THESIS

ULCERS OF THE GASTRO-INTESTINAL TRACT WITH SPECIAL
REFERENCE TO GASTROJEJUNAL ULCERS

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Submitted to the Graduate Faculty of the University of
Minnesota in partial fulfillment of the requirements
for the Degree of Doctor of Philosophy

May, 1919.
INTRODUCTION

The problem of ulcer of the gastro-intestinal tract will not let itself rest. There is still much controversy with regard to its etiology and the best method of treatment. This is especially true of the nonspecific ulcers of the upper end of the tract: the so-called peptic ulcers.

The wealth of material in the Mayo Clinic suggested the desirability of a study of the clinical findings, especially on gastrojejunal ulcer, and also the study of the experimental acid phase of the condition, not so much the gastric acidity as the relation of the blood reaction to gastric digestion, ferment injection, duodenectomy, etc. My investigation leads me to believe that the stomach conserves alkali for the body and that there is a reciprocal relation between the physiology of the blood proximal and distal to the division of the stomach and duodenum.

Ewald places gastro-intestinal ulcers into six etiologic groups:

Group 1. Ulcers which follow necrobiotic processes; peptic, duodenal, jejunal, embolic, thrombotic, amyloid, ulcers following skin burns, and those due to intestinal parasites.

Group 2. Ulcers following inflammatory processes; catarrhal, follicular, stercoral, decubital and stenosing.

Group 3. Ulcers due to acute infectious diseases; also abdominal typhus, dysentery, sepsis, erysipelas and varicous.

Group 4. Ulcers due to chronic infectious diseases; tuberculosis, syphilis, and actinomycosis.

Group 5. Ulcers due to constitutional disease; gout, scorbutas, leukemia, and arteriosclerosis.

Group 6. Toxic ulcers; uremia, mercury, arsenic, antimony and phosphorus.
Greggio divides the into eight etiologic groups:

**Group 1.** Ulcers due to irritants, alcohol, drugs, etc., producing diffuse lesions such as gastritis, and ulcers that follow acute catarrhal conditions.

**Group 2.** Lesions due to disturbances of the circulation of the gastric wall; thrombosis, emboli, hemorrhagic infarcts, stasis, ischemia, etc. Lesions of the lymphatic vessels; vascular spasm, and anomalous modification of the distribution of arteries. According to certain writers the vascular conditions follow those of a venous origin. Many admit that an ulcer in a region in which there is an alteration in the circulation is formed by local autodigestion, which is due to a direct alteration of the tissue, or because of a failure of the arrival in the tissue of substances necessary to inhibit acute digestion.

**Group 3.** Ulcers due to alteration in the constitution of the blood may be accounted for by chlorosis and anemia, hemoglobinemia, to a diminished blood alkalinity, or to the local or general alteration of different causes, in the quantity of antipepsin of the blood, to a hemorrhagic diathesis through a functional lesion of the liver, and to the alteration of the blood secondary to burns of the skin.

Many of the theories admit of autodigestion consequent to the lesion given. For example, in chlorosis and anemia there is a fatty degeneration and a thrombosis of the small vessels of the stomach and a local autodigestion. Other writers give anemia as a cause of the hyperchlorhydria which in turn is the cause of ulcer.

**Group 4.** Cases in which the alteration of the quantity of the antipepsin permits the digestive action of the gastric juice on the tissues of the wall, etc., but with the hypothesis which gives to autodigestion a decisive role in the pathology of gastric ulcer. This autodigestion is consecutive to different causes.
According to different opinions gastric stasis (dilatation, ptosis, abnormal contractions of the stomach walls, etc.), alterations of the acid secretions and of pepsin, congenital alterations or those secondary to the mucosa of vascular or nervous origin, etc., alterations in the antipeptic powers, alkalinity of the blood, the constituency of the blood, etc., all permit of the digestion of the gastric wall. In this manner, the theory of autodigestion is connected with other pathogenic hypotheses.

The augmentation is admitted of the gastric secretion, a hyper-acidity of the juice, an anomalous stasis of the juice in the stomach, perhaps by a pyloric stenosis, or of acid chyme in the duodenum due to ptosis, and the action of the acid gastric juice on the pyloric mucous membrane altered by other causes. In cases of duodenal ulcer an insufficient neutralization of the gastric contents must be considered.

Gastric autodigestion in ulcer has been explained by a lesion in the lymphatic follicles, by the existence of little foci of epithelium of the gastric mucosa, by the structure of intestinal epithelium, and by the presence of nests of special an adenic epithelium.

Group 5.- In the cases in this group the importance of autodigestion is affirmed also in many hypotheses which give to traumatism in general a great importance in the pathology of gastric ulcer. Many writers have admitted that gastric ulcer follows directly lesions of the mucosa, and lesions produced by the ingestion of substances and different bodies such as fragments of glass, bone, wood, etc. Others admit its pathologic relation with epigastric traumatism, with light and habitual compressions on this region, and with divers wounds or contusions.

In ulcers of the duodenum the influence of compression of stones or neoplasms on its wall is recognized.
Group 6.- In these cases the hypothesis of infection has also been advanced. Septic emboli, infectious alterations of the blood by septic processes general or local, and even a true direct infectious process has been given as a cause of the ulcer.

Bolton believes that chronic ulcer in man is due to endogenous and exogenous toxins, and that its chronicity depends on a secondary infection which causes muscular insufficiency.

Group 7.- In this group are considered the lesions of the central nervous system, and of the nerves as a cause of simple ulcer. Stockton calls it true neurotrophic ulcer, others believe that the nervous lesion is a cause of vascular spasm and of a muscular spasm which provokes the formation of ulcer. According to certain authors, the nervous lesion cause different alterations, because above all vasomotor of the failure of the vago-sympathetic equilibrium, or cardiospasm. It is admitted that a gastric stasis follows a pyloric spasm of nervous origin. Stuber believes in a pyloric insufficiency of venous origin and in a secondary reflex of the duodenal secretions with the stomach. Some have even given heredity a place in the pathology of chronic ulcer. To nervous troubles one writer has added autodigestion, circulatory alterations, general disease, chlorosis, anemia, etc.

Group 8.- This group comprises the constitutional diseases, such as asthenia, the enteroptoses, the general lymphatism as alterations in the lymphatics of the stomach, tuberculous habitus, hereditary hemiplegic diathesis, a special disease of the gastric wall, fibromatosis, and congenital asthenia of the trophic centers of the stomach.

Certain other writers believe gastric ulcers to be secondary to different diseases, such as morbid processes of the liver, general pyogenic processes, or processes in the abdomen, peritoneum, or appendix.

Some investigators admit of a variable origin according to the case; also complex theories have been added to the role of variable cases. The walls of
the stomach are susceptible to lesions because of their function. The repair of such lesions and of those one may produce experimentally is quite rapid, although true regeneration of the mucosa does not come until quite late. The reparative processes of the mucosa do not seem to be interfered with by the gastric juices. The contractility of the gastric wall seems to limit the extent of the wound and facilitate healing.

Cruveilhier divided the ulcers into two groups. Those having a follicular origin and which were primarily necrosis of the gastric mucosa, having different origins or causes, and those due to vascular alterations, colonies of microbes in the vessels, arteritis, endophlebitis, hyaline degeneration, toxemias, irritants, vasomotor troubles, septicemias, hemorrhagic infarcts, dyscrasias, poison, burns, and to general infection.

Cruveilhier and other writers admit that chronic ulcer may succeed the acute ulcers. Aschoff believes that a chronic ulcer may sometimes succeed the acute peptic ulcer. Hayem, on the contrary, does not believe that the chronic ulcer follows the acute.

Different types of chronic ulcer have been described. Hayem, for example, discusses an ulcer which begins at the external surface of the gastric wall and which then advances toward the mucosa. Usually two types have been considered here, the simple round ulcer, and the callous ulcer, sometimes called a perforated ulcer afterward covered and protected by peritoneal adhesions (Schnitzler). Aschoff speaks of a chronic ulcer as having formed on a pre-existing epithelial neoplasia. Clinically, however, a differential diagnosis between a callous ulcer and a tumor of the stomach is sometimes impossible. According to MacCarty the distinction is often impossible unless a histologic examination is made.

Callous ulcer very rarely occurs in the duodenum (Grüber). In the same portion of the intestine cancerous degeneration of a simple ulcer is just as rare, and although the existence of the ulcer may be frequent (Ewald) there is
such a thing as non-neoplastic callous ulcer. This ulcer has, however, a great tendency to become cancerous; one-fourth of the cases (Payr); one-third of the cases (Kelling); more than one-third of the cases (Küttner). MacCarty keeps in mind the other aspect of a secondary callousness and a preceding neoplasia.

**Etiology of gastrojejunal ulcer**

Ever since it has been known that gastrojejunal ulcers follow gastro-enterostomy, attempts have been made to discover the etiology of the condition. Why is it that ulcer occurs in such a low percentage of cases? Why is the condition not found more frequently since the same changes and the same mechanical changes anatomically and physiologically have occurred? The difference as to the time of the appearance of the ulcer, its position, etc., would lead us to believe that the etiologic factors differ in different cases.

Many writers believe that infection is the cause of the ulcer. Mayo- Robson believes that through lack of mouth care slight septic gastritis with hypochlorhydria is produced, which may lead to ulceration. He believes that all peptic ulcers are due to this infection, be they gastric, duodenal, or jejunal. Newman states that these ulcers are of mycotic origin. First there is a mycotic necrosis of the mucosa, then a peptic digestion.

The infection theory has received many adherents because in anastomosing the stomach and intestinal mucosae, wounds are produced, which become secondarily infected; these acted on by the hyperacidity of the stomach juice, become chronic. Schostak, Paterson and Gould have studied the healing of gastro-enterostomy wounds and believe that ulcer is a direct result of the operation. Most gastro-enterostomies heal by secondary intention, they become infected and are changed to chronic ulcers by hyperacidity. The extent of the necrosis may be explained as due to mechanical measures, such as instruments, Murphy button, and even suturing.
Circulatory disturbances are given as a second cause of such ulcers. The circulation may be interfered with in several ways. The loop of intestine may be too short and cause tension, or if the mesentery is kinked, the blood supply may be impeded, the suture, too, may obstruct vessels, the segment of gut anastomosed to the stomach may be abnormally fixed, there may be pressure from the colon or stomach, arteriosclerosis of the vessels, which makes kinking more effective, or injury to the mucous membrane at the time of the operation or later by food.

The peptic factor is the third hypothesis advanced for the causation of ulcers following gastro-enterostomy. Paterson, Kocher, Körte, and others hold to the hypothesis, that the high acidity of the chyme kills the cells of the normally alkali intestinal mucosa, which is subsequently digested by the pepsin. The free hydrochloric acid, not the total acidity, is the factor which causes the death of the cells. It is toxic to the mucous membrane which if its vitality is destroyed, can readily be digested by the pepsin.

Acidity or lack of alkalinity do seem to play an important part in the formation of ulcers in or around the stoma. An ulcer in the afferent limb is rarely seen; they either appear just opposite the stoma or in the efferent limb, where the acid chyme acts. Thus in the "Y" operation we have a higher percentage of ulcers than in the gastro-enterostomies, or the gastroduodenostomies. Again, even in ulcers of the duodenum, the ulcer is high up near the pylorus, seldom more than two or three inches away. It never occurs low down in the then, duodenum. Bolton writes: "It appears that any strength of hydrochloric acid above the normal can act as a protoplasmic poison for gastric cells, and will add its quota to other devitalizing influence and assist in bringing about self-digestion".

If acid is the toxic agent that causes death of the cells naturally alkali is its antidote. The cells of the mucosa must have alkali to neutralize the acid that is found with them. This increase of alkali in the stomach's blood has been demonstrated, and will be discussed later herein. The duodenum,
however, has not the power to increase or decrease the alkali content of its cells, so we have a much greater incidence of ulcer in the duodenum than in the stomach. For the same reason the point opposite the stoma and distalward is the site of election for ulceration following gastro-enterostomy.

Furthermore, since antipepsin, and antiferments have never been demonstrated, it may be that this action which we have been calling anti, is merely one of alkalinity. It is a well known fact that few cells live in acid media; in order that cells may functionate and reproduce, alkali media is necessary. The same is true of the gastric cells or the duodenum, or the jejunum. Increased acidity kills, and death produces localized acidity in the tissues, which gives the pepsin a chance to be activated and digestion to progress. If the gap of mucosa destroyed is too great for healing a chronic ulcer forms.

The frequency of duodenal and gastric ulcer

The frequency of duodenal and gastric ulcer seems to be quite well decided in favor of the former. This is especially true in the Mayo Clinic, where many more duodenal than gastric ulcers are seen. Necropsy records of Gruber, and Kreuzfuchs seem to show quite the contrary. Moynihan finds many more duodenal than gastric ulcers.

The position of the ulcer

The position of the ulcer varies. On the gastric side the greater number are on the lesser curvature near the pylorus; most all ulcers are near the pylorus (juxta pyloric region of Ewald). A number are on the posterior wall, and fewer are near the cardia and along the greater curvature. On the duodenal side they are mostly on the anterior surface within two inches of the pyloric ring. The pyloric veins make a good dividing line between gastric and duodenal ulcers. W.J. Mayo first called attention to the pyloric vein as a landmark in dividing gastric from duodenal ulcer.
Experimental research

Extensive experimental research has been done with regard to chronic gastric ulcer. Greggio has made a careful review of the literature, and he is quoted liberally in order to give an idea of the numerous and various experiments that have been tried. A true chronic ulcer is produced experimentally. Acute ulcers which heal rapidly may be produced in various ways; Mann has been able to produce them by many methods. His experiments on adrenalectomy are well known. Likewise Rosenow's work on the infectious theory of ulcer production is familiar to us all.

In order to produce an ulcer, various chemical, physical, mechanical, physiologic, and biologic methods have been invoked, using rabbits, guinea-pigs and dogs, etc.

Virchow and Ebstein used phosphorus. Filehne, and Böhm gave subcutaneous injections of arsenious acid. Jousset and Lefas injected tartar emetic. Majer, and Coen tried progressive poisoning with acetate of lead. Overback tried the cutaneous use of mercurial inunctions. Saikowski gave subcutaneous injections of corrosive sublimate. Pilliet injected glycocolate of mercury. Péron injected alcohol. Silbermann injected pyrogallic acid and tried burning the skin. Aufrecht used cantharidin. Roy, and Poncet used ergotine and scillitoxin. Westphal used pilocarpin and physostigin. Stich injected ptomaines. Rechfuss used the venom of certain lizards. Latzel used the digestive juices of the stomach and intestines of one animal and injected it into another animal. Loepcr used the extract of the gastric mucosa, or the gastric juice of a hog for his injection. Bolton used cytotoxin on gastrototoxic serum. Gundermann used an extract of liver. Favre used the blood of a uremic person. Vassale and Sacchi extracted burned tissue. Lang, and Castel glazed skin. Special organs have been taken out. Gibelli, Latzel, and Mann have taken out the adrenals. Müller, and Köllicher took out the liver. Boccardi, and Falcone took out the thyroid.
The vascular supply has been modified by the injection of wax emboli. Panum, Prévost and Cottard injected tobacco into the aorta. Payr injected dermatol and india ink into the gastro-epiploic arteries and veins. Chessin and Feldmann injected lycopodium. Kobayaaki injected liquid paraffin infected with staphylococci in order to produce ischemia by mycotic emboli.

Wilkie tried to produce retrograde embolic processes. Friedrich and Hoffman ligated the umbilical veins with aseptic precaution. Otte, and Gandy ligated the epiploic veins and the mesenteric veins. Sapiejska burnt the omentum, von Eiselberg ligated it, Friedrich resected it.

Baron ligated the vessels of the stomach. Pavy and Matthes did the same, but in addition injured the mucosa mechanically, or chemically with hydrochloric acid. Fenwick, and Gundermann ligated the portal vein to produce a stasis.

Changes in the constituency of the blood have been made by producing acute anemia with perchloride of iron, pyrogallic acid, pyrodine and a combination of pyrodine anemia and the injection of dermatol into the gastric veins. (Chessin and Feldmann). Silbermann, and Fütterer produced a pyrogallic anemia, and at the same time ligated the arteries to the stomach. Gibelli tried bleeding, and at the same time traumatic lesions of the gastric walls. Zironi injected pyrodine and at the same time resected the pneumogastric nerve. Anemias have been produced to retard healing in other experimental methods. Frouin produced a stasis, gave saline alimentation, and then hydrochloric acid. Latzol fixed the duodenum and thus prevented the normal drainage of the stomach juices. López injected gastric juice and extracts of gastric mucosa.

Artificial hyperchlorhydria has been associated with other lesions, according to Matthes, with direct lesions of the mucosa, to Koch and Ewald, with lesions of the medulla, to Saitta, with resection of the pneumogastric nerve and ligature of the gastric vessels. Boršky made ulcers at the gastro-enterostomy opening by producing a pyloric stasis and instilling hydrochloric acid. Stuber made gastric ulcers by producing pyloric insufficiency in such a manner that the
pancreatic juice flowed back into the stomach. He at the same time fed his dogs so as to produce as little acidity of the stomach as possible.

The effect of trauma has been studied by Matthes, and Gibelli. They produced direct lesions of the gastric mucosa. These wounds healed rapidly. Foreign bodies have been injected as well as caustics to produce trauma. Pavy, and Samuelson used concentrated hydrochloric acid. Sternberg used heat. Sternberg, and Decker used hot foods. Matthes sutured the mucosa in rings to the muscular coats and noticed hard ulcerations. Fiori produced a pyrodin anemia, then made a direct lesion, and thus produced a lasting loss of substance. Clairmont reports direct lesion of the mucosa associated with vessel ligation so that the two correspond. Fiebich did the same thing, but results do not correspond. Local infection and hyperchlorhydria have been tried. Burning of the stomach with small tubes of hot porcelain and at the same time injecting intravenously phosphoric acid to kill the antipepsin was tried by Katzenstein.

Infection, too, has had its advocates. Cohn injected pus into the arteries. Lebert injected it into the peritoneal cavity. Bauer injected the Bacillus coli. Wurtz and Leuici injected the Bacillus lactis; and Charrin, the Bacillus pyocyanus. Favre injected an organism extracted from the blood of a patient with eclampsia. The monumental work of Rosenow in the field of infection is well known. Turk, and Bauer kept animals undernourished with food infected with Bacillus coli. Singer mixed the food of animals with excreta. Filtered cultures of the Bacillus pyocyaneus have been injected by Charrin. Enriquez and Hallion injected diphtheria toxin. Claude injected tetanus toxin. Bolton injected gastric toxin. Wilkie produced thrombosis and septic emboli of the omentum. Kobayaski tied the cecum of a dog so the peritoneum would become inflamed and thus cause an ulcer.

Certain experiments show a relation of the lesions of the central and peripheral nervous systems and the formation of ulcers of the stomach and duodenum. For example, lesions of the optic thalamus, the cerebral peduncles, the
protuberances, the bulb, after burning of the cerebral surfaces (Brown Sequeard).
Lesions of the tubercles quadrigemini or the hemispheres (Ébstein). Section of
the cervical cord. All of these lesions together with the ingestion of 5 per
cent hydrochloric acid (Koch and Ewald). Bilateral lesions of the anterior and
posterior roots of the fifth to eighth dorsal segments (Schupfer). Lesions of
the marrow and anemia (Quincke and Daettwyler). Excitation of the pneumogastric
in the neck (Talma). Lesions produced by exciting the nerve subdiaphragmatically
(Lichtenbelt). Lesions formed by causing neuritis of the pneumogastric nerve in
the the neck, or in/abdomen by burning the nerve or by the injection of alcohol.
Donati’s, and Körte’s results from section of the vagus in the neck were negative;
only Saitta obtained any positive results when he also gave the rabbit hydrochloric
acid. Section of the vagus in the thorax has given variable results; Krehl, and
Fritsch obtained negative results, Kawamura at times obtained positive results.
Abdominal section of the nerve gives the same results; Opföls, and Kobayashi have
produced ulcers. Grünsburg and Lunch have failed to produce them. Marchetti by
double ligation of the abdominal vagi has produced chronic ulcers. Löwin produced
hyperemias, gastro-intestinal hemorrhages and mucous ulcerations by extirpating the
celiac plexus; Budge, and Lustig failed with the same operation. Kawamura
succeeded, Kobayashi failed to produce the lesion or irritation respectively of
the celiac plexus. Brancati ablated the paravertebral lumbar sympathetics and
produced lesions. Vedova did the same by injuring the great splanchnic, Duranti
by injuring the small splanchnic. Lilla’s simultaneous lesions of the celiac
plexus and pneumogastric produced small punctate hemorrhages. Samuelson had
negative results even with the addition of injection of hydrochloric acid. Auer
took away all the nerve supply of the stomach; the movements were diminished, the
reflexes suppressed, and ulceration occurred.

The gastric wall has been injected with adrenalin (Rosenbach and Eschker),
with formalin (Borszéky); with gastrotoxic serum (Bolton). With the same agents
injected into the gastric vessels Toluc-Suzuki obtained lesions, but
they healed rapidly. Licini has by the use of apomorphin, been able to convert some of these acute lesions into chronic.

The foregoing experiments are not however, to be considered positive, when compared to the *ulcus rotundum* of Cruveilhier. Different writers, using the same experiment, vary in their results. Many methods produce lesions varying all the way from small hemorrhages to destruction of the wall of the stomach and acute ulcer formation; such ulcers heal. The lesions following injury to the central nervous system are necrotic and occur also in other organs.

No one cause can be assigned to the formation of ulcer. Each case has its own special cause and whatever this may be the preferable treatment up to the present is gastrojejunostomy. In the larger number of cases this operation effects cure; in some cases only improvement, and in a few the same symptoms remain with changed or added attributes. Our attention is especially directed to the latter group since they include the greater percentage of gastrojejunal or jejunal ulcers. Just why these ulcers occur still remains a problem in surgery. Gastro-enterostomy seldom heals primarily; some parts of it may, but the greater portion of it heals by secondary intention.

**The healing of the gastro-enterostomy stoma**

Harvey, and Flint have given us detailed reports of the healing of the gastro-enterostomy stoma. Changes occur about 7 mm. from the gastro-enterostomy line. The body chief cells which are normally the cells that make ferments are changed to mucus-forming cells. The process begins at the line of contact of the two mucous membranes and in about three weeks extends to 7 mm. about the stoma. In the next 3 mm. radially about the stoma the ferment cells have a tendency to this change, but do not undergo a complete transformation. After one month a reverse transformation begins and the same cells become ferment cells. Fully to complete this process takes six and one-half months. After this the glands up to the suture line, do not differ from those remote from it.
When the gastro-enterostomy has produced only a slight disturbance of the circulation there is a minimum of inflammatory reaction and healing by first intention. The infolded serous surfaces promptly adhere by throwing out a fibrinoplastic exudate, and this also extends along the entire line of the incision. After twenty-four hours the mucosa has well regenerated and after from forty-eight to seventy-two hours any defect in mucosa may be covered. All that is necessary to complete the healing is the organization of the exudate. Such a process may be completed in five to fourteen days.

When the circulation to the mucous membrane of the stomach and intestine has been much disturbed the process is a much slower one and there are degenerative processes preceding the reparative. The mucous membrane, for varying spaces around the gastro-enterostomy, is destroyed and must be replaced. The destructive processes last about seven days, depending on the extent of the injury. After this time the restorative process begins and is completed at about the fourteenth day. The regeneration of the muscularis mucosa and the tunica muscularis takes somewhat longer.

The regeneration of the intestinal mucosa takes place from the crypts. In the neighborhood of the exudate they return to their embryonic form. The epithelium flattens as it passes up from the crypts to the exudates, where it penetrates its substance and forms a single layer of squamous cells. From this layer young crypts extend down into the organizing exudate and there produce new growing centers. After the restoration of the epithelium is complete the differentiation into typical goblet cells and regular columnar cells takes place.

The regeneration of the gastric mucosa generally begins from the less differentiated epithelium about the mouths of the gastric glands or from the tubules that have returned to their embryonic form. As in the intestine the new formed epithelium flattens as it passes up on the exudate and which it often penetrates. From this sheet of epithelium new tubules are produced by invag-
inating into the substance of the exudate. The glands are at first embryonic but later assume their normal character. The muscularis mucosa begins to regenerate about the second week. It may be a complete regeneration of the muscle, or the ends may be connected with connective tissue strands. The tunica muscularis may do about the same thing. It may heal completely or may too, be connected by new formed connective tissue. The intestinal epithelium is not modified by the gastro-enterostomy. It heals well in the presence of the gastric juice, due to antiferments or to the neutralization of the juice with succus entericus.

It should always be remembered that the new formed anastomosis is the site of a healing ulcerated surface for a period of fourteen days, that this healing is not always complete, and that the number of gastrojejunal and jejunal ulcers is on the increase, that is, their diagnosis is more and more sure.

The suture has been held responsible for the failure of the gastroenterostomy to heal. Silk or linen sutures have often been found at the site of an old ulcer. This seemed a probable explanation of the finding until the abandonment of the silk and linen for the catgut suture. However, it is safe to say these sutures were a factor but not the only one in retarding the reparative process.

**Observations on gastrojejunal ulcer**

It was not until eighteen years after Wölfler's first gastroenterostomy that a gastrojejunal ulcer was observed. The observation was made by Braun in 1899, in a patient who had had a posterior gastrojejunoostomy eleven months before for pyloric obstruction. The operation had not given him complete relief. The vomiting continued and his condition became distressing that he sought hospital relief. His stomach was dilated below the umbilicus. With treatment he improved for a short time. On the second day after his third admission to the hospital he died. Necropsy showed a perforated jejunal ulcer in the afferent limb about one inch below the anastomosis. Peritonitis was
The stoma was quite large.

After the report of this case many other observations were made. The first statistical report, 12 cases from the literature, was given out by Kieffer in 1902-1903. In 1904 Tiegel reported 6 cases and collected 16 others from German literature. In 1907 von Key reported 49 cases. In 1909 Paterson reported 63 cases. In 1910 von Roojen reported 78 cases, to which were added 14 others by Petren in 1911. Further work was done by von Schostak, Poly, and others. Lieblein, in 1915, reported 129 cases. In France the first case was reported by Quenu in 1902. In England the first case was reported by Mayo Robson in 1904. In the same year Hamann reported the first case in America. Then followed the work on the interesting problem by Moynihan, the Mayos, Balfour, Carman and others.*

In 1915 Balfour and Carman reported 13 cases from the Mayo Clinic. Up to this time (April, 1919) there have been 69 cases operated on. Forty-four followed operations done in the clinic, and 25 were done elsewhere. The present report concerns only the 44 cases.

Statistics

From Jan. 1, 1906 to April 1, 1919 complete records have been kept at the Mayo Clinic of all ulcer cases of the gastro-intestinal tract. Operations have been done in 3,480 cases of ulcer; 3,175 duodenal; 305 gastric. In the duodenal ulcer cases posterior gastro-enterostomy was done in 3,161 (99.5 per cent). Fourteen (.44 per cent) anterior gastro-enterostomies were done. In 154 cases (4.8 per cent) in addition to a posterior gastro-enterostomy the pylorus was blocked. In 847 (26.6 per cent) perforation was found at the time of the gastro-enterostomy. In 977 cases (30.7 per cent) obstruction was found.

In the gastric ulcers 279 (91.47 per cent) posterior gastro-enterostomies and 26 anterior (8.5 per cent) were made. The pylorus was blocked in 21 cases (6.8 per cent). Perforation was found in 142 cases (46.5 per cent).

*It is fitting here that I should pay special tribute to the work of Dr. W. J. Mayo, Dr. C. H. Mayo, and Sir Berkeley Moynihan in teaching the medical world the fundamental importance of recognizing and treating ulcer of the upper gastro-intestinal tract.
and obstruction in 73 cases (23.9 per cent).

The gastric ulcers showed a greater tendency to perforate; 46.5 per cent gastric as compared to 26.6 per cent of the duodenal. Duodenal ulcer has a greater tendency to obstruct; 30.7 per cent as compared with 23.9 per cent in gastric ulcer.

In 18 of the 44 cases there was a high acidity before operation. In only 6 cases was it high after operation. Four patients, however, had a higher acidity after the posterior gastro-enterostomy than before.

There were 2,689 males (77.3 per cent), and 791 (22.7 per cent) were females in the series. In the duodenal cases (3,175) there were 2,453 (77.2 per cent) males; and 722 (22.4 per cent) were females. In the gastric cases (305) there were 236 (77.3 per cent) males, and 69 (22.6 per cent) females. In the gastrojejunal cases (69) 63 (91.3 per cent) were males, and 6 (8.6 per cent) were females. The incidence of gastrojejunal ulcers is comparatively much higher in the male.
Table 1

MISCELLANEOUS

<table>
<thead>
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<th>Condition</th>
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<td>Gastrojejunal ulcers following operation for gastric ulcer</td>
<td>6</td>
</tr>
<tr>
<td>Gastric ulcers no bleeding before first operation</td>
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<td>Gastric ulcers causing melena before and after first operation</td>
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<td>No blood immanent melena before first operation but hematemesis and melena after first operation</td>
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<tr>
<td>Gastric ulcers with perforation at first operation</td>
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</tr>
<tr>
<td>Gastrojejunal ulcers with perforation at first operation</td>
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<tr>
<td>Gastric ulcers with obstruction at first operation</td>
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<td>Hematemesis before operation</td>
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<td>Perforation at operation</td>
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<td>Gastrojejunal ulcers following posterior gastro-enterostomy</td>
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</tr>
<tr>
<td>Some which had thread or suture material in ulcer area</td>
<td>11 (25%) (44%)</td>
</tr>
<tr>
<td>Gastrojejunal ulcers with thread or suture material in ulcer area</td>
<td>21 (30%) (69%)</td>
</tr>
<tr>
<td>Average time between first operation and appearance of symptoms of gastrojejunal ulcer</td>
<td>23.3 months</td>
</tr>
<tr>
<td>Average time after onset of first symptoms of gastrojejunal ulcer before operation</td>
<td>22.5 months</td>
</tr>
<tr>
<td>Gastrojejunal ulcers following excision and posterior gastro-enterostomy for gastric ulcer</td>
<td>2</td>
</tr>
<tr>
<td>Gastrojejunal ulcer following cautery excision and posterior gastro-enterostomy for gastric ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Gastrojejunal ulcer following partial gastrectomy and later posterior gastro-enterostomy for gastric ulcer</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 2.

**BEFORE POSTERIOR GASTRO-ENTEROSTOMY**

<table>
<thead>
<tr>
<th>Emesis &amp; Findings</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis with retention</td>
<td>10 (3 with food remnants at test meal)</td>
</tr>
<tr>
<td>Emesis with bleeding</td>
<td>16 (5 with blood at test meal)</td>
</tr>
<tr>
<td>Emesis with bleeding and retention</td>
<td>4 (3 with blood at test meal) (1 with food remnants at test meal)</td>
</tr>
<tr>
<td>Emesis without other findings</td>
<td>16</td>
</tr>
<tr>
<td>Emesis and dilated stomach</td>
<td>5</td>
</tr>
<tr>
<td>Bile in gastric contents</td>
<td>2 and 1 (?)</td>
</tr>
<tr>
<td>Emesis with retention, dilated stomach and pyloric stenosis</td>
<td>1</td>
</tr>
</tbody>
</table>

**AFTER POSTERIOR GASTRO-ENTEROSTOMY**

<table>
<thead>
<tr>
<th>Emesis &amp; Findings</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis with retention</td>
<td>6 (1 with food remnants at test meal)</td>
</tr>
<tr>
<td>Emesis with bleeding</td>
<td>7 (2 with blood at test meal)</td>
</tr>
<tr>
<td>Emesis with bleeding and retention</td>
<td>3 (2 with food remnants at test meal) (1 with blood at test meal)</td>
</tr>
<tr>
<td>Emesis without other findings</td>
<td>18</td>
</tr>
<tr>
<td>Emesis with dilated stomach</td>
<td>2</td>
</tr>
<tr>
<td>Blood in test meal</td>
<td>1</td>
</tr>
<tr>
<td>Bile in gastric contents</td>
<td>2 and 3 (?)</td>
</tr>
</tbody>
</table>
Table 3

AGES BY DECADES

**Gastric ulcer**

<table>
<thead>
<tr>
<th>Decade</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-20 years</td>
<td>6</td>
<td>1.9%</td>
</tr>
<tr>
<td>21-30</td>
<td>33</td>
<td>10.8%</td>
</tr>
<tr>
<td>31-40</td>
<td>51</td>
<td>16.6%</td>
</tr>
<tr>
<td>41-50</td>
<td>98</td>
<td>32.1%</td>
</tr>
<tr>
<td>51-60</td>
<td>77</td>
<td>25.2%</td>
</tr>
<tr>
<td>61-70</td>
<td>36</td>
<td>11.8%</td>
</tr>
<tr>
<td>71-80</td>
<td>4</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

**Duodenal ulcer**

<table>
<thead>
<tr>
<th>Decade</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-20 years</td>
<td>33</td>
<td>9.7%</td>
</tr>
<tr>
<td>21-30</td>
<td>468</td>
<td>14.7%</td>
</tr>
<tr>
<td>31-40</td>
<td>919</td>
<td>28.9%</td>
</tr>
<tr>
<td>41-50</td>
<td>922</td>
<td>29%</td>
</tr>
<tr>
<td>51-60</td>
<td>627</td>
<td>19.7%</td>
</tr>
<tr>
<td>61-70</td>
<td>201</td>
<td>6.3%</td>
</tr>
<tr>
<td>71-80</td>
<td>14</td>
<td>0.4%</td>
</tr>
<tr>
<td>81-90</td>
<td>1</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

**Gastrojejunal ulcers**

- **Average age**: 41.8 years
- **Oldest male**: 69 years
- **Oldest female**: 54 years
- **Youngest male**: 22 years
- **Youngest female**: 25 years
Pathologic anatomy

As in their clinical relation, so also in their pathologic-anatomic relation, ulcers of the gastrojejunal type resemble those of the gastric and duodenal types. They have a great tendency to perforate and to form inflammatory tumors. According to Key they also have great tendency to hemorrhage. The resemblance between these ulcers has been noted by many observers. In form they are sharp-edged and funnel shaped, more substance of the mucous membrane being lost at the surface of the stomach wall than deeper down. The perforated ulcers have sharp edges and seem to be punched out. The perforations vary in size from mere needle-sized holes to the size of a twenty-five cent piece or even larger.

The question of spontaneous healing of gastrojejunal ulcers is open. In jejuno-jejunocolic fistulas, all traces of an ulcerative process seem to have disappeared. Paterson even with microscopic search, was unable to locate any ulcerative process, but found wrinkled mucosa with inflammatory reaction.

As the ulcer grows older, induration increases, the ulcerative process may increase and the inflammation around its neighboring organs, the mesentery of the small bowel, the retroperitoneal tissues, the anterior abdominal wall, the transverse colon, etc., may be involved. When the process does extend inflammatory tumors are found which resemble very closely those formed in the stomach. These ulcers often penetrate into the anterior abdominal wall, into the rectus muscle, more often the left. In some cases covered perforations are found. The colon occasionally prevents the ulcer from perforating, at other times the colon in its protective role has not been able to accomplish its work and a fistula between it and the jejunum has formed. In these fistulas the mucous membrane is sometimes directly continuous and completely healed - all ulceration having been checked. These conditions often narrow the stoma and decrease its efficiency, so much so that symptoms of obstruction appear.
Generally there is only one ulcer, but there may be more. Key, Lion, Paterson, and Petren found two ulcers in some cases; Wall found four; ten each Eisberg and Pinner found four.

The position of the ulcers is usually in or around the stoma. Many of them are on the jejunum just opposite the stoma, where the chyme would be directly a guard to the intestinal wall. The efferent limb of the jejunum has more ulcers than the afferent. Roojen hesitates to associate an ulcer far removed from the stoma with the previous posterior gastro-entero-stomy but prefers to think that it is a spontaneous jejunal ulcer.

**Symptomatology**

Cases of gastrojejunal and jejunal ulcers usually have been divided into two main groups. In the second group two subdivisions have been made:

*Group 1.* Cases in which perforation occurs into the general peritoneal cavity.

None of the cases in the present series fall into Group 1. All the cases were of a chronic type. There were, however, many in which the perforation had healed and had formed a tumefaction of more or less extent.

*Group 2.* Cases in which owing to the formation of local adhesions, perforation does not occur into the general peritoneal cavity.

1. The base of the ulcer points outward toward the abdominal parietes, and if perforation occurs the result is an inflammatory exudate into the abdominal wall, which may develop a sinus.

2. Perforation into a hollow viscus, or adhesions at the site of the ulcer. The mesocolon quite frequently prevents perforation into the peritoneal cavity.

In 23 of the 69 cases perforation had occurred; 6 perforating toward the abdominal parietes and 17 inward, either toward the colon or toward the transverse mesocolon. There were four colonic fistulas. In 18 of the cases remnants of a former silk or linen suture were found. In one case a silkworm
gut was found. The position of the ulcers in a high percentage of cases, was in or around the stoma. A few of the ulcers were on the wall of the jejunum opposite the stoma and fewer still on the efferent limb. In one case in which operation was done elsewhere, an ileal ulcer was found; the anastomosis had been made high up in the ileum. In a few cases the ulcers were multiple.

The symptoms of gastrojejunal ulcers are much the same, as those of other peptic ulcers. If a patient who has been in good health following a gastrojejunostomy, begins to complain of his former symptoms, which may have added or changed attributes, an ulcer on the stoma or about it should be suspected. A complaint of hyperacidity or hypersecretion is still further evidence. The pain, usually, is constant, and if in addition a tumefaction can be felt, or if the abdominal wall is indurated, the diagnosis becomes certain. Lately the x-ray has given valuable aid in diagnosing such ulcers by showing deformity of the stoma.

**Treatment**

Since there are cases on record that seemingly have been cured medically and other cases that have healed spontaneously, it is reasonable to give the patient a chance of medical cure before surgical intervention is attempted. The treatment should be rest in bed, a carefully directed diet, with appropriate alkali treatment.

The acute perforations are at once surgical. After operation they fall into Paterson's Group 2. In these cases in which there are more or less protective adhesions the indications for surgical treatment are not always so clear. However, many cured; 40 per cent of the patients treated for such perforations at the Mayo Clinic were entirely cured, and nearly all received benefit.

The exact operative procedure to adopt depends on the individual case. The point to be kept in mind is not to do too much. Patients who have extensive operations do not get on so well. The findings at operation will indicate whether a plastic operation on the stoma, a cut off gastro-enterostomy, a Heineke-Mikulicz
a Finney pyloroplasty, a gastrogastrostomy, or a gastroduodenostomy, etc., should be done. In a few of our cases it was necessary to operate a third time before relief was obtained.

**Prognosis**

Questionnaires were sent to each of the 69 patients as follows:

We are interested to know what has been the state of your general health since your last operation here for stomach trouble, and shall greatly appreciate a reply to the following questions:

1. Have you any stomach trouble now?
2. Is the trouble the same as it was before the first operation?
3. If it is different, tell in detail how it differs.
4. Do you have pain? (a) If so, how often, and is it daily?
   (b) What time of day?
   (c) Does food ease it?
   (d) Does soda ease it?
   (e) In what part of the abdomen do you feel the pain?
5. Does food agree with you?
6. Did the last operation help you?
7. Give any other information you can about your present condition.

Reports were received concerning 34 patients; two had died. Thus the findings in 32 cases were summarized as follows:

In response to the question "have you any stomach trouble now," there were 13 frankly negative answers and 10 frankly positive answers. Nine patients who had received much benefit made modified statements. The answers were:
"yes, some" (Case 86663); "occasionally" (Case 51115); "yes, a little" (Case 119616); "very occasionally" (Case 145305); "occasionally, but slight" (Case 102407); "a little " (Case 118450), etc.

Fifty-nine per cent of the patients who had secondary trouble after gastro-enterostomy were benefited; 40 per cent were absolutely cured; 31 per cent, according to their own statements, were not benefited, and need further consideration.
In response to the question, "is your trouble the same as it was before the first operation", the replies in the frankly positive group to the first question, were all positive with one exception. One patient still had pain although the location had changed. The pain before the operation was circum-umbilical but, "since the operation it had shifted to the right side just inside the short ribs." The pain instead of being dull and growing, was sharp, and came on in attacks.

In the intermediate group the responses were again variable; "What little trouble I have now is like my former trouble (Case 102407); "my pain is gone but I have gas which bothers me" (Case 119416); and "I am better than I ever was; my occasional trouble resembles my original" (Case 86663). One patient (Case 118450) replied that she felt "easier". Another patient (Case 122474) admitted that her operation had benefited her, but stated that her trouble, though recurring less frequently, was the same as before operation. Four of these patients admit frankly that the old trouble is gone but give other slight symptoms of distress. It is clear that the patients in this group were greatly benefited. In the frankly negative group in response to the first question, none of the patients had any of their former symptoms, they were without pain and were feeling well.

Most of the answers to the questions, whether or not there were any changes of symptoms from the original after the gastro-enterostomy, that is, whether the new ulcers at the stoma developed symptoms with their own attributes, were that the trouble following the posterior gastro-enterostomy was the same as before the operation. Eight of the ten patients who were not benefited by the operation reported that their symptoms were just the same; two wrote that their pain was different, located on the left side above the umbilicus, and that the pain was more constant.

In the intermediate cases, that is, those patients having only slight trouble after the last operation, the symptoms varied. The main complaints were
gas and acidity with some pain. The pain symptom in these cases was of especial interest, and it was desirable to discover, if possible, a difference from the normal ulcer cases. The complaint was practically the same, pain came on two to three hours after eating, and food and soda gave relief. The responses were very vague as to the location of the pain in any particular part of the abdomen. When these patients were asked whether or not the last operation helped them, all answered "yes". That is, 22 of the 32 were benefited by the operation; 13 were symptomless, and 9 had some few symptoms left.

The question asking for voluntary information did not afford much data of value so far as the symptomatology of the gastrojejunal ulcer was concerned.
Several methods were used to demonstrate that the blood leaving the stomach is more alkaline than that coming into it. First the perfusion of an isolated stomach was tried, then a heart-lung preparation, and finally a method more satisfactory than either of these was developed.

1. The stomach was resected and suspended in normal saline solution kept at constant temperature. A canula was inserted into the gastric artery and connected with a constant pressure apparatus. The perfusate was normal saline with as much of the dog's own blood as could be collected. The solution was kept at body temperature and perfused repeatedly through the stomach. It was soon discovered that such an experiment was unsatisfactory, owing principally to the great edema of the cells after perfusion had continued for about half an hour. Under such conditions the stomach cells could not function normally. They were greatly swollen and the whole stomach wall was translucent.

2. It was thought that by using a heart, lung, stomach preparation the blood could be kept in circulation through the stomach and that the same blood could be made to pass through the stomach many circuits in a unit of time, and each time increase the alkalinity. The arch of the aorta, and all the vessels leaving the thoracic and the abdominal aortas were ligated. Just below the celiac axis the abdominal aorta was ligated again. This, of course, necessitated opening the chest. A tracheal canula was inserted, and connected to a Connell apparatus. None of the animals lived long enough under these conditions to obtain an accurate test. They succumbed in less than an hour.

3. The technic as follows was finally devised. A low tension of ether was maintained with a Connell apparatus. The chest was not opened. The circulation to the head and upper extremities and to the thorax was not disturbed. The circulation to the spleen, pancreas, and intestines was stopped by double ligation and section. The abdominal aorta was ligated just above the superior mesenteric artery. All the venous radicals of the portal vein, except those
draining the stomach, were ligated. This permitted the collection of venous blood from the portal vein, and thereby all the return blood, well mixed, from the stomach. The arterial blood was taken from the aorta.

The first few experiments were conducted after the animals had fasted from eight to eighteen hours. The animals did not show any appreciable increase in the alkalinity of venous blood as compared with the arterial.

The same experiments were done with the stomachs full. The esophagus was ligated to keep the fluid in the stomach from drowning the animal. An increase in the alkalinity of the venous blood, both in its hydrogen ion concentration and its carbon dioxide combining point was shown. The carbon dioxide combining point, however, in all the experiments with venous and arterial blood, was lower than normal. The carbon dioxide combining point was estimated by the Van Slyke apparatus. The hydrogen ion concentration was estimated by the colorimeter method of Rowntree. The blood chlorid was estimated in some of the experiments.

My experimental work was undertaken for the purpose of investigating more closely the autodigestion theory of ulcer production. There are two, perhaps three, phases to this theory: (1) the death of the mucosal cells, (2) the digestion of the cells, and (3) secondary infection. I was greatly impressed with the fact that on injecting solutions of stains into the gastric artery, that part of the stomach which is by far the greatest ulcer bearing area, takes stains much more deeply than the other parts of the stomach. The lesser curvature and the juxta pyloric region were much deeper stained than the fundus and the greater curvature. This picture suggested the idea that ulcer production is related in some way to blood supply. The stomach cells are dependent on the blood supply for their vitality, and resistance to autodigestion. The elements which are supposed to prevent autodigestion are known as anti-ferments. Since the ferments are the cause of the digestion of the cells after their death, it seemed worth while to make a few investigations with regard to the biologic
reaction and the commercial ferments.

Rabbits were used in these experiments for the reason that ulcers are easily produced in them, and they are easy to handle.

Three series of experiments were conducted; one with pepsin, one with trypsin, and one with peptone. Ten per cent solutions of these substances were made in very weak tricresol solution. The rabbits were injected at weekly intervals for three weeks, at which time they were sacrificed, necropsy was done, and the blood tested. The initial dose of solution was 5 c.c.; the second dose 7 c.c., and the third dose 10 c.c. Larger doses than these produced immediate death.

The first injection, intravenous into the ear, was made Dec. 13, 1918; the last Jan. 14, 1919. The stomachs of all the rabbits at necropsy were normal.

To test the blood for any increased antiferment power artificial gastric juice was used (.03 per cent acidity, .016 mg. of pepsin to 30 c.c.). In wide mouthed bottles containing 20 c.c. of the artificial gastric juice 200 mg. of tissue were placed. Five different kinds of tissue were selected, namely; fundic, pyloric, jejunal, duodenal, and colonic. In each bottle were placed 5 c.c. of the fresh serum of the rabbits. As controls another set of bottles with normal rabbit's blood and one wet with no serum were used. The test bottles were placed in the incubator at body temperature for twenty-four hours, and then the amount of digestion was noted. There was no retardation of digestion in the bottles containing the serum of rabbits which had been injected with the ferments or the peptone. The different tissues did, however, show variations in the amount of digestion. Kawamura in 1911, showed this very definitely.

Dogs were used next in the ferment experiments. The dried ferments were not used since in their preparation they might have been injured to an extent to destroy their power to produce the biologic reaction; if they had possessed it. Instead of injecting the ferments in solution intravenously, the major pancreatic duct was implanted into the splenic vein. This experiment was done on four dogs; one January 9, one January 13, one January 15, and one January 17, 1919. In three
of the animals the splenic vein was under considerable tension, and it was doubtful whether or not the pancreatic juice would run into it. The fourth operation was very successful from a technical point of view. In addition to the ferments, alkali was found to be a factor of especial interest. The blood chlorid was also studied in these days.

PROTOCOLS OF PANCREATIC DUCT EXPERIMENTS

Dog C945. Experiment 10

Blood reactions

<table>
<thead>
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<th>Date</th>
<th>P.H.</th>
<th>CO₂</th>
<th>Cl</th>
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<tbody>
<tr>
<td>Jan. 13, 1919</td>
<td>7.4</td>
<td>30</td>
<td>500</td>
</tr>
<tr>
<td>Jan. 29</td>
<td>7.7</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Feb. 18</td>
<td>7.6</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

The animal was a male, no catheter specimens or urine were obtained.

Dog C942. Experiment 11

Blood reactions

<table>
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<tr>
<th>Date</th>
<th>P.H.</th>
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<th>Cl</th>
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<tbody>
<tr>
<td>Jan. 9, 1919</td>
<td>7.2</td>
<td>40</td>
<td>540</td>
</tr>
<tr>
<td>Jan. 10</td>
<td>7.5</td>
<td>38</td>
<td>485</td>
</tr>
<tr>
<td>Jan. 13</td>
<td>7.5</td>
<td>48</td>
<td>530</td>
</tr>
<tr>
<td>Jan. 17</td>
<td>7.5</td>
<td>48</td>
<td>530</td>
</tr>
<tr>
<td>Jan. 29</td>
<td>7.6</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Feb. 18</td>
<td>7.4</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

The urine remained alkaline until January 20. There was a slight reduction of Febling's solution for three days. The animal recovered from the operation satisfactorily.

Dog C946. Experiment 20

Blood reactions

<table>
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<tr>
<th>Date</th>
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<th>CO₂</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Jan. 15, 1919</td>
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<td>36</td>
<td>425</td>
</tr>
<tr>
<td>Jan. 17</td>
<td>7.5</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Jan. 29</td>
<td>7.3</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

The dog was sacrificed March 18, 1919. At necropsy the splenic vein could be found but it was completely thrombosed. In all probability the pancreatic juice had not passed through it.
Dog C958. Experiment 43
Blood reactions

<table>
<thead>
<tr>
<th>Date</th>
<th>P.H.</th>
<th>CO₂</th>
<th>Cl</th>
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</thead>
<tbody>
<tr>
<td>Jan. 20, 1919</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan. 29</td>
<td>7.6</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Feb. 13</td>
<td>7.4</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

The urine of this animal was examined repeatedly for alkalinity but it was always acid.

Necropsy findings in the remaining animals were the same as those in the first. No ulcers were found. While no definite conclusions can be drawn from these experiments it would seem that the slight initial increase in the hydrogen ion concentration and carbon dioxide content show that for a time the pancreatic duct emptied into the vein. Further experiments will be carried out in which the duct will be inserted into a larger vein.

In a clinical review of the cases in which operations had been done on the stomach, I emphasized the fact that when the acidity of the stomach was greatly lowered no gastrojejunal ulcers resulted. Such ulcers rarely form in a gastro-enterostomy performed for cancer. None were found in the series of 3840 cases, either following resection for cancer or for multiple ulcers. These and other findings made it appear desirable to investigate the acid phase of the autodigestion theory of ulcer production.

Ulcer is produced only when the mucosa is acid, or at least when it is acid a greater part of the time. This is proved more or less by the position of such ulcers. They are either in the stomach or duodenum, and if a gastro-enterostomy is made they may occur in jejunum. In one instance, at the clinic, an ulcer was found in the ileum following a gastro-ileostomy made elsewhere. To assume that an ulcer is produced only on acid mucosa, one must establish the fact that the first two inches of the duodenum is acid. This we have tried to do, but not having the use of a fluoroscope at all times, our attempts have not been faultless. This obstacle has, however, been overcome and our later experiments
will furnish more evidence of the exact position of the bucket, and of the Rehfuss tube. Most of the duodenal ulcers are found less than two inches from the pyloric orifice, which, if we are correct in our inference that all ulcers are formed on an acid base, would indicate that this area is acid. Ulcers never occur low down in the duodenum, and very rarely in the afferent limb of the gastro-enterostomy.

Twenty patients have been examined. Four had normal gastrointestinal tracts. Four showed no free acidity with the dimethylamidoozobenzol reagent. One patient with splenic anemia and one with gastric polyposis, in which more than one-half of the stomach had been resected, had no free acid in the stomach. Ten patients had duodenal ulcers; their histories and the x-ray findings were definite, and were proved by operation. In most of these cases fluoroscopic examination was made and in one or two plates were made. The duodenal contents were collected by a technician skilled in the work. The patients were fasted from the evening before. They were allowed water up to 11:00 a.m. Between 1:30 to 2:00 p.m. the Rehfuss tube was passed. Contents were collected one-half hour to two hours later, depending on the time it took for the tube to enter the duodenum. The patients were then fluoroscoped, after which the contents was collected. In some instances the contents were collected before the patient was taken to the x-ray department. The tube remained in place from one and one-half hour to three hours.

In all of the duodenal ulcer cases an acid reaction was shown with the bucket near the pylorus; if it was allowed to descend (not verified by x-ray) the contents became alkali. In the normal cases acid was shown in 10, and alkali in 2. In the cases in which there was no free hydrochloric acid in the stomach the reaction was alkali. In the splenic anemia case, with a gastric analysis of $8 - 0 - 8$ the reaction was alkali also. In the case of gastric polyposis, with pylorectomy the reaction was alkali.

There is a border-line or rather a neutralizing zone in the duodenum the position of which depends on the relative acidity and alkalinity of the stomach.
and of the duodenum respectively. If the stomach manufactures more acid than the duodenum manufactures alkali, the zone is pushed distalward and vice versa. It is hoped that by collecting specimens, and at the same time keeping constant watch with the fluoroscope of the position of the bucket and by estimating the acidity of the stomach and the alkalinity of the duodenum, more detailed reports may be obtained.

The simplest theory of ulcer production may depend on acidity and alkalinity alone. The stomach has a method of its own to protect itself from over-acid cells, but so far as we know, the duodenum does not have this mechanism and a higher acid chyme action on the duodenal cells for any length of time could kill them.

In order to test the time element of reaction an attempt was made to place the Rehfuss tube in the duodenum, and then instill into it 5 c.c. of 0.2 per cent hydrochloric acid solution. Small specimens were collected every fifteen minutes. In this manner the neutralizing power of the duodenal alkali was estimated on definite amounts of hydrochloric acid instilled. Twenty successful experiments were done.

Beside the exogenous acidity relation there seems to be an endogenous relation. As has been stated, the stomach has its own method of protecting its mucosa.

The stomach produces acid throughout the day; the process of acid production is greatest after the ingestion of a meal, especially after a protein meal. Due to the action of the gastric cells the acid ion chlorin separates from its base, which we may quite safely assume is sodium, and leaves the body. Whether the sodium remains as hydroxid, or carbonate or acid carbonate is not known, nor does it make any material difference, since they are all alkaline. The stomach withdraws acid from the body in which the alkali remains; it therefore possesses a function with which it is not generally credited; it is an alkali manufacturer or alkali preserver, a kind of a solveny process in the human economy. To
counterbalance this other organs must form acid by removing alkali. This suggests another chain of acid-base equilibrium other than the carbon dioxid chain of the lungs, and the phosphate chain of the kidneys. The duodenectomy experiments of Mann and Kawamura show that the counterbalance is not due to the duodenum itself. The blood reaction in animals used for their experiments remained the same after the entire duodenum was removed. Thus the large digestive glands in its vicinity, the liver and pancreas, remain for investigation. All tissue metabolism leads to acid production, but not to actual removal of the alkali base. This process is associated with only inorganic acids and bases.

The organic acids produced by tissue metabolism have to be carried to their place of exit by the alkalies of the body. As chlorides (the great source of alkali for the body in the form of sodium chloride) the base sodium is of no use to the tissues as a carbon dioxid carrier. It is only when the stomach takes off the chlorin radical that the alkali becomes of real use to the body for such purposes. The alkali reserved by the stomach not only protects its own cells from hydrochloric acid death, but furnishes alkali to carry off the organic acid wastes of the body.

Protocols 1 and 2 are compiled from tests made on fasting dogs. The first one does not show anything of importance except the low carbon dioxid value. This low carbon dioxid value runs through the entire series, but the reason for this will not be discussed herein.

In Protocol 2 one may find some evidence of the increased alkalinity of the venous blood leaving the stomach; there is not so distinct a manifestation as in some of the other protocols but more pronounced evidence was not expected from the fasting stomach.

Protocol 3 shows that 100 c.c. of 10 per cent peptone solution was placed in the stomach; it was hoped to stimulate the stomach to activity. Just before introducing the slightly alkaline peptone solution the dimethylamido- azobenzol test showed no free hydrochloric acid in the stomach contents of the
animal used for this experiment. The acidity of the contents removed from the stomach at the end of the experimental period showed that some secretion of hydrochloric acid had taken place.

Protocols 4, 5 and 6 show the results obtained by feeding the animals two to three hours before beginning the experiments. The animals were fed meat, milk and dog biscuit. The stomach contents were always acid after the experiment. The venous blood was more alkaline than the arterial blood and than the venous blood of the general circulation.

In the later experiments the venous blood of the general circulation was estimated by that taken from the external jugular vein. This was to detect any possible difference in the alkalinity of the return blood from the stomach and the blood in the general circulation.

PROTOCOLS OF TYPICAL GASTRIC EXPERIMENTS

Dog C928. Experiment 793
Dec. 20, 1918 - 1:30 P.M. Blood pressure 120

<table>
<thead>
<tr>
<th>Time</th>
<th>P.H.</th>
<th>CO₂</th>
<th>Cl.</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>2:45</td>
<td>33</td>
<td>730</td>
<td>70</td>
</tr>
<tr>
<td>Venous</td>
<td>2:45</td>
<td>30</td>
<td>730</td>
<td>70</td>
</tr>
<tr>
<td>Arterial</td>
<td>3:45</td>
<td>29</td>
<td>740</td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>3:45</td>
<td>32</td>
<td>740</td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>4:45</td>
<td>8</td>
<td>750</td>
<td>40</td>
</tr>
<tr>
<td>Venous</td>
<td>4:45</td>
<td>10</td>
<td>750</td>
<td>40</td>
</tr>
</tbody>
</table>

Dog C940.
Jan. 8, 1919 - 1:30 P.M. Blood pressure 145

<table>
<thead>
<tr>
<th>Time</th>
<th>P.H.</th>
<th>CO₂</th>
<th>Cl.</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>3:00</td>
<td>7.1</td>
<td>10</td>
<td>540</td>
</tr>
<tr>
<td>Venous</td>
<td>3:00</td>
<td>7.5</td>
<td>8</td>
<td>465</td>
</tr>
<tr>
<td>Arterial</td>
<td>4:00</td>
<td>7.1</td>
<td>8</td>
<td>540</td>
</tr>
<tr>
<td>Venous</td>
<td>4:00</td>
<td>7.3</td>
<td>22</td>
<td>595</td>
</tr>
</tbody>
</table>

Dog 941
Jan. 9, 1919 - 9:00 A.M. Blood pressure 100

100pc.c. 10 per cent peptone solution placed in stomach. P.H. 7.1

<table>
<thead>
<tr>
<th>Time</th>
<th>P.H.</th>
<th>CO₂</th>
<th>Cl.</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>10:10</td>
<td>7.4</td>
<td>6</td>
<td>450</td>
</tr>
<tr>
<td>Venous</td>
<td>10:10</td>
<td>7.6</td>
<td>28</td>
<td>400</td>
</tr>
<tr>
<td>Arterial</td>
<td>11:40</td>
<td>7.2</td>
<td>10</td>
<td>450</td>
</tr>
<tr>
<td>Venous</td>
<td>11:40</td>
<td>7.3</td>
<td>22</td>
<td>440</td>
</tr>
</tbody>
</table>
Hydrogen ion concentration of peptone after experiment 6.8.

<table>
<thead>
<tr>
<th>Dog 956</th>
<th>Jan. 16, 1919 - 9:05 A.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood reaction</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>P.H.</td>
</tr>
<tr>
<td>Arterial</td>
<td>9:55</td>
</tr>
<tr>
<td>Venous</td>
<td>9:55</td>
</tr>
<tr>
<td>Arterial</td>
<td>10:05</td>
</tr>
<tr>
<td>Venous</td>
<td>10:05</td>
</tr>
<tr>
<td>Heart blood</td>
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</tr>
</tbody>
</table>

Stomach contents acid - hydrogen ion concentration 6.6

<table>
<thead>
<tr>
<th>Dog C967</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Time</td>
<td>P.H.</td>
</tr>
<tr>
<td>Arterial</td>
<td>9:56</td>
</tr>
<tr>
<td>Venous</td>
<td>9:56</td>
</tr>
<tr>
<td>Arterial</td>
<td>10:56</td>
</tr>
<tr>
<td>Venous</td>
<td>10:56</td>
</tr>
<tr>
<td>Heart</td>
<td>10:56</td>
</tr>
</tbody>
</table>

Stomach contents acid - hydrogen ion concentration 6.6

<table>
<thead>
<tr>
<th>Dog D4</th>
<th>Feb. 5, 1919 - 10:00 A.M.</th>
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</thead>
<tbody>
<tr>
<td>Blood reaction</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>P.H.</td>
</tr>
<tr>
<td>Arterial</td>
<td>11:20</td>
</tr>
<tr>
<td>Venous</td>
<td>11:20</td>
</tr>
<tr>
<td>Jugular</td>
<td>11:20</td>
</tr>
<tr>
<td>Arterial</td>
<td>12:20</td>
</tr>
<tr>
<td>Venous</td>
<td>12:20</td>
</tr>
<tr>
<td>Jugular</td>
<td>12:20</td>
</tr>
<tr>
<td>Arterial</td>
<td>1:40</td>
</tr>
<tr>
<td>Venous</td>
<td>1:40</td>
</tr>
<tr>
<td>Jugular</td>
<td>1:40</td>
</tr>
</tbody>
</table>

Stomach contents acid 6.6.

In the first series of experiments the blood chlorid was estimated in order to demonstrate whether a chlorid deficit was present. The results obtained suggest such a deficit. I should have liked to continue these estimations in all the bloods taken but I found that the loss of sufficient blood for the tests was too great a shock to the animal. The operation in itself is very severe. This added element of blood removal lowers the blood pressure so much that the chlorid estimations were necessarily abandoned. By future work I shall hope to improve the technic to such a point that more blood can safely be removed.
SUMMARY

The results of the experiments described suggest these hypotheses:

1. The stomach reserves alkali for the body.

2. The alkali has a two-fold purpose; it prevents the death of its own cells by guarding against overacidity; it replaces the alkali secreted by the kidney and pancreas, and thus keeps the body at a constant level of basic alkali, so that the acid waste products may be removed.

3. Peptic ulcer is always produced in an acid environment.

4. The first two inches of the duodenum are acid most of the time. In patients with duodenal ulcer they are probably acid all the time.

5. Most ulcers occur on the lesser curvature of the stomach because the blood is less alkaline when it first enters the stomach.

6. Food ease in duodenal ulcer is due to an increased alkalinity of the duodenal cells.
REFERENCES


10. v. Eiselberg: Quoted by Pólya.


Aufrecht: Quoted by Greggio.

Bauer: Quoted by Greggio.

Boccardi: Quoted by Greggio.

Böhm: Quoted by Greggio.

Brown Sauard: Quoted by Greggio.

Budge: Quoted by Greggio.

Castel: Quoted by Greggio.

Charrin: Quoted by Greggio.

Chessin and Feldmann: Quoted by Greggio.

Clairmont: Quoted by Greggio.

Claude: Quoted by Greggio.

Coe: Quoted by Greggio.

Decker: Quoted by Greggio.

Ebstein: Quoted by Greggio.

Eiselberg: Quoted by Greggio.

Enriquez and Hallion: Quoted by Greggio.

Falcone: Quoted by Greggio.

Favre: Quoted by Greggio.

Fenwick: Quoted by Greggio.

Fiebich: Quoted by Greggio.

Friedrich and Hoffman: Quoted by Greggio.

Filehne: Quoted by Greggio.

Fiori: Quoted by Greggio.

Fritsch: Quoted by Greggio.

Frouin: Quoted by Greggio.

Gibelli: Quoted by Greggio.

Grunenburg and Lunch: Quoted by Greggio.

Gundermann: Quoted by Greggio.

Joussat, P. and Lefas: Quoted by Greggio.
Katzenstein: Quoted by Greggio.
Kobayashi: Quoted by Greggio.
Koch and Ewald: Quoted by Greggio.
Kollicher: Quoted by Greggio.
Korte: Quoted by Greggio.
Krehl: Quoted by Greggio.
Lang: Quoted by Greggio.
Latzel: Quoted by Greggio.
Lebert: Quoted by Greggio.
Lichtenbelt: Quoted by Greggio.
Licini: Quoted by Greggio.
Lilla: Quoted by Greggio.
Loeper: Quoted by Greggio.
Löwin: Quoted by Greggio.
Lustig: Quoted by Greggio.
Majer: Quoted by Greggio.
Marchetti: Quoted by Greggio.
Matthes: Quoted by Greggio.
Müller: Quoted by Greggio.
Ophüls: Quoted by Greggio.
Otto and Gandy: Quoted by Greggio.
Overback: Quoted by Greggio.
Panum: Quoted by Greggio.
Pavy: Quoted by Greggio.
Payer: Quoted by Greggio.
Périn: Quoted by Greggio.
Pilkäst: Quoted by Greggio.
Ponscet: Quoted by Greggio.
Prevost and Cottard: Quoted by Greggio.
Quincke and Daettwyler: Quoted by Greggio.
Rechfuss: Quoted by Greggio.
Rosenbach and Eschker: Quoted by Greggio.
Roy: Quoted by Greggio.
Saikowski: Quoted by Greggio.
Saitta: Quoted by Greggio.
Samuelson: Quoted by Greggio.
Sapiejko: Quoted by Greggio.
Silbermann: Quoted by Greggio.
Singer: Quoted by Greggio.
Sternberg: Quoted by Greggio.
Stich: Quoted by Greggio.
Talma: Quoted by Greggio.
Telma: Quoted by Greggio.
Turk: Quoted by Greggio.
Vassale and Sacchi: Quoted by Greggio.
Vedova: Quoted by Greggio.
Virchow: Quoted by Greggio.
Westphal: Quoted by Greggio.
Wilkie: Quoted by Greggio.
Wurtz and Leudet: Quoted by Greggio.
Zironi: Quoted by Greggio.


27. Kocher: Quoted by Paterson.


50. Pinner: Quoted by Pólly.


64. Wölfler, A.: Quoted by Roojen.