University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE

University of Nebraska Medical Center
DigitalCommons@UNMC

MD Theses

Special Collections

1961

Method and evaluation of a new experimental approach to decrease gastric acids

Edward Allen Rhodes
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Recommended Citation

Rhodes, Edward Allen, "Method and evaluation of a new experimental approach to decrease gastric acids" (1961). *MD Theses*. 2570.
https://digitalcommons.unmc.edu/mdtheses/2570

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

METHOD AND EVALUATION OF A NEW EXPERIMENTAL APPROACH TO DECREASE GASTRIC ACIDS

Edward Allen Rhodes

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1961

Omaha, Nebraska

TABLE OF CONTENTS

		Page
I.	Introduction	1
	(a) Definition, distribution, and incidence of peptic ulceration.	1
	(b) Causes of peptic ulcers	2
	(c) Difficulty of prevention	5
	(d) Review of present treatment	6
	(e) Disadvantages of present treatment	9
II.	Present Investigations of New Techniques . .	11
	(a) Present work with excision of gastric mucosa	11
	(b) Present work with replacement	20
	(c) Present work with alteration	25
	(d) Additional techniques	27
III.	Research Project	28
	(a) Materials and Methods	29
	(b) Tabulation of results and statistics . . .	33
	(c) Graph I	37
	(d) Graph II	38
IV.	Evaluation and Conclusions	39
V.	Summary	42
VI.	Bibliography	44

I. INTRODUCTION

The treatment of many diseases has advanced today to the point of prevention. In many diseases, polio myelitis for example, prevention of the disease is possible but treatment for the actual developed case is poorly known. Still in other disorders the treatment of the developed disease is known but the prevention is unknown. In this latter category we find, among many, the peptic ulcer.

The peptic ulcer is a circumscribed area of tissue loss occurring only in those portions of the digestive tract exposed to the action of acid gastric juice. Ulcers are found in all peoples, in all regions of the earth, in all occupations, in all ages and all walks of life. There is a decreased occurrence in sections of northern India and the Malay natives of Java and Sumatra. The factors which allow these people to escape peptic ulceration are being investigated.

The exact incidence of peptic ulcer is unknown; however autopsy and X-ray studies have shown from ten to twelve percent of all peoples suffer at some time from peptic ulceration. Of these, a ratio of four to one, male to female, suffer from duodenal ulcer while a ratio of three or four to one, male to female, have gastric ulceration. Gastric lesions are encountered more frequently at autopsy, but the duodenal ulcer is

recognized most often clinically.

In considering the management of peptic ulcer, it would be ideal to handle it on a preventative basis. To do so means preventing the cause or causes of this condition. As Portis says, "Theories of the cause - have been legion." He gives these six broad headings for causes: bacterial inflammation, nonbacterial inflammation, trauma, infarction, chemical inflammation, and nerve lesions. The theory of infarction is now no longer tenable. Trauma is a very rare cause, but sufficient cases have been reported to require its mention. Under the heading bacterial inflammation are found acute ulcers resulting after acute infectious diseases which have come to autopsy. No organism has ever been consistantly found as a possible cause of ulceration, and histologically ulcers appear as the result of chemical inflammation.

Nonbacterial inflammation is a relatively new concept associated with antral gastritis. There is much present dispute going on concerning whether or not gastritis is the original process leading to ulceration. If this theory stands the test of time, its cause still remains to be found.

Since the vast majority of ulcers are caused by chemical inflammation and nerve lesions, this discus-

sion is given last and in greater detail.

Chemical inflammation may take several forms, but hyperacidity is generally considered paramount. It has been found, however, that the contents and amount of gastric juice formed by ulcer patients does not differ from the juice of normal subjects. Also, the ulcer patient's gastric juice does not differ between periods of remission or exasserbation. This indicates a variable factor inherent in the gastric mucosa to resist digestion. If such a factor exists, it is yet to be found. This factor may be a thin protective layer of mucus over the mucosa which is absent in the ulcer patient. The possible operation of this factor is poorly understood. However, it has been experimentally shown many times that ulceration occurs only in those portions of the digestive tract exposed to acid gastric juice, and that ulceration does not occur in the absence of an acid gastric juice. Quoting Schwartz, "No acid - no ulcer" is a true dictum for practical and functional purposes.

Nerve lesions, a function of the cephalic phase, can best be covered by quoting Harvey Cushing who states experimental evidence strongly suggests

...the presence in the diencephalon of a parasympathetic center. From this center, apparently tuberal in situation, fiber tracts pass backward to relay with the cranial-autonomic stations of midbrain and medulla of which the vagal nucleus is by far the most important because of its influence on the activity of the lungs, heart and upper alimentary canal.

Experimental lesions anywhere in the intracranial course of these fiber tracts from anterior hypothalamus to vagus center, presumably from parasympathetic stimulation (or possibly from vagal release due to sympathetic paralysis) are prone to cause gastric erosions, perforations or ulcers. Intracr nial injuries and diseases affecting these same basilar regions of the brain are known to be accompanied by ulcerative lesions of the upper alimentary canal. It is reasonable to believe, therefore, that the perforations following the cerebellar operations forming the basis of this study were produced in like fashion by an irritative disturbance either of fiber tracts or vagal centers in the brain stem....

Stimulation of the postulated parasympathetic center by intraventricular injections of pilocarpine or pituitrin cause, in man, an increase in gastric motility, hypertonis and hypersecretion leading to retching and vomiting which ultimately contains occult blood. The same effects, associated with observable patches of hyperemia of the gastric mucous membrane, have been shown to follow direct electrical stimulation of the tuber cinereum in animals....

The parasympathetic apparatus, in all probability, under normal conditions is ... strongly affected by cortical or psychic (Pavlov) influences. However, this may be, direct stimulation of the tuber or of its descending fiber tracts, or what theoretically amounts to the same thing, a functional release of the vagus from paralysis of the antagonistic sympathetic fibers, leads to a hypersecretion, hyperchlorhydria, hypermotility and hypertonicity, especially marked in the pyloric segment. By the spasmodic contractions of the musculature, possibly supplemented by accompanying local spasms of the terminal blood vessels, small

areas of ischemia or hemorrhagic infarction are produced leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices.[1]

On this precept it has been shown experimentally that anxiety, frustration, guilt, resentment, insecurity, and other tensions resulting from psychodynamics such as suppressed, stron and receptive dependent wishes cause an increase, over normal, of those factors previously mentioned.

From the preceding discussion it will be evident how very difficult prevention of factors causing peptic ulceration would be. Consider only the last two causes discussed, where the majority of patients fall. In the category of chemical inflammation, where the exact mechanics are unknown, no treatment for the total population is possible. It also seems highly unlikely that in any human society those psychic factors, predisposing or causing ulcer formation, could ever be removed. By today's methods there is no treatment practical for the entire population to reduce gastric acidity, the one universally acceptable factor as a primary cause of peptic ulcer. Since this is so, it becomes necessary to treat the disease at whatever stage of development may be severe enough to bring the patient to the doctor.

Under present concepts of ulcer treatment conservative care forms the first line of defense in both acute and chronic types. The object of therapy is the healing of the ulcer and the prevention of its recurrence. Healing the ulcer, carried out under inpatient care especially if gastric, is generally not too difficult. This excludes carcinoma as the cause.

The aim of conservative or medical management is directed toward reducing gastric secretion and motility. The patient is placed on hourly cream or milk feedings. If the ulcer is located in the duodenum, cream is used since food containing fat in excess of ten percent when in the duodenum causes a decrease in gastric secretion and motility. If the ulcer is located in the stomach milk is used. Milk will not cause decreased motility and secretion; for this reason it will not hold the acid gastric secretions in the stomach. These feedings do not exceed five ounces. A feeding greater than five ounces causes distension of the pyloric antrum which stimulates both motility and secretion.

In conjunction with these hourly feedings an antacid is given every hour on the half hour. This combats a rising acidity resulting in these stomachs

which will empty the milk feeding in approximately thirty minutes. Magnesium hydroxide is the drug of choice in constipated patients because of its laxative effect. Since aluminum hydroxide has a constipating effect, it is chosen if there is a problem of hypermotility.

It is desirable to use milk feedings and antacid in the proper time relationships. If this is done, the gastric acidity of the patient will be held at a pH of 3.5 or above. When secretions are more alkaline than pH 3.5, pepsin is not formed to further aggravate the ulcer.

Rest, both physical and mental, is very important. This is usually augmented by the use of sedatives such as elixer of phenobarbital or tranquilizers.

Frederick F. Paustian, M.D. concluded this Gastroenterology lecture on March 11, 1961 telling seniors that bella donna drugs such as atropine are used to block the neuro-effector junctions and further reduce gastric secretions. Since anticholenergics tend to decrease motility, they are desired only for those patients with a hypermotility problem involving the large and small bowel.[2]

Under hospital supervision results of this treatment are good. When healing has begun, the patient is

and widely used, many disadvantages are present. In conservative forms of treatment the long term nature is a heavy, tiresome burden for the patient to bear, particularly if he is symptom free. Such length treatment is dependent on a cooperative individual. Soft diet, abstinence from alcohol, and constant surveillance may become very unpleasant to the patient. Long term therapy, though cheap day by day, may amount to many dollars, and still the possibility of recurrence is great.[1]

The disadvantages of operating are many. A portion of the gastric reservoir is lost, often permanently if compensatory dilation does not occur. Reservoir loss with a large stoma between small intestine and stomach results in the "dumping syndrome" [3] as shown by Abbott, Kreiger, Levey, and Bradshaw. Vagotomy, severance of vagal fiber descending about the esophagus, not only removes this innervation from the stomach but also destroys parasympathetic stimulation of liver, biliary tree, pancreas, small bowel, portions of the kidney, and the proximal one third of the colon.

Also note that a gastrojejunostomy is not a physiologic anastomosis. From this (without explanation) may occur obstruction of the stoma, short-circuiting

a portion of the bowel, afferent loop malfunction, anemia, undernutrition, reactive hyperinsulinism, diarrhea, and as already mentioned the "dumping syndrome." Aside from these complications which can and do occur, the operation may be obviated by the development of a marginal or stomach ulcer. That is a peptic ulcer developed on the jejunal portion of the gastrojejunostomy. These ulcers tend to be treatment resistant and often require another operation.

The disadvantages mentioned above are overshadowed by a greater good derived in the majority of patients; however, the incidence is high enough that a method of treatment of lower morbidity is being sought by many. This is the stimulus which prompted the evaluation of gastric acidity presented in this paper.

The second section reviews the methods and results of other investigators. The third section reports original work on this subject.

II. PRESENT INVESTIGATIONS OF NEW TECHNIQUES

In the last five years a growing number of investigators have attempted to find a definitive treatment for peptic ulcer. This research has been pointed at the reduction of gastric acidity by various methods. The object of these endeavors has been to find a means of permanently establishing a hypochlorhydria without disrupting physiology or permanently reducing the gastric reservoir.

The methods used may be classed broadly in three categories according to Longmire, et al.[4] First, excision, that is full thickness removal of the gastric mucosa, leaving the denuded gastric wall to heal by filling the defect with granulation tissue. Second, replacement of acid secreting gastric mucosa with non-acid secreting mucosa; this is accomplished by autogenous grafting. The third category is alteration in the cellular structure of the gastric mucosa, a phenomena occurring for a time after partial thickness mucosal excision.

In the category of excision Williams, Pisesky, and Mackenzie have developed a procedure making use of dogs. Their method is as follows: The stomach is freed along the greater curvature from the proximal antrum to the esophagus. Atraumatic clamps are then placed across the proximal antrum one-half inch from

the junction with the body and across the gastro-esophageal junction. Blood flow to the area is controlled by means of the gastroesophageal clamp and a Blaloch clamp through the same hole in the mesentary to the left gastric artery. The mucosa is exposed by an incision along the greater curvature. The mucosa is then held taut with tissue forceps and peeled away from the seromuscular coat by blunt and sharp desection along the cleavage plane. This stripping is completed on the anterior and posterior walls so that the separations meet on the lesser curvature. The bridge of mucosa is severed leaving funnel shaped mucosal flaps leading to either antrum. The freed mucosa is then resected leaving only intact mucosa at either end. A direct end to end anastomosis between the two mucosal edges is then performed. At this point there is formed a circular pouch of excess seromuscular layer about the anastomosis. The bases of this pouch are closed over the anastomosis, and due to contraction very little dead space results.

This was done to fifteen dogs who tolerated the operation well and were back on a normal diet within a week. Three dogs were sacrificed at intervals of one, five, and twelve weeks to observe the sequence of healing. At one week the dead space within the sero-

muscular pouch was filled with clot which was completely resorbed by the fifth week. At this time also the seromuscular pouch had contracted to form a thickened fold about the anastomosis. By the twelfth week there was little evidence of this thickening and the reservoir had dilated to approximate its original size. The stomach allowed free passage of peristaltic waves, and examination with barium indicated a normal emptying time.

Unfortunately the authors are vague about the effect on gastric secretion. It is stated that repeated tests using food and histamine for stimulation failed to produce acid in the gastric secretion. How long this condition held true is not mentioned. The authors also report that a group of ten dogs were given daily injections of forty mg. histamine base in beeswax for four weeks beginning six weeks postoperatively. Five control dogs were treated similarly. All controls developed ulcers, two perforated, while the animals operated upon showed no evidence of ulceration at sacrifice. This series covers only ten postoperation weeks. It would be of great interest to know what the acid studies showed beyond this time with a series of gastric analyses to back it up. [5]

An identical operation has been performed on cats by Johnstone and is mentioned here to point out some of the variable responses between species. Thirty animals were operated upon, only seventeen of which survived beyond two months. Five of these gained weight, six maintained their weight, and six lost. The cats operated upon were subjected then to histamine stimulation. This first group was given twenty mg. in beeswax initially every day six days weekly. If the animals maintained their well being and weight the dose was increased until 75 mg. histamine was given daily. This was continued until the control cats, receiving the same dosages, died or were in extremis. When the controls died the operated cats were killed for examination.

Four cats, in which a two cm. of mucosa had been left at either antrum, showed no ulceration. One animal was left after operation with six cm. of mucosa at either end of the stomach; he died of perforated esophageal ulcer. Another animal left with six cm. of cardiac mucosa and three cm. of pyloric mucosa developed a perforated duodenal ulcer. In two cats the mucosa of the lesser curvature was left intact. Both died of perforated duodenal ulceration. Two cats having had gastrectomies with jejunal anastomosis developed

and died of stomach ulceration. All control cats died from peptic ulceration. Whether any outlived the experimental animals is not mentioned. It is also unclear about the condition of the five remaining cats operated upon.

Gastric analysis on cats, according to the author, is impractical due to contamination by saliva and intestinal juice. There is indication, however, that the experimental cats were much more ulcer resistant than were the control cats. It is also apparent that postoperative gastric dilatation is less in cats than in dogs with this procedure.[6]

Longmire, Lippman, et al have been using a technique of mucosal excision on dogs and cats, the basic concept of which takes origin from the work of Howes. Howes while investigating the role of mucus cells in the production of gastric carcinoma had been causing gastric hypochlorhydria in his experimental cats. He did this by causing ischemic injury to the gastric mucosa in the presence of hydrochloric acid. A differential response was noted on the cellular level. Pepsin producing serous cells and acid producing parietal cells were more affected than the basophilic mucus secreting chief cells. Thus in the face of early regeneration a predominantly mucus secreting epithelium was

produced which resulted in a relative gastric hypochlorhydria. Although this hypochlorhydria was present one month after injury, one year later the animals produced gastric juice with a pH ranging from 1.5 to 2.5 in response to histamine stimulation. Thus the early predominance of a mucus secreting epithelium is transient, relative to the slower regeneration of the more specialized acid secreting cells.[7]

In 1952 Longmire and associates attempted to refine, promote, and make permanent this type of regeneration. Thus although this procedure employs gastric mucosal excision, it must also be classed, at least partly, under alteration of the gastric mucosa since this is the desired result. First using six dogs and later fifteen cats, the stomach was entered in the longitudinal axis approximately two cm. from and parallel to the greater curvature. The mucosal layer was then stripped from the muscular wall with the exception of a small area about the pyloris and cardia. Stripping was done with blunt and sharp disection, and the wound then closed. In addition to this, a gastrojejunostomy was done on two of the cats.

In dogs it was possible to remove with relative ease between seventy and ninety percent of mucosa. The plane of cleavage runs just superficial to the

muscularis mucosa, this organ being left essentially intact. It is noted however that the bases of glandular foveolae penetrate the muscularis mucosa making it impossible to remove all the glandular elements without removing the muscularis. To leave these glandular elements behind results in complete regeneration of a normal gastric mucosa in approximately twenty-one days. To remove the muscularis mucosa and thus all glandular elements results in fatal contraction of the stomach, often, and at least the destruction of the gastric reservoir.

The regenerative powers of the gastric mucosa in cats was found to be virtually non-existant. Many of the animals died, and those that did live had severely scarred and contracted gastric walls. The cleavage line for the gastric stripping, like in the dogs, was found to be superficial to the muscularis mucosa; unlike the dog, however, no glandular elements penetrated this structure. No doubt, this accounts greatly for the failure of denuded areas to be re-epithelialized, but even so there was little advance of new tissue from intact mucosal borders in the cat. This was not found to be true in dogs. Ivy has made the distinction that ulcers result when mucosal destruction is deep enough to remove all mucosal elements and penetrate the mus-

cularis. This causes granulation and scarring. If tissue destruction is not this deep, the lesion is an erosion.

At this point the authors speak of studies of the gastric acidity of these animals, but no data is given. Later in 1956 the second article was published. At that time the study had been carried on long enough for a good follow up study. The data given is from dogs only.

Since the object was to cause regeneration of a non-acid secreting, or relatively so, gastric mucosa, the stripping of mucosa was not carried beyond the muscularis mucosa. Gross and histologic regeneration was complete in three to eleven weeks. Within twenty-one days mucosal regeneration was usually complete, but without folds. Some small irregularity in mucosal folds seemed to be permanent. Microscopically there was a moderate irregularity of the mucosal glandular pattern, but over all there was a normal distribution and variety of cells; parietal cells were abundant.

The information gathered on nineteen experimental dogs over a twenty month period concerning their gastric analysis is quite extensive. The volume of gastric juice excreted over a thirty minute period after histamine stimulation one month post-operative was less

than twenty cc. This value rose to forty cc. by the eighth month post-operation where it remained throughout twelve more months. The control animals excreted an average of sixty cc. of gastric juices.

The mucus content of the gastric juice one month following operation was just over an average of forty percent. Over a twelve month period this fell gradually to a level of eight percent where it held steady. The control animals averaged a four percent mucus content over the same twenty month period.

The pH of gastric juice one month after operation was slightly more than six. This fell sharply by the third month to approximately a pH of three. From here it fell slowly to hold at a pH of 1.8 some sixteen months after operation. The control averaged a pH of 1.4 for the same twenty month period.

The free acid content of the gastric juice one month post-operation was zero. From here it climbed by the fourteenth month to level off at 60 mEq./L of hydrochloric, while the control animals averaged approximately 83 mEq. of hydrochloric acid per liter of gastric juice.

The pepsin content of the gastric juice one month after operation was six mg. per cubic cm. of gastric juice. Over the twenty month follow-up period the

values increased steadily and at the time of reporting had reached an average value of 25 mg./cc. The control average was 22 mg./cc. during this period.

Parallel to these results a series of figures are given which were obtained from dogs which not only had undergone mucosal stripping but also had vagotomy. These dogs were then compared with vagotomy only controls. In all instances vagotomy alone had a greater effect than mucosal stripping alone, and the total effect in combination the greatest effect.[8]

Having now covered that experimentation which involves excision, replacement of acid secreting mucosa with non-acid secreting mucosa is of consideration next.

Longmire and Lippman were also pioneers in this type of procedure. In 1954 their operations on fourteen dogs were performed thus: The stomach was entered through a 10 cm. incision in the body of the organ, 2 cm. from and parallel to the greater curvature. From thirty to ninety percent of the mucosa was stripped from the stomach in a plane just superficial to the muscularis mucosa. Then a 10 to 20 cm. segment of jejunum was resected at a point 10 to 20 cm. from the duodenojejunal juncture. The segment was divided longitudinally along its antimesenteric border. The mucosa and submucosa were separated as one layer and taken from the

muscularis and serosa. This then formed a free graft 8 to 15 cm. by 3 to 8 cm. It was placed to cover the defect of stripped gastric mucosa. It was secured to the bed with a running 4-0 chromic suture about the border. Interrupted 4-0 chromic sutures were placed variously through the body of the graft. Several small incisions were then made in the graft for drainage. After closure pressure was maintained on the graft by means of an inflated rubber balloon. Pressure was controlled by a tube brought out through a gastrostomy wound. An entero-anastomosis re-established the continuity of the small bowel.

Only five of the fourteen animals survived. One survivor was operated upon again two weeks after primary surgery and a biopsy taken through the graft site. Three weeks later this animal was sacrificed. A second animal was killed ten weeks after operation, the rest of them three months after operation.

Two weeks after operation there was evidence of early mucosal regeneration, the epithelium appearing basophilic with no evidence of parietal cells. At five weeks parietal cells still were not seen and the mucosa in some areas vaguely suggested jejunal epithelium. At ten weeks there was definite growth of jejunal mucosa. There was some patchy regeneration of

gastric mucosa with parietal cells withing the graft site, and occasional gastric glands were present between jejunal glands. Three months after operation mature jejunal villi were seen in strips measuring up to 9 or 10 mm. long. Small islands of regenerated gastric mucosa would separate these strips.[9] No ulceration of grafted jejunal mucosa was reported.

No gastric acid studies are reported in this thesis. It can be easily seen, however, that the procedure has not only reduced the original parietal cell mass but has replaced it with mucus secreting epithelium. This then would result in increased nutrilization and dilution of the gastric juices.

In 1956 Free, Mannix and Beal performed a very similar operation; however rather than using jejunal mucosa for the free graft these men used split thickness skin grafts taken from the anterior abdominal wall. The procedure was performed on fourteen dogs, nine of which lived. Five died during the operation or in the first twenty-four hours post-operation. Biopsies taken between the third and seventh week showed the presence of viable white skin. There was no evidence of contracture. The percentage of viable graft varied from one percent in four animals to twenty-five to eighty percent in the remainder.

Biopsy demonstrated in the first four dogs, whose grafts ranged between 0.020 and 0.025 of an inch in thickness, that subepithelial cysts including hair follicles, sweat glands, and sebaceous glands were present. This no doubt accounted for a portion of the poor "take." The rest of the animals were given thinner grafts, increasing the amount of "take" although not greatly in some cases. There was no gross or microscopic evidence of digestion or ulceration on the grafts.

Here again, motion of the recipient bed has been a problem. The authors have employed vagotomy to reduce the gastric peristaltic waves. Also the pressure balloon was used. Longmire and Lippman felt that gastric dilatation occurring with the pressure balloon caused their high mortality.[10] Though aware of this the authors make no comment, feeling that the balloon was necessary to approximate the graft to the concave gastric wall and to assist hemostasis.

No studies of the gastric secretions were made.[11]

Beal and associates published a second article in 1959 reporting that they operated on thirty-one dogs, in the previously explained manner, of which twenty-two lived. Initially there was a graft take of from zero to eighty percent. The average was fifteen percent. A group of these dogs were followed over a seven month

period, and only two were found to have persistant epithelial element and in these only fragments of skin remeined. Vagotomy and pyloroplasty did not improve the graft "takes."

Owing to the poor results on dogs, the authors next subjected twenty-one young pigs to the procedure of gastric mucosal stripping. Only nine pigs survived. They reported that Nembutol sensitivity caused the high mortality. In eight of these pigs the average graft "take" was forty-five percent. There was a slough of the graft in the ninth pig evidentally due to the formation of a hematoma beneath. In those which took, there was a sharp line of demarcation between gastric mucosa and the grafted skin. Where grafted skin did not cover the stripped gastric wall the area was covered by fiberous tissue and inflammatory cells with mild contraction. The grafts did not show evidence of digestion or ulceration and appeared to be adherent to the underlying submucosa without inflammatory reaction.[12]

A major factor responsible for the canine failures is the difficulty of removing all the gastric mucosal elements. To do so results in extensive contraction. Pigs, on the other hand, do not share this regenerative capacity, nor do they show the degree of contraction after a complete stripping. If the failure to regener-

ate the mucosa and the lesser degree of contraction after a complete stripping assist in the "taking" of a graft, as figures tend to indicate, then the future of the procedure looks better for use in man, since man shares these characteristics with the pig. Any application to man, however, is yet remote since many technical difficulties remain to be overcome. Also the effects on gastric acidity in the experimental animals have not been investigated. The authors are absorbed in perfecting the procedure and have not looked to see if their goals are being achieved.

Another major method of reducing gastric acidity concerns the use of X-rays. The effect is to alter the function of the existing cellular components. These effects of X-rays upon gastric acidity were studied by Ivy[13] as long ago as 1923. Doses, 160 percent of a dog's erythema dose (400 percent of a human's), were used, and gastric secretory response was abolished - all acid disappearing, the free acid being absent three weeks. Six weeks after exposure the acidity returned to normal. The acid secreting glands were found to be forty percent of a dog's erythema dose more sensative than the mucous glands. The acid cells underwent atrophy, while the mucous cells were not greatly affected. Dawson states that the chief cells undergo cytolysis while parietal

cells are not as readily broken down.[14] In a careful study of serial histological gastric response to radiation, Goldgraber and associates found the changes patchy in nature. Coagulation necrosis to the depth of the fundal glands involving all cells was the first change. At the peak of the process there was partial to complete loss of glandular substance with mucosal thinning and edematous interstitial tissue. There was also a chronic inflammatory infiltration with marked changes in the superficial epithelium.[15] Shell and Bollman found that in dogs any lasting reduction in gastric acidity required dosages of Reontgen rays just short of the amount which would produce fatal cachexia.[16]

In the largest reported series concerning humans, 800 cases, a greater incidence of post radiation achlorhydria was found in patients with gastric ulcer than in those with duodenal or jejunal ulcers. The time length of acid depression proved to be very irregular, in some individuals lasting a few days, and in others eight months.[17]

Decrease in gastric acidity achieved with the use of X-rays is generally transient, lasting for unpredictable periods of time. This improvement may be related not only to chief cell damage but to factors such as alteration of neutralizing buffer secretion and the

relief of pylorospasm. As yet X-ray therapy is primarily useful in cases of intractable pain, where operation has failed and in stopping unfavorable progress so that conventional forms of treatment may gain a foothold. Its use has not proved successful in the production of a permanent hypochlorhydria. [18]

Also within this category of "alteration of cellular structure" it is necessary to mention a field of research which has developed a hypochlorhydria. In the search for the cause of gastric carcinoma many workers have been producing atrophic gastritis in dogs and other animals by means of injecting an extract of human gastric juice. The purpose of this research is to isolate a substance in human gastric juice which is responsible for gastric carcinoma. There has been no success yet; however it has been possible to produce a permanent atrophic gastritis in Heidenhian pouches in dogs. Essentially an inhabition of parietal cells results which should in turn produce a hypochlorhydria. Since these investigations have not been directed this way, no testing of the acid secretory powers on these preparations has been made. [19]

III. RESEARCH PROJECT

It has been pointed out in previous discussion that the incidence of peptic ulcer is high and is spread throughout the world population. Present methods of treatment for this condition are good, and the results, in the majority of cases, are excellent. Nevertheless, treatment is not perfect. A simpler, more effective treatment would be welcome. Therefore this study and evaluation of a new approach has been made.

The various methods of treatment which have been discussed, those in common usage and those experimental ones, have a common goal. This goal is the reduction of gastric acidity. This reduction has been accomplished by blocking the function of the gastric mucosa or removing and destroying it. The aim of the procedure to be discussed here is not unique, but the direction of approach is different.

Phenol, the standard tissue preservative, was chosen as the agent to be used for the destruction of the gastric mucosa. The choice was made because of these advantages: (1) Tissue contacted by phenol is fixed, and complete death results; (2) Phenol, because of its very nature, is sterile; (3) Phenol is easily obtainable at minimal expense.

The early phase of this project was carried out on dogs. These animals were used because they stand up well under the stress of operation and because more information is available in current literature about the use of dogs. Guinea pigs were chosen as the animals to be used in the second portion of the project. This choice was made on the basis of reports in the current literature stating the ease with which gastric analysis could be done on unanesthetized guinea pigs.[20]

Four dogs were used in the first phase. They were prepared thirty minutes prior to operation with atropine 1/150 gr. and morphine sulfate 1/4 gr. intra-muscular. Surgical anesthesia for the procedure was obtained with intravenous Nembutol, sixty mg. per five pounds of body weight. The anterior abdominal wall was then shaved, prepared, and draped using standard sterile techniques. A skin incision was made just lateral to the midline extending from the xiphoid process to the level of the umbilicus. The peritoneal cavity was then entered through a pararectus incision.

Just prior to the administration of Nembutol anesthesia, and approximately thirty minutes after the administration of atropine and morphine sulfate Histolog U.S.P. was given to promote maximum gastric secretory activity. The dosage given was the amount

recommended for humans. This dose was five mg. per kg. of body weight, given intra-muscular. Thirty minutes after the injection of Histolog a single sample of gastric secretion was taken. This was obtained through a nasogastric tube which was placed in the stomach during surgical anesthesia and prior to incision with the aid of direct laryngoscopy. This sample of gastric secretion was taken for a control base line.

When the gastric sample had been drawn, the abdomen was entered as previously described, and the stomach identified. The gastroesophageal and gastroduodenal junctions were identified. The posterior mesenteric attachments were incised at these locations and Penrose drains were placed loosely about the junctions. A gastric biopsy was then taken from the anterior gastric wall. A purse-string suture of 0 chromic cat gut was placed about the defect. In dog number one only a five cc. Foly catheter was introduced into the stomach through the wound, the bag inflated, and the purse-string suture drawn tight about the catheter. The placement of the Foly catheter was omitted in later operations.

With the catheter secure in dog number one the Penrose drains were drawn tight to occlude the stomach from below and above. At this point Phenol solution

was put into the stomach via the catheter. The Phenol was then removed in the same manner and the stomach was washed with tap water through the catheter. The catheter was then removed and the wound closed by a purse-string suture with inverting interrupted silk sutures. The Penrose ligatures about the cardia and pyloris were loosened and removed.

In dogs number two and three the biopsy was taken as indicated and the defect closed immediately, without insertion of the catheter. The Phenol solution in these animals was introduced into the stomach through the nasogastric tube. This was the only variation from the procedure as described for dog number one.

Dog number four was treated differently. When a gastric analysis was done on the above preparations, general anesthesia was required to pass the nasogastric tube. It has been reported that general anesthesia, particularly Nembutol anesthesia, may result in as much as a forty percent decrease in the secretory activity of the gastric mucosa. In order to avoid this factor, two operations were performed on dog number four. The first operation was a gastrostomy. A six by ten cm. flap of anterior gastric wall was formed into a tube with running inverting mattress sutures. The formed tube was then brought to the outside through a stab

wound in the right upper quadrent where it was sutured to the skin.

When healing had occurred, a series of base line gastric analyses were performed under histamine stimulation without anesthesia for a control. After these were accomplished, the second operation was performed. This consisted of entering the abdomen, occluding the stomach as previously described, and introducing phenol solution through the gastrostomy. The phenol was then withdrawn and the stomach washed with tap water. Again when healing had occurred, acid analyses of the gastric secretion by Histolog stimulation were done under the same conditions as prior to the phenol instillation and without anesthesia. (See statistics and Graphs 1 and 2.)

Layer closures were done on all dogs. O chromic interrupted sutures were used on the facial planes. The skin was closed in all cases with subcuticular stitches. No bandages were placed over the wounds. At the time of operation and three days post-operatively the dogs were given 500,000 U. aureomycin and 500,000 U. streptomycin.

The animals were allowed only water for the first twenty-four post-operative hours. Thereafter they were given water soaked half rations of Purina Dog

Chow for three days. During this time they were confined to their cages and not allowed any exercise beyond standing. At the end of this four day period the dogs were allowed to go into the dog run for exercise and were started on full rations of dry Chow.

RESULTS AND STASTICS

Titration of gastric juice samples were done using the technique described by Miller.[21] Acidity was expressed in clinical degrees, that amount of 0.1 N sodium hydroxide necessary to neutralize the acid present in 100 cc. of fluid.

Dog Number One:

Date of operation: January 10, 1961
Weight - 36.5 pounds
Anesthesia - Nembutol 1 gr./5 lb. Atropine 1/150gr.IM
Gastric Stimulation - Histolog 0.2cc. IM
Gastric Analysis prior to phenol: Free 55° Total 91°
Phenol instilled into stomach: 1% solution for three minutes

Follow up Gastric Analyses:

Date: January 21, 1961
Weight - 36 pounds
Anesthesia - Nembutol 1 gr./5 lb. at time of stimulation IV
Atropine 1/150 gr. IM
Stimulation - Histolog 0.2cc. IM
Gastric analysis: Free 0° Total 45° at thirty minutes

Date: February 6, 1961
Weight - 47.5 pounds
Anesthesia - Nembutol 1 gr./5 lb. at time of stimulation IV
Atropine 1/150 gr. IM
Stimulation - Histolog 0.25cc. IM
Gastric Analysis: Free 10° Total 30° at thirty minutes.

Date: March 9, 1961
Weight - 39 pounds
Anesthesia - Nembutol 1 gr./5 kg. thirty minutes after stimulation IV
Stimulation - Histolog 0.2cc. IM
Gastric Analysis: Free 2° Total 103° at thirty minutes

Date: March 23, 1961
Weight - 40 pounds
Anesthesia - Nembutol 1 gr./5 kg. thirty minutes after stimulation IV
Stimulation - Histolog 0.3cc. IM
Gastric Analysis: Free 95° Total 101° at thirty minutes

Dog Number Two:

This animal died ten days after operated. No studies were performed. Death resulted from exsanguination secondary to wound dehiscence.

Dog Number Three:

Date of operation - February 6, 1961
Weight - 42 pounds
Anesthesia - Nembutol 1 gr./5 lb. given at time of stimulation IV Atropine 1/150gr.IM
Stimulation - Histolog 0.2cc. IM
Gastric Analysis prior to phenol: Free 11.5° Total 30° at thirty minutes
Phenol instilled into stomach - 5% solution for three minutes

Follow up gastric analyses:
Date: March 7, 1961
Weight - 42 pounds
Anesthesia - Nembutol 1 gr./5 lb. given at time of stimulation IV Atropine omitted.
Stimulation - Histolog 0.2cc. IM
Gastric Analysis at thirty minutes: Free 4° Total 100°

Date: March 17, 1961
Weight - 42 pounds
Anesthesia - Nembutol 1 gr./5 lb. given thirty minutes after stimulation IV
Atropine omitted

Stimulation - Histolog 0.2cc. IM
Gastric Analysis at thirty minutes: Free 31°
Total 44°

Date: March 24, 1961
Weight - 41 pounds
Anesthesia - Nembutol 1 gr./5 lb. given thirty minutes after stimulation
Atropine omitted
Stimulation - Histolog 0.25cc. IM
Gastric analysis at thirty minutes: Free 14°
Total 24°

Dog Number Four:

Date of operation - February 24, 1961
Gastrostomy performed
Weight - 60 pounds
Anesthesia - Nembutol 1 gr./5 lb. IV
Atropine 1/150 gr. IM
Morphine sulfate 1/4 gr. IM
Stimulation - none
Gastric analysis: none

Follow up gastric analysis prior to phenol introduction:
Date: March 7, 1961
Weight - 55.5 pounds
Anesthesia - none
Stimulation - Histolog 0.3cc. IM
Gastric analysis:

Before stimulation	Free 0°	Total 84°
15 min. after stimulation	Free 0°	Total 102°
30 min. after stimulation	Free 0°	Total 128°

Date: March 8, 1961
Weight - 55.5 pounds
Anesthesia - none
Stimulation - Histolog 0.3cc. IM
Gastric analysis:

Before stimulation	Free 27°	Total 76°
15 min. after stimulation	Free 24°	Total 63°
30 min. after stimulation	Free 38°	Total 80°
45 min. after stimulation	Free 56°	Total 82°
60 min. after stimulation	Free 39°	Total 64°

Date of operation: March 10, 1961 Procedure: instillation of phenol
Weight - 55 pounds
Anesthesia - Nembutol 1 gr./5 lb.
Stimulation - none
Gastric analysis: none

Follow up gastric analyses after phenol introduction:

Date: March 16, 1961
Weight - 55.5 pounds
Anesthesia - none
Stimulation - Histolog 0.5cc. IM
Gastric analysis:

Before stimulation	none	
15 min. after stimulation	Free 10°	Total 35°
30 min. after stimulation	Free 69°	Total 84°
45 min. after stimulation	Free 45°	Total 74°
60 min. after stimulation	Free 7°	Total 40°

Date: March 24, 1961
Weight - 54 pounds
Anesthesia - none
Stimulation - Histolog 0.25cc. IM
Gastric analysis:

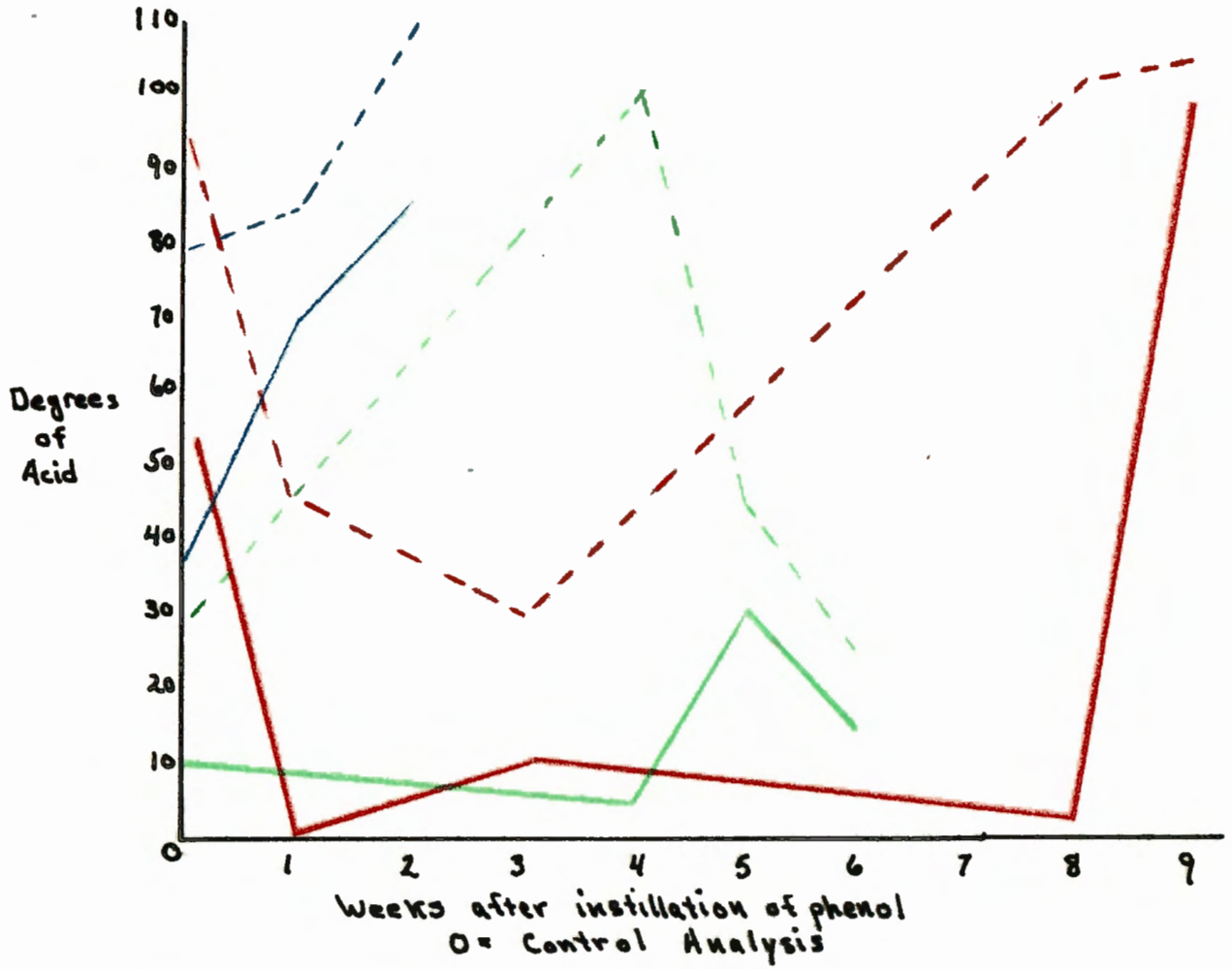
Before stimulation	Free 14°	Total 47°
15 min. after stimulation	Free 15°	Total 34°
30 min. after stimulation	Free 84°	Total 108°
45 min. after stimulation	Free 88°	Total 98°
60 min. after stimulation	Free 35°	Total 51°

For graphic illustration of the comparison of base line acidity to the acidity resulting after treatment with phenol, refer to Figure 1. Figure 2 is a graph of base line analyses and analyses taken after introduction of phenol in dog number four.

The second phase of the project dealing with guinea pigs is not completed, and reporting of statistics will be done later in an adendum.

Graph I

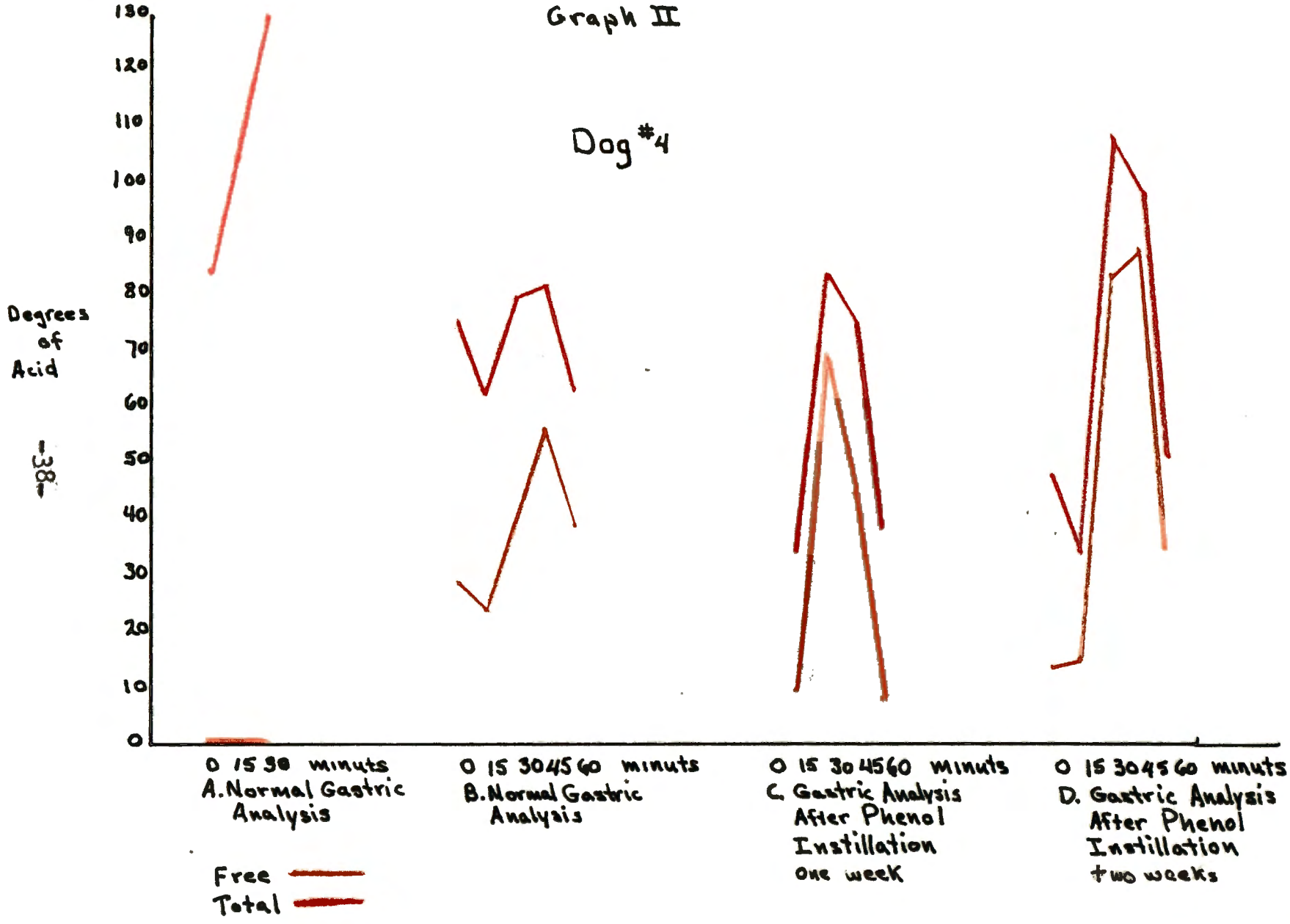
Serial Gastric Analyses



Dog #1 Red Dog #3 Green Dog #4 Blue Free —— Total - - - -

Graph II

Dog *4



IV. EVALUATION AND CONCLUSIONS

The graphs and tabulation of results show that a decrease in gastric acidity was obtained only transiently in dogs number one and three. The depression of acid in dog number three, even then, was only of the free portion. Perhaps this could be considered a transient effect, but unfortunately these reductions can be accounted for on other grounds. These dogs were given Atropine 1/150 grain and morphine sulfate 1/4 grain IM as preoperative anesthesia. Atropine is very effective in blocking the gastric secretions. On top of this, as was previously stated, Nembutol anesthesia will cause as much as a forty percent reduction in the gastric secretions. Since in these instances the drugs were given before histamine stimulation, they were certainly in full effect.

The comparison of tissue sections taken before and after treatment with phenol also throws light on the results. The second biopsy taken from dog number one was obtained almost five weeks after the instillation of one percent phenol for a period of three minutes. Comparison of these slides shows no gross variation. There was no evidence of fibroblastic activity or inflammatory cell infiltration. Any damage which may have resulted could not be detected histologically.

Gastric tissue was taken from dog number three at the time of death ten days after operation. This gastric mucosa had been subjected to five percent phenol for three minutes. Comparison of this and the first biopsy demonstrated dead and necrotic cells present in the second sample. This necrosis involved only one half to one millimeter of the gastric mucosa. This represents a destruction of approximately 1/4 of the total thickness of the mucosa. There was minimal fibroblastic activity and virtually no inflammatory infiltration.

The rise of gastric acidity, both free and total, in dog number four after phenol had been given is difficult to explain. It is doubtful that this is laboratory error. The response may well be explained on the basis of gastritis. The response may also be due to growing apprehension on the part of the dog.

A great deal of investigation is necessary to fully evaluate the use of phenol as an agent in the production of hypechlorhydria. The methods described failed to destroy the full thickness of the gastric mucosa. Stronger solutions should be used for longer periods of time. It is necessary to determine the uniformity of phenol penetration and cell death. What will result when all gastric mucosa is destroyed

in this manner? A slowed tissue reaction to the insult may result which will not end in contracture of the stomach. Regeneration of gastric mucosa may not be complete with this method. More important is the quality of the replacement tissue in the face of regeneration. It has been noted previously that parietal cell response differs from the response of the other cells comprising the gastric mucosa. Perhaps the regenerated or often damaged mucosa will be replaced with impotent epithelium which produces a decreased concentration of acid.

What effect if any will phenol have on the organism? Very small amounts of this agent if absorbed may cause death. This was avoided in the procedure through isolation and washing of the exposed tissues. However, exposure to stronger solutions over greater lengths of time may decide the issue. It is necessary to take biopsy specimens of liver, heart, kidney, adrenal glands, and pancreas. These tissues should be studied for any damaging effects. The long term effect of phenol irritation is not known. It is not known if denuded gastric wall or grafted tissues will be prone to develop carcinoma.

These and many more questions must be answered, not only about this procedure but those being tried

by other investigators, before this technique should be discarded.

V. SUMMARY

The Introduction reviews the incidence, distribution, and treatment, both medical and surgical, of the peptic ulcer. A new method which could produce a permanent hypochlorhydria by a relatively simple method has been studied.

The second portion of this paper is a review of the literature dealing with investigations of methods to reduce gastric acidity permanently. The techniques used all attempt to avoid reduction of the gastric pouch, nonphysiologic anastomoses, and the necessity of long term follow up treatment. These procedures are grouped in three classes: Excision of the gastric mucosa, alteration of the gastric mucosa, and replacement of the gastric mucosa. The methods and results of work in each classification are described. All methods have achieved reduced gastric acidity, in experimental animals.

The third section of this paper is a report and evaluation of a new experimental technique done at the University of Nebraska College of Medicine. The gastric

mucosa in a series of dogs was damaged using phenol. The method of phenol instillation is described. Resulting damage to the gastric mucosa is evaluated by a series of gastric acid analyses accomplished before and after the use of phenol. Tissue sections of the gastric mucosa taken before and after phenol damage are also described. Two graphs are presented which illustrate the findings. The paper ends with a discussion of the finding and the information still necessary for full evaluation.

I wish to thank the Department of Surgery of the University of Nebraska for their assistance in conducting this project. In particular, I want to thank Dr. John Porter for his help and guidance.

BIBLIOGRAPHY

1. Portis, S. H., Diseases of the digestive System, 2nd Ed. Lea and Febiger, pp. 196.

2. Paustian, F. F., M.D., Department of Internal Medicine of University of Nebraska College of Medicine, Gastroenterology Senior Lecture Series March 11, 1961.

3. Abbott, W. E. and others, The Etiology and Management of the Dumping Syndrome After a Gastroenterostomy or Subtotal Gastrectomy, Gastroenterology 39:12-27 (July) 1960.

4. Longmire, W. P.,Jr. and others, Studies in the Regeneration of gastric mucosa in the experimental animal, Surgery:32:384, 1952.

5. Williams, H. T. and others, Total Excision of Acid Secreting Gastric Mucosa in the Dog, Surgical Forum; Clinical Congress of the American College of Surgeons, Vol. 9 pp. 451-4, 1958.

6. Johnstone, F. R. C., Full Thickness Mucosal Excision in Cats with Prolonged Survival: Resistance to Nutamine induced ulceration, Surgical Forum, Vol. 9, pp. 446-450, 1958.

7. Howes, E. L., The Role of Mucous Cells in the Production of Gastric Neoplasms, J. National Cancer Institute 10:377, 1949.

8. Longmire, W. P.,Jr. and others, Studies in the Regeneration of gastric mucosa in the experimental animal, Surgery 32:384-394, 1952
Longmire, W. P.,Jr. and others, Further observations on the Return of Secretory Function Following Mucosal Stripping in the Dog, Surgery 40:212, 1956.

9. Lippman, H. N. and Longmire, W.P., Studies in the Transplantation of Free Jejunal Mucosa-Submucosa Autografts to the Mucosa Stripped Stomach of the Dog, Annals of Surgery 140:86, 1954.

10. Longmire, W. P., Jr. and others, Further observations on the Return of Secretory Function Following Mucosal Stripping in the Dog, Surgery 40:212-221 1956.

11. Beal, J. M. and others, Replacement of Gastric Mucosa with Autogenous Skin Grafts, Surgery 40 (3):554-559 (Sept.) 1956

12. Dineen, J. P. and others, Application of Autogenous Skin Grafts to the Gastric Wall, Surgery 45(2):251-257 (Feb.) 1959.

13. Ivy, A. C. and others, Studies on the effect of X-rays on Glandular Activity:The Effect on Gastric Secretion, Radiology 1:39, 1923.

14. Dawson, A. B., Histologic Changes in the Gastric Mucosal (Pawlow Pouch) of the Dog Following Irradiation, Am. J. Roentgenology 13:320, 1925.

15. Goldgraber, M. B. and others, The Early Gastric Response to Irradiation: A Serial Biopsy Study, Gastroenterology 27:1-21, 1954.

16. Bollman, J. L. and Snell, A. M., Gastric Secretion following Irradiation of the Exposed Stomach and Upper Abdominal Viscera by Roentgen Rays, Am. J. Digest. Dis. 1:164, 1934.

17. Richetts, W. E. and others, Peptic ulcer: An analysis of Results, Gastroenterology 11:789, 1948. Radiation Therapy in Peptic Ulcer: Study of Selected Cases, Gastroenterology 11:807-817, 1948.

18. McCullough, J. V., The effect of Roentgen Therapy Upon Gastric Acidity, A. M. A. Arch. Surgery 80:226-233 (Feb. 4) 1960.

19. Smith, W. O. and others, Experimental Gastritis (Atrophic) Associated with Inhibition of Parietal Cells, Transactions of the Assoc. of Am. Physicians 71:306-311 1958.

20. Watt, J.E. Gastric Acidity in the Guinea Pig, Quarterly J. of Experimental Physiology 40: 364-369, 1955.

21. Miller, Seward E.,M.D., A Textbook of Clinical Pathology, Williams and Wilkins Pub., 1955. 5th Ed., pp.1079-1080.