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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

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BY

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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

LII. STUDIES ON GASTRIC ULCER *

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The studies on gastric ulcer as presented here are the first of a series of studies on the pathologic physiology of the stomach and duodenum in the condition of ulcer of these parts of the gastro-intestinal tract.

I. THE OCCURENCE OF ULCER AND OTHER PATHOLOGIC LESIONS IN THE STOMACH AND THE DUODENUM OF THE DOG AS JUDGED FROM ONE THOUSAND NECROPSIES

In a series of studies to be made on a pathologic physiologic condition it is obviously essential to make a study of the frequency of the occurrence of that condition in the animal used. A large amount of work has been done on gastric ulcer in which the dog has been the chief experimental animal. There are only two reports in the literature concerning the frequency of the occurrence of ulcer in the dog. Turck[1] reports a series of necropsies on 189 healthy and 82 diseased dogs in which the findings of "peptic ulcer" were absolutely negative. Other pathologic lesions, if they occurred, are not reported. Mann[2] reports a series of more than two hundred normal dogs and cats in which no "lesion of the gastric mucosa was found at necropsy." From the findings of these two observers one might conclude that the occurrence of lesions of the gastric mucous membrane of the dog are very rare. Since the data offered in the literature is meager, it was considered important to ascertain more completely the occurrence of lesions of the gastric mucous membrane in the dog.

METHODS

The stomach and duodenum of healthy, diseased and experimental dogs was removed immediately after death and placed in cold running water where they were examined immediately, or always within one hour after removal. Quite a number of stomachs were examined a

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* From the Hull Physiological Laboratory of the University of Chicago.

1. Turck, F. B.: J. A. M. A. **67**:1784 (Dec. 9) 1916.
2. Mann, F. C.: J. Exper. M. **23**:203 (Feb.) 1916.

longer period after death than one hour, but observations on these were not recorded because of the possibility that any lesion present might be the effect of autodigestion.

The lesions observed were classified as follows: (1) Petechial hemorrhage, applied to the condition in which the red blood corpuscles are abundantly packed in the tissues of the mucosa and lie in the mucosa adjacent to the lumen; (2) superficial hemorrhagic erosion, applied to the condition in which there is an evident petechial hemorrhage accompanied by a superficial erosion of the cells of the mucous membrane; (3) acute ulcer, applied to the condition in which there is a well defined break in the continuity of the mucous membrane; (4) chronic ulcer, applied to the condition in which the edges of the ulcer are raised, undermined and thickened, and the base of the ulcer indurated; (5) diffuse inflammation, applied to the condition generally referred to as gastritis in which there occurs a swelling and hyperemia of the mucous membrane together with the production of a viscid adhesive mucus exudate and in acute cases with the occurrence of petechial hemorrhages and superficial erosions; (6) and tumors involving the mucosa. I agree with Bolton[3] that it is neither useful nor correct to call a superficial hemorrhagic erosion an ulcer.

RESULTS

Table 1 shows the occurrence of pathologic lesions in the stomach and duodenum of healthy dogs that had been subjected to ether anesthesia for a period of two or three hours, while students used them for acute laboratory experimentation.

TABLE 1.—Showing Lesions of the Stomach and Duodenum (900 Dogs)

Lesions	Cardia		Fundus		Pylorus		Duodenum		Remarks
	No.	%	No.	%	No.	%	No.	%	
Petechial hemorrhages	11	1.2	..	....	2.6	2.9	13	1.4	
Superficial hemorrhagic erosions	1	0.09	1	0.09	23	2.5	6	0.6	
Acute ulcer	..	....	..	....	1	0.09	..	....	Old emaciated dog
Diffuse inflammation	..	....	4	0.44	4	0.44	23	2.5	
Tumors	..	....	..	....	3	0.33	..	....	Adenomatous polyps

The petechial hemorrhages and hemorrhagic erosions occurred chiefly in the last 2 inches of the pyloric portion of the stomach and in the first inch of the duodenum. In the case of the acute ulcer of the pyloric portion of the stomach there were two ulcers (2 by 1 mm.), involving the entire thickness of the mucosa within one-half inch of the sphincter. The stomach was taken from on old emaciated

3. Bolton: Quart. J. Med. **5**:434, 1911.

animal. No apparent cause for the gastritis could be found. Worms accompanied the enteritis in all except five animals, and may have been the cause in most cases.[4]

TABLE 2.—Lesions Occurring in Thyroid Parathyroidectomized Dogs (Twenty-Four Dogs)*

Stomach	Stomach, No.	Duodenum, No.
Petechial hemorrhages	16	20
Superficial hemorrhagic erosions	13	15
Acute ulcer	1	3
Diffuse inflammation	9	18

* One acute ulcer, 15 × 3 mm., almost perforated was found in the fundus. Otherwise all the lesions in the stomach were confined to the pyloric portion.

Table 2 shows the occurence of ulcer and of lesions of the mucous membrane of the stomach and duodenum in animals dying of thyroid parathyroidectomy. The paramount symptom that was manifested in the animals was depression, as reported by Carlson,[5] only 60 per cent. of them showing tetany. These animals lived from three to twenty days. The severity of the intestinal findings was directly portional in most cases to the longevity of life following the operation.

Eight out of forty dogs dying of distemper (snuffles) showed petechial hemorrhages and superficial hemorrhagic erosions of the pyloric and duodenal mucous membrane. Acute gastritis and enteritis was present in every dog in this series. Hypoacidity is a constant occurrence in these animals. I have seen several cases in which raw meat would pass through the gastro-intestinal tract of a dog sick with distemper without being changed in color. Diarrhea is also present in practically every case, as is anorexia and emaciation.

In ten dogs dying of shock and symptoms of raised intracranial pressure following cerebral ablations, every one showed petechial hemorrhages and superficial erosions of the fundic and pyloric mucous membrane. In four of these dogs the stomach was acutely dilated. No free acid was present in the stomach of these animals.

Out of twenty dogs that had been injected intravenously with ether twenty-four hours previous to death, five showed petechial hemorrhages and superficial erosions of the fundic and pyloric mucous membrane.

Superficial hemorrhagic erosions occur frequently in dogs dying of experimental diabetes.

A deeply eroded and indurated ulcer (4 by 6 mm.), typically chronic, was found in the first quarter of an inch of the duodenum

4. Food was present in the stomachs of about one half of the animals. The lesions had no relation to the presence of food, however.

5. Carlson, A. J.: Am. J. Physiol. **30**: 1912.

in a cachectic dog whose pancreatic ducts had been ligated five months previously and who had been kept on a diet of bread and milk. Hypoacidity was present in this dog. The dog died of acute stomatitis accompanied by rapid emaciation. The stomach and duodenum of twenty-four dogs, in which the pancreatic ducts had been ligated, were examined without finding ulcer. Four of these animals showed superficial erosions. In these dogs emaciation was marked and they died of distemper. The other animals were killed in other experiments, no lesions being present. With the exception of six of these animals, the pancreas was from macroscopic appearance atrophic and fibrotic. Jona[6] reports the presence of ulcers in the duodenum and small intestine following ligation of one pancreatic duct. From his picture and his description, I am led to believe that what he called ulcers were nothing more than Peyer's patches, which occur in the duodeum of the dog, made more conspicuous by emaciation and postmortem digestion. These patches are easily mistaken for ulcers, if a microscopic study is not made.

My observations on suprarenalectomized animals partly confirm those of Mann.[2] In forty suprarenalectomized dogs I have only seen one acute ulcer and twenty instances of petechial hemorrhage and hemorrhagic erosion of the gastric and duodenal mucous membrane, which is less frequent than reported by Mann.

Dogs dying immediately after section of the vagi and splanchnics not infrequently show petechial hemorrhages of the pyloric and duodenal mucous membrane. But in ten dogs that died or were killed from one week to four months following double vagotomy and splanchnotomy with extirpation of the celiac plexus, no gastric or duodenal lesions were found. Durante[7] reports that he observed lesions that were similiar to acute and chronic ulcers in man. He does not state how long the ulcers were present and only states that such animals survive a short time. Most of my animals lived indefinitely and the nerve sections were verified at necropsy. Such animals become cachectic, however, and have to be cared for rather carefully for some time in order to keep them in a normal state of health.[8]

In a personal communication from Dr. S. A. Mathews, I was told that in Eck fistula dogs, which are kept alive for a long period on a diet of bread and milk and which are emaciated and cachectic, chronic ulcers of the stomach are frequently found.

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6. Jona, J. L.: M. J. Australia **1**:316 (April 19) 1919.

7. Durante, L.: Surg., Gyn., Obst. **22**:399 (April) 1916.

8. In an emaciated dog with gastrostomy and both splanchnics cut, Dr. A. B. Luckhardt found a chronic ulcer about one inch from the gastrostomy. The ulcer was about to perforate.

The three tumor formations found were adenomatous polyps which were confined in each case to the mucosa of the pyloric portion of the stomach.

No scars were found in the stomach or duodenal mucous membrane. These were looked for as probable evidence of healed acute ulcers. Such scars are reported to occur frequently in man.

SUMMARY AND DISCUSSION

It is apparent from the results of this study that chronic ulcer of the stomach and duodenum in healthy dogs and even diseased dogs, if it occurs at all, is very rare. In diseased and cachectic experimental animals only two marked ulcerations were found: one, very acute and almost perforating, the second, typically chronic. On the other hand, petechial hemorrhages and superficial hemorrhagic erosions do occur in the gastric and duodenal mucosa of the healthy dog. (I have seen them in the mucosa of the stomach even though the animal had not been subjected to ether anesthesia previously.) These lesions, however, occur more frequently in experimental, diseased and cachetic animals.

Comparing these observations with those reported to occur in man, it is seen that the dog is much less subject to gastric lesions than man. According to Adami[9] "hemorrhages into the stomach wall are quite common" in man, and Birch-Hirschfield[10] reports that they are found in 50 per cent. of cadavers. Osler[11] states that hemorrhagic erosions are common. Chronic ulcer occurs in man as often as from 2 to 4 per cent. Why there is such a difference between man and dog is a matter open for speculation. If gastric juice digestion was a basic factor, we would expect more ulcers in the dog than in man as the dog's acidity is on the average greater than man's. The dog being an animal generally of higher resistance and less subject to dietary, toxic and nervous factors, which cause gastric disturbance of motor, secretory and circulatory activity, than man, we would expect to find fewer ulcers. The dog not being so subject to focal infections and hemorrhagic erosions as man, the dog would be less likely to have an ulcer hematogenous in origin. Also, the dog being less subject to nervous influences, which cause hypomotility and hyposecretion, there would be less chance to infect a point of lowered resistance, a petechial hemorrhage or erosion, by bacteria swallowed. These observations

9. Adami, J.: Principles of Pathology, Philadelphia, Lea & Febiger, 1911, **2**: 414.

10. Birch-Hirschfeld: loc. cit., Adami.

11. Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton & Co., 1916, pp. 490, 447, 480.

suggest at least that there is some factor present in man causing the chronicity of the ulcer which is absent in the dog; also, that if chronic ulcer can be produced in the dog's stomach or duodenum, it can be produced in man by the same method.

The fact that chronic gastric ulcer does not occur and that gastric carcinoma is not found in the dog is comparative evidence, I take it, in favor of Mayo Robson's[12] theory of the etiology of carcinoma of the stomach in man. Mayo Robson suggested that gastric ulcer was the source of gastric carcinoma. Wilson and McCarthy[13] have presented evidence in support of this theory.

2. THE EXPERIMENTAL PRODUCTION OF CHRONIC GASTRIC ULCER IN THE DOG

Petechial hemorrhages, superficial hemorrhagic erosions and acute ulcers have been produced experimentally in many ways: mechanically, chemically, by heat, drugs, toxins, peptones, serums, by section of the vagi and the splanchnics, by embolism and thrombosis, anemia, by feeding bacteria, by the intravenous injection of specific and nonspecific bacteria, by abrasions, by lesions to the central nervous system, by removal of the suprarenals and parathyroids, and by many other methods. In other words, they are produced by anything that causes a local necrosis of the membrane by direct toxic or chemical action on the mucosal cells or by interfering or disturbing the normal condition of the capillaries of the mucosa. All biologic methods of producing the hemorrhages seem to point toward a marked susceptibility of the gastric and duodenal mucosal capillaries to injury by toxic and nervous influences.

Although acute ulcers have been produced in many ways, few investigators have claimed to have produced chronic ulcers of the gastric and duodenal mucosa. Bolton[14] and Friedman and Hamburger[15] were able to delay the healing of experimental acute ulcers by producing partial pyloric stenosis. Turk[1] reported that he was able to produce perforating ulcers of the duodenum and stomach by feeding *B. coli.* Durante,[7] by ligating and cutting the splanchnic nerves, reports the production of chronic ulcers. Rosenow[16] has reported the production of gastric and duodenal ulcers that "resemble those in man in location and tend to become chronic, to perforate and to cause hemorrhage" by the intravenous injection of alleged specific streptococci.

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12. Robson, A. W. M.: Lancet **2**:1547, 1904.
13. Wilson, L., and McCarthy, W. C.: Am. J. M. Sc., 846 (Dec.) 1909.
14. Bolton: Proc. Roy. Soc., Lond. **82**:236, 1909.
15. Friedman, J. C., and Hamburger, W. W.: J. A. M. A. **62**:380 (Aug. 1) 1914
16. Rosenow, E. C.: J. Infect. Dis. **19**:333 (Sept.) 1916.

The chief views held at the present time concerning the etiology of chronic gastric ulcer are as follows: (1) Infection of the mucous membrane through the blood by specific or nonspecific bacteria from a focal infection is the primary factor and the source of reinfection; (2) the digestive action of the gastric juice on mucosal cells that have had their normal resistance to acid peptic digestion diminished in some way; (3) a localized trophic disturbance is responsible for the chronicity of the ulcer; (4) the infection of the mucous membrane by swallowed bacteria.

Most investigators in this field agree with Bolton[17] that chronic ulcer originates from an acute lesion and that most of the acute lesions heal rapidly.

This study was undertaken as an attempt to throw more light on the experimental production of chronic ulcer in the dog.

METHODS AND RESULTS

Healing of Experimental Acute Ulcers.—The time required for the healing of acute ulcer produced by Roth's method (the injection submucously of 1.0 c.c. of a 5 per cent. silver nitrate solution) in the fundic and pyloric portions of the stomach and in the duodenum. Ulcers made in the mucous membrane of the fundic portion of the stomach healed in from nine to thirteen days; when ulcers were made in the pyloric portion of the stomach, healing required from twelve to eighteen days; if the dogs had the distemper, healing required from eighteen to twenty-two days. In the duodenum from sixteen to twenty-four days were required for the healing of the ulcer.

This difference in the rate of healing is explained, I believe, by the anatomy and physiology of the different portions and the way in which ulcers of the mucosa heal. The manner of healing has been described in detail by Bolton[14] and Griffini and Vassale.[18]

Aseptic Embolism.—Injections of finely divided animal charcoal suspensions were made into the branches of the gastro-epiploic arteries with negative results. Suspensions of lead chromate and pigments were injected into branches of the gastro-epiploic arteries with resulting petechial hemorrhages and hemorrhagic erosions. Acute ulcers resulted in three of the animals injected with lead chromate. The results with lead chromate and pigments confirm the observations of Cohnheim[19] and Klebs and Welti.[20] Why the injection of animal charcoal gave negative results cannot be stated. The findings suggest

17. Bolton: Ulcer of the Stomach, London, 1913.
18. Griffini and Vassale: Ziegler's Beitr. **3**:425.
19. Cohnheim: Lect. on Gen. Path. (New Sydenham Soc.) **3**:878, 1890.
20. Klebs and Welti: Handb. d. path. Anat., 1869.

that effects produced by pigments and lead may be toxic and that an embolism produced by an inert, nontoxic substance, charcoal, will not result in hemorrhage or acute ulcer.

Ligation of Blood Supply.—Six to eight of the branches of the gastro-epiploic vessels supplying the pyloric portion of the stomach were ligated with negative results. This confirms the results of Littauer[21] who found that the blood supply to one third of the stomach could be cut off without producing dileterious effects and demonstrates a marked freedom of anastomosis.

Silver nitrate ulcers were made in such an area to which the large blood vessels had been ligated with the result that they healed in normal time. The ulcers were made at the same time that the vessels were ligated.

Partial Pyloric Stenosis and Healing of the Ulcer.—The effect of partial pyloric stenosis on the rate of the healing of the ulcer was studied in eight dogs. In five the healing time of the ulcer was delayed from two to four weeks. No marked induration of the edges occurred in any case. The ulcers in the three dogs which did not manifest rapid loss of weight healed in normal time. To ascertain the condition of the ulcer, the dog was killed in some cases, in other cases operated on aseptically and the ulcer examined by direct inspection through an incision in the stomach wall. These findings confirm the observations of Bolton[14] and Friedman and Hamburger,[15] who report delayed healing in acute experimental ulcers accompanied by partial pyloric stenosis. Bolton reports delayed healing only, while Friedman reports a chronic ulcer at eight weeks after the production of the acute ulcer. Bolton accounts for the delayed healing as "due to necrosis of the base of the ulcer or excessive formation of sclerotic tissue therein, such conditions being the result of the low resistance which the connective tissues possess to digestion by gastric juice, or possibly in some cases to a secondary bacterial infection." Friedman and Hamburger account for the delayed healing by the prolonged action of the gastric juice and hyperperistalsis. Loss of weight and disturbed nutrition, which I observed in my animals and which is reported by both of the above investigators, although not emphasized, and bacterial infection of the acute ulcer must also be considered as possible factors in the delayed healing following partial pyloric stenosis.

Injections of Bacteria.—Injections of streptococci (one tube of a twenty-four-hours-old culture in dextrose ascites broth) were made into two or three branches of the gastro-epiploic arteries in a series of

21. Littauer: Virch. Arch. **195**: No. 2, 328.

dogs with negative results. The dogs were killed from two to four weeks after the injection, so if any acute effects were produced, they did not persist nor leave scars. In two dogs killed twenty-four hours after the operation petechial hemorrhages were found. Perigastritis resulted in every case. Two strains of streptococci were used, one a *Streptococcus viridans* isolated from a tonsil, the other a *Streptococcus hemolyticus* from a case of septicemia. Dr. Clawson of the department of bacteriology, from whom the bacteria were obtained, stated that both were fatal for rabbits. The *S. viridans* when injected (three tubes of a twenty-four-hours-old culture of dextrose ascites broth) into dogs caused no symptoms; the *S. hemolyticus* when injected into dogs caused a rise in temperature, inactivity and loss of appetite of three days' duration. Although the bacteria were virulent enough to produce a dense fibrinous and fibrous perigastritis at the site of injection, no acute ulcers of the stomach resulted. These results suggest that either a markedly virulent or a specific bacterium is required to produce an acute ulcer of the stomach. I have injected streptococci beneath the skin and the mucosa of the stomach at the same time and in the same dog; in the former instance an abscess developed, while nothing resulted from the submucosal injection.

Feeding Bacteria.—The effect of feeding bacteria to dogs in which an experimental abrasion of the pyloric and duodenal mucous membrane had been made was studied. The laceration was made under aseptic procedure through an incision in the anterior wall of the stomach by pinching and tearing the mucosa with a hemostat or extirpating it with the knife. Ten tubes of a twenty-four-hour-old culture of streptococcus were given daily by the stomach tube at a time when the stomach was empty. This was done in five healthy dogs with negative results, the laceration healing in from six to ten days and the extirpations in from twelve to fifteen days. In other words, Wilkensky and Geist's[22] observations were confirmed. The work was about to be given up when a sixth dog developed distemper after the operation and had recovered three weeks later. The dog was killed and a necropsy was made six weeks after the operation. A large hyperemic, edematous, inflamed ulcer (three-quarters of an inch in diameter) was found at the point of laceration. This dog had been fed *Streptococcus viridans,* which Dr. Clawston isolated from the deep tissues adjacent to the ulcer. The work was continued on two other distemper dogs and in two cachectic dogs with ligated pancreatic ducts. Six weeks after the production of the acute ulcer a necropsy was done on one of the distemper dogs. It revealed an ulcer with con-

22. Wilkensky, A. O., and Geist, S. H.: J. A. M. A. **66**:1382 (April 29), 1916.

gested and edematous edges with a thickened base. This dog had been fed *Streptococcus hemolyticus* which was isolated from the deep tissues about the edges of the ulcer by Rosenow's technic.[23] The second distemper dog which recovered from the distemper four weeks after the operation was killed four weeks later, or eight weeks after the production of the abrasion of the mucosa, and a healing ulcer (Fig. 1)

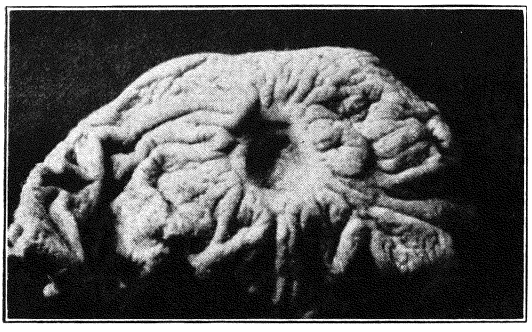


Fig. 1.—Chronic ulcer (eight weeks) of the pyloric portion of the stomach produced experimentally.

Fig. 2.—Chronic ulcer (ten weeks) of the duodenum produced experimentally.

was found at the site of the abrasion. The edges were congested, edematous and markedly indurated. The cachectic ligated pancreatic duct dog showed at the site of the duodenal abrasion, which was made in this dog, an indurated ulcer with edematous edges (Fig. 2) ten weeks after the production of the lesion. This dog continued to get more emaciated and weaker until it was killed.

23. Rosenow. Jour. Infect. Dis. **17**:219, 1915.

The gastric juice and stomach contents of these dogs were examined at intervals for free acid. Free acid was not found at any time during the attack of distemper or during marked cachexia. This fact is well known to anyone who has worked with Pavlov pouch dogs sick with distemper or showing a disturbance of nutrition.

This study is being continued by a new method that will be more subject to experimental control.

DISCUSSION

The chronic ulcers produced in this study suggest that two other factors are necessary other than an abrasion with a trophic disturbance, infection via mouth or blood stream and acidity, namely, (1) a general lowered resistance, and (2) a temporary hypoacidity or achylia. The animals in which it was possible to delay healing of the acute lesion and to cause it to assume signs of chronicity by feeding streptococci were diseased and cachectic, and showed no free acid in their gastric

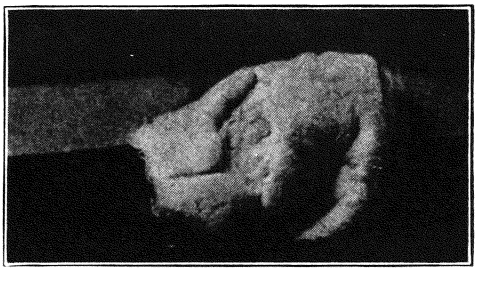


Fig. 3.—Ulcer found by Dr. A. B. Luckhardt one inch from a gastrostomy opening in an emaciated dog with both splanchnics sectioned.

juice or contents. It is to be recalled that it was observed in the first study on the occurrence of gastric and duodenal lesions that erosions are much more frequent in the experimental, diseased and cachectic animals. It is well known that diseased and cachectic animals show gastric juice that is deficient in free acidity and often entirely absent. This, of course, makes it possible for any bacteria swallowed or administered to become implanted in the abrasion or local area of hemorrhage or erosion, if present—free acid to the extent that occurs normally in the stomach being incompatible with life for most bacteria. Further, it should be pointed out that an infected lesion in a pathologic mucous membrane—for the mucosa of the stomach is pathologic when it is not secreting its normal gastric juice—is more likely to assume signs of chronicity and to become chronic than a lesion in a normal mucous membrane functioning normally. Therefore, given an abrasion of a pathologic gastric mucosa, a general lowered resistance by disease or disturbed nutrition accompanied by a hypoacidity, we have factors that

make it possible for bacteria swallowed or in the blood stream to become implanted in the abrasion and to produce local inflammation, induration, congestion and edema, and a chronic ulcer. Further, it is reasonable to believe, as observed and pointed out in one animal, that after the edges and base of the abrasion have become infected, inflamed and finally indurated—normal blood supply being diminished thereby—the general condition of the patient may improve or become normal, and yet have the ulcer remain chronic—because of the local diminution of blood supply and edema — and even to become more extensive because of mechanical irritation of coarse foods and tonic gastric activity associated with the action of acid pepsin on the devitalized tissue in the base and about the edges of the ulcer; or even a reinfection may occur during a period of hyposecretion following some digestive disturbance.

It is interesting to recall that acidity is generally considered the all-important factor in the chronicity of the ulcer, which is hardly tenable in light of my observations or those of Rosenow.[16] I recognize, however, that the chronic ulcer that I report might be considered by some to be different from the ordinary peptic ulcer seen clinically. My ulcers may be similar to those found in some cases of achylia gastrica, which some clinicians believe to have a different etiology than peptic ulcer, i. e., trophic.

These results explain the reports of many investigators who have ascribed some other cause to the delayed healing or chronicity. The results of Durante,[7] who produced ulcers chronic in character by section of the splanchnics, are in accord with this conception when the petechial hemorrhages, erosions, temporary hypoacidity and disturbed digestion and loss of weight, that often results along with the temporary lowered resistance from this operation, are taken into account. Durante reports that his animals lived only a short time, which supports my contention. Our double vagotomized and splanchnectomized dogs at this laboratory live indefinitely, but their feeding has to be carefully attended to for the first week or two—in a good state of health, which explains, I believe, why we found no ulcers in our series. Durante's ulcers were infected, as was shown by Rosenow. This conception is also in accord with the findings of Bolton[14] and Friedman and Hamburger,[15] who report that partial pyloric stenosis delays the healing of ulcer. The former investigator suggests that bacterial invasion may have been the cause. Both investigators report that such animals with partial pyloric stenosis vomit, lose weight and become cachectic. This also occurred in some of my dogs. Bolton reports that in some of his animals the gastric contents were neutral or alkaline, but Friedman and Hamburger state that "hyperacidity" resulted in

their animals. The effect of pyloric stenosis upon gastric secretion has not been thoroughly worked out, so this point cannot be settled. Turck's[1] results are in agreement with this conception. Turck produced ulcers by feeding *B. coli* in large amounts over long periods of time to animals that were confined and that manifested abnormal "systemic conditions" with "modified conditions of the alimentary tract." I was surprised to find that this conception is not contrary to Rosenow's observations. In looking over his protocols,[16] I find that the animals that showed chronic ulcers in his series had distemper or some general malaise as shown by anorexia and loss of weight. I do not accept the results of Rosenow as he interprets them with respect to chronic ulcer. Even if his specificity idea is accepted, that does not prove without question of a doubt, that this specific infection is the cause of the chronicity of the ulcer. A mycotic embolus is one of the factors causing acute gastric lesions, or the bacteria may infect an acute lesion otherwise produced. But it is agreed by most workers that acute ulcer in healthy animals heal rapidly no matter how produced. So it is very probable in the light of the results of other investigators and of the results obtained in this study that chronic gastric ulcer has its origin in an acute lesion of the mucous membrane which is infected by swallowed bacteria, or by bacteria from the blood stream, during a time at which the mucous membrane is pathologic—secreting none or but little free acid—and the general resistance is lowered by disease or disturbance of nutrition.

3. METHOD FOR MAKING A PYLORIC POUCH TO BE USED IN THE STUDY OF GASTRIC ULCER

Although several investigators have reported that they were able to produce ulcers of the chronic type, no one has seen a chronic gastric ulcer in the process of development. The method generally employed has been to produce an ulcer in the stomach by some means and then kill the animal some time later and ascertain the condition of the ulcer. Such a procedure is very unsatisfactory experimentally because of the presence of numerous uncontrollable factors. Hardt[24] and Dragstedt[25] approached nearer to the ideal experimental procedure when they studied ulcer in the Pawlow pouch. But in the Pawlow pouch one is working with a part of the stomach that seldom has ulcer, that heals rapidly, and that produces an acid secretion. The mucous membrane of the pyloric portion of the stomach, on the other hand, is the frequent site of ulcer, heals slower than the fundic mucous membrane

24. Hardt, L. L. J.: Am. J. Physiol. **40**:314 (April) 1916.
25. Dragstedt, L. R.: J. A. M. A. **68**:330 (Feb. 3) 1917.

and does not produce an acid secretion but a mucous secretion slightly alkaline in reaction. So it seems that the ideal experimental procedure, in which all factors might be controlled and chronic ulcer most likely to be produced under daily observation, would be to study the factors (acid, alkalies, irritation, motility, infection, with specific and non-specific bacteria, emaciation, etc.) that influence healing, positively or negatively, in a pouch of the pyloric portion of the stomach.

Hence the operative technic for making such a pyloric pouch has been worked out.

METHOD

Two methods are presented, one for making a pouch with nerves intact, the other for making a pouch with extrinsic nerve supply severed.

With Nerve Supply of the Pouch Intact.—Approximately at a point on the anterior wall of the stomach where the fundic mucous membrane merges into the pyloric mucous membrane an incision one inch long is made through the wall into the lumen of the stomach (Fig. 4, *a*). Through this incision the mucosa is everted and the original incision (a) is continued around the stomach (b), cutting only the mucosa without cutting deeper than the submucosa (as in the Pawlow operation), thus dividing the mucosa into fundic and pyloric portions. The anterior and posterior edges of the fundic mucosa is then sewn together (Fig. 5, c) with a continuous Lembert suture, as is also the anterior and posterior edges of the pyloric mucosa (d), thus forming a wall of the two mucous membranes, which divides the stomach into two compartments, the fundic and pyloric. The incision in the wall of the stomach (a) is then closed by a continuous suture. Next a posterior gastro-duodenostomy (e) is done connecting the fundic compartment with the duodenum. Then a pylorectomy (Fig. 6, f) is done and the pyloric compartment is opened to the outside by a stab wound (g), the pyloric portion of the stomach being anchored to the abdominal wall by a series of interrupted sutures.

With Extrinsic Nerve Supply Severed.—The pyloric portion of the stomach is separated from the rest of the stomach and from the duodenum by incisions "A" and "B" (Fig. 7), care being taken not to interfere with the blood supply of the pyloric portion, which is to be the pouch. An end to side anastomosis (Fig. 8, a′) of the stomach to the duodenum is done and the cut end of the duodenum is closed (b′). Then the opening at the pyloric orifice (b) is closed. Next a large stab wound is made in the abdominal wall and the pouch is anchored in place. The reversal of the pouch so that "a" is brought to the outside instead of "b" makes a larger rosette and the mucosa of the pouch more accessible.

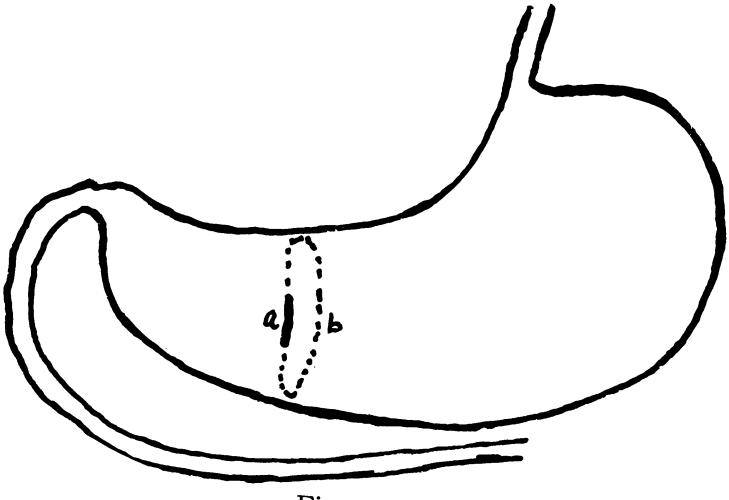


Figure 4

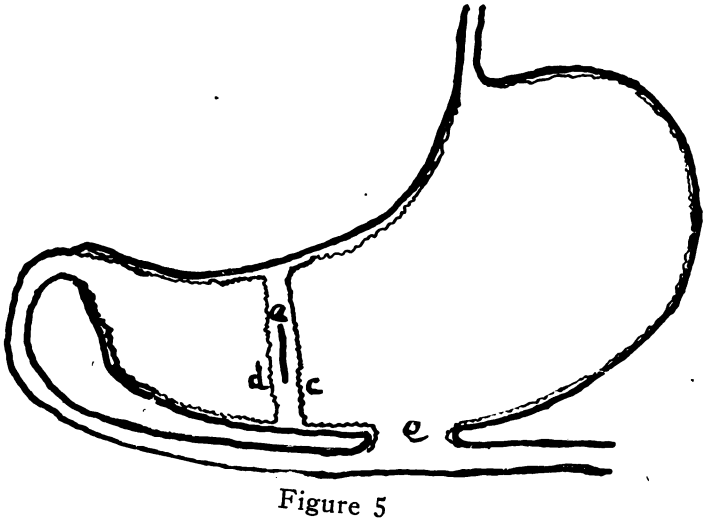


Figure 5

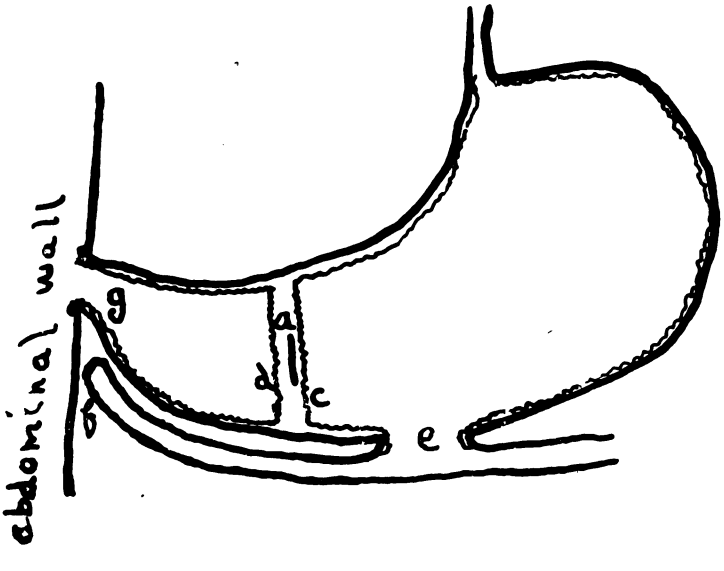


Figure 6

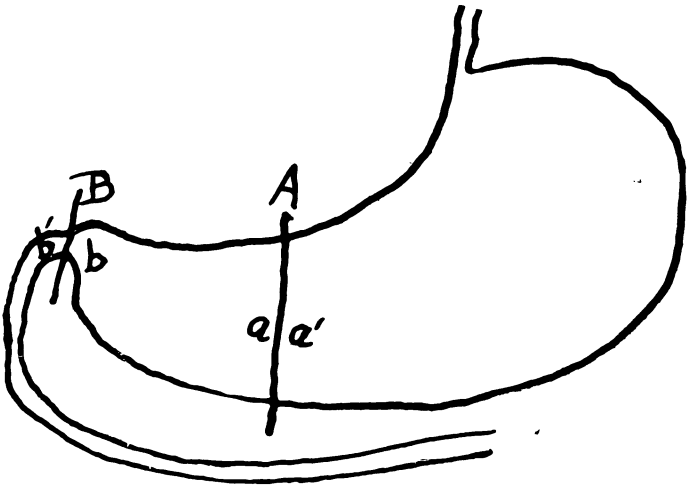


Figure 7

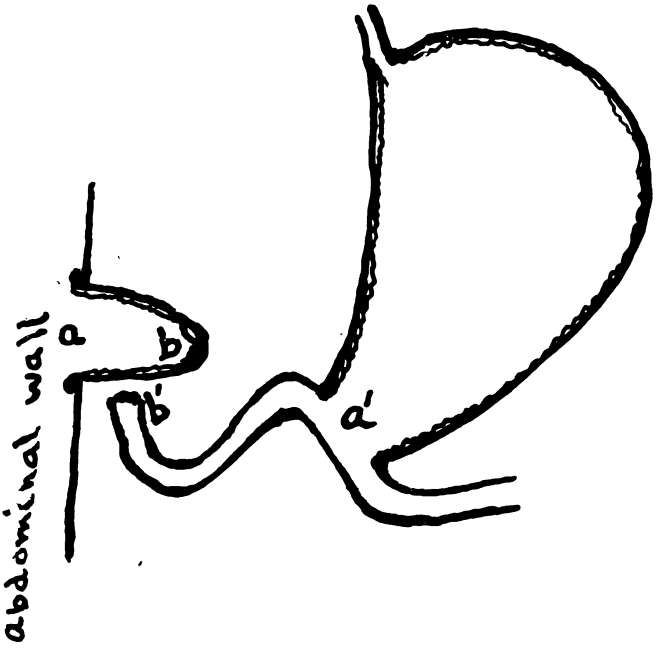


Figure 8

RESULTS

Dogs operated on as described by these methods live indefinitely in a good state of health. Their feeding must be looked after carefully for the first week or two. Bones should not be fed until two or three months after the operation. They cause obstruction at the point of gastroduodenostomy.

The study of the experimental production of chronic ulcer and the factors influencing the healing of acute ulcers is being continued by this method.

4. THE RELATION OF THE LOCATION OF THE ULCER TO CHANGES IN MOTILITY AND EMPTYING TIME OF THE STOMACH

All clinicians are generally agreed that in duodenal ulcer there is a retention of gastric contents and a hyperperistalsis of the stomach. The literature, however, is somewhat at variance concerning the motility of the stomach in ulcers of the pyloric portion of the stomach, unless a stenosis has been produced when the effects upon motility are practically identical with those of a duodenal ulcer. Dundon[26] studied the motility of the empty stomach in the condition of ulcer of the pyloric portion of the stomach and the duodenum. He concluded from his work that the motility of the empty stomach was greater in the condition of ulcer of the stomach and duodenum.

Desiring more complete and definite data on the relation of the location of the ulcer upon changes in motility and emptying time this study was undertaken.

METHODS

The motility of the empty stomach was studied three to five weeks previous to the making of an acute ulcer. The criteria used were: (1) the height of the contraction, (2) the frequency, (3) the length of the hunger and rest periods, (4) the type of the contractions, and (5) the postural and tonic activity of the stomach, the latter being determined by measuring the required amount of air necessary to be put into the balloon to raise the manometer level one inch.[27] This

26. Dundon, J. R.: Am. J. Physiol. **44**:234 (Sept.) 1917.

27. The amount of air required is practically constant from day to day, never varying more than 5 c.c. There is quite a variation between different dogs, varying from 15 to 40 c.c. After section of the vagi the amount required is from 10 to 20 c.c. more than normal. This is only temporary; after from ten to twelve days the amount required becomes normal again. It is a question whether this is a true measure of the postural or tonic activity of the stomach. It points in that direction, however. The normal amount required is not influenced by ulcer of the stomach or duodenum. For a day or two after making the ulcer the amount required may be from 5 to 10 c.c. below normal, however.

method of putting a fixed amount of air in the balloon gave a constant base line from which one could comparatively judge more accurately the character of the motility. The size of the balloon, the time of starvation, and as far as possible, the diet were controlled. Bones were not allowed to be fed because they are sometimes found in the stomach twenty-four hours after feeding. The state of nutrition of the dogs was guarded carefully. Dogs with the mange, sniffles, or any other disease were discarded. Ulcers were made by injecting 1.5 c.c. of a 5 per cent. silver nitrate solution beneath the mucosa. Ulcers were made in the anterior wall of the fundus in three dogs, in the anterior wall near the lesser curvature of the pyloric portion of the stomach from one-half to one inch proximal to the sphincter in five dogs and in the first inch of the duodenum in six dogs. Observations were made on the motility of the empty stomach for from three to seven weeks following the making of the ulcer.

Observations were also made on the emptying time of the stomach in ulcer of the fundic and pyloric portions of the stomach and the duodenum. A meal of 100 gm. of ground meat mixed with 50 c.c. of water was fed and its emptying time determined either by gastric fistula, emesis (morphin), and in some cases roentgenographically.

RESULTS

Ulcer of the fundic portion of the stomach had no effect on the motility of the empty stomach, save a slight temporary inhibition for the first two or three days following the making of the ulcer. The same held true for the emptying time, no delay occurring. Healed ulcers were found at necropsy.

TABLE 3.—Motility of the Stomach Before and After Ulcer of the Duodenum; Twenty-Four Hours' Starvation

Dog		Average Height of Contraction	Type	Average Length of Hunger Period	Average Length of Rest Period
IX	Before	5 cm.	I	40 min.	1½ hrs.
	After	7 cm.	I, II, III	2 hrs.	1 hr.
XII*	Before	Had to starve 80 hrs. before contractions occurred			
	After	5.5 cm.	I, II	30 min.	1 hr.
XVI	Before	7 cm.	I, II	1¼ hrs.	1¼ hrs.
	After	9 cm.	I, II, III	3 hrs.	30 min.
XXI	Before	4.5 cm.	I	1¼ hrs.	2 hrs.
	After	9.5 cm.	I, II, III	2¼ hrs.	1¾ hrs.
XXXII	Before	5 cm.	I	50 min.	2¼ hrs.
	After	5 cm.	I, II, III	3 hrs.	1½ hrs.
XXXIII	Before	5 cm.	I	1 hr.	3 hrs.
	After	7 cm.	I, II, III	3 hrs.	1 hr.

* An old animal.

Ulcer of the pyloric portion of the stomach caused in three out of five dogs an increase in the motility of the empty stomach. Here, too, a temporary inhibition of the motility for two or three days following the making of the ulcer occurred. The emptying time of the stomach was only interfered with in one of the dogs, in which there was a delay of two hours. In this dog at necropsy an extensive scar was found extending to the pyloric sphincter, but not involving it.

TABLE 4.—Showing Emptying Time of the Stomach Before and After Ulcer of the Duodenum

Dog	Normal Time of Emptying	Emptying Time after Ulcer, Duo.	Time Delayed	Remarks
IX	3 hrs.	5½ hrs.	2½ hrs.	
XII	3½ hrs.	5 hrs.	1½ hrs.	
XVI	3 hrs.	5¼ hrs.	2¼ hrs.	
XXI	2¾ hrs.	5½ hrs.	2¾ hrs.	
XXXII	4 hrs.	9 hrs.	5 hrs.	On a full meal this dog often had food in the stomach 24 hours after feeding
XXXIII	3¼ hrs.	5 hrs.	1¾ hrs.	

Ulcer located in the first inch of the duodenum caused an increase in the motility of the empty stomach in all of the six dogs (Table 3, Figs. 9, 10, 11 and 12). This increase was very marked in three of them. A delayed emptying time was observed (Table 4) in every animal. One animal showed a high grade retention to the degree that frequently food, that is on a full meal, was present in the stomach twenty-four hours after feeding. The hypermotility and retention only lasted from two to four weeks. On all these animals a necropsy was done and scars were found.

DISCUSSION

These results show that the clinical symptoms of chronic ulcer with respect to disturbed motility and emptying time of the stomach can practically be duplicated experimentally by an acute ulcer. The inhibition occurring for two or three days after making the ulcer is explained by the observations of Luckhardt[28] to the effect that gastritis inhibits motility, for a temporary gastritis is produced about the area of the injection of the silver nitrate. Why ulcer of the pyloric portion of the stomach and duodenum should disturb motility and ulcer of the fundic portion of the stomach is a question yet to be answered.

28. Luckhardt: loc. cit. Carlson, The Control of Hunger in Health and Disease, Chicago, 1916.

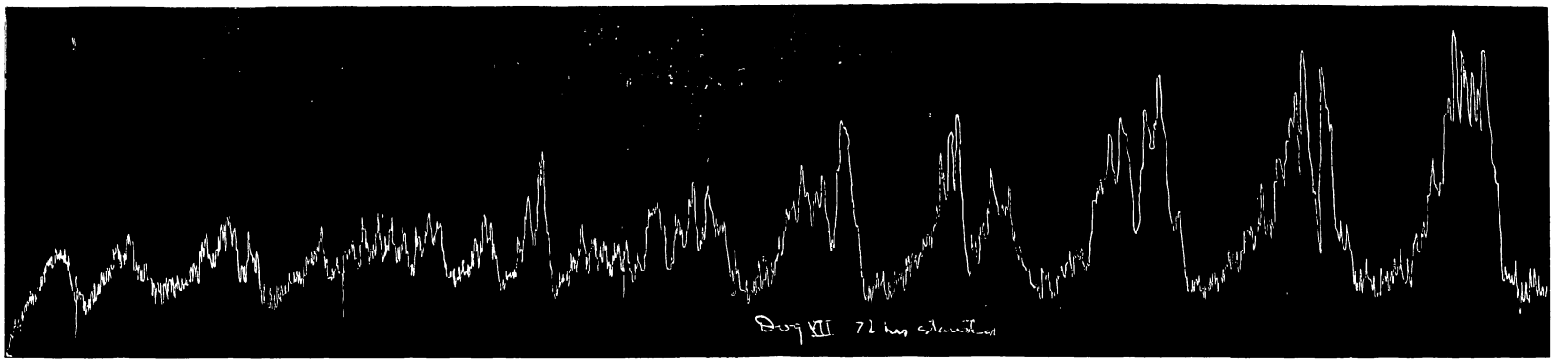


Fig. 9.—Contractions from an old dog (Dog 12, Tables 3 and 4) which had to be starved seventy-two hours before contractions occurred.

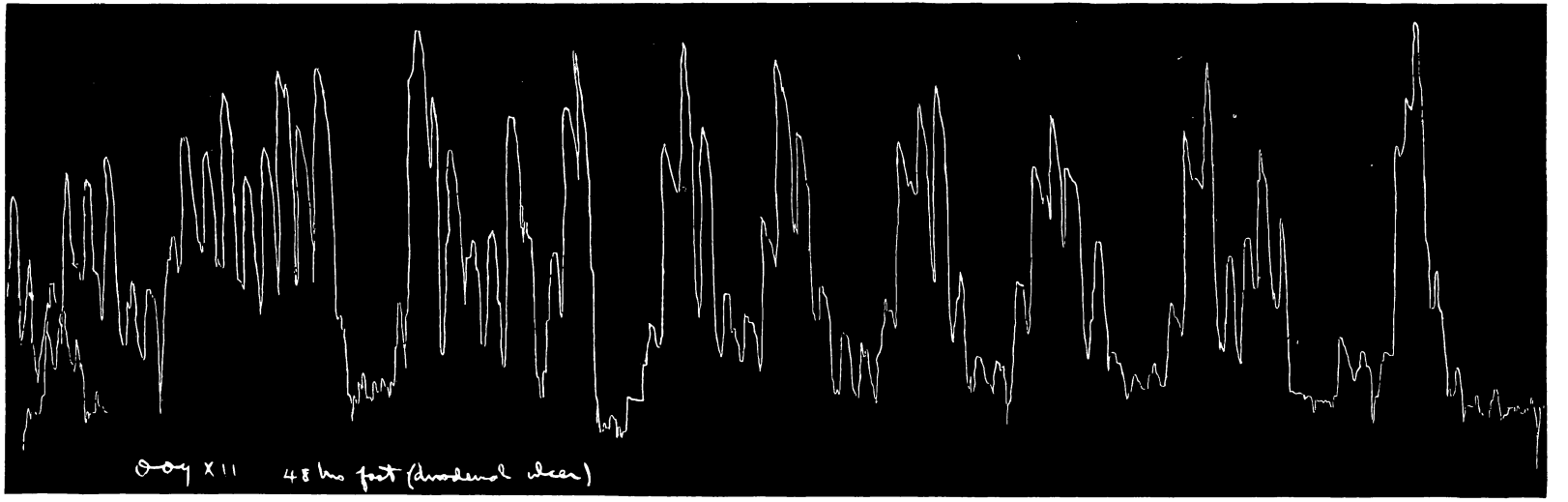


Fig. 10.—Contractions from the same dog after forty-eight hours' starvation following a duodenal ulcer.

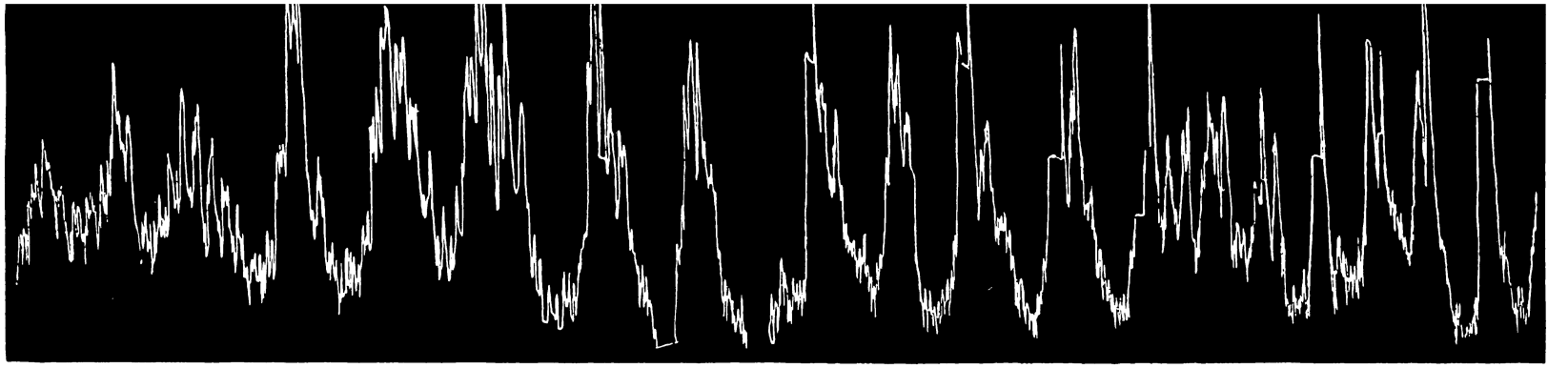


Fig. 11. — Contractions from Dog 9 (Tables 3 and 4) before making the duodenal ulcer.

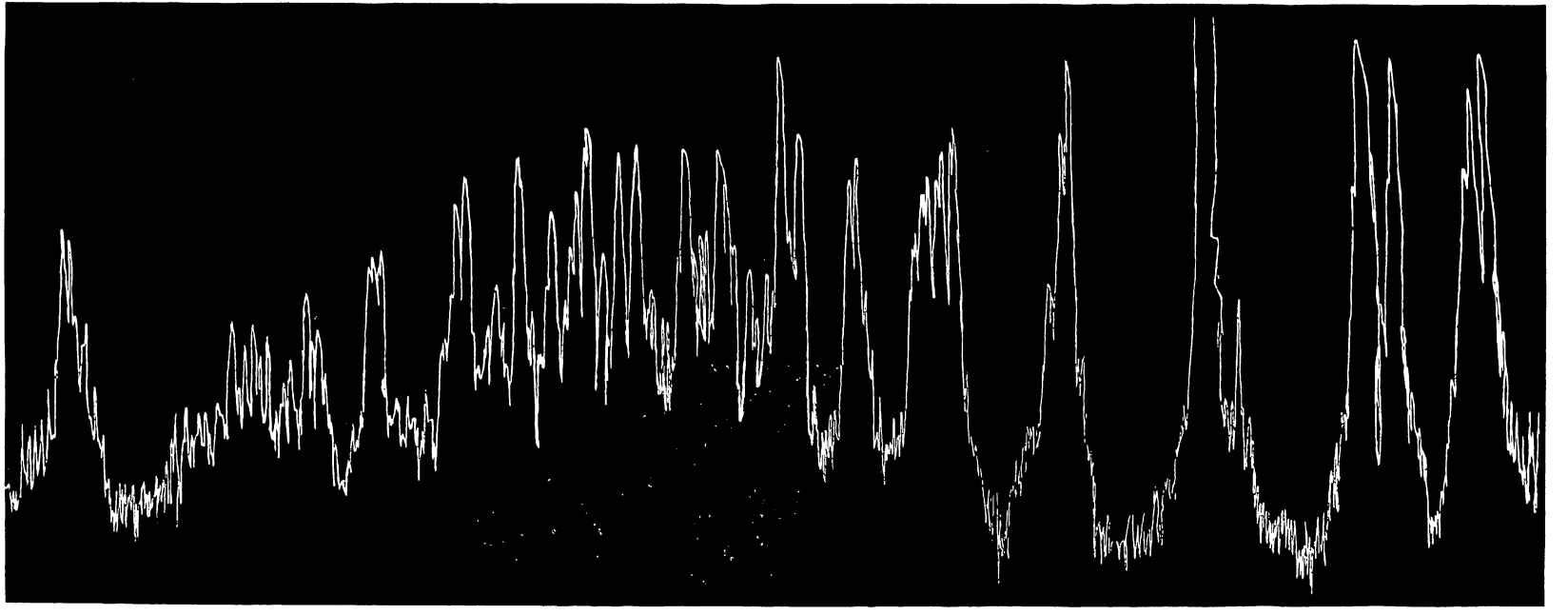


Fig. 12. — Contractions from same dog after making the duodenal ulcer. Dog was starved twenty-four hours in both cases.

5. IS HYPERMOTILITY AND DELAYED EMPTYING OF THE STOMACH IN DUODENAL ULCER DUE TO AN INTRINSIC OR EXTRINSIC MECHANISM?

Hypermotility and delayed emptying of the stomach as a result of duodenal ulcer may be caused by either one or a combination of four mechanisms: (1) to a long reflex to the cord and medulla, (2) to a short reflex to the celiac ganglion, (3) to a local intrinsic reflex, (4) or to an altered metabolic rate. Carlson[29] and Cannon[30] have shown that the isolated empty or full stomach, that is, with the extrinsic nerves sectioned, manifests normal movements. The movements of the isolated empty stomach are chiefly Type I, Types II and III, contractions seldom appearing. Brunemeier and Carlson[31] found that inhibition of contractions by acids, alkalies, water, milk, etc., occur in the isolated stomach, showing that it was possible to inhibit movements of the stomach via local or short nerve paths. Hicks and Vischer[32] showed that duodenal regurgitation when acid was in the stomach and that the characteristic movements by which this was accomplished occurred in the isolated stomach and duodenum. But the literature presents no evidence as to whether augmentation, or increased motility, can be brought about by local reflexes. On the other hand, the literature draws our attention to the importance of the extrinsic mechanism and uses the vagus nerve to explain all conditions of hypermotility, retention, pylorospasms, etc., without considering the possible importance of an intrinsic mechanism.

METHODS

Both vagi and splanchnics were sectioned and the celiac plexus was extirpated. Records were made of the motility of the empty stomach, using the criteria mentioned in Study 3. An acute ulcer was made in the first inch of the duodenum and changes in motility were observed.

Observations were made on the emptying time of the stomach before and after the ulcer. A meal of 100 gm. of ground meat mixed with 50 c.c. of water was fed.

RESULTS

An increase in the motility of the isolated empty stomach occurred (Table 5) following the making of the acute ulcer in the duodenum (Figs. 13, 14, 15 and 16). The degree of increase was not as great as that noticed when the extrinsic nerves were intact (Table 3). All

29. Carlson, A. J.: Am. J. Physiol. **32**:369, 1913.
30. Cannon, W. B.: Am. J. Physiol. **36**:191, 1915.
31. Brunemeier and Carlson: Am. J. Physiol. **36**:191, 1915.
32. Hicks and Vischer: Am. J. Physiol. **39**:1, 1915.

TABLE 5.—Motility of the Stomach Before and After Ulcer of the Duodenum in Dogs with Both Vagi and Splanchnics Sectioned and Celiac Plexus Extirpated, Twenty-Four Hours' Starvation

Dog		Average Height of Contraction	Type	Average Length of Hunger Period	Average Length of Rest Period
I	Before	6 cm.	I	1 hr. 40 min.	2 hrs.
	After	9 cm.	I	3 hrs. 20 min.	2 hrs.
I-A	Before	4 cm.	I	1 hr.	1 hr.
	After	8 cm.	I	2 hrs.	45 min.
XXXIII	Before	Contraction negligible on 24 hrs. starvation			
	After	8 cm.	I	3 hrs.	30 min.
XXI	Before	5 cm.	I	30 min.	1½ hrs.
	After	7 cm.	I	3½ hrs.	20 min.

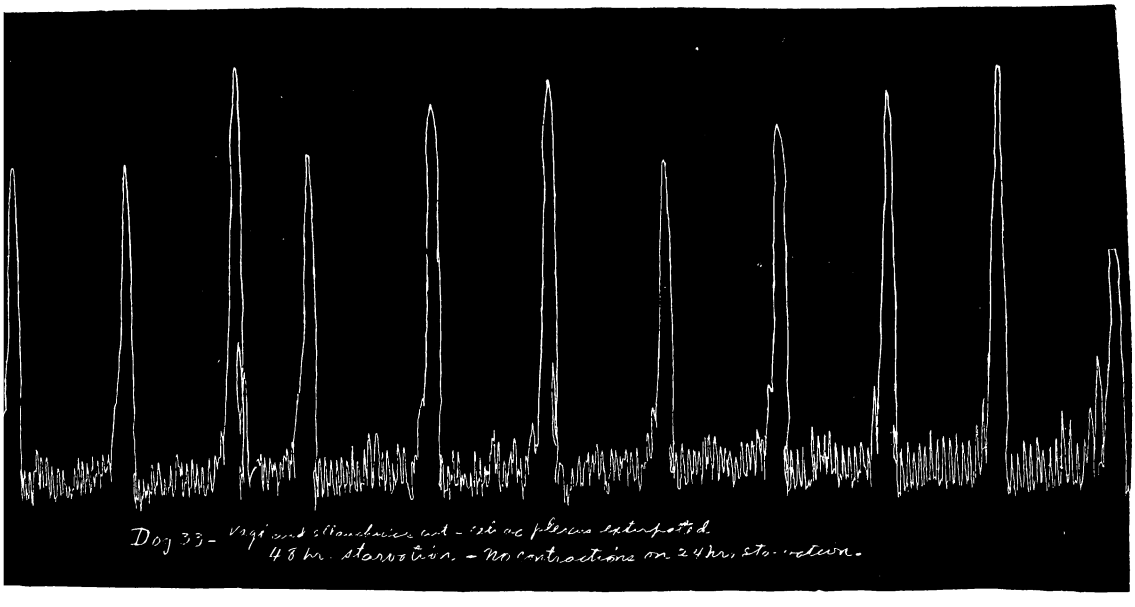


Fig. 13.—Contractions from Dog 33 (Tables 5 and 6) with both vagi and splanchnic sectioned and celiac plexus extirpated and starved twenty-four hours. Note type of contractions in the isolated stomach.

TABLE 6.—Showing Emptying Time of the Stomach Before and After Ulcer of the Duodenum in Dogs with Both Vagi and Splanchnics Sectioned and Celiac Plexus Extirpated

Dog	Normal Time of Emptying of Isolated Stomach	Emptying Time after Ulcer of Duodenum	Time Delayed
I-A	3¼ hrs.	4¾ hrs.	1½ hrs.
XXXIII	3¾ hrs.	5 hrs.	2¾ hrs.
XXI	3 hrs.	5 hrs.	2 hrs.

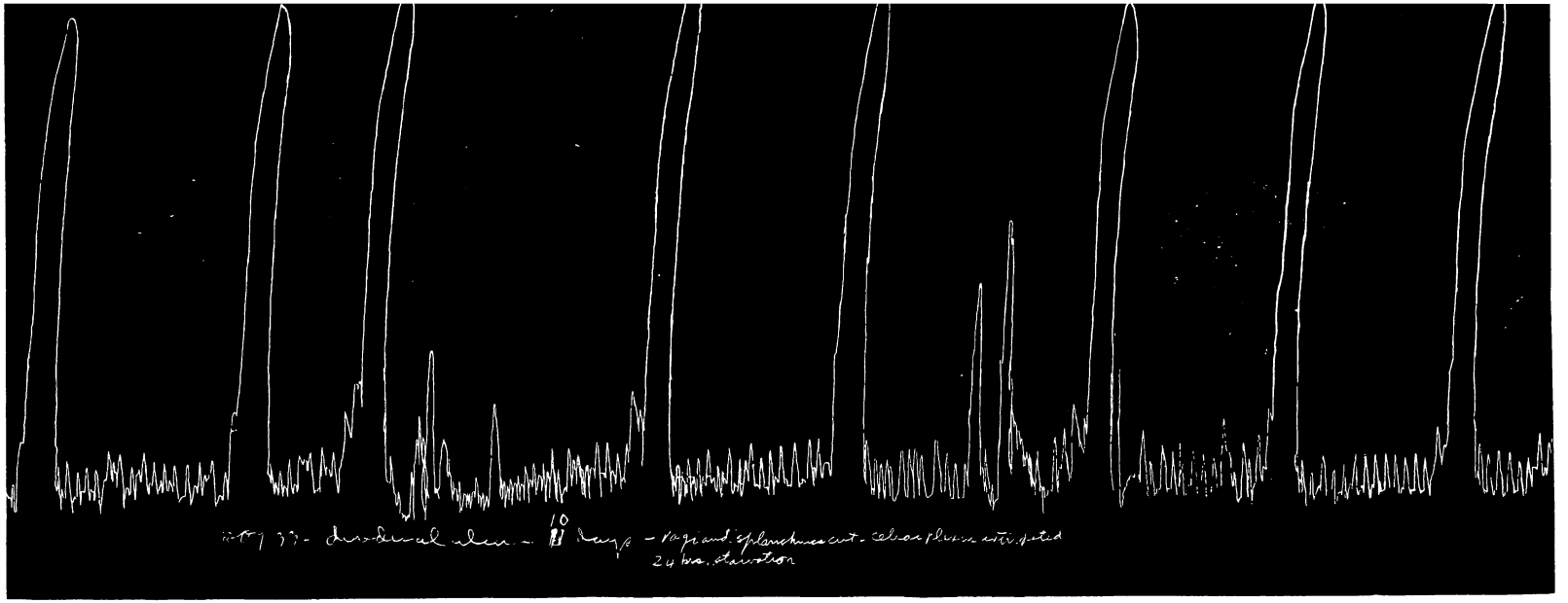
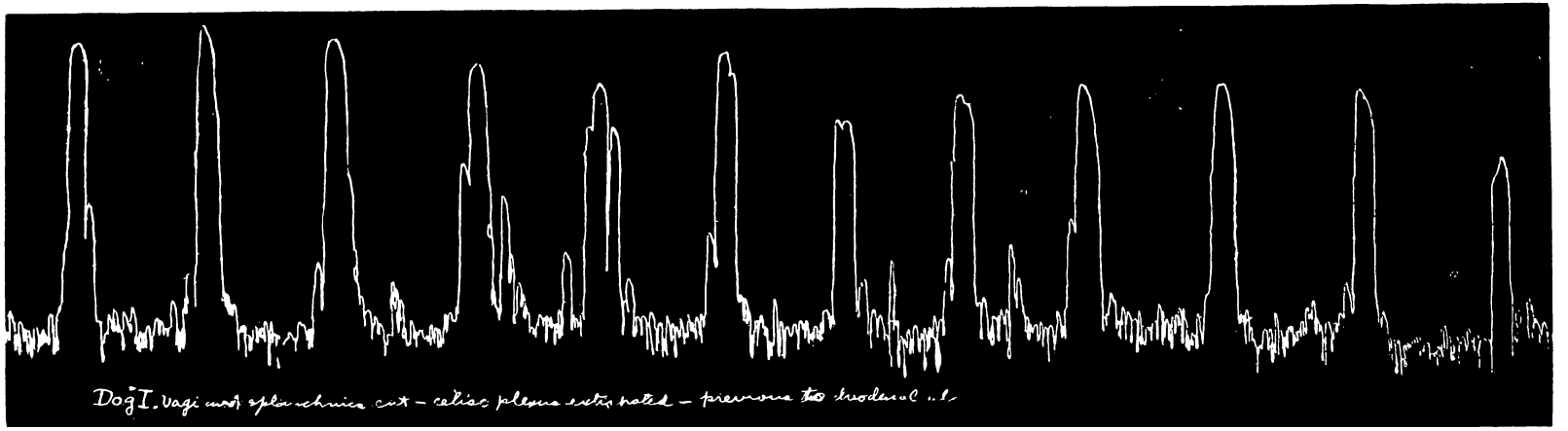


Fig. 14.—Contractions from the same dog after twenty-four hours' starvation with duodenal ulcer.



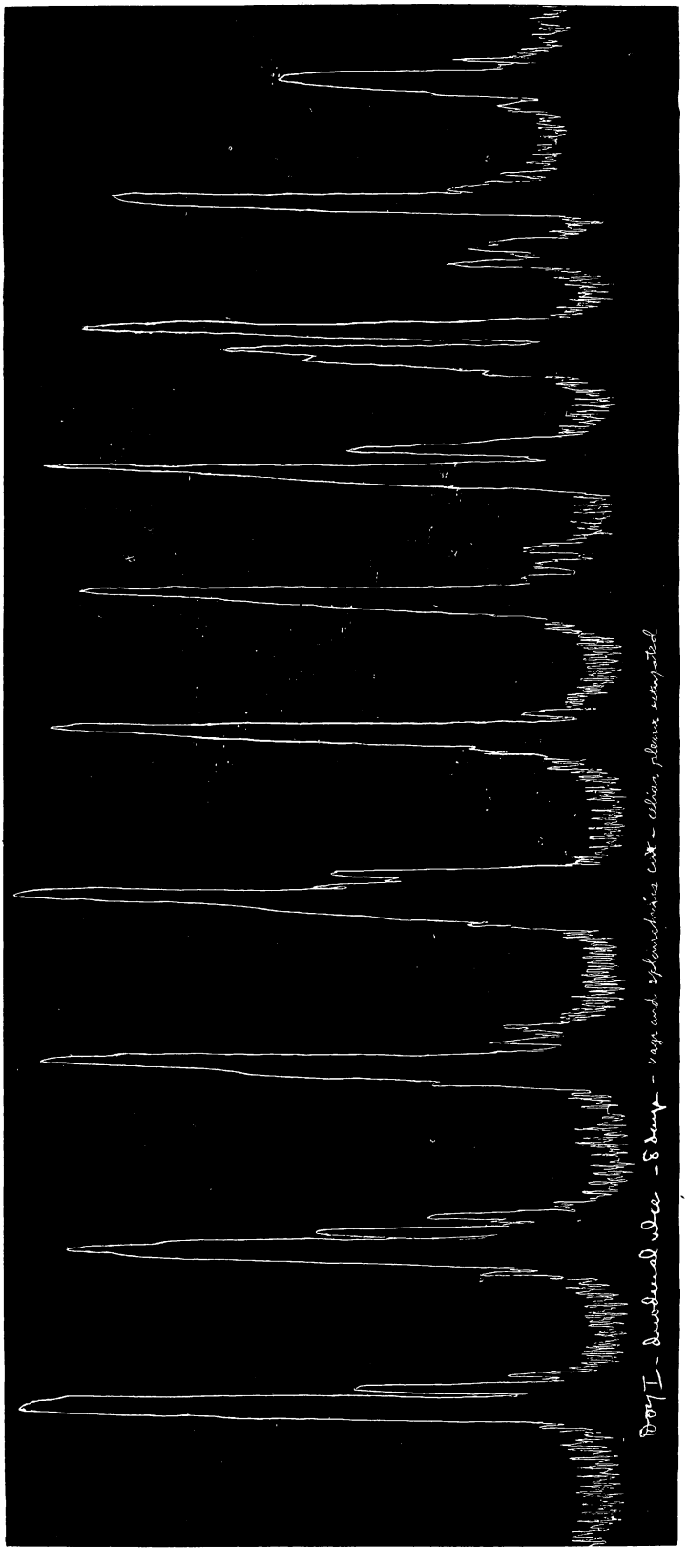


Fig. 16.—Contractions from the same dog after twenty-four hours' starvation with duodenal ulcer.

contractions were Type I, showing that the prevalence of Types II and III in normal animals (Table 3) with duodenal ulcer was due to an extrinsic mechanism.

The emptying of the stomach was delayed (Table 6), not so much as when the extrinsic nerves were intact (Table 4).

During the course of this study Brunemeier and Carlson's[31] observations on the inhibitory effect of alkalies and acids on the motility of the isolated stomach was repeated and confirmed.

DISCUSSION

These results show that the fundamental cause of the gastric hypermotility and delayed emptying of the stomach in duodenal ulcer is intrinsic, and that it is enhanced by the presence of the extrinsic nervous mechanism, the rôle of the latter being to increase the frequency of the contractions occuring on gastric tone, or Types II and III.

Although these results show that hypermotility and delayed emptying of the stomach in duodenal ulcer are due to intrinsic mechanism, they do not teach us the nature of the mechanism. There are two possibilities: (1) an increased irritability of the intrinsic nervous reflex, and (2) an altered metabolic rate.

ADDENDUM

Since writing this article my attention has been called to an article by Carman[33] in which he differentiates between extrinsic and intrinsic spasm by the use of atropin. He states that "intrinsic spasm plays an important part in the roentgenologic evidence of duodenal ulcers, and that in the absence of spasm no deformity of the bulb would be seen in many instances, and the case passed as negative." It is very interesting and important to note that my experimental results corroborate this clinical finding.

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33. Carman, R. D.: J. A. M. A. **66**:1283 (April 22) 1916.