectious or allergic mechanism, as in an aphthous ulcer of the buccal mucosa. The acute lesion extends or is kept from healing by (a) acid-pepsin in normal or hypernormal amounts, or (b) mechanical and chemical trauma from rough and irritating food, or (c) hypermotility or hypertonicity of the musculature. In some populations a dietary deficiency is probably concerned. In some cases, secretion of excessive amounts of acid causes the initial lesion and prevents it from healing. In many cases, excessive secretion of acid does not occur and hence some deficiency in the mucosa must be concerned. In any case, a bland, non-mechanically irritating diet which buffers and neutralizes acid should promote healing of the ulcer."[3]

Available statistics from Scandinavia, Germany, England and the United States may be interpreted to show that five to ten percent

of these populations develop a peptic ulcer in their lifetime.[4] The ratio of the duodenal ulcer to the gastric ulcer is set at "at least 3 DU: 1 GU."[5]

Symptomatology, diagnosis and differential diagnosis are not within the scope of this paper.

As regards therapy, E. N. Collins[10] wrote of the present status of peptic ulcer therapy at Cleveland Clinic in July, 1950. He re-emphasized that in most instances gastric resection was the treatment of choice for gastric ulcer. With conventional treatment you have to assume that you are dealing with a benign lesion, a dangerous assumption. He has found that resection is rarely followed by the formation of a jejunal ulcer and that results of the operation are excellent.

At Cleveland Clinic surgery in the treatment of duodenal ulcer is reserved for its complications, i.e. acute perforation, two or more hemorrhages, or obstruction. Operative treatment has consisted of bilateral vagotomy with gastroenterostomy. Only 15% of duodenal ulcer patients has been subjected to surgery, leaving 85% to be handled medically and, according to Collins, "Satisfactorily". Considering the incidence of this type of lesion[4,5] susceptable to medical management, medical therapy assumes an important role.

Management included general hygienic measures, diet and antacids. In their experience adequate antacid therapy didn't call for complete neutralization of acid but just such control that would keep the acid below the pH required to activate pepsinogen. According to Hollander, and Eyerly and Brenhaus a pH of 3.5 was the critical level and toward this their therapy was directed. A brief note was made to the effect of Banthine in the treatment of twenty patients having complicated duodenal ulcer: "Initial response to the use of

this drug has been favorable. Several physicians requested the use of Banthine before resorting to vagotomy with gastroenterostomy and they have obtained satisfactory results without surgery." Significantly he adds that "a long-term follow-up study will be required before evaluating this on any other form of treatment for peptic ulcer".

Exclusion of other forms of therapy for peptic ulcer and its complications and consideration of only vagotomy, atropine, and Banthine is dictated by the available literature at this point in the clinical trial of Banthine and the similarity of the ultimate effects of the three approaches. As the preponderance of experimentation has been with duodenal ulcer patients, this further limits the discussion as to type of lesion dealt with.

Dragstedt and Woodward[11] wrote on "The Appraisal of Vagotomy for Peptic Ulcer After Seven Years". As a result of their experimentation they concluded that there is satisfactory proof that patients with duodenal ulcer secrete an excessive amount of gastric juice in the fasting stomach and as a result of food stimulus; and that the beneficial effect of vagotomy is due to the decrease in gastric secretion.

Average Twelve-Hour Night Gastric Secretion in the Empty Stomach of Normal Persons and Peptic Ulcer Patients[11]

Condition of Patient	Number of Cases	Volume cc.	Free Acid Clinical Units	HCl Output M.Eq/L
Normal	81	551	33	18
Duodenal ulcer	135	1,085	52	60
Ulcer after vagotomy	70	521	22	11

Vagotomy alone was performed on 234 patients referred to their surgical service with duodenal ulcer. Dragstedt has noted that 76% secured a good result, 9% a fair result and in 15% a poor result. Sixteen patients subsequently had to have additional surgery.

"Complications of vagotomy.....are chiefly due to motor disturbances in the stomach (and) are for the most part trivial and self-limited and can be controlled or eliminated entirely."[11]

"Nearly 85% of the patients who present themselves for treatment of peptic ulcer are maintained satisfactorily on a medical regimen"[14] Perforation, pain, hemorrhage and obstruction were considered indications for surgical treatment. In Glenn's series[14] massive hemorrhage and obstruction were considered contraindications for surgery. Vagotomy alone was performed on 33 patients. Eight of the results were failures and Glenn concluded that the results were "somewhat discouraging".

Walters and Bilding[24] wrote of the previous abandonment of vagotomy by surgeons because of resultant reactions from interference with motility of the stomach and intestine. Reactions were listed as: dilatation of the stomach with gastric retention; dehydration and hypochloremia postoperatively; later symptoms of fullness, gas and diarrhea; and in some patients stasis ulcers developed. These annoying symptoms occasionally necessitated further surgery. Dragstedt's recent series prompted Walters et al to review the results of vagotomy at Mayo Clinic during the past five years. Excellent results were noted in 57.5% of 29 cases.

In the above three series "excellent results" were noted to be increased where vagotomy was employed with gastroenterostomy, but for the purposes of this thesis only the results of vagotomy alone were noted.

Grimson writes[15] that "after five years of thorough study and review by C. Keith Lyons of results obtained following several types of ulcers, the conclusion reached by us, but not all colleages, the vagotomy with gastroenterostomy, because of its low operative risk and low recurrence rate, was a safer procedure than subtotal resection.

Side effects of gastroenterostomy remain troublesome in some cases, and for this reason during the past four years a search has been made for drugs which might alleviate these complications. Some encouraging results have been obtained." Banthine, a "medical vagotomy"[23] has been employed in a clinical trial by this author.

Banthine is the trade name of beta-diethylamino-ethyl xanthine-9-carboxylate methabromide which is put out by the G. D. Searle & Co. Experiments with the drug were conducted by Hambourger, Cook, Winburg and Freese and reported.[18] Its action as an autonomic ganglion blocking agent was demonstrated. Employing cats, the proximal end of the cervical vago-sympathetic trunk was stimulated to produce contraction of the nictitating membrane. Banthine administered intravenously relaxed this contraction. During the relaxation of the nictitating membrane while under the influence of Banthine, it can be made to contract briefly by administering epinephrine. This, plus the observation that Banthine has no influence in protecting mice subjected to a minimal lethal dose of epinephrine, suggests that its action is possibly on the ganglion and not as an anti-epinephrine drug.

Changes in dogs' bladder tonicity were recorded by a water-manometer-lever system. The pelvic nerve was stimulated and increase in intravesical pressure noted. Banthine was administered and there was only a slight or no response at all to further stimulation.

Inhibition of intestinal motility was demonstrated by employing three trained, unanesthetized dogs (Thiry Vella dogs with ileal fistulas). A balloon was inserted into the fistula and normal contractions noted. Contractions ceased for from 5 to 40 minutes after Banthine injection. Similar results were recorded employing anesthetized dogs.

Twelve of sixteen guinea pigs were saved by previous Banthine administration before being exposed to fatal dosage of Mecholyl, death being produced by bronchospasm.

Similar mydriatic reactions were noted in rabbits upon comparing the actions of atropine and Banthine.

Inhibition of salivary secretion was demonstrated by the stimulation of the chorda tympani nerve in experimental dogs before and after administration of Banthine. Banthine was shown to inhibit the secretion.

The production of hypotension by Mecholyl and cardiac arrest by stimulation of the vagus was inhibited by previous administration of Banthine in experimental animals.

Inhibition of sciatic nerve stimulation on the gastrocnemius muscle of five anesthetized cats was demonstrated after administration of increasing doses of Banthine.

Transient but definite falls in blood pressure and depression of respiration were noted in anesthetized dogs and cats.

Hambourger et al concluded that the predominate action of Banthine was its action in blockading the parasympathetic neuro-effector. Also noted were its possible sympathetic ganglion blocking actions and curare-like actions in larger doses.[18]

Longino, Grimson, Chittum and Metcalf of the Department of Surgery at Duke University have conducted tests with Banthine in both experimental animals and man.[21] Employing dogs the group administered successively increasing dosages of Banthine to them and noted their physiologic responses:

In dogs:

Hypotension and pulse acceleration were produced with larger doses, the extent depending on the dosage of the drug. Respiratory

depression was produced with Banthine, and complete respiratory arrest was produced after administration of 16.5 mgm/Kg. of Banthine. The probability of respiratory arrest being the cause of death if a curare-like action were produced was expressed by Hambourger et al.[18]

Banthine was shown to prevent cardiac arrest or slowing of the heart after stimulation of the distal end of the vagus. They demonstrated that they could block the carotid sinus reflex up to ten minutes employing Banthine. The reflex back pressure response of the femoral artery was studied by employing epinephrine before and after Banthine. Without Banthine epinephrine produced a slight drop in blood pressure followed by a rise in pressure. With Banthine administered before epinephrine, the epinephrine produced on administration an immediate rise in blood pressure. "This monophasic rise resembled that occuring in the sympathectomized extremity." The dosage required to produce this effect was larger than that employed in other phases of the experiment.

Barium meals were fed ten dogs and fluoroscopically emptying time was determined. Initial emptying was 3.3 minutes and at four hours 79% of the meal had passed and in six hours 95%. Banthine was administered prior to another test meal on the following day. Initial emptying time was found on an average to be 30-plus minutes and at four hours only 15% of the meal had been emptied and 54% at six hours.

In man:

Effects of Banthine on the human cardiovascular and gastrointestinal systems were noted. Dosage was 100 mgm. administered orally. The average blood pressure of a group of twenty patients was 134/84 mm. of mercury. After Banthine administration the average was 140/90. There was a uniform, slight rise in pulse rate noted. "There was no marked change of blood pressure in any patient. Also, postural hypotension did not occur." Temperature gradients were determined from

the umbilicus to the toes in eight patients. No significant changes in temperature were noted with the administration of Banthine.

Effects on motility were determined by employment of intragastric balloons and the fluoroscopic following of barium meals. Aspiration was employed to determine effects on gastric secretion. Control periods were observed in all tests before administration of Banthine. Approximately 20 minutes after administration of 100 mgm. of Banthine orally contractions ceased in the stomachs of three subjects for an average of 1½ hours. Similar results were obtained after intravenous administration in eight subjects.

Passage of a barium meal in six normal subjects showed an average gastric residual of 20% at the end of 1 hour, complete emptying in five subjects at 2 hours with one subject retaining 15%. On the following day, after 100 mgm. of Banthine had been administered orally, passage of a barium meal showed an average retention at 1 hour of 82%, 73% at 2 hours, 43% at 4 hours and 18% at 6 hours. 0.45 mgm. of atropine was administered orally on the third day in three subjects before a barium meal. A slight decrease in peristalsis was noted, but gastric emptying was as rapid during this test as on the first day.

Aspirations were done on seven control patients prior to administration of 100 mgm. of Banthine orally. Results were compared with the findings on aspiration after drug administration. The average pH of the specimens went from 1.67 to 2.67; the average volume/15 minute period went from 30 to 9 cc.; the M.Eq. free acid/15 minute period went from 1.19 to 0.28; and the M.Eq. total acid/15 minute period went from 1.62 to 0.49.

They concluded with "Eleven patients with duodenal ulcer have been treated by giving 100 mgm. of Banthine orally 3 to 5 times daily for periods of 3 to 5 months. Although this period of time is too short

for evaluation each patient has been subjectively improved. There have been no disagreeable side effects, and abnormality of blood counts or of urinalyses has not occurred. These preliminary results are encouraging and treatment is being continued."

Noting the effect of complete vagotomy in the healing of various peptic ulcers, Smith et al became interested in the possibility of producing a "medical vagotomy".[23] Citing Palmer, Kersin and Levins' experience that atropine, even in toxic doses, proved ineffective in reducing the hypersecretion encountered in duodenal ulcer, the authors employed Banthine to determine its effects on gastric secretion in man and animals.

With a series of vagotomized dogs, Banthine was shown to have no effect on gastric secretion and motility; the effectiveness of the vagotomy being determined by the Hollander test. 17% and 42% reductions in hydrochloric acid were noted in 24-hour secretions in dogs with intact vagi.

No attempt to treat the selected patients with duodenal ulcer was made. The effect of Banthine on 12-hour night secretions was noted with administration of 100 mgm. doses orally every 4 hours. The reduction noted in the six patients ran from 30 to 86%. There were no significant side effects although one patient complained of dryness and two noted a slight blurring of vision on reading fine print.

On the basis of their work the authors concluded that "it seems likely that the drug would exert a favorable influence since the depressant effect on gastric secretion was quite marked, though not so great as may be secured by complete vagotomy." This was concluded on the slight work done by the authors in the face of the weight of material they had after observing vagotomies for some time.

"The present study (of Banthine) indicates that Banthine inhibits secretions by its cholinergic blocking or atropine-like action."[5] For comparison's sake the effects of atropine as recorded by several researchers are noted. Gill and Jessup[13] performed a series of experiments with atropine, rating its effect on various gastric functions. They were stimulated to do so by a review of conflicting reports as to the place of atropine in peptic ulcer therapy. They quoted two authorities who questioned atropine's place in peptic ulcer therapy: 1. "In doses usually employed by mouth atropine and belladonna are practically without effect on the secretory and motor functions of the stomach"---Bastedo; 2. "There is little basis for the clinical use of belladonna drugs in peptic ulcer or hyperchlorhydria in the attempt to reduce the volume and acidity of gastric juice" and "that on the whole, the normal gastric secretion is not significantly altered by the belladonna drugs" and "atropine does not significantly affect the gastric evacuation time in normal subjects"---Goodman and Gilman.

Gill and Jessup briefly reviewed the six detailed reports on the effect of atropine in the treatment of uncomplicated duodenal ulcer where hypersecretion plays such an important part. Moore and Kilroe reported that free acidity was reduced in six patients 1 hour after eating with the employment of tincture of belladonna. However, the volume of gastric secretion was not found to be diminished. Lockwood and Chamberlain[20] employed atropine sulfate prior to a test meal and found that free acid was reduced on an average of 45.9 units, the total acid an average of 36 units and delayed emptying time 15 minutes. Atkinson and Ivy[7] employed atropine before histamine injection to determine its effects in eight patients with chronic duodenal ulcer. These tests were done on fasting patients whose stomachs were aspirated every 10 minutes for 2 hours before and after the histamine injection.

The volume of secretion and the total output of hydrochloric acid were reduced, but the free and total acidity were unchanged. Seventeen patients with healing duodenal ulcers were administered atropine by Kirsner and Palmer[19] and its effect was noted on a series of aspirations. They concluded that no appreciable reduction in acidity was obtained. Volumetric determinations were not made. Effect on gastric contractions by atropine was noted by Anderson and Morris[6] in six fasting patients. Subcutaneous administration of atropine increased the frequency of contractions in three, had no effect in two and decreased contractions in one. Fifteen patients with duodenal ulcer were studied by Means[22]. Continuous suction was started and after an interval atropine was administered. Twelve of the patients showed a decrease in total volume, ten a decrease in free acidity and eight a decrease in total acidity.

Gill and Jessup[13] concluded that "the results of these studies have not been conclusive." Differences in results were attributed to the variability in methods and the known variability in gastric function from patient to patient. They designed an experiment to study the effects of atropine on certain gastric functions. The experiment adhered as closely as possible to a clinical regimen with the employment of a bland diet, frequent feedings and sedation. Six male patients were selected with histories averaging five years. All of the patients had duodenal ulcer craters demonstrable roentgenographically. The study covered four weeks. The patients were ambulatory throughout and the first week was devoted to determinations of gastric function without the administration of atropine. Atropine was administered the second and third weeks and then discontinued; 1.2 mgm. of atropine sulfate was given orally every four hours the second week and increased to 2.4 mgm. the third week. Methods employed were as noted in the article[13].

The results noted that average fasting volumes of gastric secretion were approximately halved for the two week-periods of atropinization i.e. *69.2 ml, 37.8 ml, 40.7 ml and 70.0 ml. pH determinations were less acid during atropinization, i.e. 1.5, 3.2, 2.8, and 1.5. Fasting free and total acidity showed decreases while under atropinization, i.e. free acid 3.7, 1.5, 1.5, and 4.2 millimoles per 100 ml. During atropinization the rate of gastric secretion was markedly reduced, i.e. 4.70 ml, 2.19 ml, 1.98 ml and 3.99 ml per minute. Combined hydrogen ion concentrations were decreased during atropinization: pH values were 1.9, 3.4 3.5 and 2.1. There was a decrease in the production of total and free acid, i.e. total acid 0.245, 0.075, 0.067 and 0.223 millimoles per minute, and free acid 0.224, 0.058, 0.052, and 0.23 millimoles per minute. Rate of pyloric evacuation was found to be decreased, i.e. 10.06, 6.10, 5.67 and 8.25 ml per minute. They noted that "in general, ulcer symptoms improved while the studies were in progress. The ulcer craters had healed in the five patients, who had follow-up gastrointestinal X-rays after the study." and that "our results with atropine are similar to the immediate results of vagotomy."[13]

As regards toxicity, each patient experienced dryness of the mouth and a blurring of vision. Considering the large dosage and the side effects they concluded that clinical implications of these results were limited. Significant was the consistent finding that increasing the dosage of atropine, i.e. from 1.4 mgm every six hours to 2.4 mgm, showed no appreciable advantage.

Benjamin et al[8] commented on the need for a drug which would inhibit acid secretion by the stomach. They noted the side effects of

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* Where four successive figures occur they refer to average weekly determinations on four successive weeks. The first and fourth figures cover the weeks without atropine administration and the second and third the weeks with atropine.

atropine and that in all instances it did not inhibit secretion in some duodenal ulcer patients. They proceeded to compare the action of Banthine and atropine in man and dogs.

Basal secretions were determined in three healthy, young adults. Atropine and Banthine were administered parenterally and the degree of inhibition was approximately the same. In two ulcer patients atropine and Banthine were given on separate days. Compared results showed that they depressed secretion equally, but that atropine raised the pH more effectively than Banthine. However, Banthine was given parenterally and in ten milligram doses. Depression of histamine stimulated secretion in seven healthy adults was approximately the same with both drugs.

In the animal phase of the experiment three dogs were used with vagotomized pouches of the entire stomach. The degree of inhibition produced by the drugs was approximately the same, with a greater dosage of Banthine required.

As a follow up to his article on peptic ulcer therapy[10], E. N. Collins in conjunction with Charles H. Brown reported further on the use of Banthine in the treatment of duodenal ulcer and the possibility of its use as a "medical vagotomy"[9].

The period of management was approximately two months. Twenty-five patients were selected who had either experienced recurrance of the ulcer or some other complication. Preferably the patients had ulcer craters, so that progress could be followed roentgenographically within four to eight weeks after onset of treatment. Dosage was 100 mgm of Banthine every six hours and there was no strict management of diet nor employment of antacids. Of the twenty-five patients, one discontinued therapy due to intolerance of the drug, three achieved only partial relief, and two obtained none at all. One of these two

subsequently underwent surgery. The remaining nineteen became symptom-free in one to four days on Banthine alone, not requiring multiple feedings nor antacids.

Roentgenologic observations were made in only eighteen patients. These were made four to eight weeks after onset of therapy. As all the patients exhibited a defect at onset of therapy, findings would be significant. Seventeen of these patients showed no crater at all on subsequent examination and the eighteenth showed only a "questionable crater".

These findings prompted the authors to remark that "we have not observed such remarkable results with any other type of ulcer therapy".[9]

As regards toxicity, side reactions were mild. Dryness was noted in eleven patients, slow urinary stream in six and impaired visual focus in five. Reduction of dosage alleviated these symptoms in all but four. Reactions were most severe initially and subsided after a week or so.

Interestingly, it was noted that a 67-year-old man was admitted to Cleveland Clinic with the complaint of "retention". Subsequent history revealed that the patient had been given Banthine by a druggist. The physical examination revealed that the patient had prostate enlargement, pointing up a possible contraindication to the use of Banthine.

The authors were enthusiastic over the results achieved with Banthine and its use as a "medical vagotomy". It gave promise where belladonna and atropine produced severe side effects, and possibly ruled out the necessity of frequent feedings and antacids. They soberly concluded with this statement: "Whether long-continued use of this drug will result in intolerance to the medication or severe toxic reactions has not, as yet, been determined, inasmuch as none of our patients have undergone the therapy for a significant interval."[9]

A. I. Freidman[12] treated fourteen patients with duodenal ulcer and one with a gastric ulcer with Banthine. All of the patients were males and all had roentgenographically demonstrable lesions. Other than 100 mgm of Banthine four times daily only a bland diet was prescribed. The report covers only the first month of treatment.

Two of the patients described their symptoms as "worse" and four noted "no effect". The remaining nine were definitely improved. Two of the patients within the month showed roentgenographically that the lesion had disappeared. Ten of the patients complained of dryness, one of cycloplegia and one of slight urinary retention. There were no severe toxic manifestations.

One patient had been treated for four years with bland diets, frequent feedings, antacids, belladonna and phenobarbital. His course was such that surgery had been advised. Seven days after starting treatment with Banthine this individual was symptom-free. This was the most "spectacular" result noted in the series, which was reported on one month after its inception.

In May of 1949 Grimson, Lyons and Reeves[16] started a clinical trial of Banthine. Previous work on animals and test dosage of patients determined that the optimum dose orally was 100 mgm. Secretion and motility of the stomach were observed to be depressed from two to six hours after administration of Banthine. Dosage was prescribed every four or every six hours. When healing was manifest dosage was cut to 50 mgm.

The results were summarized by Grimson in the New York State Journal of Medicine[17]. 100 patients were selected who had failed to respond to conventional medical management. The patients were encouraged to eat regular meals and diet, frequent feedings, antacids and

other medications were discontinued. Banthine was the sole therapeutic agent. 100 mgm. were administered every four to six hours for approximately two weeks to two months, i.e. until such time as there was roentgenologic evidence of healing. Dosage was then cut to 50 mgm. four times daily and continued as a maintenance dose.

Seven patients had postoperative jejunal ulcers, two had both gastric and duodenal ulcers, two had channel ulcers and the rest had duodenal ulcers. Surgical intervention was indicated in the seven patients with jejunal ulcers and in 55 of the patients with duodenal ulcers. Signs and symptoms were such that Banthine had to be discontinued in only five of the patients, who then went to surgery after 5, 6, 6, 6 and 10 weeks of treatment.

As regards pain, 80 patients were relieved within $\frac{1}{2}$ hour after the first dose. Occasional ulcer pain was experienced in 11 patients initially, but subsided in all in from 14 to 103 days of treatment. Four patients who, at the time of this report, had been only 47 to 97 days under treatment had not as yet achieved complete relief.

15 of the 91 patients who achieved relief had recurrence of pain lasting from 3 to 47 days. Recurrence occurred when the patient was on maintenance dosage and subjected to considerable strain. With full dosage and supplementary antacids and bland diet, the patients again achieved relief. Vomiting was present in 52 of the cases before therapy. A recurrence occurred only in seven, all of whom were among the above fifteen. Major and repeated hemorrhages had occurred in 19 patients and melena was evident in 12 patients prior to Banthine administration. There has been no recurrence of bleeding as far as the clinical trial has gone.

Symptomatic relief necessitated the following of the ulcer's course roentgenographically at the third and sixth weeks and at two

or three months intervals afterward to determine healing. Excluding the seven patients with jejunal ulcers and the five patients who went to surgery, there were 88 patients left to be followed roentgenographically. At onset of therapy there were 45 patients with marked deformity of the duodenum, i.e. three-quarters or more narrowing of the duodenum. Lessening of the deformity was noted in 35 patients, no change in 8 and increase in deformity in 2. 21 patients had a moderate deformity, i.e. between one-quarter and three-quarters narrowing of the duodenal lumen. After onset of therapy improvement was noted in 12 patients, no change in 7 and an increase in deformity in 2. 22 patients had a slight deformity before treatment, i.e. narrowing of the lumen one-quarter less than normal. Improvement was noted in 6, no change in 10 and an increase in deformity in 6. The author speculated[17] that this was possibly due to contraction resulting from healing. Craters were demonstrable in 29 patients prior to onset of therapy. In 14 to 77 days roentgenograms and fluoroscopy showed that 22 craters had filled. In 6 patients craters were demonstrated on examinations on the 14th, 14th, 24th, 36th, 47th and 55th days, but not on subsequent examinations.

Of the 88 patients, after healing, only one ulcer was demonstrated in the group and this on the 263rd day after onset of therapy during a severe respiratory infection. The ulcer healed after 5 weeks of treatment with 100 mgm. of Banthine four times daily, antacids and rest.

Routine blood and urine analyses have been normal throughout the test and no development of tolerance to the drug has been noted. Dryness of the mouth and dilatation of the pupils were noted by most at the onset of therapy. Constipation and slowing of the urinary

stream were noted by a few. These symptoms proved less troublesome as therapy continued.

Five to ten percent of selected populations have peptic ulcers sometime during their lives.[4] The ratio of duodenal to gastric ulcer is approximately 3 DU: 1 GU.[5] 85% of duodenal ulcers can be handled medically[10,14] leaving surgery for the treatment of its complications.

Dragstedt and Woodward appraised the results of vagotomy over seven years performed on 234 patients for the treatment of duodenal ulcer. Good results were secured in 76% of the cases.[11] Glenn wrote of the "somewhat discouraging" results in 33 cases where vagotomy alone was performed and 8 failures were encountered.[14] Walters and Bilding listed reasons for previous abandonment of vagotomy in the treatment of peptic ulcer and reviewed the results obtained in 29 cases employing this procedure. Excellent results were noted in 57.5% of these cases.[24] In all series[11,14,24], excellent results were increased when vagotomy was employed with some other procedure. It was agreed that effectiveness of vagotomy resulted from the reduction of gastric motility and secretions.

Grimson and Lyons[15] concluded that vagotomy with gastroenterostomy was one of the best surgical approaches to duodenal ulcer treatment, but admitted its disadvantages. Their work has been directed toward approximating surgical results with drugs, i.e. a "medical vagotomy".[23] One of the drugs used was Banthine.

Hambourger et al concluded on the basis of their experimentation that the predominate action of Banthine was its action in blocking the parasympathetic neuroeffectors and also noted its possible blocking actions on the sympathetic ganglia and its curare-like actions in larger doses.[18] Results with 43 subjects tested with Banthine by

Longino et al[21] were noted as reducing gastric motility and acid secretion. Subjective improvement was noted in 11 of the 43 who had had duodenal ulcers prior to onset of treatment. Depression of secretion was noted in 6 subjects with ulcers tested by Smith[23] employing Banthine.

Atropine's place in peptic ulcer therapy was noted by Gill and Jessup.[13] Controversy over its efficacy was noted.[13,20,7,19,6,22] Methods and thoroughness of investigators listed were questioned. A satisfactory four-week test was conducted. Results with atropine were noted to be "similar to the immediate results of vagotomy". Benjamin et al[8] found Banthine as effective as atropine, but in their comparison as regards the respective drugs' effect on reducing motility and secretion they found no advantage of Banthine over atropine.

Collins and Brown[9,10] commented enthusiastically on results obtained employing Banthine on 25 patients in a clinical trial. They noted Banthine "gives promise where belladonna and atropine produced severe side effects, and possibly ruled out the necessity of frequent feedings and antacids". Side effects were noted. Results of a clinical trial of Banthine for one month on 14 patients with duodenal ulcers were noted by A. I. Freidman. Equivocal results were obtained and no clear cut explanation was given as to his method.[12] Grimson et al employed Banthine in clinical trial with 100 patients starting in May 1949.[16,17] The trial was unique in that Banthine alone was used to the exclusion of barbiturates, antacids, antispasmodics, and bland diet. Results were as noted and "gratifying". Radiological evidence of healing was noted[10,16,17] and continued dosage seemed advisable after healing in their experience. No tolerance was developed to the drug as yet. Side effects were noted.

On the basis of experimentation it can be concluded that Banthine is an anticholinergic drug. Of therapeutic interest is its action in depressing gastric motility and secretions with subsequent symptomatic relief. Objective radiological evidence of healing has been noted. Methods and results of clinical trials were as noted above. Remissions have been noted in the series listed. It would appear that the continuance of a maintenance dosage of Banthine after healing might preclude recurrence. The fact that Banthine alone has produced healing should be of interest to the physician who has to set up a dietary and medical regime for the patient, and of even more interest to the patient who must carry it out. Considering that the patients considered, who have undergone treatment with Banthine, had uniformly been referred first to surgical services after failing under medical management, and considering the results achieved, Banthine would seem to have a place in the treatment of peptic ulcer. It would seem that even better results could consistently be obtained when employing Banthine on patients patently eligible for medical management alone.

Whether or not patients receiving Banthine will develop a tolerance to it, what side effects might develop as a result of its prolonged usage and what effect the drug might have on cutting down the incidence of exacerbations of peptic ulcer only continued trial and observation will tell.

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