Henry Ford Hospital Medical Journal

Volume 8 | Number 3 Article 9

9-1960

An Experimental Study On The Action Of Bile In The Normal Dog And Its Protective Role In Dogs With Ulcerogenic Operation

Eduardo Camacho

AN EXPERIMENTAL STUDY ON THE ACTION OF BILE IN THE NORMAL DOG AND ITS PROTECTIVE ROLE IN DOGS WITH ULCEROGENIC OPERATION*

EDUARDO CAMACHO, M.D.**

INTRODUCTION

During the last 30 years duodenal ulceration has been the subject of extensive study, particularly in the field of experimental surgery. The amount of literature published on the subject reflects its importance. The divergence in approach to the problem and the variety of methods speak eloquently of the lack of adequate therapy.

This report is concerned with some experimental changes regarding the acidity of the gastric contents obtained with a new type of surgical procedure in the dog: a shunt operation to physiologically deviate the gallbladder bile to the stomach without disturbance of the anatomy or function of either gallbladder or stomach, and its effects on dogs with ulcerogenic operations. This work was completed at the Surgical Research Laboratories of the Henry Ford Hospital.

HISTORY

Bickel, as cited by Graves[1] in 1909, produced jejunal ulceration after gastro-jejunostomy on a dog, in which he ligated the common bile duct and produced a total biliary fistula by means of a cholecystostomy. In 1916, Gray[2,5,14] did the first experimental work on the action of bile on the gastric chemistry after cholecysto-gastrostomy was performed on 6 dogs. No changes were reported on the total acidity of the gastric contents. Babcock[3] in 1920, applied in humans the supposed virtue of bile to the treatment of peptic ulcer and suggested the use of this for persistant hyperacidity and pyloric spasm. He stated that, "contrary to general opinion, bile was a normal stomach fluid and played an important, but poorly recognized part, in gastric digestion; its entrance into the stomach is associated with the cessation of stomach activity and does not produce nausea or discomfort. Thus, at the completion of each period of digestion the pylorus normally relaxes, bile flows into the stomach neutralizing and permanently arresting the activity of the acid pepsin of the chyme. The antrum, which has felt the brunt of the irritation, is coated with a protective film of the alkaline mucilaginous film fluid and then the peristaltic movements of the stomach cease."

In 1923, Mann and Williamson[8], with the introduction of a method by which jejunal ulcers could be produced in the dog by the so-called "surgical duodenal drainage" or diversion of the duodenal contents to the lower small bowel, aroused great interest in the degree of protection afforded by duodenal secretions, especially bile, in peptic ulcer. In Russia, in 1923, Bogoraz[4] advocated cholecystogastrostomy as a means of controlling one of the principal conditions for the development of peptic ulceration; namely, the hyper-acidity of the gastric contents. His theory of attaining prolonged neutralization of acid contents by continuous flow of bile into

*Abridgement of a Thesis submitted to the Horace H. Rackham Graduate School, University of Michigan in partial fulfillment of the requirements for the Degree of Master of Science of Surgery.
**Division of General Surgery.

the end of the stomach was substantiated by the excellent results achieved by him on these 25 cases.

Nasarov[4], in 1926, published the results of 32 cases of cholecystogastrostomy at the 17th Congress of Russian Surgeons in Moscow. After operation these patients were free of symptoms. The gastric juice was analyzed at various periods during the next 1½ years. A decrease in gastric acidity and the constant presence of bile was found. One year later, on publishing results of subsequent laboratory studies done on these patients, Nazarov made a few points of practical inference regarding the outcome of the anastomosis and stressed the great tendency toward stenosis and constriction of the anastomotic site. He recommended that the anastomosis should be at least 2-3cm. in length to be sufficient and he reported cases of failure of the operation due to this factor.

Braithwaite[6], in 1926, reported 18 cases of cholecystogastrostomy with satisfactory results in the treatment of gastroduodenal ulcer. In the same year, Kapsinow[7] devised a method for exclusion of the bile from the intestine. This consisted essentially of an implantation of the fundas of the gallbladder transcortically into the pelvis of the right kidney, thus establishing a cholecysto-nephrostomy. Of 43 dogs prepared in this manner, 17 developed typical chronic gastroduodenal ulceration.

Houston and Jobling[9], in 1928, produced duodenal and gastric ulcers in dogs with biliary fistulae using a choledochostomy on 9 dogs. Seven of these developed duodenal ulcer and 2 of these 7 a concomitant gastric ulcer. The remaining 2 dogs died within the first 15 days without evidence of ulceration at that time. Berg and Jobling[9,11,12] in 1930 stressed once more the role of the biliary and hepatic factors in the experimental peptic ulcer. In 23 dogs with biliary fistula, some of which were complicated by liver damage, 13 developed ulceration. This led to the conclusion that one of the effects of biliary exclusion may be the disturbance of the regulatory mechanism of mucous secretions which exposed the surface epithelium to the action of the gastric juice. In 1934 Berg[11] studied the comparative frequency of ulceration after deprivation of bile and pancreatic juice in 16 dogs with pancreatic fistula. Of these, only one developed ulceration. He concluded, "The preponderance of evidence indicates that peptic ulcers develop more readily in dogs after exclusion of bile than after loss of pancreatic juice."

Ochsner[16], in 1934, stressed the importance of the bile as a protecting mechanism in the development of ulceration in a series of dogs with Pavlov and Heidenhain pouch formation and subsequent anastomosis of these pouches to the jejunum. Ulcers in the efferent loop of the anastomosis developed in 100 per cent of these; however, on anastomosing the gallbladder to these pouches the incidence was reduced from 100 to 43 per cent. Smith and Owings,[15] in 1935, after production of ulceration in 7 dogs with total biliary fistulae, re-operated and verted the biliary secretion over the area of ulceration. This resulted in the cure of 4 dogs.

The most recent study of the protective value of the alkaline duodenal juices in peptic ulceration was made by DeBakey.[17] In 1937, he reported the reuslts of four different groups of experiments with 60 dogs. In group one were 20 dogs with pyloric occlusion and anterior gastrojejunostomy. When the duodenal secretion was absent

from the anastomosis, 50 per cent of the dogs developed ulceration. In group two, of 10 dogs with the same preparation, after deviation of pancreatic juice to the ileum, 70 per cent developed ulcers in a period of 46 to 57 days. In group three, of 20 dogs with the same preparation and deviation of bile juices, 90 per cent developed an ulcer in one month. In the fourth group of 10 dogs, on which the previously mentioned preparation was utilized but with both bile and pancreatic juices absent, there was 100 per cent incidence of ulcer formation, with death of all the animals, from within the second postoperative week to 25 or 30 days.

McCann[10], in 1929, after gastrojejunostomy, brought into the fundus of the stomach the total of duodenal secretions and obtained ulcers in the jejunum in 80 per cent of 23 dogs. He showed in this experimental work the inability of duodenal secretion to control the acidity of the stomach. He concluded that the chemical characteristics of the gastric contents were unaltered and that the concentration of the acid that passed the pylorus remained the same or constant. He attributed the development of ulceration to the lower buffer power on pylorus and also to the mechanical action of the pyloric contraction over the place of jejunum just in front. Noteworthy at this point is the fact that Graves[1], in 1935, repeating the same experiment but diverting the secretions to the antrum instead of the fundus, found the ulceration did not occur. Maier[20] defied McCann's procedure by anastomosing the proximal cut end of jejunum to the fundus of the stomach with a side-to-side anastomosis. In anastomosing the pylorus to the jejunum both opposing ends were cut in angle to obtain a large stoma. In his series, only one jejunal ulcer developed.

Wilhelmj[19] poured the duodenal secretions into the stomach by creating a side-to-side anastomosis between the anterior gastric wall and almost all of the duodenum. This was performed in such a way that the latter virtually formed a part of the anterior wall. The Mann-Williamson procedure then was accomplished and in a series of 6 dogs no ulceration developed. Kesavalau and Mann[18], in 1943, on promoting the enterogastric drainage, were unable to reach any definite conclusions regarding the changes in the gastric acidity.

Little evidence exists concerning the effect of duodenal secretions on the gastric acidity in humans. Schmilinsky[21] is credited with the first attempt at total intragastric regurgitation. In 3 patients with jejunal ulcer following gastroenterostomy the results were distressing. There was perforation of the ulcer in one case and very severe gastristis in the others. Wangensteen,[18,20,21] in 1942, reported 3 cases in which he performed total intragastric regurgitation with development of ulcers in 2 of the 3. Later, in 1943, Braithwaite[6] reported follow-up results of his cases on whom he had performed cholecystogastrostomy. The abdomen was reopened 1½-2 years after surgery in 6 cases. In all of them the anastomosis was found to be closed. Reconstruction of the anastomosis relieved the symptoms in 6 out of 7. He claimed that 50 per cent of his anastomoses probably were closed at the end of 18 months.

In 1954, Farmer and Smithwick[22] reported 4 cases of subtotal gastrectomy and vagotomy in which a duodenostomy tube was used because of difficult duodenal stump closure. On study of the effect of partial exclusion of bile and pancreatic juice on the acidity of the gastric contents they found in one case that diversion of the bile

and pancreatic juice made a striking fall in pH. When duodenal suction was applied, it fell from 7 and 6 to 1.3 or 1.0, showing the influence of duodenal bile and pancreatic secretions upon acidity. In two other cases changes were slight but very definite. They concluded that the effect of duodenal regurgitation on the acidity of the gastric contents may be a decisive factor in the achievement of good results.

PROCEDURE

Our animals were kept in clean cages designed for them. All the dogs were healthy mongrel type, both male and female. They were kept fasting for a period of 5 days prior to operation and were allowed to have only water the day of surgical procedure, in order to assure an empty stomach. Anesthesia employed was Nembutal intraperitoneally with a dosage of 50 mg. per Kg. At the time of surgery 500cc. dextrose saline solution was given routinely with penicillin (400,000 units per day) for a period of three days after surgery to avoid complication, especially pneumonia. The dog was allowed to have water 24 hours postoperatively and one can of commercial dog food in 48 hours. They were allowed to have clean water at all times, except when fasting specimens were taken. The procedure in general was tolerated very well without any evidence of vomitus, diarrhea or weight loss.

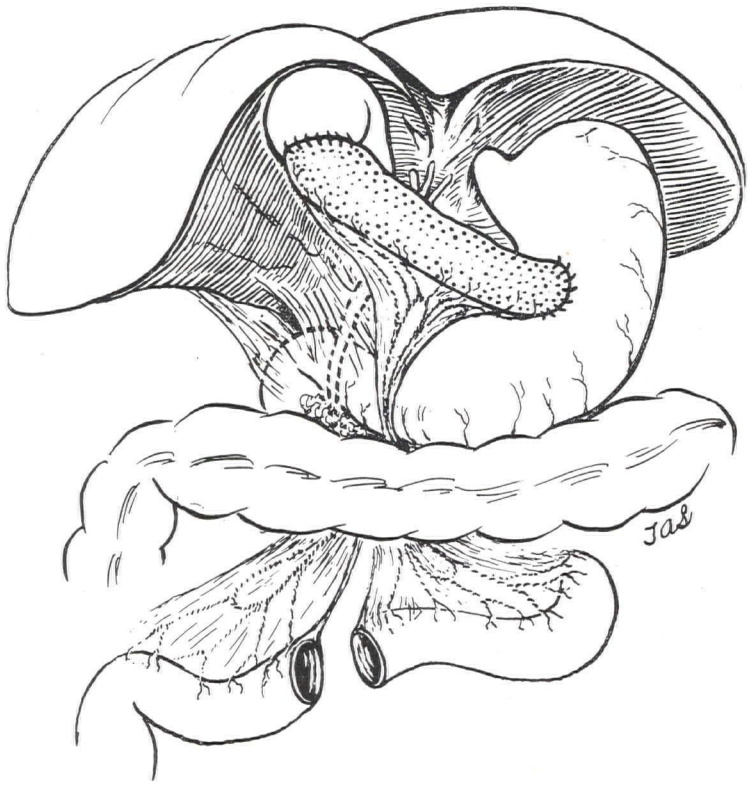

Figure 1

Jejunal segment connecting gallbladder and stomach. The segment keeps the original blood and nerve supply.

The operation consisted essentially of a cholecystogastromy with an interposed segment of jejunum isolated with its own blood supply and innervation (Fig. 1). This was arranged in peristaltic fashion from the gallbladder to the stomach and described in a preliminary report by Barron and co-workers[24] in 1958. This jejunal loop was taken, in all cases, from a distance of 10cm. distal to the duodenojejunal junction. By performing this procedure we endeavored to: (1) eliminate tension on anastomotic lines of suturing, since the length of the loop permits an easy-to-do anastomosis on either side. (2) avoid disturbance of the anatomical location of the organs involved. (3) prevent food particles or any gastric contents from reaching the gallbladder cavity. This was essential to avoid cholangitis, obstruction and liver abscess so common in cholecystogastrostomy as described by Beaver[14] in his experimental work, and (4) permit drainage of alkaline secretions into the duodenal area. Twenty dogs were operated upon and all were allowed to recuperate for a period of at least 20 days. A Dragstedt-Ellis cannula then was inserted in 14 dogs. Of the 14 dogs 4 died prior to any obtaining of postoperative specimens. The remaining 10 dogs lived for a period of 20 days to 2 years (Table I).

Table I

DOG	CONDITION	TIME	LOOP	LENGTH	ANASTOMOSIS	PH	FREE HCL	TOTAL ACID
No. 601	Sacrificed	one year	Isoperistalsis	30 ctms.	Body of Gallbladder to Fundus of stomach	5.5	None	40
No. 603	Sacrificed	six months	Isoperistalsis	15 ctms.	Body of Gallbladder to Fundus of stomach	4.5	12-16	50
No. 610	Sacrificed	five months	Isoperistalsis	10 ctms.	Fundus of Gallbladder to Body of stomach	5	0-20	50
No. 611	Death Distemper	one month	Isoperistalsis	15 ctms.	Body of Gallbladder to Fundus of stomach	5.5	None	40
No. 615	Sacrificed	ten weeks	Isoperistalsis	10 ctms.	Fundus of Gallbladder to Body of stomach	1.5	40-50	60-80
No. 616	Sacrificed	two years	Isoperistalsis	25 ctms.	Body of Gallbladder to Body of stomach	4	Occasional 12-20	50
No. 618	Sacrificed	one year	Isoperistalsis	15 ctms.	Body of Gallbladder to Antrum of stomach	5.5	None	40
No. 624	Sacrificed	two years	Isoperistalsis	15 ctms.	Fundus of Gallbladder to Fundus of stomach	4.5	Occasional 0-12	50
No. 625	Death Gastrostomy Leakage	three weeks	Isoperistalsis	15 ctms.	Fundus of Gallbladder to Antrum of stomach	5	None	40
No. 628	Death Pneumonia	three weeks	Isoperistalsis	15 ctms.	Fundus of Gallbladder to Antrum of stomach	4	Occasional 12-30	50

Table I

Survival of dogs with Dragstedt-Ellis cannula.

RESULTS

A minumum of 200 specimens taken during fasting conditions were obtained and showed reduction on the acidity of the gastric contents, with a pH as illustrated by dog No. 601 (Fig. 2). Of these 10 dogs, 4 were sacrificed, 2 at 5 and 6 months

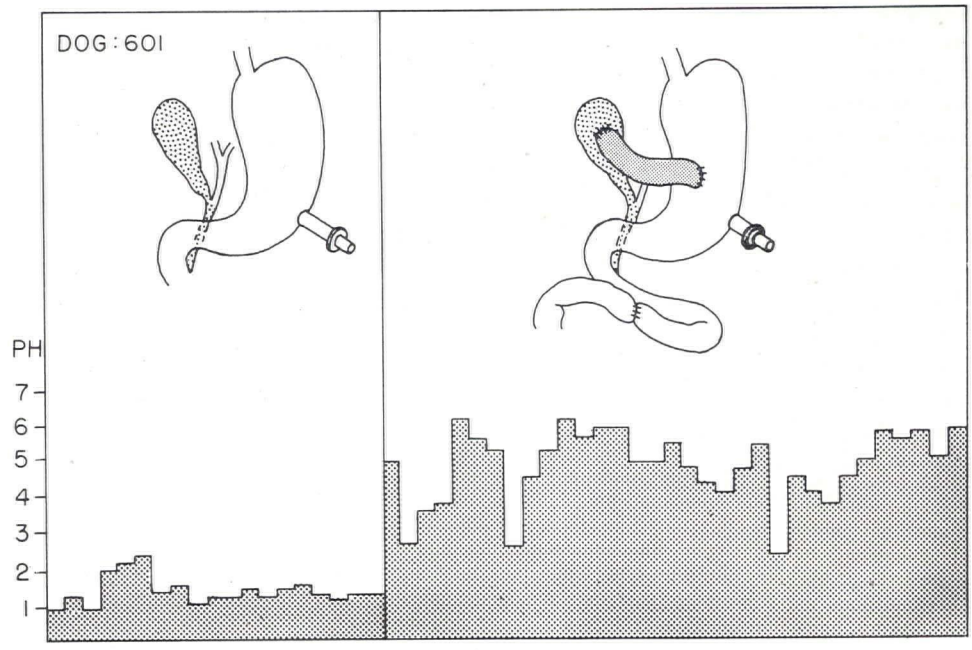

Figure 2

The changes on the pH are best illustrated by Dog 601. Notice the reduction on the acidity of the gastric contents.

respectively, and 2 at a year and 2 at 2 years. There was only one in our series with no results in which complete occlusion of the jejunal loop due to adhesions made impossible the flow of bile through the loop into the stomach. One death occurred from distemper and 2 more of pneumonia and leakage from the gastrostomy with localized peritonitis. In all 10 cases, isoperistalsis anastomosis was accomplished. The site of anastomosis and length of the loop was varied in order to evaluate any differences in results. (Table I). From the overall results there does not seem to be any difference as far as the gastric chemistry is concerned.

The function of the gallbladder was tested on 7 dogs. Cholecystographic studies were obtained on these animals, 4 of them with Telepaque at doses of 1.5 Gm. (iodopanoic acid) orally. The gallbladder shadow was obtained and visualized in a 12 hour period on 4 cases. In 3 cases, cholographin was used. This study demonstrates that the gallbladder still functioned normally after the anastomosis to the jejunal loop (Fig. 3).

At autopsy, special attention was directed toward the possible presence of abscesses of the liver, particles of food in the gallbladder, patency of anastomoses, evidence of changes in mucosa and evidence of ulceration in the jejunum. The anastomoses were evaluated for evidence of stenosis or obstruction. No ulceration was found in the jejunal loop or in the duodenum; no abscesses were found in the gallbladder or ulceration in biliary ducts or liver. No stenosis or obstruction found at the level of any anastomotic sites (Fig. 4).

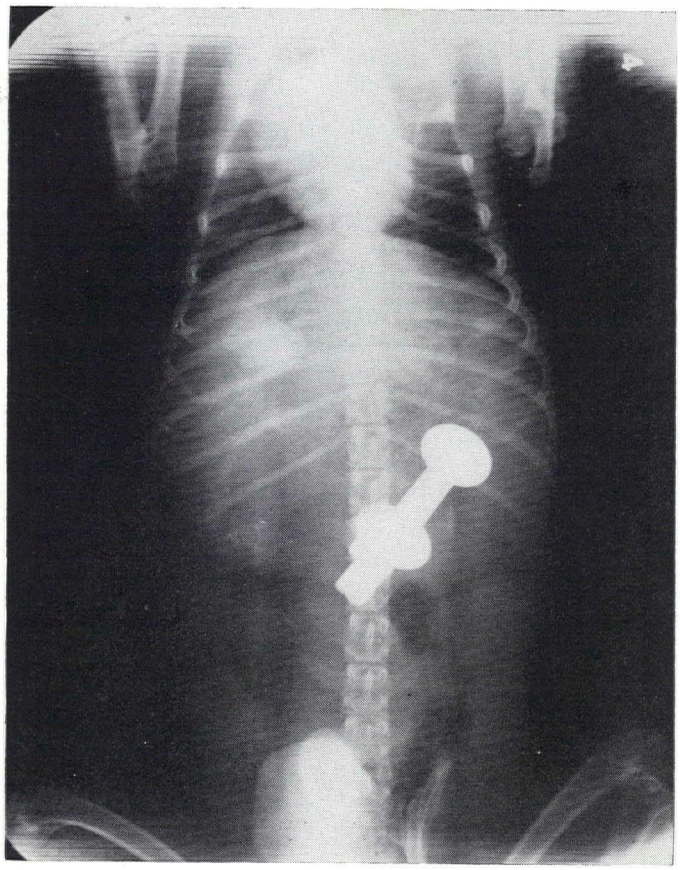

Figure 3

Cholographin visualization of the gallbladder two hours after intravenous injection. Some dye has been excreted into the bladder already.

After these results were obtained, a series of experiments were then undertaken in an effort to clarify the effects of bile transported in this fashion into the stomach of the Mann-Williamson dog. Twenty healthy mongrel dogs were used for this purpose, on whom 10 had the original Mann-Williamson procedure carried out. The second group of 10 had, in addition, the procedure described previously to divert the bile into the gastric cavity. Following recovery from surgery both groups received identical care and diet. Specimens were obtained for free hydrochloric acid determination and pH. Weight was recorded prior to surgery and daily after surgery for two weeks, then twice a week until the time of death.

In the first group (Mann-Williamson alone) there was steady recovery within the first week, during which time the dogs were able to eat and their general condition was satisfactory. Postoperative anorexia appeared the second week and by the third week there was a progressive weight loss noted. In some animals perforation of the ulceration occurred in the fourth week, while in others melena,

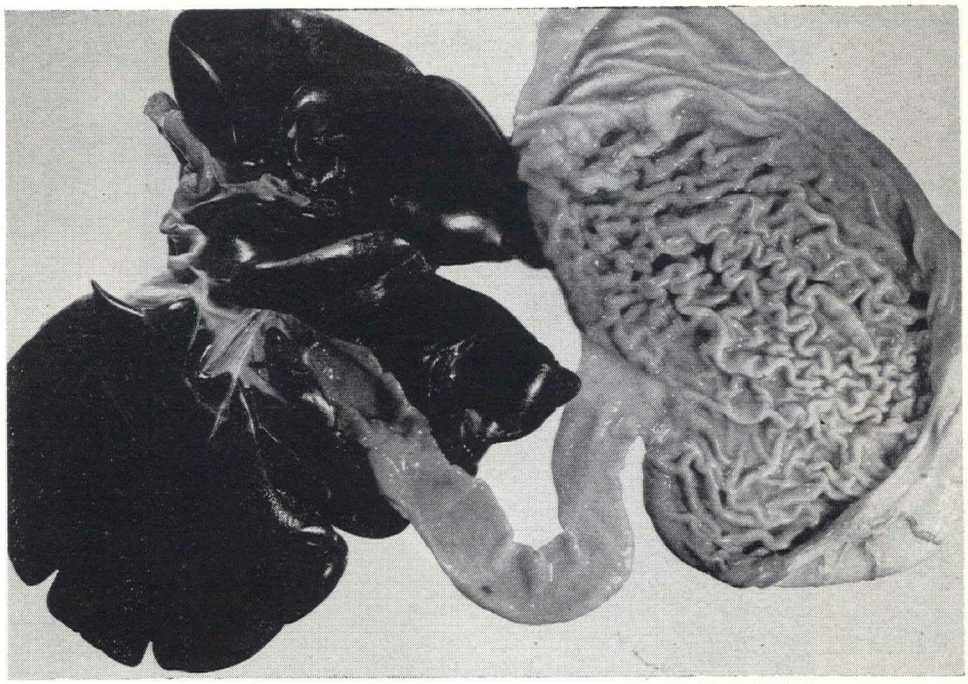

Figure 4

Dog 603. Sacrificed six months after operation; notice the absence of abscesses, stenosis or ulceration.

Table II

Group 1

Mann-Williamson

Dog No.	Anorexia	Weight Loss	Melena	Ulcer Perforation
622	10 days	15 days	25 days	30 days
667	7	10	12	15
668	10	15-20	25	25
671	10	18	20	23
672	10	15	20	36
675	10	10	25	34
689	10	15	25	34
708	7	Downhill with death at 14 days.		
710	5	Downhill course with death at 10 days.		
711	5	Downhill course with death at 11 days.		

Group 2

Mann-Williamson Bile Protection

Dog No.	Anorexia	Weight Loss	Melena	Ulcer Perforation
632	40 days	50 days	69 days	Ulcer perforation
636	40	45	53	Ulcer perforation
640	20	40	37	No ulcer
661	18	30	35	No ulcer
678	20	22	25	No ulcer
694	25	30	47	Ulcer perforation
697	25	30	47	Ulcer perforation
699	20	33	38	Ulcer perforation
706	20	30	34	No ulcer
709	20	30	32	No ulcer

Table II

Complications in the Mann-Williamson dog with and without bile protection.

diarrhea and exanguination followed in a period of 26 to 34 days (Table II).

In the second group, recovery was complete within the first week. Appetite was consistently good during the first month (Table II). Between the twenty-fifth and thirty-seventh postoperative day, 4 died without evidence of ulceration. Death from ulcer perforation occurred in others between the fifty-third and sixty-ninth day (Fig. 5, 6). In contrast to those of group one, weight loss, anorexia and melena did not occur in any of these animals until the fourth week.

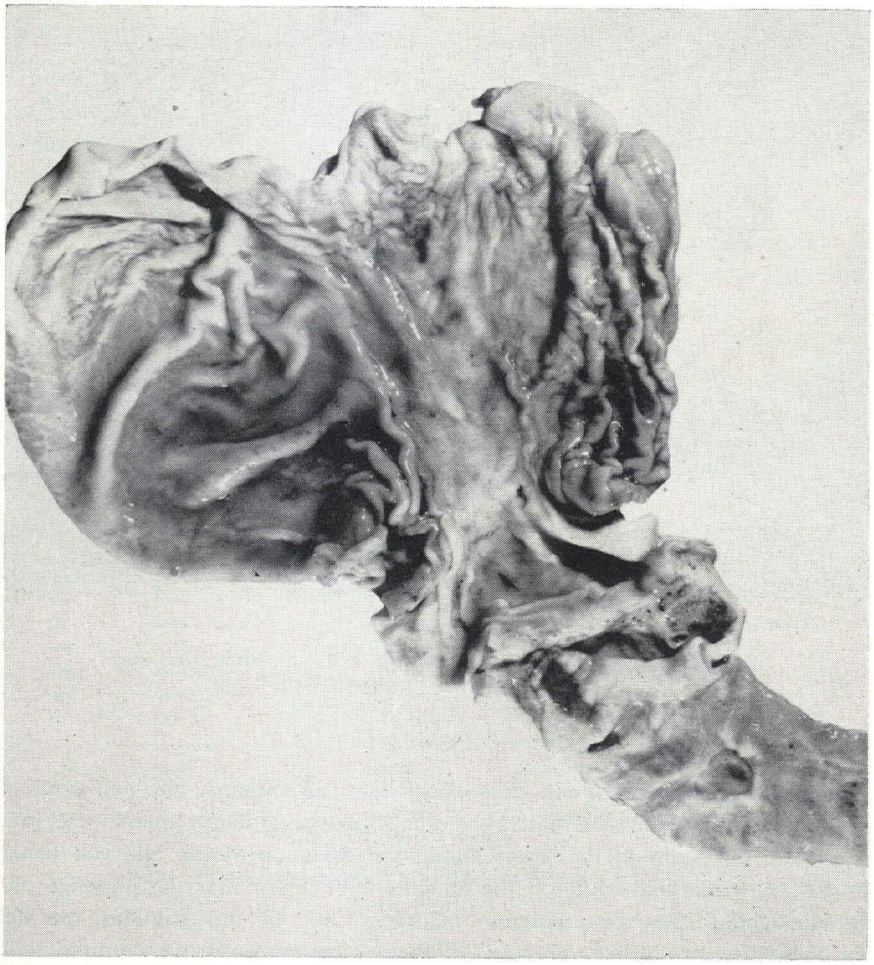

Figure 5

Dog 672. Mann-Williamson. Notice one stomal ulcer and one large jejunal ulceration 36 days after operation.

No appreciable difference in the pH was detected in either group, nor was any difference noted between the pH of these experimental animals and the average pH of the normal dog. These confirm the experimental findings of Friedman, Sandweiss, and Salztein.[25]

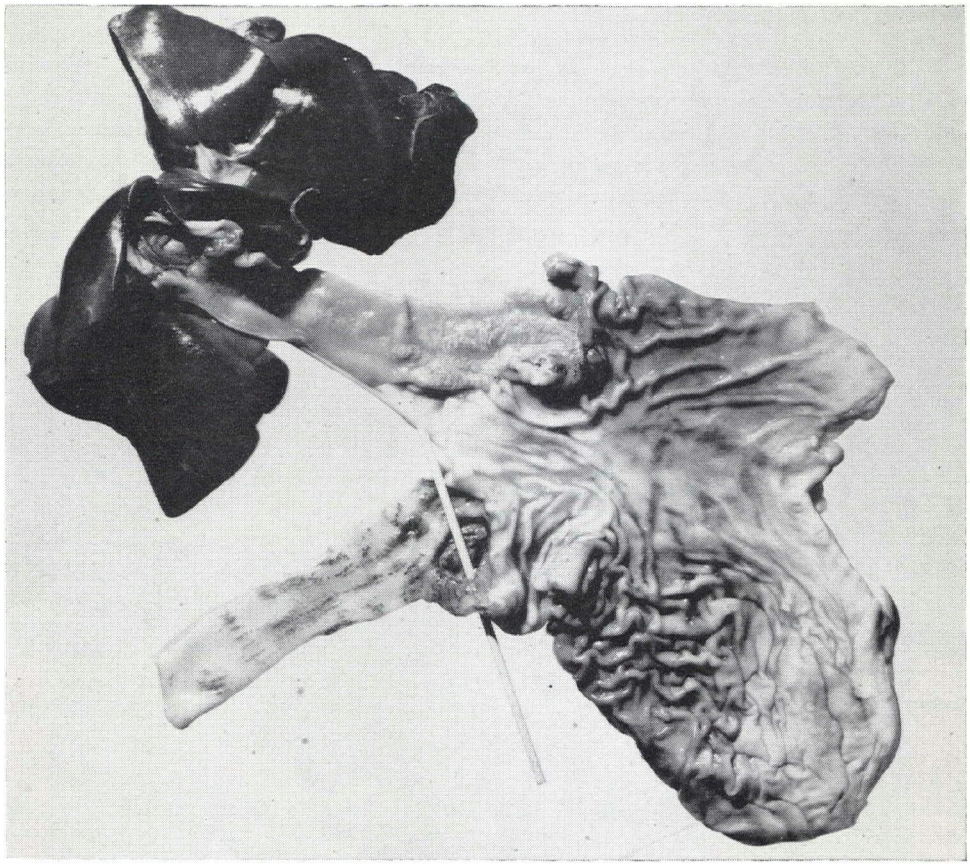

Figure 6

Dog 632. Mann-Williamson of Group No. 2. Bile protected, with ulcer perforation 69 days after operation.

COMMENT

The nutritional problem in these dogs was outstanding, 90 per cent having developed diarrhea within the first 10 days. This was probably due to the presence of pancreatic secretions in the lower ileum; the deviation of the bile and pancreatic secretions has a marked effect on the appetite. We know that the presence of food in the duodenum stimulates secretion of bile. Lack of this stimulus, we believe, lowers the daily production of bile. Clinical experience would confirm that the absence of bile decreases the appetite, thus establishing a vicious cycle. The fact that the acidity is not higher than that of the normal dog suggests very strongly that poor nutritional status plays a major role in the production of ulceration. The fact that no change in gastric content points also to the probability that bile production is strikingly decreased. In our opnion this deserves more study.

Due to the fact that the animals with the Mann-Williamson preparation often became markedly cachectic and dehydrated before the ulcers appeared, some question

may be present in regard to the genesis of the ulceration (local factors and systemic alterations). We sought an operation that produced ulcers resembling the clinical lesions and at the same time preserved the nutritional status of the dogs until the onset of the ulcer. From the work of Dragstedt and associates[26], we know that a persistent and excessive secretion of gastric juice by the body and fundus of the stomach occurs when the antrum is transplanted into the colon. Dragstedt, Oberhelman and Smith[27] in 1951 reported the regular production of experimental gastric and gastrojejunal ulcers in dogs when a hypersecretion is obtained in this fashion. They reported ulceration in 80 per cent of the dogs in which the antrum of the stomach was transplanted to the colon with restoration of gastrointestinal continuity by gastrojejunostomy.

In order to further clarify the question of how much protection the bile affords, 2 groups of experimental series were performed. In the first group of 10 dogs the antrum was transplanted to the side of the transverse colon and gastrojejunostomy was done. In a second group our previously described cholecystogastrostomy with jejunal segment was performed following the antrum transplantation and gastrojejunostomy. In all cases the portion of jejum used for reconstruction of intestinal continuity was just proximal to the ligament of Treitz.

RESULTS

The recovery from the operation was uneventful in group one. No weight loss was seen before the forty-fifth day (Table III). One animal exhibited marked

Table III

Dog No.	Weight Loss	Melena	Death
Group 1 Antrum Transplantation			
502	None	60 days	60 days massive bleeding
503	None	50 days	60 days massive bleeding (2 ulcers)
504	70 days	90 days	100 days large ulcer
513	45 days	None	70 days perforation (2 ulcers)
516	45 days	52 days	Massive bleeding
517	None	45 days	Perforation 2 ulcers
518	45 days	54 days	Massive hemorrhage
520	None	None	25 days perforation
522	None	32 days	Perforation large stomach ulcer
525	70 days	90 days	No ulcer found
Group 2 Antrum Transplantation and Bile Protection			
505	70 days	80 days	100 days
511	70 days	70 days	90 days
515	Sacrificed 8 months with no ulcer.		
519	Sacrificed 5 months with no ulcer.		
523	70 days	70 days	80 days
664	Sacrificed one year with no ulcer.		
687	Sacrificed one year with no ulcer.		
704	Sacrificed six months with no ulcer.		
720	Sacrificed 3 months with no ulcer.		
721	75 days	80 days	90 days

Table III

Bile protection in antrum transplantation.

weight loss. At autopsy it was found that this dog had a sealed perforation of the jejunum and because of this finally succumbed. Melena was a feature present in 6 of the animals and resulted in death. Perforation occurred in 4 dogs. One dog had a perforation and an ulcer with bleeding (Fig. 7). The shortest time of

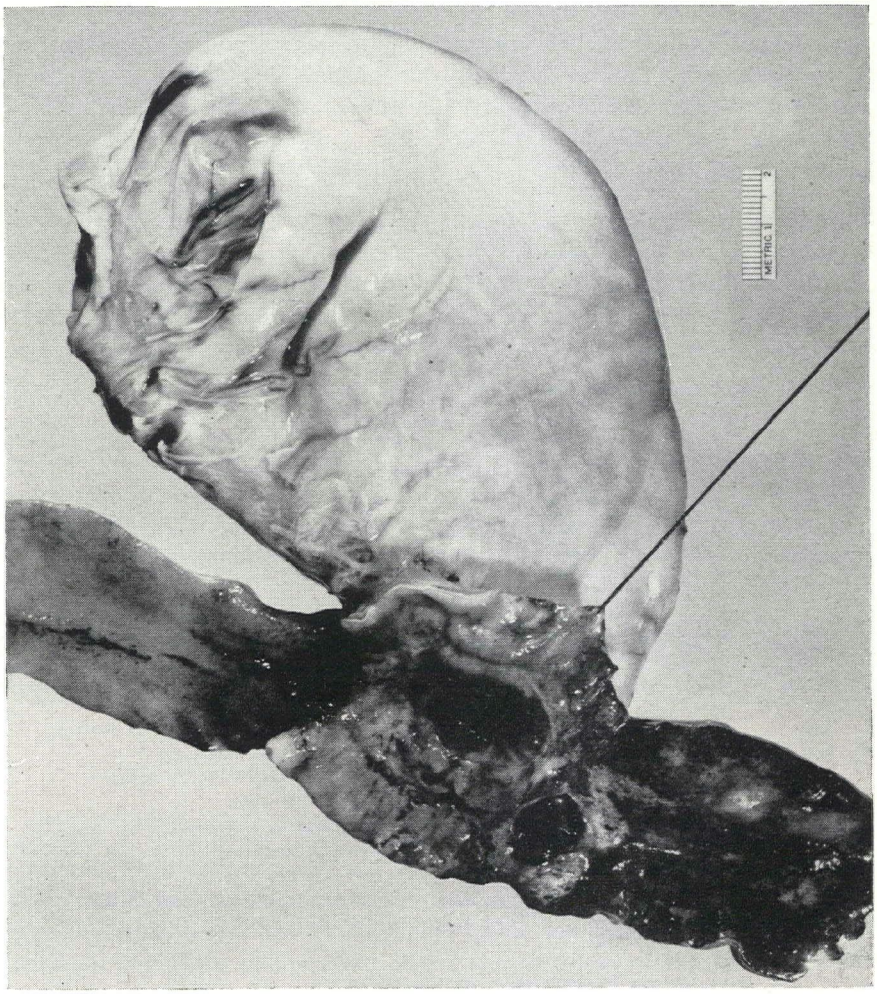

Figure 7

Dog 502. Antrum transplantation and gastrojejunostomy 60 days after operation. Notice ulceration and erosions on jejunum. Death occurred from massive bleeding.

ulceration onset was 25 days and the longest 90 days. The location of the ulcers varied widely but was more often stomal in type, this leading to hemorrhage in most cases. When the ulcer appeared in the jejunum, perforation was frequently seen. Although in one animal no large ulcer was found on postmortem examination, melena was the cause of death and diffuse redness and erosion of the jejunum was present. In any event, an incidence of 90 per cent ulceration was seen in this group.

In group two, with the bile protection, 6 of the 10 dogs, in varying periods from 3 months to one year before sacrifice, showed no evidence of ulceration. Ulceration occurred in 4 dogs in periods which varied from 80 to 100 days. From this fact we elicit that some protection was afforded these animals. In a careful scrutiny of the post-mortem findings on dogs 523 and 511, it was interesting to note that a small portion of the antrum (one inch) was left behind connected to the duodenum. The author believes that this may be a decisive factor in the ulcerogenesis in these dogs (Fig. 8).

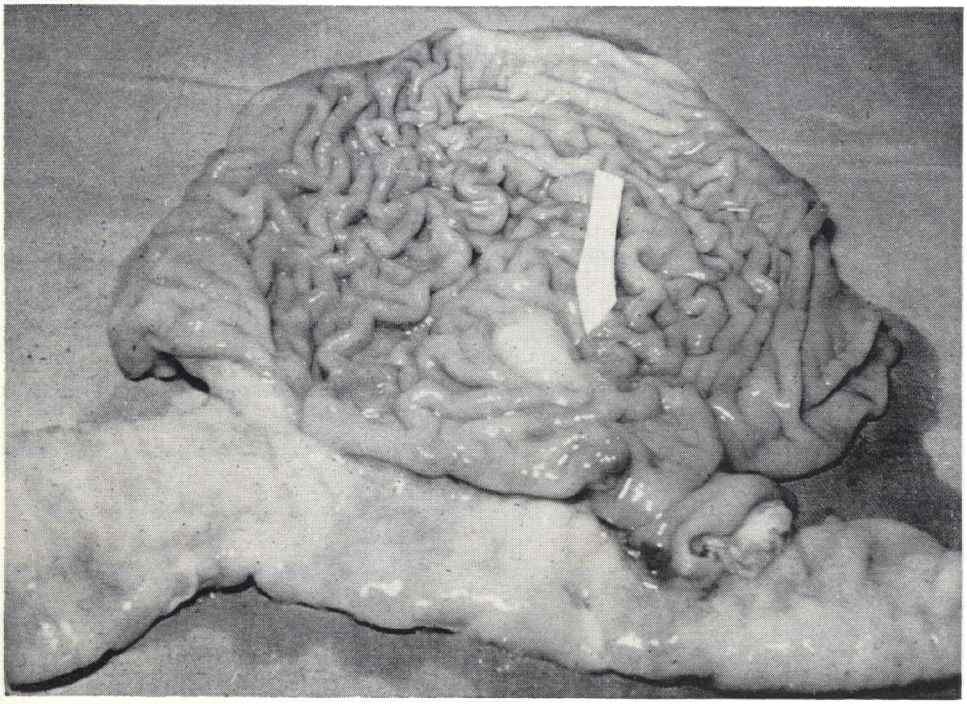

Figure 8

Dog 704. Sacrificed six months after antrum transplantation with bile protection. Notice opening of the anastomosis (arrow) of the jejunal segment into the stomach and the intact jejunum.

CONCLUSIONS

The pH of the gastric contents of the normal dog is suitable to be changed by the bile to pH levels of 4.5 or above. A reduction is obtained in the total acidity and neutralization of the HCL acid is produced.

The isoperistalsis of the isolated loop of jejunum avoids empyema of the gallbladder and hepatitis. The gallbladder maintains functional capacity after anastomosis to the jejunal loop as shown by cholecystographic studies. There is no manifestation of intolerance in the dog to the presence of bile in the gastric cavity.

The pH of the Mann-Williamson dog is not changed by the action of bile transported into the stomach through jejunal transplants, and the pH of the normal dog does not differ from that of the Mann-Williamson dog.

The influence of the nutritional status in the production of bile and the onest of ulceration merits investigation. Bile, under the conditions of the present experiments, fails to prevent the Mann-Williamson induced ulceration. In 90 per cent of the dogs with gastric antrum transplantation to the colon and gastrojejunostomy ulceration is produced. Bile protection, as afforded by the operation presented in this work, reduces this incidence to a 40 per cent on the basis of these experiments. The role of bile alone on the genesis of ulceration is of prime importance as shown from these experimental findings and should deserve intensive study on the basis of the modern physiological concepts.

Acknowledgement: The author is indebted to Dr. James Barron for the encouragement and constructive criticism during the progress of the experimental work.

Eduardo Camacho, M.D.
Avenida del Sur 275
Guadalajâra Jalisco
Mexico

REFERENCES

1. Graves, A. M.: Combined and separate effects of bile, pancreatic secretion and trauma in experimental peptic ulcer, Arch. Surg. 30:833, 1935.

2. Gray, E. G.: Experimental study of effect of cholecystogastrostomy on gastric acidity, J. Exper. Med. 23:15, 1916.

3. Babcock, W. W.: The control of hyperchlorhydria and its consequences by cholecystogastrostomy, Med. Rec. 98:476, 1920.

4. Nazarov, N. N.: Cholecystogastrostomy for gastric ulcer, Surg., Gynec. & Obst. 45:474, 1927.

5. DuBose, F. G.: Cholecystogastrostomy and cholecystoduodenostomy, Surg., Gynec. & Obst. 39:295, 1924.

6. Braithwaite, L. R.: Role of bile in duodenal regurgitation (Bradshaw lecture), Brit. J. Surg. 31:3, 1943.

7. Kapsinow, R.: The experimental production of duodenal ulcer by exclusion of bile from the intestine, Ann. Surg. 83:614, 1926.

8. Mann, F. C., and Williamson, C. S.: The experimental production of peptic ulcer, Ann. Surg. 77:409, 1923.

9. Berg, B. N., Johnston, A., and Jobling, J.: Duodenal and gastric ulcers in dogs with biliary fistulas, Proc. Soc. Exper. Biol. & Med. 25:334, 1928.

10. McCann, J. C.: Experimental peptic ulcer, Arch. Surg. 19:600, 1929.

11. Berg, B. N., and Jobling, J. W.: Biliary and hepatic factors in peptic ulcer; an experimental study, Arch. Surg. 20:997, 1930.

12. Berg, B. N.: Peptic ulcers; comparative frequency after deprivation of bile and pancreatic juice, Arch. Surg. 28:1057, 1934.

13. Braithwaite, L. R.: Surgical treatment of chronic duodenal ulcer and gastric ulcer; cholecystogastrostomy as the operation of choice for inaccessible gastric ulcer, Lancet 1:900, 1926.

14. Beaver, M. G.: Cholecystogastrostomy; an experimental study, Arch. Surg. 18:899, 1929.

15. Owings, J. C., and Smith, I. H.: Experimental production and cure of jejunal ulcers, Proc. Soc. Exper. Biol. & Med. 29:832, 1932.

16. Ochsner, A., Gage, M., and Hosoi, K.: Relationship of peptic ulceration to gastric chemism, Proc. Soc. Exper. Biol. & Med. 31:1260, 1934.

17. DeBakey, M. E.: Peptic ulceration; relative protective value of the alkaline duodenal juices, Arch. Surg. 34:230, 1937.

18. Kesayalau, A., and Mann, F. C.: The influence of duodenal contents of intragastric acidity, Surgery 14:578, 1943.

19. Wilhelmj, C. M., Henrich, L. C., and Hill, F. C.: Influence of duodenal secretions on acid gastric contents, Am. J. Physiol. 111:293, 1935.

20. Maier, H. C., and Grossman, A.: Relation of duodenal regurgitation to development of jejunal ulcers, Surgery 2:265, 1937.

21. Wangensteen, O. H., and Lannin, B.: Criteria of acceptable operation for ulcer, importance of acid factor, Arch. Surg. 44:489, 1942.

22. Farmer, D. A., and Smithwick, R. H.: Effect of partial exclusion of bile and pancreatic juice on the acidity of gastric contents in postgastrectomy patient, Surgery 35:557, 1954.

23. Glenn, F., Evans, J., Hill, M., and McClenahan, J.: Intravenous cholangiography, Ann. Surg. 140:600, 1954.

24. Barron, J., Camacho, E., Gray, E. J., and Duffy, F. H.: Neutralization of gastric acid by bile transported through jejunal transplants; preliminary report, Henry Ford Hosp. M. Bull. 6:180, 1958.

25. Friedman, M. H. F., Sandweiss, D. J., and Saltzstein, H. C.: Effects of ACTH, cortisone and urinary anthelone on gastric secretion in normal and Mann-Williamson dogs, Am. J. Physiol. 167:786, 1951.

26. Dragstedt, L. R., Woodward, E. R., Storer, E. H., Oberhelman, H. A., Jr., and Smith, C. A.: Quantitative studies on mechanism of gastric secretion in health and disease, Ann. Surg. 132:626, 1950.

27. Dragstedt, L. R., Oberhelman, H. A., Jr., and Smith, C. A.: Experimental hyperfunction of gastric antrum with ulcer formation, Ann. Surg. 134:332, 1951.