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THE ULCER PROBLEM*

(I) Etiology, with Special Reference to an Inter-relationship Between the Vascular and the Acid-Peptic Digestive Factors.

(II) Characterization of a Satisfactory Operation Which Will Protect Against Recurrent Ulcer.

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IT is indeed a rare privilege to be asked to give one of the triennial lectures of your Association commemorating Lister, easily first amongst all surgeons of all time. My sense of genuine appreciation of this high honour is marred not alone by the knowledge that this compliment is ill-deserved, but also by serious personal misgivings over being able to bring something to you suitable to the occasion.

Pope once said: "His praise is lost who waits till all commend". So many eulogies have been spoken of Lister, his life and his great work, that it would ill befit me on this occasion to attempt to tell again what others before have said with lustre. If I were to attempt to add another stone to the coping-stone of encomiums with which Lister's life and work has been crowned, it would appear out of place and a slight to those who have done their work so well. Your own inimitable Archibald on a similar occasion said: "The chorus of his praise has become almost a liturgy, and one can only hope to write the liturgy in somewhat different phrases". It is fitting in contemplating the life of this great benefactor of surgery and society that we resign ourselves to the piety of memory, renew acquaintance with his ideals and reflect for a moment upon the arduous labours and glory of this great and good man. We need the example of men like Lister more than they need our praise. On the occasion of the Lister commemoration, it is fitting that we rededicate ourselves to the noble tasks which he so greatly advanced.

Accompanying publication of the first Listerian Oration by your own late John Stewart, of Halifax, the Lister Memorial Club of your Association made this announcement: "The first Listerian Oration published herewith is very properly concerned with the life and work of Lord Lister himself; subsequent orations may draw not only upon the various items associated with Lister's life, but may include also the story of all great and important advances in scientific surgery and medicine". I hesitate to be the first to break with the tradition of dealing with surgery in a historical manner on this important occasion, but with the kind permission of your officers, I shall attempt to tell you briefly something of the skirmishes that my associates and I have been having with the ulcer problem. Did not Lister himself break more forcibly with tradition in surgery than anyone else has before or since? Having the permission of your officers and the precedent of Lister's own example, I will embark on this undertaking without attempts at further justification.

THE ASPECTS OF THE ULCER PROBLEM TO BE DISCUSSED

This is not the place nor would time permit a general survey of the problem of ulcer. Your own Babkin (1944) has reviewed in a comprehensive manner the whole problem of gastric secretion and its relation to the ulcer problem. Rather, it is my intention in the time available to me to acquaint you with studies which my associates and I have been prosecuting on phases of the ulcer problem: (1) etiology, with special reference to an inter-relationship between the

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vascular and the acid-peptic digestive factors in the genesis of ulcer; (2) characterization of a satisfactory operation which will protect against recurrent ulcer.

My associates who have lent special impetus to the experimental phases of the work reported herein are: Drs. R. L. Varco, L. J. Hay, B. G. Lannin, K. A. Merendino, F. Kolouch, and I. Baronofsky. These men have successively spent a year or more in the Experimental Laboratory of Surgery. And during the last seven years, covering the period of their tenure in the laboratory, various phases of the ulcer problem have been worked upon intently. All of these men have had an important rôle in wresting from nature the observations reported herewith.

I.

ULCER PRODUCTION

Ulcer of the stomach and/or duodenum may be produced experimentally by several means. A number of occurrences have suggested the great importance of the acid-peptic digestion factor in the origin of ulcer. Foremost amongst these are: (1) the Mann-Williamson operation (1923) in which the bile and pancreatic juice are diverted away from the gastric outlet; and (2) the attachment of an isolated gastric pouch to a short intestinal loop, attached in turn to the jejunum or ileum (Matthews and Dragstedt, 1932). In both these procedures, no opportunity being available for the usual neutralization of the acid-peptic digestive juice by the alkaline digestive juices, ulcer follows both these procedures in nearly 100% of instances.

These circumstances, though they serve to emphasize the significance of unneutralized gastric juice in the genesis of ulcer, are nevertheless quite artificial. An important deterrent to general acceptance of the acid-peptic theory in the genesis of ulcer as suggested by these experiments was failure to produce ulcer by histamine, the most profound known stimulant of gastric secretion. Orndorff, Bergh and Ivy (1935) carried out a diligent attempt to provoke ulcer in dogs with histamine. Ten dogs were injected subcutaneously with 2 mgm. of aqueous histamine every 2 hours, day and night, 10 times a day, the dogs being allowed a 4 hour rest period daily. These daily injections extended over a period of 66 days. No ulcers were produced, but 4 of the 9 dogs in which the experiment was completed exhibited superficial erosions in the duodenum.

In 1939-1940 Charles Code, a graduate of the Medical School of the University of Manitoba at Winnipeg was working in our department of physiology at the University of Minnesota with Professor M. B. Visscher. Code was interested in the effects of histamine intoxication. Our laboratory in surgery was concerned with the problem of gastric secretion. We fused our efforts and through Code's interest a tool was created that has proved of real worth in studying the ulcer problem. Code and Varco (1940) implanted histamine-in-beeswax to permit its gradual liberation and thereby were able to elicit a prolonged histamine action. Employing 30 mgm. of histamine implanted in beeswax and injected once a day into dogs, ulcer could be produced quite regularly with doses not much larger than the total daily dose which was ineffective in the hands of Orndorff, Bergh, and Ivy (1935) when injected in aqueous solution.

The implantation of histamine-in-beeswax has proved a useful tool not alone in indicating the importance of the acid-peptic factor in the origin of ulcer, but at the same time it has constituted an excellent means of assaying the protective influence of a given operation against the ulcer diathesis.

In the earlier observations reported from this laboratory upon ulcer genesis, stress was placed primarily upon the acid factor. Subsequent observations have demonstrated that the peptic factor too is an item of importance in augmenting the injury occasioned by unneutralized acid. Kolouch (1945) observed that, when gastric juice containing both acid and pepsin, obtained from dogs with isolated gastric pouches under the influence of histamine stimulation, was dripped on to exposed mucosal surfaces of the antrum or duodenum in the dog, mucosal injury was greater than when hydrochloric acid alone of the same pH was employed as the dripping agent. Furthermore, observations made during the past two years suggest definitely that, ulcer may be produced by a variety of means which fail to augment gastric secretion. In these very experiments, acid peptic digestion is nevertheless an important agent in causing erosion and/or ulcer; that is, without the acid peptic digestive mixture gliding over the mucous membrane of the stomach or duodenum, ulcer would not occur. Before detailing some of these experiments, however, I would like to summarize the evidence on ulcer production in various animals with histamine stimulation.

A. *The histamine-in-beeswax provoked ulcer.*[29] —In Table I is shown in summary, the incidence

of ulcer production in various animals employing the histamine-in-beeswax technique. Only in the monkey and in the rabbit was it difficult to produce ulcer by stimulating the endogenous mechanism of the stomach to secrete. In the dog, the usual site of ulcer after histamine was very much like the spontaneous ulcer in man, the duodenum and the antrum being the sites of predilection. In the chicken and duck, the ulcers occurred in the gizzard; in the pig the squamous epithelium of the upper end of the stomach seemed most sensitive to acid-peptic

TABLE I.

INCIDENCE OF ULCER PRODUCTION IN VARIOUS ANIMALS ACCOMPANYING DAILY INTRAMUSCULAR IMPLANTATION OF HISTAMINE-IN-BEESWAX

Animal	*No. in series*	*Daily amount of histamine base milligrams*	*No. of days of injections*	*No. of ulcers*	*%*
Dogs.....	12	30	4-37	11	87.5
Guinea pigs.	8	5	2-11	6	75.0
Cats.....	5	5	3-28	4	80.0
Chickens...	3	7.5	4- 9	3	100.0
Ducks.....	2	20	20-26	2	100.0
Swine.....	3	40	13-15	3	100.0
Woodchucks	3	15-20	5-30	2	66.0
Calves.....	4	30 to 150	1-50	2	50.0
Monkeys....	4	20-50	23-59	1*	25.0
Rabbits....	8	7.5 to 30	5-41	1*	12.5

*Superficial erosive ulcer.

digestion and all the ulcers occurred in the cardia with perforation on to the pancreas. Perforation was frequent in the cat and guinea pig. In the main, the duodenum in most of our experimental animals, as in man, appeared to be a favourite site of ulcer formation; in many, however, the ulcer was in the stomach, and a number of animals presented both gastric and duodenal ulcers.

It is interesting that it was possible to produce ulcer quite regularly in the rabbit employing the histamine-in-beeswax technique, upon discarding the cellulose pulp of cabbage, carrots and lettuce, feeding only the juice which went through the press. By this means it was possible to get the rabbit's stomach empty, permitting the acid-peptic digestive mixture an opportunity to attack the gastric or duodenal wall directly. Perforated ulcers of the duodenum were produced in all of 4 rabbits subjected to this modification of the experiment.

B. *The vascular factor in ulcer genesis.*—Most of us come slowly to conclusions which are at variance with our previously held ideas. The import of the production of ulcers by the histamine-in-beeswax technique was to re-emphasize the significance of the acid-peptic digestion factor in the genesis of ulcer. No ulcer without free hydrochloric acid has come to be a commonplace expression. The frequency with which a bleeding ulcer becomes manifest for the first time in persons in the sixth or seventh decade has, undoubtedly, seemed a little unusual to clinicians who hold to the acid-peptic factor as being the important determinant in ulcer genesis. If those patients harboured the ulcer diathesis, why did they not manifest symptoms earlier in life?

In 1931, suction applied to an indwelling duodenal tube became standard practice in this clinic in the postoperative management of abdominal cases to prevent intestinal distension. Prior thereto, hæmatemesis was observed occasionally as a postoperative complication, especially in peritonitic distended abdomens. With the commencement of the use of suction as a routine postoperative measure to prevent the occurrence of distension, hæmatemesis disappeared as a postoperative complication. Eiselsberg, it is to be recalled, described this occurrence in 1899, and attributed it to retrograde thrombosis of the gastric wall, reaching the stomach via the omentum and mesentery. Payr (1907, 1910), and Wilkie (1911) both observed that retrograde embolism of the veins of the stomach with resultant formation of gastric erosions and/or ulcer could be produced by injection of particulate matter into the veins of the omentum. Wilkie's paper is written with that clarity of style that characterized all his work. In addition, his paper is accompanied by beautiful illustrations, several of which are in colour.

1. *Fracture and hæmatemesis.*[69]—

CASE 1

In 1940, severe hæmatemesis was observed in a man, L.W., aged 36, admitted December 9, 1940, with multiple fresh fractures sustained in an automobile accident. Fat was demonstrated in the urine the day following admission. A few days later repeated hæmatemesis and melæna, persisting a week and necessitating several transfusions of blood, occurred. The prothrombin time and vitamin C level in the blood were normal. The patient eventually made a satisfactory recovery and was dismissed to his physician on February 26, 1941. There had been no antecedent story of ulcer or bleeding.

CASE 2

The above occurrence was looked upon as a fortuitous circumstance until Mrs. K.A., aged 82, was admitted directly after having sustained a fractured neck of the left femur in a fall on March 15, 1942. During the next few days, the patient was mentally

confused and also incontinent. The hæmoglobin was 11.9 gm. On March 25 vomiting of blood and melæna occurred. There was quickening of the pulse and mild shock. Transfusions of blood and a constant intragastric drip of Varco formula No. II was begun on March 26; despite the transfusion of 1,000 c.c. of blood, the hæmoglobin was only 7.8 gm. The patient's condition worsened and death occurred March 29. There had been no antecedent story of ulcer prior to the fracture. At autopsy, an ulcer 15 x 22 mm. was found in the first portion of the duodenum on the posterior wall. The edges and floor of the ulcer were soft and the base appeared somewhat necrotic. Bronchopneumonia was present and the presence of a fracture was verified. Microscopically, the ulcer extended through the circular muscle of the duodenum and an interstitial antral gastritis was found.

CASE 3

Soon thereafter, a third patient, a young man, aged 17, was admitted on July 31, 1942, 11 days after having been injured in an automobile accident. He was unconscious for 5 days following the accident. When admitted here, a compound fracture of the right femur was present with considerable comminution of the shaft; there was also fracture of the right ankle, a hæmatoma in the scalp and a deep laceration of the right hand. Hæmatemesis occurred on August 8, 1942, and coffee-ground emesis thereafter was not infrequent, until death, which occurred August 15. The patient's course was febrile and stormy. Blood cultures were repeatedly negative. At autopsy the presence of multiple fractures was verified. A mucosal erosion 5 mm. in diameter was present in the midportion of the corpus of the stomach along the greater curvature. There was submucosal hæmorrhage about it. A submucosal area of hæmorrhage measuring 4 mm. in diameter was present at the lesser curvature, 2 cm. above the pylorus. Four additional hæmorrhagic areas were present in the antral mucosa measuring approximately 2 mm. in diameter. Microscopically, minute miliary abscesses were observed in the heart, liver, pancreas and brain.

CASE 4

In the meanwhile, a fourth patient, a Mr. E.C., aged 68, was observed in whom melæna occurred after fracture; he gave the following story. He was admitted with a fresh fracture of the neck of the right femur on March 27, 1942. On May 1, 1942, hæmatemesis and melæna occurred. The stools were consistently positive for blood. The patient had undergone gastrojejunostomy elsewhere 18 years previously for a duodenal ulcer. He had experienced occasional transient epigastric distress in the intervening years, but this was the first hæmorrhage since operation. An x-ray film on May 27, 1942, showed a large stomal ulcer 2 cm. in diameter. The patient did well on an ulcer regimen and was dismissed to his home on crutches on May 29, 1942. There has been no recurrence of melæna.

The pathological records of Dr. Bell's department revealed, over a 7 year interval (1926-1932) 15 additional cases of fracture in which hæmatemesis, ulcer and/or erosion, gastric and/or duodenal, was noted in the records of the postmortem examinations on fracture cases.

2. *Experimental production of ulcer and/or erosion by fracture or curettement of bone marrow.*[49, 50]—These observations just reported suggested the necessity of determining whether ulcer could be produced by fracture. A series of 6 guinea pigs was subjected to fracture of a femur. Some of the guinea pigs received repeated fractures of other long bones at weekly intervals. One developed a gastric ulcer. Two others exhibited a gastroduodenitis. An equal number of cats was treated in a similar fashion. No gastro-intestinal pathological results were noted.

Fifty-two dogs were subjected to a drill hole through both cortices of the humerus, a drill hole with curettage of the bone marrow, or fracture. These animals were sacrificed at various periods of time up to 23 days: 53% developed gastroduodenal disease. Erosions and/or ulcer of the stomach or duodenum were produced in 11 dogs (21%). In one instance a perforated duodenal ulcer was observed.

This evidence suggests a causal relationship between fracture and acid-peptic ulceration of the stomach and duodenum. Three possible explanations have been proposed: (1) A histamine effect from the fracture site with stimulation of gastric secretion; (2) fat embolism; (3) a combination of these two factors.

The fasting gastric samples of 10 fracture patients were analyzed for acid and volume. These samples were obtained the day following fracture and for several subsequent days. No stimulatory effect on the gastric secretory mechanism was observed as judged in the light of responses of normal patients without fracture.

Six dogs with isolated gastric pouches were studied. The operative trauma consisted of a drill hole through both cortices of the humerus, a drill hole with curettement of the bone marrow, or fracture. One animal exhibited a prolonged (24 hour) stimulation of gastric acid and volume following fracture. This result could not be reproduced in the same dog during a subsequent experiment.

Subsequently 18 intact dogs (including 3 controls) were subjected to a drill hole through both cortices of the humerus. Gastric aspirations were carried out daily for 23 days. No stimulation of the gastric response was observed in excess of that of the control animals nor of each individual dog's standard fasting curve prior to the trauma to the bone. In consequence, it may be concluded that a histamine effect is not the primary cause of the observed erosions or ulcerations of the stomach and duodenum following fracture.

3. *Ulcer production by the intravenous injection of fat.*[3]—It next remained to be determined whether ulcer could be produced experimentally

by the intravenous injection of fat. Human breast or omental fat was employed, obtained from surgical procedures and extracted with ether. One and one-half c.c. of fat per kilogram of body weight was injected intravenously. It has previously been stated that rabbits are quite refractory to ulcer production by histamine alone. In each of 6 rabbits, whose weights averaged 1.74 kilograms, a single intravenous injection of 1.5 to 2 c.c. of fat was made. Then 30 mgm. of histamine-in-beeswax was implanted once daily for from one to four days. No dietary strictures were imposed on the rabbits. A perforated ulcer occurred in each instance save one, and that rabbit died of pulmonary embolism shortly after the fat injection (Fig. 1). Three rabbits were injected with fat but were given no histamine. Ulcer did not develop. In two additional rabbits, a daily implantation of 30 mgm. of histamine-in-beeswax was made; in one over a period of 28 days, in the other for 28 days; neither developed ulcer.

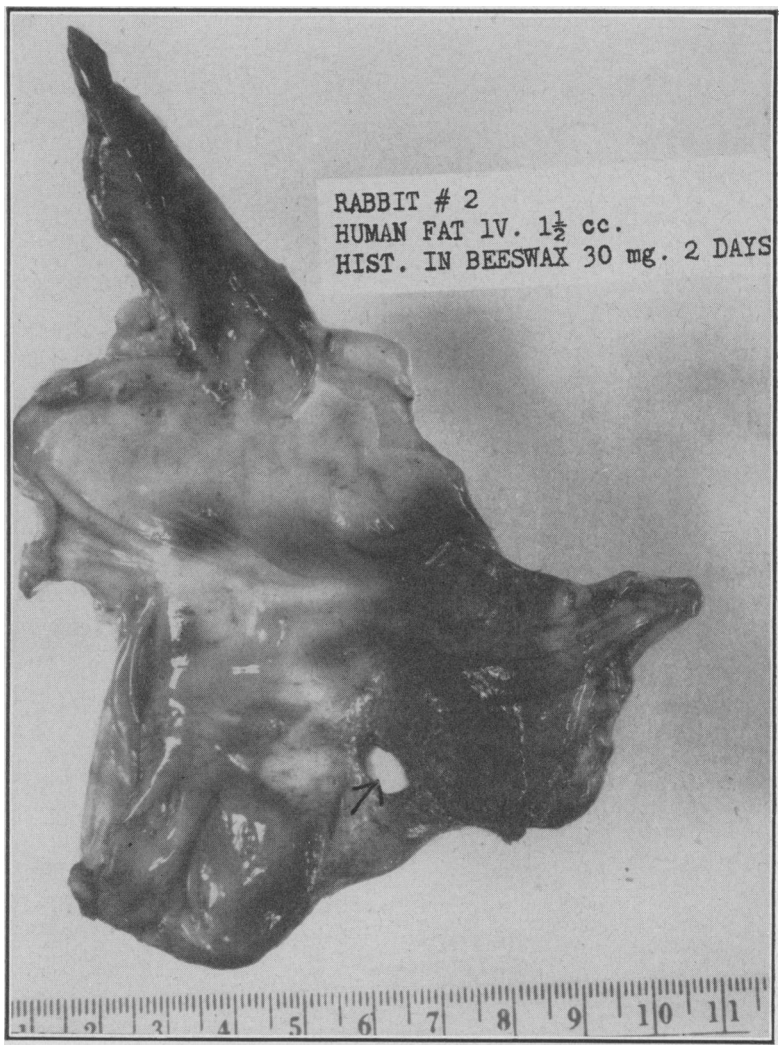


Fig. 1.—Perforated ulcer in stomach of a rabbit after single injection of 1.5 c.c. of human omental fat. Histamine-in-beeswax (30 mgm.) was given for 2 days. The rabbit is quite refractory to the production of ulcer with histamine. In other words, the intravenous injection of fat sensitized the rabbit to ulcer. (Illustrations of ulcer produced in various animals by histamine accompany the paper by Hay *et al.*, in *Surg., Gyn. & Obst.*, **75:** 170, 1942).

Similar studies were carried out on cats, dogs and guinea pigs which received no histamine. A single intravenous injection of fat, 1.5 c.c. per kilogram in amount, was made into each animal; of 6 cats injected, 2 developed ulcers; one at 4, the other 18 days after the fat injection. Of 2 guinea pigs injected with fat, both exhibited typical gastric ulcers. Of 7 dogs given a single intravenous injection of fat, a bleeding duodenal ulcer was found in one dog sacrificed 14 days after the fat injection. Of 3 dogs that received 30 mgm. of histamine-in-beeswax daily following a single intravenous injection of fat, all developed multiple bleeding duodenal and gastric ulcers, within 3 days after the first injection of histamine.

Microscopic studies were made of tissues stained with Sudan III in all the 52 animals receiving fat intravenously, a single block of brain, lung, kidney, and stomach being studied in each instance. It is to be noted in Table II

TABLE II.

INFLUENCE OF TIME INTERVAL ON OCCURRENCE OF FAT EMBOLI ATTENDING THE INTRAVENOUS INJECTION OF FAT

Sacrificed from 1 to 4 days after fat injection: No. of animals	*Amount of fat injected*	*% of tissues revealing fat emboli:*			
		Lung	*Brain*	*Kidney*	*Stomach*
(A) 23	1½ c.c./kg.	91	60	73.9	47.8
Sacrificed from 5 to 21 days after fat injection:					
(B) 29	1½ c.c./kg.	41	11.1	34.4	3.7

that the identification of fat in the stained sections was considerably higher, especially in the stomach, in the animals sacrificed and studied within one to four days after the fat was injected intravenously.[4a]

4. *Interpretation of these observations.*—Fat injected intravenously does not stimulate nor augment gastric secretion in dogs with isolated gastric pouches. The mechanism of ulcer production undoubtedly is that of plugging the end vessels to the mucosa; the resultant anæmic areas in the mucosa become less resistant to injury and digestion by the acid-peptic juice, than is the normal mucosa. The rate of disappearance of the fat from the mucosal and submucosal gastric vessels is rapid as indicated in Table II. This circumstance undoubtedly accounts for the fact that hæmatemesis, erosions or ulcer have not been observed more commonly to accompany fracture of long bones in man. That fat emboli in the lung and brain are common occurrences in patients dying early after fracture of long bones is well known (Le Count and Gauss, 1915; Bissell, 1916). In response to an injury addressed to 50 American orthopædic surgeons concerning the occurrence of hæmatemesis or ulcer after fracture, 42 replies were received. None reported observing ulcer or hæmatemesis in patients not previously having ulcer. However, one instance very similar to Case 4 above was reported to me by Dr. R. C. Webb, of Minneapolis. His patient, like my Case 4, had undergone gastrojejunostomy previously for a duodenal ulcer; a temporary bleeding stomal ulcer appeared shortly after the fracture, which responded promptly to conservative management. Two surgeons each reported having observed hæmatemesis once after the manipulation of a stiff joint under anæsthesia.

The only previous allusion to the occurrence of erosion and/or ulcer following fracture, that I have been able to find in the literature, is to be found in a discussion of a paper by Sternberg (1907), entitled, "Experimental Production of Gastric Ulcers in the Guinea Pig". Sternberg was discussing the influence of alcohol in the production of ulcers and the process by which acute erosions become chronic ulcers. In the discussion of Sternberg's paper, Schridde stated that he had twice observed fat embolism at postmortem in the submucosal gastric arteries accompanying fracture. In one patient, a 70-year old man, there were numerous erosions and 20 superficial ulcers. The patient died of coma which had persisted following the fracture. Schmorl in a 6-line discussion at the same meeting of the German Pathological Society (1907) stated that, he, too, had observed punctate hæmorrhages in the gastric mucosa due to fat embolism following fractures and severe bodily contusions.

Florer and Ochsner (1945) recently reported the instance of a boy of 14 who sustained rupture of the thoracic duct and chylothorax following injury. The chyle was reaspirated and injected intravenously. The boy died of a perforated duodenal ulcer 25 days after receipt of the injury. Is one justified in wondering whether the fat from the injected chyle attained larger particulate size on standing in the pleural cavity thus giving rise to embolism on injection? In other words, did the intravenously injected fat play an important rôle in the development of the ulcer?

These studies on the relation of erosion and/or ulcer to fat embolism following fracture or amputation are by no means complete. With the helpful co-operation of Professor E. T. Bell and his associates of the Department of Pathology, we are now beginning to collect evidence on the presence or absence of fat emboli in the mucosal and submucosal vessels of patients dying of multiple fractures shortly after receipt of injury. In the few patients thus far studied, it would appear that fat embolism of the gastric end-vessels is just as common as it was in the experimental studies reported herein. It may be justifiable to ask whether bacterial emboli may not also give rise to gastric hæmorrhage.

5. *The epinephrine provoked ulcer.*[4]—The production of ulcer by the intravenous injection of fat suggested that an attempt be made to produce chronic vasomotor arterial spasm, to note whether ulcer would follow.

Fourteen rabbits were subjected to daily intramuscular injections of 2 mgm. of powdered epinephrine and 30 mgm. of histamine dihydrochloride computed as histamine base, each implanted in beeswax. The difficulty of producing ulcers in rabbits by implantation of histamine in beeswax alone has already been mentioned; however, in the 14 rabbits in which implantation of powdered epinephrine was made in beeswax, accompanied by the simultaneous administration of histamine-in-beeswax, ulcer or erosion occurred in each instance. Seven rabbits had 1

or more perforated gastric or duodenal ulcers. Of the remainder, 2 showed bleeding gastric ulcers and the rest had multiple bleeding gastric ulcers in the fundus or pylorus. There was evidence of gross hæmorrhage into the gastrointestinal tract in all. The average length of survival was 4 days. Controls given histamine-in-beeswax alone up to 10 days showed no evidence of either erosion or ulcer.

Two dogs were given intramuscular injections of 8 mgm. of epinephrine in beeswax daily. One animal died of gastrointestinal hæmorrhage after 4 injections and the other after 2 injections. Marked dilatation of the stomach and a severe gastritis and duodenitis with multiple erosions and bleeding points in both stomach and duodenum were noted in both of these dogs. A small shallow duodenal ulcer was noted in one. Fresh blood was present in the stomach and duodenum in both dogs. In 2 guinea pigs, 2 mgm. aqueous adrenalin was suspended in gelatin and injected intramuscularly. In both guinea pigs erosions and shallow ulcers were observed in the stomachs after the daily administration of this dose of adrenalin for 3 days. Repeated tests with adrenalin in aqueous form failed to reveal any definite stimulation of gastric secretion in Heidenhain and Pavlov pouch dogs.

6. *The pitressin provoked ulcer.*—Dodds and associates (1934) produced superficial erosions and hæmorrhages in the mucosa of the fundus of the stomach of several laboratory animals by a single injection of pitressin. Later (1935) Dodds and his associates reported having produced chronic ulcer with perforation in rabbits by giving 40 c.c. of the British Pharmacopœia pituitrin by stomach tube once a week over 8 weeks. Ulcer was also produced by giving 5 c.c. of the British Pharmacopœia extract subcutaneously to rabbits every other day for 4 injections.

Dodds and his associates (1935) failed to obtain evidence of stimulation of gastric secretion with pituitrin. On the contrary, they observed evidence that pituitrin inhibited the usual stimulating effect of a small dose of histamine. Nedzel (1938) confirmed these observations of Dodds and his associates and stated that vascular interference with local nutrition of the gastric mucosa is the primary factor in the production of hæmorrhages and erosions. Byrom (1937) observed that the giving of large single doses of pitressin (740 pressor units) produced gross lesions in the kidney, liver, and other organs characterized by ischæmia and necrosis. Hæmorrhagic erosions also were observed in the stomach. Byrom believed these changes to be caused by an intense arterial spasm which produced ischæmia and necrosis.

The observations of Dodds and his associates and of Nedzel were confirmed in our own observations on cats, guinea pigs and rabbits. The depressant action of pitressin on gastric secretion also was verified on dogs with isolated Heidenhain or Pavlov pouches. The conclusion is that the chronic arterial spasm invoked by epinephrine or pitressin produces local areas of anæmia in the gastric mucosa which then become susceptible to the acid-peptic digestive activity of the gastric juice.

7. *The production of bleeding from gastric and œsophageal erosions and/or ulcer invoked by obstruction of the portal circulation.*—Gastric hæmorrhage in obstruction of the portal vein or its tributaries is not an uncommon clinical occurrence. Such bleeding usually has been attributed to the bursting of mucosal or submucosal œsophageal varices. Patients with obstruction of the superior vena cava exhibiting œsophageal varices, do not bleed however. May not the increased venous pressure resulting from portal obstruction render the gastric mucosa more susceptible to erosion of the acid-peptic digestive juice? It appears safe to conclude that arterial spasm of the gastric end-vessels invites erosion of the gastric mucosa by the acid-peptic digestive activity of the gastric juice. Why should not mucosal congestion brought about by venous stasis lead to the same result?

To test the validity of this hypothesis, the following experiments were carried out on rabbits and dogs in three series. In each series a partial obstruction to the normal venous return of blood from the stomach to the portal system was made. In two of the series, the normal flow of venous blood from the left gastro-epiploic vein into the splenic was obstructed by a tie placed proximal to their juncture. In the third series cellophane was placed snugly around the portal vein as it lay in the gastrohepatic omentum. Pearse (1940) has shown that cellophane, when placed around the aorta, will slowly obliterate this vessel, an occurrence occasioned through the agency of a severe fibroblastic reaction within six weeks of the placement of the cellophane ligature. These procedures were tolerated very well by the animals, and all ani-

mals were eating and drinking normally as soon as the effects of the anæsthetic wore off. After an interval of 2 days after operation in the splenic-tie series and an average of 113 days in the portal-tie series, the daily administration of 30 mgm. of the histamine-in-beeswax mixture prepared after the method of Code and Varco (1940) was commenced. The time of sacrifice in the dogs was determined by the occurrence of spontaneous hæmatemesis, melæna or extreme weakness. The rabbits were sacrified at varying periods of time. In all animals the stomachs were weighed. An effort was made simultaneously to garner control data on the weights of normal stomachs in both rabbits and dogs.

Results.—Transient immediate increase in size of the spleen attended partial venous obstruction of the stomach and splenic vein. In the dogs with obstruction of the portal vein, a well-developed collateral circulation was noted. The veins of Retzius, the anastomosis of the superior hæmorrhoidal vein, the œsophageal veins and the veins coursing through the omentum were uniformly enlarged and prominent.

In series I consisting of 5 dogs, the splenic, the left gastric and the left gastroepiploic veins were divided and tied. Two days later the administration of 30 mgm. of histamine-in-beeswax was commenced. The dogs were sacrificed when they appeared ill, 4 on the fourth day after ligature of the splenic vein, and the other on the sixth day. All dogs exhibited severe bleeding and there were large duodenal and/or gastric ulcers in all. Three exhibited erosions in the

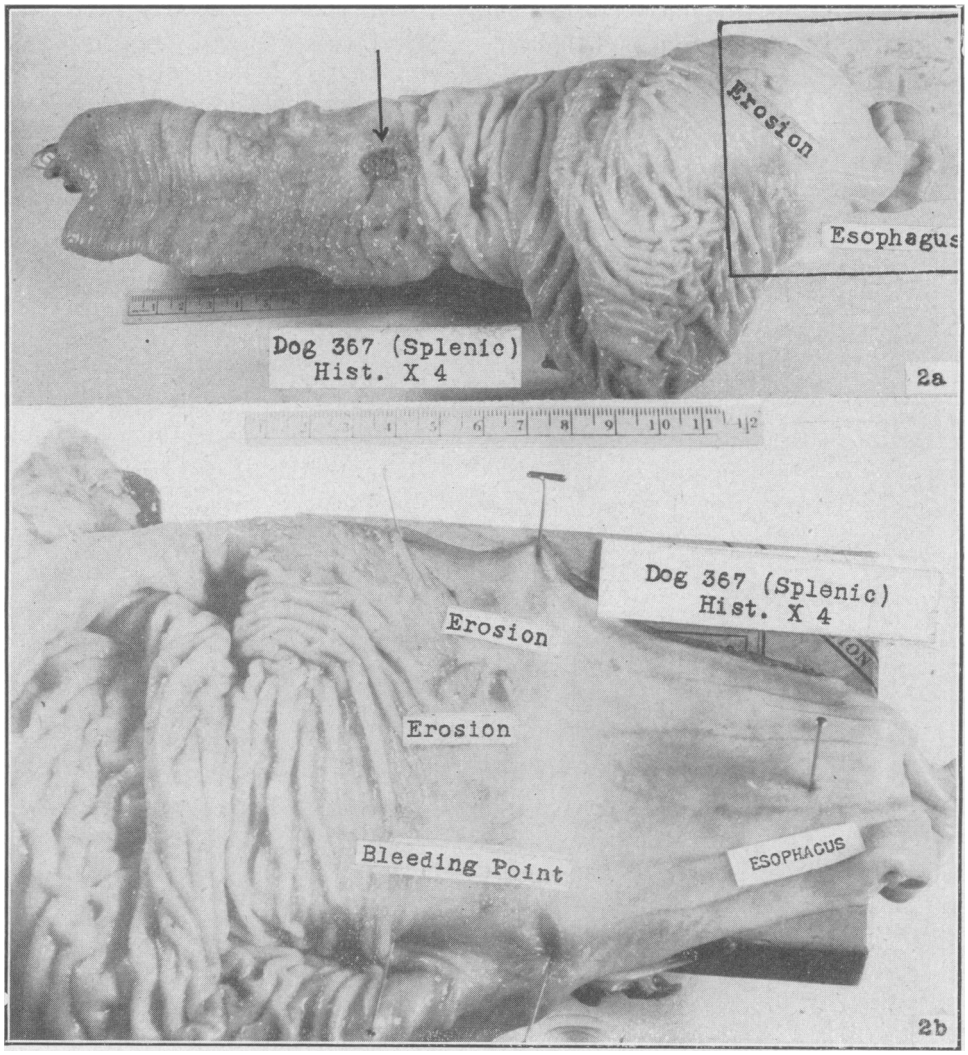


Fig. 2.—Duodenal ulcer (a) and peri-œsophageal erosions (b) in the upper end of the stomach in a dog after ligature of the splenic, left, gastric and left gastro-epiploic veins. The dog received 30 mgm. of histamine-in-beeswax daily for 4 days. There was considerable blood in the stomach. (a) Orientation photograph. (b) "Close-up" of bleeding erosions in upper end of the stomach.

lower end of the œsophagus (Fig. 2). Five other dogs were employed as controls. In 2 the veins were tied, but no histamine was given. These dogs were sacrificed 71 days later. No ulcers or erosions were found. In 3 other dogs, no vein ligatures were made, but the dogs were given 30 mgm. histamine-in-beeswax daily, for 2 to 4 days before sacrifice. None of these exhibited erosions or ulcer. The stomachs of all dogs with vein ligatures were distinctly heavier than the 2 control dogs which received histamine alone.

In Series II, there were 4 dogs, in all of which the portal vein was obstructed by a cellophane ligature. Two received histamine-in-beeswax; 2 did not. The 2 dogs receiving histamine were killed within 3 days after commencement of its administration. Both these dogs exhibited large perforating duodenal ulcers. In one there was bleeding from an eroded œsophageal varix. The other dog exhibited multiple bleeding gastric ulcers. The 2 dogs not receiving histamine had heavy stomachs, but exhibited no ulcers. In one there was a submucosal hæmorrhage in the lower end of the œsophagus. The portal vein had been obstructed 150 days before.

TABLE III.
WEIGHTS OF STOMACHS OF RABBITS SUBJECTED TO SPLENIC VEIN LEFT GASTRIC AND GASTRO-EPIPLOIC VEIN LIGATION WITH OR WITHOUT HISTAMINE

No. of rabbits	*Procedure*	*Average weight of rabbits*	*Average weight of stomachs in grams*
13	Splenic-tie Histamine	1.8 kg.	32.03
11	No splenic-tie No histamine	1.8 kg.	21.4
Controls: 4	Histamine-in-beeswax 30 mgm. every day for 17, 21, 21, 28 days respectively. No splenic-tie	1.8 kg.	21.3

In Series III, there were 18 rabbits. The vein ligatures were the same as in the dogs in Series I. In 9 rabbits, the vein ligatures were followed by the daily administration of 30 mgm. of histamine-in-beeswax for 1 to 7 days before sacrifice. In 8 of these 9 rabbits, bleeding erosions and/or ulcer were present. In two, bleeding erosive lesions in the lower œsophagus were present. There were 9 controls. In 4 rabbits, the vein ligatures were carried out, but the animals received no histamine. There were no erosions or ulcers. Five received histamine, but the veins were not obstructed. Neither erosions nor ulcers were observed in this group.

It is apparent from these experiments that obstruction of the venous drainage from the stomach abets the ulcer diathesis. That is, erosions and ulcer are far more readily provoked with histamine in the presence of portal hypertension than when there is no obstruction to venous outflow of blood from the stomach. The difficulty of producing ulcer in rabbits by histamine alone has been mentioned already. However, as is indicated herein, bleeding ulcers and erosions follow regularly when histamine administration is preceded by ligature and division of the splenic vein. In the dog too, ulcer is produced regularly in a surprisingly short time when the venous drainage from the stomach is obstructed, accompanied by the administration of histamine. Œsophageal varices were observed regularly in the experiments of longer duration, in which the portal vein was obstructed. Œsophageal erosions were observed in several of the dogs.

Another striking finding was the uniform increase in weight of the stomachs of both rabbits (see Table III) and dogs, in which obstruction to the venous outflow from the stomach had been established. Microscopically, this occurrence appears to be due to an œdema of the entire gastric wall, but especially of the submucosa. Erosion of the mucosa by acid occurs readily when the blood supply has been altered by obstructing the venous outflow.

C. *Clinical observations.*—In this section it is my purpose to draw attention to two clinical features relating to the preceding recitation of experimental observations. The first of these relates to a group of cases presenting occult bleeding from the gastro-intestinal canal, in which antecedent studies, if made before shock and severe anæmia supervened, are negative. The conditions, represented in the case histories to be recited are well-known pathological entities. The cause of the bleeding remains obscure and death supervenes because of uncontrolled hæmorrhage. At autopsy, the surprise finding is usually a small superficial erosion with a sclerotic artery in the base of the erosion. If no ulcerative lesion in the mucosa is detectable grossly, microscopic examination discloses either an arterial thrombosis of a segment of the gastric wall or an ulcerative gastritis with atrophy of

the mucous membrane. My special purpose in listing these cases is to indicate that the gastric mucous membrane is frequently a source, if not the *usual* source of occult bleeding from the gastro-intestinal canal; and that a 75% gastric resection, as is done for ulcer, usually will rescue these patients from death from hæmorrhage.

The second group is represented by 4 patients with portal hypertension caused by cirrhosis of the liver or thrombophlebitis of the portal and/or splenic vein. In this group of patients, all of whom have presented severe anæmia from hæmatemesis and/or melæna, an extensive (90%) gastric resection has been done on the thesis that the bleeding was an erosive process occasioned by acid-peptic digestion of the gastric and lower œsophageal mucous membrane in the presence of portal hypertension causing venous stasis. The clinical and x-ray diagnosis of the cause of bleeding in all these patients has been *œsophageal varices.*

1. *Hæmatemesis and melæna from superficial gastric erosion, arterial thrombosis of a gastric vessel or ulcerative gastritis.*—

CASE 1

Mr. H.J., aged 44, admitted June 5, 1944, because of hæmatemesis and melæna. Four transfusions for bleeding and shock before admission. Hæmoglobin on admission, 4 gm. Hæmatemesis continued and despite several transfusions hæmoglobin was brought only to 6.5 gm. Exploration on June 7. No lesion felt in the stomach or duodenum. A 75% gastric resection was done and in the excised specimen, high on the lesser curvature there was a tiny shallow ulcer about 2 mm. in diameter. The removed stomach weighed 130 grams. Microscopically, there was atrophy of the mucosa. There has been no recurrence of bleeding. On January 30, 1945, the hæmoglobin was 14.2 gm. The patient reported in again on May 2, 1945, stating that he was well and working.

CASE 2

Mrs. S.P., aged 56, admitted July 26, 1944, because of hæmatemesis and melæna. Five transfusions were given prior to admission and the hæmoglobin on arrival was 6 gm. By July 31, 1944, the hæmoglobin had risen under large daily transfusions of blood to 11.6 gm. Exploration was done July 31, 1944, under cyclopropane anæsthesia. No lesion in the stomach could be seen or felt, but a 75% gastric resection was carried out. The removed stomach weighed 130 gm. High up on the lesser curvature, and just a little removed from it on the posterior wall, there was a shallow ulcer 3 mm. in diameter. Microscopically, its base was necrotic; there was also atrophy of the mucous membrane, with some leucocytic infiltration.

CASE 3

Mr. R.E., aged 48, admitted January 10, 1944, because of hæmatemesis. The hæmoglobin was 4 gm. %. A diagnosis of carcinoma of the fundus of the stomach was made. After multiple transfusions, hæmoglobin came up to 14.2 gm. %. On admission blood pressure was 120/65, but the patient gives a story of previous hypertension and the retinal vessels show evidence of sclerosis. The patient was prepared for operation by constant intragastric dripping of a high protein and carbohydrate and low fat diet (Varco II). Transthoracic exploration was done February 14, 1944. The spleen was larger than normal, and the main splenic artery appeared to run directly into the fundus of the stomach, high up on the greater curvature. The fundus of the stomach to the left of the œsophagus felt rather thick and imparted a "corrugated feel" to the palpating finger. The spleen was excised and a piece of fundic stomach 6 x 4 cm. This excised specimen was then subjected to x-ray examination. The arteries in the gastric wall exhibited considerable calcification in the x-ray film. On microscopic study calcification as well as thrombosis was apparent. The bleeding apparently was occasioned by the plugging of the end vessels in the gastric wall. The patient returned for observation on September 19, 1945. He was well and there has been no further bleeding.

CASE 4

Mrs. A.S., aged 49, admitted November 9, 1944, because of repeated melæna. The patient is quite obese. She was hospitalized 5 times during the past year because of melæna. X-rays of the alimentary tract were negative as were also gastroscopic and proctoscopic examinations. Hæmoglobin 7.9 gm. Exploration on November 10, 1944. No findings. A 75% gastric resection was done on the thesis that a small bleeding point, not palpable through the gastric wall, was present. The removed specimen weighed 140 grams but showed no bleeding point. Microscopically an ulcerative gastritis was present. The patient did well and the hæmoglobin had risen to 12 gm. % at time of dismissal. There has been no recurrence of melæna and when the patient returned for observation on May 29, 1945, the hæmoglobin was 13.1 grams.

CASE 5

Mr. F.K., aged 45, admitted July 5, 1944, because of hæmatemesis and melæna. The hæmoglobin was 7 gm. The patient had been studied in the outpatient clinic on several occasions over the preceding 6 years because of abdominal distress. Repeated x-ray studies of the gastro-intestinal tract had been negative. Seven litres of blood were given prior to operation on July 11, 1944, at which time the hæmoglobin was 6.9 gm. Exploration save for a few hæmorrhages in the upper jejunum was negative. Dr. R. L. Varco called me to the operating room. I advised him to resect the stomach, indicating that one such resection already had been done by me for occult bleeding. The hæmorrhages in the jejunum however appeared to be a more tangible source of the bleeding and he removed a segment of the upper jejunum which exhibited several hæmorrhagic areas but no ulceration. The patient did poorly after operation, and continued to bleed. Six litres of blood were given in the postoperative period. The patient died of hæmorrhage on July 17, 1944.

At autopsy a very shallow erosion 2 mm. in diameter and less than 2 mm. in depth was found on the lesser curvature near the incisura angularis. There was an open vessel in its base. Additional areas of hæmorrhage, very much like those observed at operation were noted in the jejunum. Both the lumen of the ileum and the colon contained considerable blood. Microscopic study of the ulcer base revealed fresh granulations and a rather large arteriosclerotic artery in the submucosa beneath the ulcer.

DISCUSSION

The older pathological literature contains numerous references to patients who have come to autopsy in which death occurred from bleeding from a small, superficial erosion in the gastric mucous membrane, in which there was an

open artery in the base. Lewin (1908) reviews the earlier literature and lists additional cases of his own. Instances of this sort already had been described by Gallard in 1884. Buday (1908), in reporting such an instance of fatal hæmorrhage from a small erosion in the gastric fundus, located with difficulty at autopsy, states that the intimal thickening of the gastric arteries in the submucosa is frequently greater than in far larger vessels. Even extensive formal pathological studies relating to sclerosis of visceral arteries rarely mention the gastric arteries (Brooks, 1906; Dow, 1925). Arteriosclerosis, out of proportion to that found in the arteries of the body as a whole, may be encountered as a surprise finding in any vessel. Schwyzer (1907) reports such an instance, in which only the coronary arteries exhibited more arteriosclerotic changes than the gastric arteries.

Ophüls (1913) and Boles and associates (1939) stress arteriosclerosis of the gastric arteries in patients with ulcer as a part of a general process. Fetterman (1935), reporting from the Toronto General Hospital, indicates that intimal thickening of the submucosal arteries in resected stomachs removed at operation from patients with ulcer is a frequent finding.

Whereas such erosive processes as those reported herein appear ordinarily very innocent when the specimens are examined, the persistent bleeding from these areas belies their harmlessness. A sclerotic vessel does not close readily, and it is to be remembered that it is an artery that is opened usually. In a fatal hæmorrhage, attending a mediastinitis following perforation of the cervical œsophagus in which the carotid sheath was opened by me at operation to effect a more secure closure of the œsophageal perforation, I was very much surprised to note that the bleeding occurred from the carotid artery (1938). My inference was that, the thinner walled jugular vein should have been opened. Undoubtedly, however, the pulsations of the artery caused it to be the more easily eroded by the suppurative process.

Disse (1904) states that an end artery going out to the mucosa from the submucosal vessels supplies an area 2.5 mm. in diameter. The plugging of such vessels in older patients may be the precursors of bleeding from an erosive lesion.

2. *Extensive (90%) gastric resection for erosive hæmorrhage in portal hypertension.*—

CASE 1

Mr. F.K., aged 59, admitted to medical service January 27, 1945, because of recurrent hæmatemesis first noticed in 1938. In March of 1944, œsophageal varices were ligated elsewhere through a left thoracic approach. The patient bled again before leaving the hospital and there have been three additional spells of hæmatemesis since. A carcinoma of the right bronchus close to the carina also has been demonstrated since the ligation of the œsophageal varices. The hæmoglobin, when the patient was first seen in the medical outpatient department, was 7.52 gm. %. On February 6, 1945, a few days after admission to the medical service, the hæmoglobin was 9 gm. On February 9, 1945, patient began bleeding again and 500 c.c. of blood was given daily by the medical service over a period of 5 days, a total of 2,500 c.c. being given. At the end of this time, the hæmoglobin was 7 gm. After transfer to surgery, a litre of blood was given daily for 9 days including the day of operation, the hæmoglobin rising slowly to 12.3 gm. %. Blood was demonstrated constantly in the stool. Gastric analysis without histamine showed a maximum of 27 free acid and a total of 39°. A bronchoscopy done on February 5, 1945, showed a squamous cell carcinoma to be present in the right main bronchus. The x-ray findings of the chest were consistent with a carcinoma of the right lung. Liver function studies were normal. There was no ascites.

On February 23, 1945, a 90% gastric resection was done on the thesis that an increased portal pressure produced a passive congestion of the gastric mucous membrane, which, in the presence of free hydrochloric acid, made the mucous membrane more vulnerable to acid-peptic digestion. In other words, it is believed that bleeding from œsophageal or gastric varices is primarily an erosive rather than a bursting process. The blood loss in the operation was 1,190 gm.

The spleen was also large and was removed. It weighed 870 gm. The removed stomach weighed 225 gm. The portal and splenic veins were both large and their walls, as in an atheromatous process, were somewhat thick. The portal pressure was 25 cm. of saline solution. The liver appeared normal. The operative diagnosis was, therefore, primary thrombophlebitis of the portal and splenic veins.

The microscopic study on the spleen showed a condition of fibrosis consistent with the diagnosis of Banti's disease. The liver was normal microscopically. There were no areas of atrophy in the gastric mucosa and there was a moderate amount of intestinal antral gastritis present, as is commonly observed in duodenal ulcer.

The patient did well after operation and the hæmoglobin promptly rose to 14 gm. There has been no further evidence of bleeding. The patient was dismissed on March 6, 11 days after operation. On March 27, he returned for excision of the right lung which also was done by me on April 4. The lesion in the bronchus was quite near the carina, necessitating amputation close to the bifurcation of the trachea. The lung was universally adherent but was excised without difficulty. The lung weighed 620 gm. There was no tumour in the removed lymph nodes. The tumour in the bronchus extended over a distance of 3 cm. and practically occluded the bronchus. The biopsy diagnosis of squamous cell carcinoma was confirmed.

A transfusion of 1,000 c.c. of blood was given for this operation, the blood loss in operation being 1,450 gm. This is the only transfusion the patient has had since gastric resection. The patient did very well after operation and manifested very little operative reaction and was dismissed on April 15, 11 days after operation. The hæmoglobin on April 11, was 10.5 gm.

There has been no melæna nor hæmatemesis since the gastric resection in February. The hæmoglobin on May 18, 1945, was 10.9 gm. and 12.2 gm. on June 5. The patient's weight was 122 pounds, 10 pounds less

than before gastric resection and 6 pounds more than at the second admission for excision of the right lung. He believes he is making definite progress and appears to be doing very well.

CASE 2

Baby boy, R.O., aged 3. On July 28, 1944, splenectomy was done because of repeated hæmatemesis and melæna. The removed spleen weighed 170 gm. The liver appeared nodular and cirrhotic. A piece removed for biopsy showed definite cirrhosis microscopically. The patient was dismissed August 8, 1944. On April 11, 1945, the parents brought him back because of recurrent melæna. In hospital, vomiting of blood occurred necessitating transfusions for shock. The hæmoglobin, which had been 13.4 gm. on the first admission, fell to 5.6 gm. Under daily transfusions of 250 to 500 c.c. of blood, the hæmoglobin rose to 10.7 gm. on April 23, 1945, at which time a 90% gastric resection was done. The liver appeared somewhat more nodular than at the last operation. The portal venous pressure was not determined. A specimen withdrawn prior to operation for gastric analysis contained largely blood. No transfusions were given after operation and the hæmoglobin rose to 14.2 gm. Blood disappeared from the stool and when the patient left the hospital on May 6, 1945, he was eating well.

CASE 3

Mrs. M.V., aged 62, periodic melæna, vomiting, and diarrhœa over a period of years have been the patient's complaints. She also has pain in the back and x-ray examination discloses a hæmangioma in the twelfth dorsal vertebra. The spleen is palpable and is believed to be enlarged. There has been blood in the stool persistently and the hæmoglobin was 4.5 gm. upon admission. There was free hydrochloric acid in the gastric juice (59°). Recently ascites has developed. The hæmoglobin in July, 1942, done elsewhere was 7.4 gm. Between episodes of melæna and diarrhœa the hæmoglobin improves. After the transfusion of 3 litres of blood and iron and liver extract therapy, the hæmoglobin rose from 4.5 to 12.9 gm.

Operation was done May 24, 1945, the spleen was large and weighed 520 gm. upon removal. The liver appeared to be definitely cirrhotic. A small piece of the liver edge was removed for biopsy. The portal venous pressure measured in one of the veins of the great omentum was 35 cm. of saline solution. There was a good deal of new vessel formation in the mesenteries. The veins of the mesentery and bowel appeared very prominent. The spleen was excised. A 90% gastric resection also was done with the consideration in mind of reducing the capacity of the stomach to secrete acid. The resection was very difficult and tedious because of the vascularity and thickening of the suspensory ligaments of the stomach. The removed stomach weighed 160 gm.; there were no erosions. Microscopically there was antral gastritis and cirrhosis of the liver with marked fibrosis. The present hæmoglobin is 10.8 gm. and the patient is still in the hospital under observation because of fever suggesting the possibility of a subphrenic abscess.*

CASE 4

Mrs. E.H., aged 27, admitted May 21, 1945, because of hæmatemesis, melæna and a feeling of faintness. Blood has been present persistently in the stool since May 19, 1945. The hæmoglobin was 8.8 gm. In 1938, I removed this patient's spleen because of recurrent hæmatemesis, and melæna. There were a number of accessory spleneculi found. The diagnosis was thrombophlebitis of the splenic vein. The liver appeared normal. There has been no recurrence of hæmatemesis or melæna until just before admission. There is no ascites; liver function tests are normal. The patient had free hydrochloric acid in all of 4 samples, the highest value being 36°. Three transfusions of blood were given and the hæmoglobin rose to 11.7 gm. on the day of operation. On June 4, 1945, a 90% gastric resection was done. The liver appeared normal, no surviving splenic tissue was observed. The portal venous pressure measured in an omental vein is 49 cm. of saline solution. The mesenteric veins appeared full and were very prominent. The suspensory ligaments of the liver were extremely vascular and thick making dissection difficult. The omentum was universally adherent in the upper right quadrant and contained prominent veins. The fundic portion of the stomach was intimately adherent to the left diaphragm and pancreas over a wide extent. The removed stomach weighed only 114 gm. There has been little operative reaction and the patient is convalescing nicely from the procedure and was dismissed from hospital 7 days after operation.

* This patient died subsequently of a subphrenic abscess which was managed in too dilatory a manner.

DISCUSSION

The first operation in this group of patients with portal hypertension was done just a few months ago, and a longer lapse of time will have to be awaited before one can say with assurance that this is a satisfactory manner in which to control the bleeding in such patients. A fairly large number of patients with cirrhosis of the liver, as Eppinger (1937) has indicated, die of hæmorrhage before ascites or liver insufficiency supervene. The operations proposed by A. O. Whipple (1945), of excising the spleen and left kidney and uniting the veins of these two organs over a Blakemore tube, or of making a direct Eck fistula between the portal vein and the vena cava, obviously constitute a more direct attack upon the problem of portal hypertension. However, an Eck fistula *per se* apparently does not constitute an altogether harmless diversion of portal venous flow, as indicated by the earlier report from Pavlov's laboratory (see Enderlen *et al.*, 1914) as well as by the more recent report of G. H. Whipple and his associates (1945).

It perhaps should be indicated, too, that gastric resection in a patient with portal hypertension may be a more difficult operation than in a patient with ulcer. The omenta and tethering membranes and ligaments of the stomach are thickened up, owing to the new vessel proliferation. Dissection, in consequence, may be difficult, because of obliteration of normal tissue planes. In the ordinary gastric resection for ulcer, the operation may be accomplished with a blood loss of 300 c.c. or considerably less; owing to a tendency for all the dissected surfaces in portal hypertension to bleed, the blood loss is usually much greater. The employment of dry gauze sponges and weighing them at operation (1942)[66] however, keeps the surgeon apprised continuously of the magnitude of the blood loss, which loss may be replaced by an equal amount of transfused blood.

At the moment, we are engaged in determining whether the bleeding from gastric and œsophageal erosions, which can be created experimentally by the administration of histamine in the presence of portal obstruction, can be prevented by preliminary extensive gastric resection. If such should prove to be the case, it would augur well for the proposal of subjecting patients with hæmorrhage from increased portal venous pressure to the operative procedure described herein.*

II.

Characterization of a Satisfactory Operation for Ulcer

The second portion of this presentation will concern itself with an attempt at evaluation of the criteria of a satisfactory operation for ulcer. As indicated in the reports of vital statistics by the Department of the Census of the United States, there has been a significant drop in the mortality of both appendicitis and intestinal obstruction in the last decade. On the other hand, the mortality of duodenal and gastric ulcer per 100,000 population has continued very much the same over a period of 30 years. The complications of perforation, hæmorrhage and obstruction account largely for this mortality. In order to prevent perforation, we must learn to control the ulcer diathesis. The very frequency with which the tragic complication of perforation occurs, suggests that much remains to be learned concerning the control of the ulcer problem by conservative means. The opportunity should not be neglected to point out, however, that, the general application of the principles of closure of such perforations, as first enunciated by Roscoe Graham (1937) of the University of Toronto, have had a telling effect upon the mortality of perforation.

Surgeons have concerned themselves in an empirical fashion with the problem of attempting to relieve the ulcer diathesis for a period of more than 50 years. Out of this experience has grown a mass of conflicting data with reference to the accomplishment of the surgeon in the management of ulcer, without a clear cut definition of the criteria of an acceptable operation for ulcer. The surgeon knew only that the object of his craftsmanship was to prevent ulcer recurrence, but he did not know how that end was to be attained, nor did he know nor understand the items promoting or abetting the ulcer diathesis. Little wonder that he groped about aimlessly, striving to devise new procedures or modify old ones which might achieve his objective. Little wonder that the high incidence of recurrent ulcer after operation justified internists, actuaries, and the medical departments of our Allied Forces in their distrust of what surgeons affected to be able to accomplish for the patient with an ulcer refractory to medical management.

Evaluation of the criteria of a satisfactory operation for ulcer.—This story has been told in part previously.[37, 38, 68] The histamine-in-beeswax technique has proved a most useful instrument in assaying the worth of a given operation. Before that tool became available, however, this study already was on its way in patients. In brief, it may be said that in patients as well as in dogs to which histamine-in-beeswax is administered to note whether a given operation will protect against the histamine-provoked ulcer, the results are in concurrent agreement. In man, a study of the incidence of recurrent stomal ulcer after each type of operation is the method of procedure; obviously not a commendable manner in which to determine the criteria of a satisfactory operation.

From these studies, the characters of a satisfactory operation which protects against recurrent ulcer appear to be: (1) an extensive gastric resection (75%) affording promise of reduction in gastric secretion; (2) excision of the antral mucosa. This proof emanates from operations on man alone, but appears to be well substantiated in the reports of Ogilvie (1938), Wangensteen and Lannin (1942) and McKittrick, Moore and Warren (1944). The patient reported upon previously[68] from this clinic continues well, now almost five years after excision of the antral fragment of mucosa, left behind in the first operation, in which a three-quarter resection was followed by a recurrent stomal ulcer. (3) Fairly complete excision of the lesser curvature of the stomach appears justified in that ulcer occurs primarily in the unrugated portions of the first portion of the duodenum and along the lesser curvature of the stomach. Kolouch's (1945) drip experiment apparently suggests that unrugated mucosal strips are more susceptible to injury in that periodic momentary escape from

* Preliminary experiments on dogs suggest definitely that, a 90% gastric resection affords real but not absolute protection against the histamine-provoked ulcer, in the presence of portal hypertension. Under these very same circumstances, a 75% gastric resection affords no protection against the histamine-provoked ulcer—an occurrence which indicates how strongly portal hypertension abets the ulcer diathesis.

the unrelenting dripping of the acid-peptic digestive juice is not permitted the unrugated surface. Hence the greater vulnerability of the unrugated duodenal cap and the lesser curvature to the ulcer diathesis. (4) The importance of a short afferent duodenal loop in effecting gastro-intestinal continuity after an extensive gastric resection appears to have been established. This is an item as susceptible of proof in the dog as in the patient. Both the proof from the experimental laboratory and the clinic will be cited herein, because it is my belief that this item is still, in many hands, an important factor in ulcer recurrence after an otherwise satisfactory operation for ulcer. The matter is important enough to warrant recitation in some detail.

The problem was subjected to experimental scrutiny in the following manner: Three series of experiments were carried out in dogs. In each series, a three-quarter gastric resection (75%) including excision of the pylorus and antrum was carried out. The only variable was the length of the proximal afferent duodenojejunal loop, the operations being carried out on the Billroth II plan of procedure with the Hofmeister modification of dealing with the lesser curvature.

A. *Proof of the importance of a short afferent duodenal loop in gastric resection.*[47]—

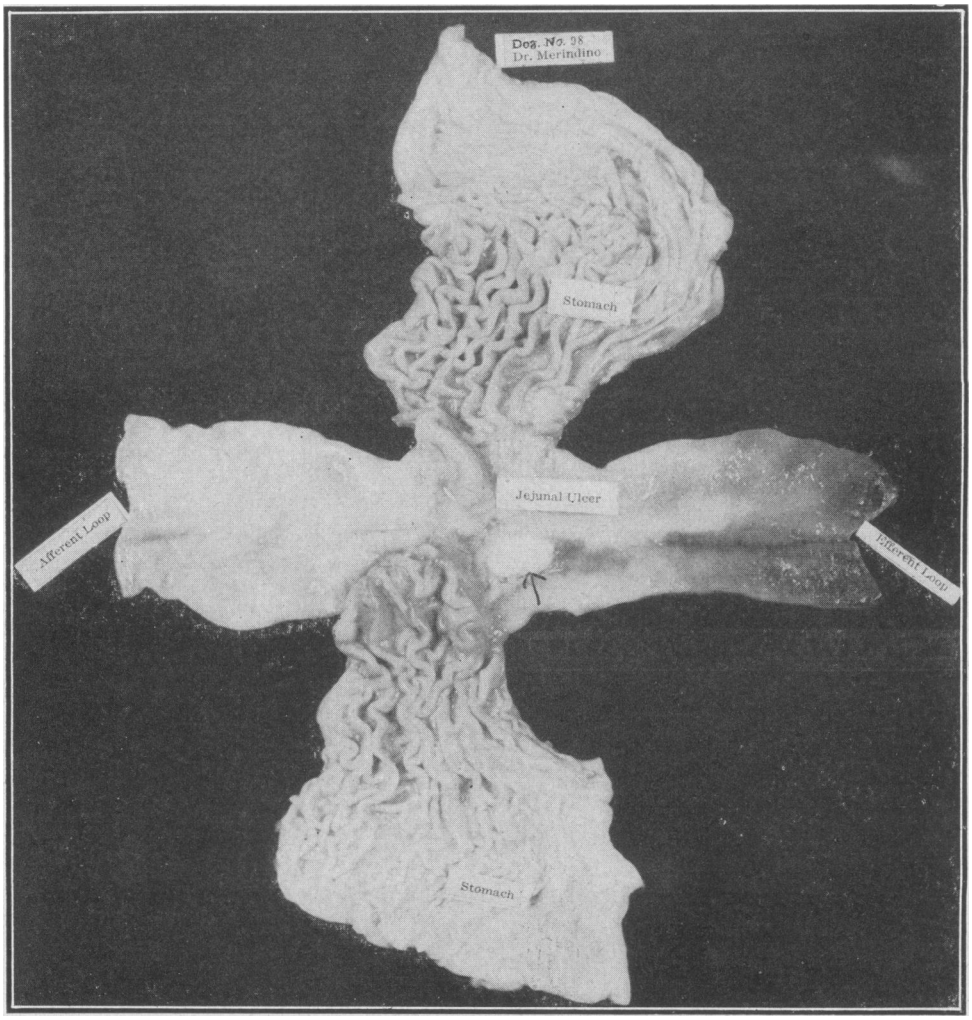


Fig. 3.—Spontaneous perforation of a stomal ulcer (no histamine) in a dog in which a 50% gastric resection (Billroth II) had been done, employing a long afferent duodenojejunal loop measuring 78 cm. in length from the inverted duodenal end. Death occurred from peritonitis 420 days after the operation. The overall length of the small intestine was 323 cm. Of 7 dogs in which 75% gastric resection was done, employing a long afferent duodenojejunal loop, followed by the administration of histamine-in-beeswax, all developed perforating or perforated stomal ulcer. In dogs that have had a 75% gastric resection accompanied by a short afferent duodenal loop, a stomal ulcer can not be produced by histamine.

Series I.—Eleven dogs were used. These dogs were subjected to an extensive gastric resection (75%). The gastrojejunostomy was performed as close to the inverted duodenal end as was technically feasible, the distance from the blind duodenal end varying from 12 to 15 cm. After this operative procedure, three months were allowed to elapse. Then 30 mgm. histamine base in beeswax, prepared after the method of Code and Varco (1940) was injected intramuscularly each day. A total of 40 to 45 injections was carried out on each animal. The animals were sacrificed after the last injection. In spite of severe histamine stimulation, not one gastrojejunal ulcer was encountered. This is significant.

Series II.—The identical operation described above (75% gastric resection) was performed on 7 dogs, with one difference. In these animals a longer afferent duodenojejunal loop was employed. The distance from the inverted duodenal end to the site of gastrojejunostomy varied from 27 to 78 cm. Similarly, a rest period of 3 months was allowed to intervene. Following this, 30 mgm. of histamine base in beeswax was injected intramuscularly daily.

A large, frequently perforated gastrojejunal ulcer was observed in each instance (100%). These results are in striking contrast to the results in Series I. Three of the 7 dogs in Series II died of generalized peritonitis attending perforation of a stomal ulcer. The dogs with the longest afferent duodenojejunal loops had the shortest survival periods.

Series III.—In a group of 4 dogs, gastric resection was done, varying in extent from 50 to 75%. The length of the afferent duodenojejunal loop in these 4 experiments varied between 78 and 144 cm. These dogs received no histamine. Two of the 4 dogs died of spontaneous perforation of a gastrojejunal ulcer located just beyond the efferent outlet (Fig. 3). One dog, in which a 50% gastric excision had been done accompanied by an afferent duodenojejunal loop of 78 cm., was sacrificed 210 days after operation. There was no stomal ulcer. One other dog is still alive and apparently well more than two years after operation.

COMMENT

The results of these experiments are striking. In 11 dogs (Series I), with an extensive gastric resection (75%), in which the afferent duodenal loop was short (12 to 15 cm.) stomal ulcer could not be provoked in a single instance by profound stimulation of gastric secretion with histamine-in-beeswax. In 3 of the 11 dogs, superficial gastric erosions were noted. In 7 dogs (Series II), in which the extent of the gastric resection was the same (75%), the only difference being that, the afferent duodenojejunal loop was longer (27 to 78 cm.), a gastrojejunal ulcer occurred following histamine stimulation in each instance. In a third series of 4 dogs with long afferent duodenojejunal loops, which received no histamine after gastric resection, varying in extent from 50 to 75%, 2 (50%) developed spontaneous perforated gastrojejunal ulcer.

B. *The importance of the length of the afferent duodenojejunal loop in indicating whether stomal ulcer will occur in the Schmilinsky-McCann operation.*—There has been much confusion and conflict of opinion concerning the item of complete intragastric regurgitation as it relates to the Schmilinsky-McCann operation. Schmilinsky (1918) suggested placement of the afferent duodenojejunal loop, in the Billroth II type of gastric resection, back on to the stomach in such a manner that complete drainage of all the duodenal contents occurred back into the stomach. He termed this arrangement an "internal pharmacy" for neutralization of gastric acidity, an item that is looked upon as a desirable factor in gastric resection for ulcer. McCann (1929) reported that he had produced gastrojejunal ulcer in 80% of 26 dogs operated upon according to the Schmilinsky plan. A number of other investigators, Ivy and Fauley (1931), Weiss, Graves and Gurriaran (1932), Graves, (1935), Maier and Grossman (1937), and Wangensteen and his associates (1940) repeated the McCann experiment with rather indifferent results. None of these investigators was able to confirm McCann's observations of a high incidence of gastrojejunal ulcer following complete drainage of the duodenal loop back into the stomach. Wangensteen and his associates (1940) indicated that disastrous results attended performance of the Schmilinsky operation on man and suggested that constant regurgitation of the duodenal loop content back into the stomach might stimulate the second or gastric phase of gastric secretion interminably. Kesavalu and Mann (1943) have shown, in dogs with isolated gastric pouches, that the Schmilinsky procedure definitely enhances secretion from the pouch.

Methods of study and results.—A total of 17 dogs was studied. The Schmilinsky-McCann operation of complete intragastric return of the entire content of the duodenal loop was performed in each animal.

In the first series of 11 dogs, the operation was accomplished in the following manner: These dogs were anæsthetized and under septic conditions, a laparotomy was performed. The pylorus of the stomach was excised. The duodenal end was then closed and inverted in the usual fashion by means of interrupted cotton sutures. At distances of 8 to 15 cm. from the inverted duodenal stump, the intestine was transected. The proximal transected intestine was anastomosed on to the stomach. Thereby complete intragastric regurgitation of the duodenal contents including bile and pancreatic juice was assured. The end of the distal loop of intestine was closed and inverted. A gastrojejunostomy, end-to-side was then performed between the end of the stomach and the side of the distal transected intestine.

Following operation, convalescence was rapid. After a brief period of time, normal activity was assumed and appetite regained. At various intervals from 72 to 360 days these animals were sacrificed. In the 11 dogs in which a short proximal duodenal loop

was employed in the Schmilinsky-McCann procedure, gastrojejunal ulcer occurred only once (9.1%).

A second series of Schmilinsky-McCann operations subsequently was carried out on 6 dogs. The operation was identical in all details with that described in the first series of animals with one exception. In the first series, the intestine was transected a short distance from the inverted duodenal stump. Thus, a short proximal loop was obtained. However, in this second series of dogs, the transection of the intestine was carried out at a lower level. The length of the proximal loop from the inverted or "blind" duodenal end varied from 76 to 90 cm. The transplantation of the proximal loop was high on the stomach in some instances, low in others. In this second series, a short period of normal response was noted. As time progressed, however, the dogs became irritable, anorexic and languid, followed by coma and death. The average survival period was 79.7 days. The area of the transplantation (high or low) of the proximal loop on to the stomach, did not appear to alter the end result. The incidence of gastrojejunal ulcer in this series was 83.3% (5 out of 6 dogs). Four of the six dogs exhibited perforated peptic ulcers.

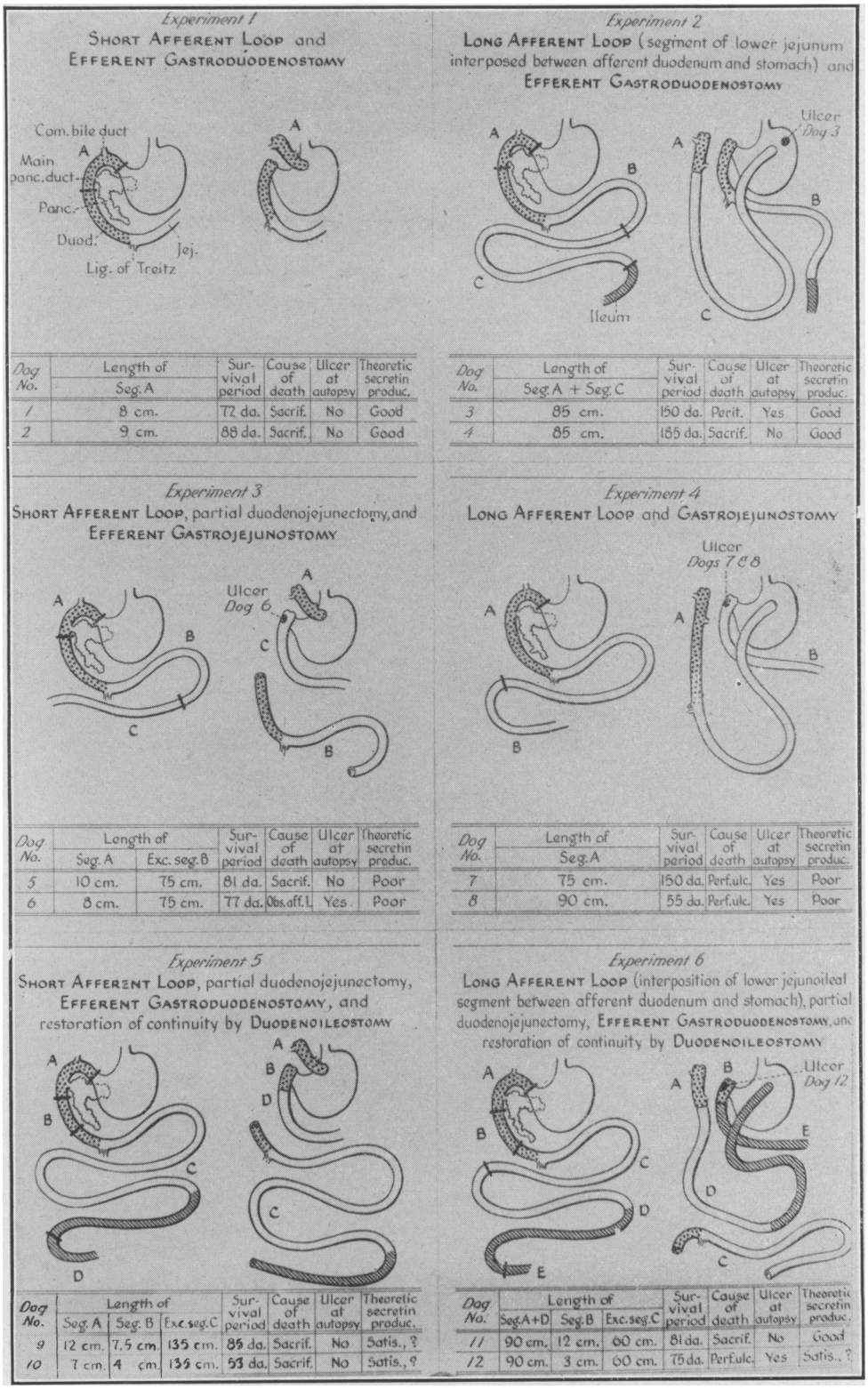
Comment.—These results clarify the confusion in the literature concerning the results of complete intragastric drainage of the duodenal loop in dogs. The results of the experiments reported herein suggest that the divergent results obtained by previous investigators are explicable on the basis of the length of the afferent loop employed. The agency through which the length of the afferent loop in the Schmilinsky procedure influences so definitely the occurrence of stomal ulcer is not apparent. One thing is clear however: exclusion of hydrochloric acid, the best physiological stimulus for the secretion of pancreatic juice with high buffer value, from contact with the duodenal mucosa, the segment of mucosa richest in secretin, affords a plausible explanation for the greatly increased incidence of stomal ulcer in the experiments in which the long efferent loop was employed.

C. *Why does a long afferent duodenojejunal loop invite stomal ulcer?*[34]—An attempt was made, without too much success, to determine definitely what the factor or factors are in a long afferent duodenojejunal loop that contribute to the occurrence of stomal ulcer. The operations depicted in Fig. 4 were carried out in 12 dogs. The 3 items examined with respect to their importance in the genesis of stomal ulcer were: (1) secretin factor; (2) the factor of spatial separation of alkaline and acid digestive secretions; (3) the sensitivity factor, implying an increased susceptibility of the mucosa of successively lower segments of the small intestine to injury by the acid gastric secretions.

Methods.—Six modifications of the total intragastric duodenal drainage operation of Schmilinsky and McCann were carried out in a series of 12 dogs (Fig. 4). The operations were devised to study the influence of both short and long afferent duodenojejunal loops on the development of stomal ulcer just beyond the efferent gastric outlet with special reference to an attempt to evaluate the significance of the three factors enumerated above. In other words, in addition to varying the length of the afferent loop, the site of the efferent outlet of the stomach was varied, permitting testing of the importance of the secretin factor and the item of mucosal susceptibility to corrosion by the acid gastric secretions. These latter objectives of the study necessitated the making of some rather complicated operative procedures. By transecting the duodenum just beyond the major pancreatic duct and interposing a loop of ileum between the proximal portion of the duodenum and the stomach, or by excising a portion of the duodenum and the upper jejunum in other experiments, it became possible to vary all the factors which we wished to scrutinize. In some experiments the afferent loop was long, yet the requirements of a functional secretin mechanism were met satisfactorily by placement of the entire length of the duodenojejunal segment beyond the major pancreatic duct at the efferent gastric outlet. By interposing a short segment of duodenal mucosa between a high ileal segment and the gastric outlet, it was possible to note when stomal ulcer followed, whether it occurred in the short duodenal segment or in the more susceptible high ileal mucosa beyond.

Results.—Five of the 12 dogs died of ulcer; in 4 of these, perforation was present. All ulcers were stomal in character, that is, just beyond the gastric outlet on the efferent loop, save one which occurred in the fundus of the stomach (dog No. 3). In dog No. 6 the ulcer was not perforated, death being due apparently to obstruction of the short afferent loop, an item which probably had something to do with the occurrence of the ulcer. The dogs which did not succumb to ulcer were sacrificed at intervals of from 53 to 185 days.

In only one of 5 dogs (20%) in which the theoretic quality of the secretin mechanism was good, did a stomal ulcer occur. In 3 of 4 dogs (75%) in which it was poor stomal ulcer occurred. In one of 3 dogs (33%) in which the quality of the secretin mechanism was questionably satisfactory, stomal ulcer occurred.



Dog No.	Length of Seg. A	Sur-vival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
1	8 cm.	72 da.	Sacrif.	No	Good
2	9 cm.	88 da.	Sacrif.	No	Good

Dog No.	Length of Seg. A + Seg. C	Sur-vival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
3	85 cm.	150 da.	Perit.	Yes	Good
4	85 cm.	185 da.	Sacrif.	No	Good

Dog No.	Length of Seg. A	Exc. seg. B	Sur-vival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
5	10 cm.	75 cm.	81 da.	Sacrif.	No	Poor
6	8 cm.	75 cm.	77 da.	Obs. aff. l.	Yes	Poor

Dog No.	Length of Seg. A	Sur-vival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
7	75 cm.	150 da.	Perf. ulc.	Yes	Poor
8	90 cm.	55 da.	Perf. ulc.	Yes	Poor

Dog No.	Length of Seg. A	Seg. B	Exc. seg. C	Sur-vival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
9	12 cm.	7.5 cm.	135 cm.	85 da.	Sacrif.	No	Satis., ?
10	7 cm.	4 cm.	135 cm.	53 da.	Sacrif.	No	Satis., ?

Dog No.	Length of Seg. A+D	Seg. B	Exc. seg. C	Sur-vival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
11	90 cm.	12 cm.	60 cm.	81 da.	Sacrif.	No	Good
12	90 cm.	3 cm.	60 cm.	75 da.	Perf. ulc.	Yes	Satis., ?

Fig. 4.—Types of operation performed in an attempt to separate out the relative importance of the secretin "distance" and "sensitivity" factors in the rôle of the long afferent loop in the production of stomal ulcer in the Billroth II type of gastric resection.

In 6 dogs in which the spatial factor was satisfactory (short afferent duodenal loop), stomal ulcer occurred only once (16.2%). In 4 of 6 dogs, in which the spatial factor was unsatisfactory (long proximal loop) stomal ulcer occurred 4 times (66.6%).

In 8 dogs the gastric outlet emptied over duodenal mucosa. Stomal ulcer occurred twice (25%). In 4 dogs, the gastric outlet met jejunal mucosa. Stomal ulcer occurred 3 times (75%).

Comment.—It is apparent from this analysis that, it is difficult to separate out the eventual rôle of any single factor. That is especially true of the secretin and distance factors. Experiments 10 and 12 constitute an excellent example of the difficulty (see Fig. 4). In dog No. 10, the afferent loop was short; in dog No. 12 it was long. In dog No. 10, only 4 cm. of duodenal mucosa remained at the efferent outlet for the gastric secretions to glide over in provoking the usual secretin effect; in dog No. 12, only 3 cm. of duodenal mucosa remained at the efferent gastric outlet. Spontaneous perforation of a stomal ulcer killed dog No. 12; 75 days after the operation no ulcer was present in dog No. 10, when he was sacrificed at 53 days. In dog No. 10, however, with the short afferent loop (7 cm.) containing good secretin containing duodenal mucosa, regurgitation of gastric secretions into the short afferent loop may have sufficed to augment the secretin effect of the 4 cm. duodenal mucosal segment at the efferent gastric outlet. In dog No. 12, on the contrary, retrograde regurgitation of gastric secretions into the long 90 cm. afferent loop could not reach the rich secretin bearing area of the duodenal segment. This same dog, No. 12, provides a striking lesson in another respect. The stomal ulcer occurred in the short (3 cm.) duodenal segment at the efferent gastric outlet and not in the ileal mucosa just beyond (Fig. 5).

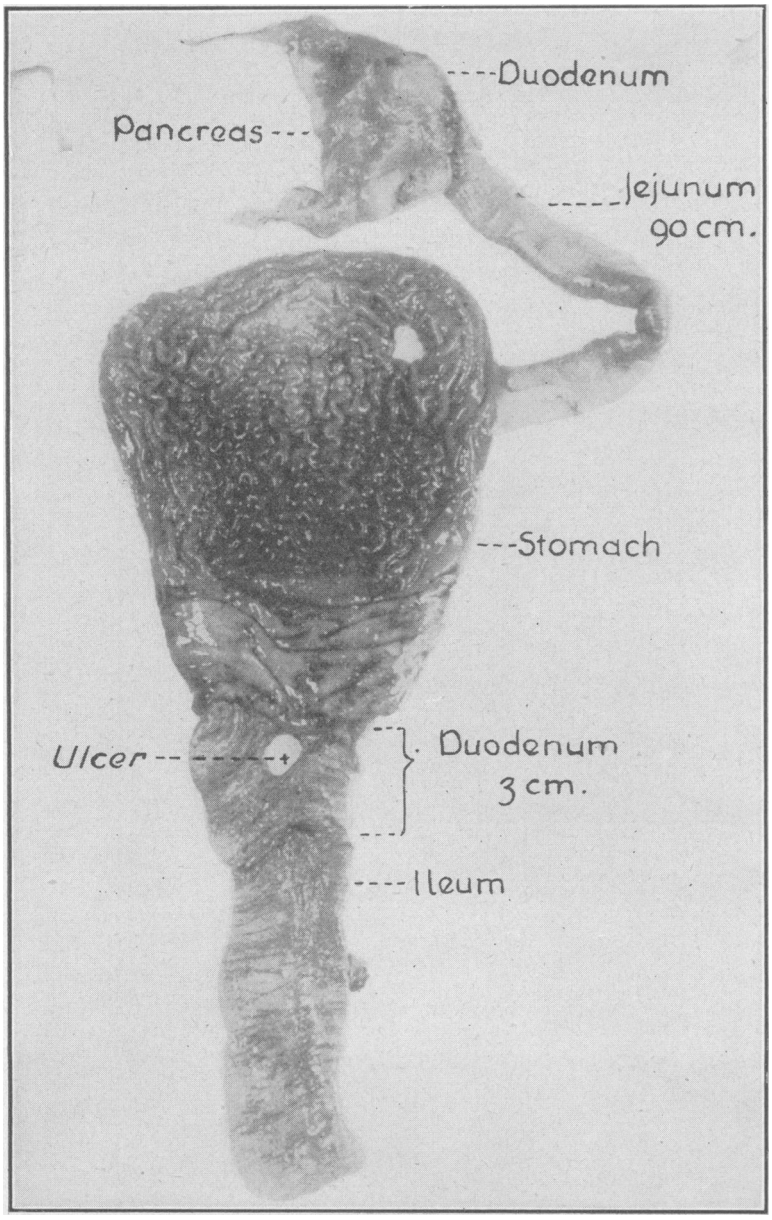


Fig. 5.—Spontaneous perforation of stomal ulcer in dog 12 (Experiment 6, Fig. 4). The afferent loop was 90 cm. in length, the stomal ulcer occurred in the duodenal segment. The "distance" as well as the "secretin" factors were both poor in this experiment. The sensitivity factor was good; in other words, one might reasonably have expected the ulcer to skip the 3 cm. duodenal segment and to have occurred in the ileum just beyond, if the ileal mucosa is more sensitive than the duodenal to corrosion by gastric juice.

In this group of experiments stomal ulcer occurred only once in a dog with a short afferent loop (dog No. 6); in this instance, however, stenosis of the afferent inlet stoma was present, interfering with delivery of the alkaline secretions from the duodenal loop. Moreover, in long afferent loops, in which extraneous factors might influence the

motility of the segment and hence delivery of the content of the loop, it would appear that such long afferent loops invite stomal ulcer.

A larger number of experiments in each group would undoubtedly be helpful in resolving the importance of each of the factors scrutinized in this study. In addition, the animals not dying of spontaneous perforation of a stomal ulcer should be allowed to survive longer before sacrifice. It is not unlikely that employment of additional modes of attack may help to separate out more definitely, the component important parts in the predisposition of stomal ulcer presented by the long afferent duodenojejunal loop. Three such methods are now being applied to the problem in this laboratory: (1) assaying the secretin potency of intestinal mucosa from varying levels of the bowel in both dog and man; (2) determination of the loss in titratable alkalinity, if any, of the content of the long afferent duodenojejunal loop as delivered at the afferent gastrojejunal stoma; (3) experiments in which the sensitivity of the mucosa of various segments of the intestine is examined by allowing hydrochloric acid to drip upon isolated surfaces.

It is difficult to separate out with finality the rôle of the various factors contributing to the development of stomal ulcer attending employment of a long afferent loop in the operation of complete intragastric drainage of the content of the duodenal loop. The "secretin" factor can not be divorced completely from the considerations of the "distance" factor. Experiment No. 12 (Fig. 4) suggests rather definitely that, the "sensitivity" factor is not as important as the other two.

The evidence garnered in this study lends strong confirmation to the deductions arrived at in the two studies listed under A and B indicating that, a long afferent duodenojejunal loop invites stomal ulcer in any gastric operation carried out on the Billroth II plan of procedure.

D. *The clinical aspects of the problem of the length of the afferent loop in gastric resection for ulcer.* — The experimental data described above under captions A, B and C suggest definitely that, the antecolic anastomosis with a long proximal duodenojejunal loop, even when accompanied by an extensive gastric resection, is not a satisfactory operation for ulcer in man. Man's small intestine is approximately twice the length of the small intestine in the dog. The length of the duodenum in man is stated by anatomists to vary between 25 and 30 cm. It has been common practice for some gastric surgeons to make the anastomosis 30 (Balfour, 1935) or more (Lahey, 1939) cm. beyond the suspensory duodenojejunal ligament of Treitz. Kiefer (1942) has reported a series of 173 extensive gastric resections for duodenal ulcer in which the incidence of gastrojejunal ulcer was 11.4%, posited on recurrence verified at operation, roentgen demonstration of a crater or the occurrence of bleeding. In that series the antecolic long proximal duodenojejunal loop was employed in the anastomosis.

In this clinic, a series of patients comprising now more than 400 consecutive gastric resections all carefully followed, has been operated upon for ulcer, employing the criteria of a satisfactory operation for ulcer described herein. In this group only one stomal ulcer has developed thus far. In that patient, Mr. L.B., aged 50, an antecedent gastrojejunostomy had been done elsewhere for a duodenal ulcer. At the operation performed by me on May 5, 1944, for a gastrojejunal ulcer, only 155 gm. of tissue were removed including 6 cm. of jejunum. In the usual three-quarter (75%) resection for ulcer, the removal of 185 gm. or more is ordinary. In the re-operation done on May 2, 1945, 86 additional grams of stomach were removed suggesting that, at the first operation, the site of the resection was inadequate. A 75% gastric resection, employing a short afferent duodenojejunal loop with a retrocolic anastomosis made at or just proximal to the suspensory duodenojejunal ligament of Treitz has been standard practice in operating upon patients for ulcer in this clinic for several years.

E. *Would a less extent of excision suffice to protect against the histamine provoked ulcer if gastric resection is carried out on the Billroth I plan of operation?*[2]—Inasmuch as the short afferent duodenojejunal loop is so important in a satisfactory operation for ulcer, would it be equally satisfactory to sacrifice less stomach (25 or 50%), but to effect gastrointestinal continuity by end-to-end suture between the stomach and the duodenum by the Billroth I operation? Experiments were carried out on 12 dogs in three series to attempt to answer this question. Each series had a different amount of stomach resected, but the residual gastric pouch in each dog in all series was anastomosed to the duo-

denum just beyond the inverted duodenal end by means of an end-to-side gastroduodenostomy. This procedure, known as the Billroth I (Haberer-Finney) plan of operation is technically more feasible in the dog than the straightforward Billroth I operation which requires an end-to-end gastroduodenostomy. After an interval averaging 46 days, the administration of 30 mgm. of the histamine-in-beeswax mixture, prepared after the method of Code and Varco (1940) was injected intramuscularly daily. Unless the dogs succumbed from the complications of ulcer invoked by the histamine implantation, the injections were carried out for 45 days.

Results: *Series I.*—Four dogs were used. A 25% gastric resection and gastroduodenostomy was performed at the inverted duodenal end. After a sufficient recovery period from the operation, the daily administration of the histamine-in-beeswax mixture was begun. Three of the four dogs (75%) developed a stomal ulcer.

Series II.—The identical procedure was used on four dogs in this series with one difference: a 50% gastric resection was carried out, followed after a suitable interval by the administration of histamine. Stomal ulcer occurred in 3 of the 4 dogs (75%).

Series III.—In this series a three-quarter gastric resection (75%) was done, followed subsequently by the administration of histamine. Stomal ulcer did not occur.

These experiments would suggest that a 75% resection carried out on the Billroth II plan of operation, employing a short afferent duodenojejunal loop, the anastomosis being made at the suspensory duodenal ligament of Treitz, is just as satisfactory an operation for ulcer as is the Billroth I operation.

F. *Intractable or incurable recurrent ulcer a myth.*—The success with which the three-quarter (75%) resection has been carried out in the surgical management of ulcer suggests that a satisfactory operation has been found. It is to be admitted freely, however, that excision of 75% of the stomach is not an ideal therapeutic measure. It is to be hoped that some day the

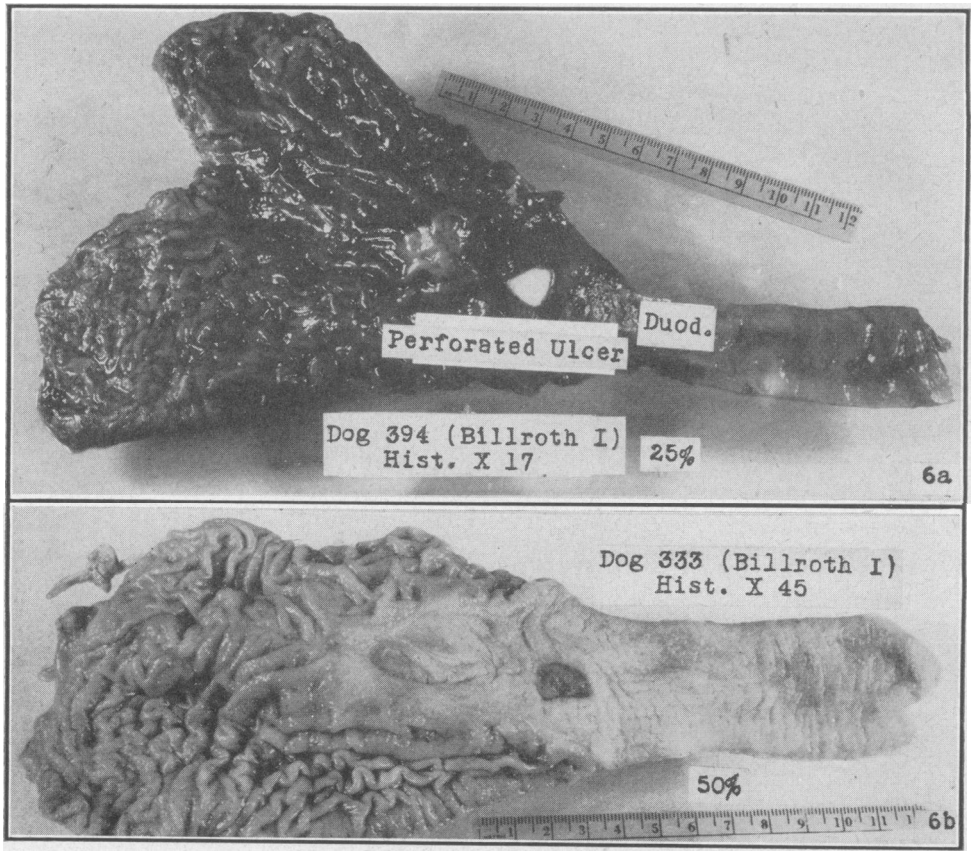


Fig. 6a.—Perforated stomal ulcer in a dog after a 25% gastric resection on the Billroth I operation. The dog died 17 days after the daily administration of 30 mgm. of histamine-in-beeswax was commenced. **Fig. 6b.**—Large perforating stomal ulcer in a dog in which a 50% Billroth I resection was done. The dog was sacrificed 45 days after the administration of histamine was started.

same objective may be achieved by lesser means. The mortality of the procedure in the experience of this clinic is approximately 2% in gastric resections of election. The surgical mortality of all procedures for ulcer including perforation and hæmorrhage has been 5%. Over a period of more than four years, during which we have been assaying the capacity of various operations to protect against the histamine-provoked ulcer in the laboratory, we have found the Group III operation (75% resection), herein described, uniformly resistant to ulcer ordinarily provoked by histamine. In the single instance in which stomal ulcer has been observed to follow such a resection in a patient, an inadequate operation was done. Whereas caffeine and alcohol are anathema to the patient with an ulcer, we have observed no need to enjoin dietary strictures upon patients who have undergone the type of procedure described herein.

Rienhoff (1945) in a recent paper replete with beautiful illustrations advocates return to a "conservative" gastric resection for duodenal ulcer, carrying the excision proximally to include the incisura angularis of the stomach. Rienhoff appends several tables in which he analyzes his data carefully. His Table III is particularly instructive. Of 260 patients operated upon by Rienhoff, he has found it necessary to subject 29 of the 255 that survived operation to re-operation, an incidence of 11.3%. If hæmorrhage is counted as synonymous with recurrent ulcer, 21.1% of the survivors have gastrojejunal ulcer. In addition, 16.3% of the survivors complain of pain. Obviously, Rienhoff's own analysis of the results of his operation may be employed to suggest that the conservative resection is an inadequate operation for ulcer. Our own observations suggest that it is not necessary to excise the ulcer itself in difficult duodenal ulcers to prevent ulcer recurrence.

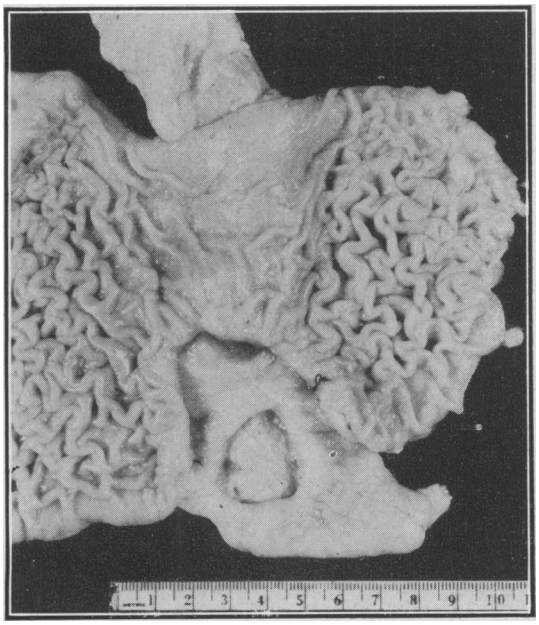


Fig. 6c.—Perforating stomal ulcer in a dog after Billroth II resection (33%); the dog was moribund from hæmorrhage 35 days after the administration of histamine was started.

We have been unable to produce stomal ulcer in the dog with histamine after a three-quarter resection (75%) whether carried out on the Billroth I or II plan of operation.

It perhaps is not out of place to point out too that the Billroth II plan of operation abets the ulcer diathesis.[67] Spontaneous ulcer in dogs is virtually unknown or, at any rate, is a great rarity. When, however, gastrojejunostomy is established in dogs, an incidence of gastrojejunal ulcer is observed in 6.6% (Montgomery, 1923). If, in addition, pyloric exclusion is performed, gastrojejunal ulcer occurs in dogs in approximately 50% of instances (McMaster, 1934; De-Bakey, 1937), indicating definitely that the Billroth II plan of operation abets the ulcer diathesis. As a matter of fact, Eiselsberg (1895) who devised the procedure of combining gastrojejunostomy with pyloric exclusion, did it on the basis of affording complete rest to a duodenal ulcer. Within a very few years thereafter, however, he observed that the high incidence of gastrojejunal ulcer following this procedure (37.5%) warranted its discontinuance. Wherein does the explanation of the increased susceptibility to gastrojejunal ulcer lie following performance of gastrojejunostomy combined with pyloric exclusion? I am inclined to believe it resides in this, that the exclusion of acid gastric juice from the duodenum prevents normal operation of the hormonal secretin mechanism described by Bayliss and Starling (1902). In other words, the small gastric resection is no better and probably inferior to gastrojejunostomy, which also is a poor operation with which to combat the ulcer diathesis.

G. *Implantation of a pedicled jejunal patch on to the gastric wall.*—Andrus and his associates (1943) contend that a jejunal graft transposed to the gastric wall will depress gastric secretion and have employed this procedure in the therapy of ulcer in man. Grossman and his associates (1945) from Ivy's laboratory, and Kolouch and associates (1945) from our labora-

tory failed to obtain confirmation of Andrus' contention.

H. *Supradiaphragmatic vagotomy.* — Dragstedt and Schaefer (1945) report having performed supradiaphragmatic section of both vagi nerves in 14 patients with ulcer with striking improvement. Many of the patients have been relieved completely of their symptoms. In 3, however, a subsequent gastrojejunostomy became necessary for the relief of persistent obstruction. We are now trying to determine whether vagotomy carried out in this manner in dogs will protect against the histamine provoked ulcer.* It is to be remembered that whereas vagotomy ablates the cephalic phase of gastric secretion, vagotomy has been employed to produce ulcer experimentally. In his Balfour lecture at Toronto, Cushing (1932) considered the neurogenic factor and its relation to the ulcer problem at length.

CONCLUSIONS

The clinical observations and experiments reported herein appear to justify the following conclusions:

1. The ease of production of perforating gastric and/or duodenal ulcer in most laboratory animals by the implantation of histamine-in-beeswax emphasizes the great importance of the acid-peptic digestive activity of the gastric juice in ulcer genesis.

2. It is obvious that fat embolism may occur following fracture of long bones and plug the end-vessels of the gastric mucosa and produce erosions, and/or ulcer, which in turn in the presence of active gastric secretion, may result in bleeding, hæmatemesis and/or melæna. This occurrence has been observed clinically and its counterpart has been produced experimentally.

3. The production of severe bleeding from erosions and/or ulcer, attending the administration of vasospastic agents such as epinephrine or pitressin accompanied by histamine-in-beeswax, definitely suggests the important rôle of the ischæmia resulting from an over-active vasomotor influence in ulcer genesis, when attended by active gastric secretion.

4. Partial obstruction to the venous outflow from the stomach increases the weight of the stomach, traceable to resultant œdema of the gastric wall, especially of the submucosa. Such venous obstruction abets the ulcer diathesis. Bleeding gastric and/or duodenal erosions and/or ulcers, as well as erosions of the lower end of the œsophagus, may be produced by such obstructions.

It is suggested that, the threatening bleeding of portal vein obstruction may be corrected by an operation (90% gastric resection) which reduces materially the capacity of the stomach to secrete. Case records of 4 patients in which this procedure has been carried out are cited. Moreover, it is suggested that, occult hæmorrhage from the alimentary canal frequently has its origin in the stomach and that, gastric resection is indicated as a therapeutic measure in many such instances. The case records of 4 patients in which this procedure was carried out successfully for profound occult anæmia are cited.

5. The histamine-in-beeswax technique has proved a useful instrument in appraising the characterization of a satisfactory operation for ulcer. It would appear that a three-quarter resection (75%), carried out on the Billroth II plan of operation, employing a short afferent duodenal loop in which the antral mucosa and the lesser curvature of the stomach are excised, meets the requirements of a satisfactory operation for ulcer. Our experience with this procedure in patients as well as in dogs receiving histamine would suggest that the intractable ulcer may be a myth.

* Experiments completed since this presentation indicate definitely that, in the dog and even in the rabbit, vagotomy affords no protection against the histamine-provoked ulcer.

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