Pathogenesis of gastric and duodenal ulcer

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Senior Thesis

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The Pathogenesis of Gastric and Duodenal Ulcer

Introduction

Historical

In considering the pathogenesis of ulcer, I shall first give a sketch of the historical, showing the earlier conceptions as to the nature and cause of ulcer.

Galen and Celsus presented vague and doubtful references to ulcer in their description of passia cardiaca, hematemesis and melena. The earliest reported cases were those of Dontatus of Mantua in 1586, who had made a diagnosis of ulcer and later proved it at autopsy. Bonetus of Geneva in 1700 published a case of perforating ulcer which was followed shortly by reports of Littre, Courtial and Morgani. Baillie in 1799 was the first to publish an accurate study of the anatomical peculiarities of ulcer. In 1828 John Abercrombie of Edinburgh who gave an excellent account of the symptoms of gastric ulcer was the first to differentiate clearly ulcer from cancer and gastritis and suggested that gastritis may be the precursor to ulcer.

A half a century elapsed before any further reference was made to duodenal ulcer. Duodenal ulcer was at that time thought to be a rare malady. Busquoy in 1887 again brought attention to it. In 1898 Dieulafoy gave a clear description of acute and chronic ulcers - suggesting that the acute was caused by a toxic-infective factor and that the acute was the precursor to the chronic.
Moynihan in 1901 and 1905 published the results of his pioneer surgical work in which he gave a complete account of the symptoms now known to be characteristic of duodenal ulcer.

Progress in the knowledge of ulcer was not given the impetus it deserved following the advent of the stomach tube. Gastric disorders were described in terms of altered secretion and motility and not of structure. The X-Ray and more recent advances in the methods of gastric analysis have given the final impetus which has thrown not only light on the cause but rendered therapy more exact.
Definition of Terms

By the term ulcer is usually meant the dissolution or break in the continuity of tissue, with a crater of variable depth and shape which is composed of fibrous and inflammatory tissue extending to the submucosa, muscularis propria and subserosa. Irregular shallow areas of dissolution invading the mucosa are usually spoken of as erosions and ulcerations. Erosions usually are characterized by the absence of fibrosis in the base and margins.

In considering the pathogenesis of gastric and duodenal ulcers, it is obvious that the so called chronic ulcers originated as acute ulcers. Accepting this view the study will be simplified.

It will also be considered that the causes of duodenal and gastric ulcers are the same, in that they are in close proximity and subjected to the same influences.

For the sake of brevity, the term "peptic" ulcer will be used to include both duodenal and gastric ulcers.
Anatomical Considerations of the Ulcer Bearing Area

The statistics of Necropsies on gastric and duodenal ulcers have shown that practically all duodenal ulcers occur in the first part of the duodenum, the duodenal cap; and that of gastric ulcer thirty-five per cent occur on the lesser curvature; thirty per cent on the posterior wall; twelve per cent at the pylorus; nine per cent on the anterior wall; seven per cent in the cardia and seven per cent in the fundus. Monynihan (1) in his book "Duodenal Ulcer" states that ninety-five per cent of the total number of cases are within one and a half inches of the pylorus. Einhorn (2) reviews the statistics and finds similar figures.

The ratio of duodenal to gastric ulcer is usually stated to be 4.5 or 5 to 1.

Since it is shown that ulcers are more often in the duodenal cap, lesser curvature, pylorus and posterior wall, it is expedient to review the more important anatomical features of the stomach and duodenum.

The stomach can be divided into a larger cardiac part and a smaller pyloric part. The cardia consisting of the fundus and body. There is usually a well marked depression, the incisura angularis, are seen on the lesser curvature which separates the body from the pyloric part. The pyloric part consists of the pyloric vestibule and canal which terminates as the pylorus.

In Hurst's (3) study of the anatomy and physiology of the
duodenum it was found that the usual subdivision of the duodenum into four divisions is misleading and that that part of the duodenum immediately adjoining the stomach differs more from the rest of the duodenum than it does from the stomach.

The pyloric wall is firm, strong and well developed—being composed of thick longitudinal and circular muscular fibers, while in the fundus the walls are thinner and the internal layer of oblique fibers are limited to the cardiac part of the stomach.

The mucosa in the pyloric region is thick (2.2 mm), smooth, and more closely attached while in the fundus it is thin (0.5 mm). The pylorus has few folds and the convolutions are numerous, freely movable and without definite arrangement.

The longitudinal mucosal folds in the lesser curvature are stretched and under tension, while in the fundus they become redundant and convoluted.

In the contracted stomach the rugae are stellate in the cardiac portion and parallel to the long axis in the pyloric region.

Gastric juice containing about 0.4 per cent of hydrochloric acid and pepsin is secreted by the glands of the fundus and body of the stomach. The glands of the pyloric vestibule secrete an alkaline fluid containing no digestive ferment and probably identical with that secreted by the duodenal mucous membrane.

The fundus receives its blood supply from the main source through three branches, the left gastro-epiploic, right gastro-epiploic and left gastric, while the pylorus is supplied from
the same source through two branches only, the right gastric and the gastro-duodenal artery. The volume of blood is greater in fundus than in the pylorus. The arteries in the pylorus are practically all terminal vessels, sparsely distributed and tortuous. They anastomose infrequently and are subject to powerful contractions by numerous interlacing muscle fibers. Arteries in the fundus are not terminal, less tortuous and less subjected to contractions.

The muscles of the pylorus are bulky where it bears the burden of digestion, while the fundus serves chiefly as a reservoir.

The muscles are bulkier in the first part of the duodenum than in the remainder and the sphincteric rings and mucosal folds, which are lacking else where are located here.

The first part of the duodenum is under a greater tension than the remainder of it because of the force exerted by the food which is expelled from the pylorus.

The lymphatic vessels and glands which are associated with those of the celiac artery are in three sets - the gastric, hepatic and pancreatico-lineal. The celiac group of glands receives the afferent - establishing an intimate connection and possible mode of spread of infection from one organ to another.

Minute lymphoid follicle are present in the gastric mucous membrane at the base of the glandular crypts and are superficial to the muscularis mucosae. They are more numerous and larger in the pyloric vestibule than in the cardiac part of the stomach and also more numerous on the lesser curvature than
on the greater curvature. They are also very numerous in the duodenal bulb.

The stomach and first part of the duodenum receive their nerve supply by the vagus which when stimulated increases peristalsis and secretion and by the sympathetics which are inhibitory in function.
Predisposing Causes

In the past few years there has been a growing tendency to regard many diseases as having a constitutional basis or certain individuals as having a diathesis toward certain diseases. A recent experimental contribution by Wade Brown (4) of the Rockefeller Institute has been made. He has demonstrated that the three factors which influence the pathogenesis of disease are: (1) The size of the individual organ in relation to body size, (2) physicochemical changes in the blood, and (3) fluid tissue particularly of the lymph and lymph nodes. The organ-body relationship and organ balance may differ in individuals by virtue of inheritance and may vary from month to month and year to year in response to environmental influences. He explains the frequency of disease during certain seasons and why the reaction of individuals to disease differ in spring and fall, each being a transectional period when the individual must make adjustments, explaining in part why ulcer symptoms recur in mathematical regularity during these periods.

Hurst (3) lays particular stress on the hypersthenic and hyposthenic gastric diathesis. Those individuals who possess short stomachs, with active peristalsis, rapid evacuation, hyperchlorhydria and with digestive hypersecretion are termed hypersthenic and have a tendency to develop duodenal ulcers. Those having a long stomach and who retain the acid chyme and food longer are termed hyposthenic and are predisposed to gastric ulcers.

Other important investigations of this diathesis were
carried out by Cambell and Conybeare (5). They examined a large number of students using both the X-Ray and gastric analysis. They found that the position of the stomach is mainly influenced by the shape of the trunk; that the tone of the abdominal musculature is important; that in health high acidity of gastric juice is most commonly associated with a high hypertonic stomach which empties quickly and that low acidity of gastric juice is generally associated with a hypotonic stomach which empties slowly. Their conclusion being that the anatomical and physiological variations present in health may be the physical basis of the subjects diathesis to develop certain gastric disorders under appropriate influences.

Held and Goldbloom (6) writing on the constitutional basis of ulcer, believe that the above statements should be modified - stating that the constitutional status, whether hypersthenic or asthenic so long as there is no definite pathology in the organ, will by virtue of accommodation and training succeed in preventing disease of the organ and if either the asthenic or hypersthenic individual does develop ulcer, the site of the lesion is not necessarily determined by the status. The asthenic individual may have a duodenal ulcer and the hypersthenic individual may have a gastric ulcer.

Regarding heredity as a constitutional factor in relation to disease, there is a growing tendency among present day investigators to consider it important. An appreciation of this factor is evidenced in the occurrence of peptic ulcer in several members of a family in direct blood relation, fathers and
sons, brothers and sisters and even in the more distant relatives. Hurst in considering the familial tendency has shown a number of family histories with several cases of ulcer in each family. In other cases he was able to show several members of the family who gave a history of indigestion.

Other predisposing causes will be considered in the discussion which is to follow on the theories of the pathogenesis.
Vascular Insufficiency Theory

The oldest concept or explanation of the cause of peptic ulcer was on the basis of vascular insufficiency. Virchow (3) originated this idea in 1853. His concept was that an ulcer began as a local ischemic necrosis induced by an embolic occlusion or thrombosis of a vessel. This vascular occlusion mechanically removed the alkalinizing influence of the blood and permitted the local destruction of the mucosa by the corroding hydrochloric acid.

Janeway in 1871, quoted from McCann (7), presented a case of perforating ulcer of the stomach with a fibrinous plug in a branch of the gastro-epiploic artery leading to the ulcer. About this same time Klebs announced his theory as that of local ischemia due to spastic contraction of the arterioles. Others thought it due to a stasis of the venous return and still others to a mechanical hyperemia caused by an abnormal contraction of the gastric musculature leading to hemorrhage and formation of ulcer. Quincke believed it due to a general anemia but this was soon disproved.

The experimental work at this time on embolus or vascular occlusion was carried out by Cohnheim in 1890, quoted from McCann, by injecting a lead chromate suspension into the gastric branches of the splenic artery, he was able to produce ulcers which healed in three weeks. These results were not confirmed by other investigators. Ivy (8) tried similar experiments, using finely divided emboli of animal charcoal and getting negative results. By using lead chromate, he produced ulcers which he believed
due to a toxic origin.

Cæelen, quoted from Held and Goldbloom, contended that in most cases arteriosclerotic vessels in the vicinity was the primary cause of ulcer. It is possible that the arteriosclerosis was a result and not the cause, as it is found that in most cases, arteriosclerosis is not present. In those diseases in which vascular changes are most marked, notably lues, ulcer is not especially prevalent.

Von Bergmann (9) sponsored the theory that spastic contraction of the arteries causes a local ischemia which is the starting point for digestion by the digestive juices and subsequent ulcerations. This is purely theoretical, but as Held and Goldbloom have suggested, it is probable that a purely functional disturbance of the localized blood vessels may spastically so close the vessels that the circulation is disturbed and on autopsy nothing of note would be seen which would suggest vascular occlusion.
Bacterial Theory

The theory that there is an infective factor which is the primary cause of peptic ulcer is not a new one. Dieulafoy in 1897 described two cases of pneumococcal infection involving the lungs, peritoneum and stomach. Severe hematemesis occurred in both cases and at autopsy minute acute ulcers were found in the stomach with pneumococci in the surrounding tissues.

Numerous experimental investigations have brought forth proof that the invasion of different micro-organisms can in reality cause erosions in the gastric mucosa. It was also found that these organisms produced similar erosions in the rest of the gastro-intestinal tract and that these erosions were the result of the toxic effect of an excessive injection of bacteria. Acute ulcers were first produced in animals by the injection of a culture of Staphylococcus aureus by Letulle in 1888.

The bacteriological work of prominence is that of Rosenau (10), who applied his theory of selective affinity of streptococci. Using dextrose-brain broth, he cultivated the organisms isolated from ulcers and from foci of infection in patients with ulcer. Injecting these specific strains of streptococci into rabbits, hemorrhagic erosions and ulcerations developed in 61 per cent. of the rabbits injected with ulcer strains and in 28 per cent. of those injected with strains from foci of the patients with ulcer. He found these organisms constantly in the depths of the ulcers. Other bacteria were sometimes found but always in smaller numbers. More recently, he has obtained the same results with
dead bacteria and with filtrates of active cultures showing that these bacterial toxins are also effective, though the lesions were less severe and as no bacteria were present to produce more toxins, healing occurred more rapidly. On immunizing rabbits with the specific streptococcus, but not from streptococci obtained from other sources, the liability to the formation of ulcers was greatly reduced from 82 to 17 per cent.

The experimental work of Nickel (11) has confirmed Rosenau's work. He experimentally produced lesions by streptococcal injections from surgical resected ulcer bearing tissue and from other foci of infection. Cultures were obtained from 21 patients who had duodenitis without ulceration. Eighteen of these patients had one or more foci of infection which contained streptococci with selective affinity for the stomach or duodenum. Hemorrhagic lesions were found in the duodenum in 57 per cent of the rabbits which received injections of cultures from teeth of patients, 49 per cent developed ulcers in the stomach or duodenum which came from patients with a streptococcal tonsil infection and 53 per cent of the patients developed ulcers which developed following the surgical resection of inflamed duodenum.

He found that 93 of the 134 patients with duodenal ulcer had a focus of infection containing streptococci with affinity for the stomach or duodenum. In 52 per cent, of the patients with ulcer, streptococci were found in the teeth; 51 per cent had infected tonsils; 50 per cent showed cultures from prostate and 72 per cent showed cultures of streptococci from
surgical resected duodenal ulcers.

Cultures taken from ulcers of the stomach and injected into rabbits produced gastric ulcers in 64 per cent. He concluded that those cultures taken from gastric ulcers more often reproduced lesions in the stomach than in the duodenum and those with duodenal ulcer or duodenitis more often produced lesions of the duodenum than in the stomach. He found also that the cultures obtained which produced the lesions were predominantly of the streptococcus viridans type. The lesions produced very closely resembled those of the patients, Judd (12).

Hurst (3), commenting on the experimental work of specific affinity of the streptococci, concludes that the teeth, tonsils and prostate may be infected with streptococci, the toxins of which have a specific destructive effect on the gastric and duodenal mucous membrane. If the organisms pass into the blood stream and lodge in the mucous membrane, they may set up a sub-infection, produce toxins which devitalize the tissue and produce a neurosis which when acted upon by the gastric juice forms an ulcer. Often as soon as the original foci are eradicated, the process is prevented and healing rapidly takes place. The healing process may be prevented and then a chronic ulcer develops.

Frequently oral sepsis is found in patients with gastric and duodenal ulcer. At the New Lodge Clinic, 70 per cent of the 157 patients with peptic ulcer had pyorrhoea alveolaris, apical infection or both. Ten per cent of these were edentulous and most of these had oral sepsis at the time when the
ulcer first developed and in some residual infection was still present.
Toxic Theory

In as much as toxins other than toxins of a bacterial nature have been used to experimentally produce ulcer, it is considered appropriate to discuss this separate from the infective theory.

Bolton (13) advanced the theory that ulcer is due to toxins which develop as a result of absorbed end-products of digestion. He experimentally produced a substance which he called gastro-toxin and which he injected into the peritoneal cavity of animals and produced lesions of the stomach. Injections of this substance directly into the gastric mucosa caused ulcerations. He found that complete neutralization of the gastric contents with sodium bicarbonate not only prevented the development of the acute ulcers but also the localized areas of necrosis which formed the first stage in their production.

Enriquez and Hallion, quoted from Hurst, in 1893 produced ulcers in animals by the injection of diphtheria antitoxin.

It is commonly recognized by the profession that hemorrhagic ulcerations and ulcers very frequently occur following severe superficial burns. Maes (14) has found an incidence of six per cent of duodenal ulcer in fatal cases and that this occurs mostly in children. He states that these ulcers are very apt to be overlooked and suggests that the cause is probably a toxemia.

Hunter (15) was able to produce ulcers in dogs by the injection of a toxic substance, toluylendiamin. He believed a toxic substance is elaborated in the burned tissues excreted
in the bile and finally coming in direct contact with the duodenal mucosa.

Harris (16) advanced the theory that the action of the toxin was to reduce the natural alkalinity of the intestinal wall causing necrosis and hemorrhage - the areas being transformed into ulcers by the action of the pancreatic juice.

Levin (17) came to the conclusion that shock incident to all burns causes either a true or relative hyperacidity and hypoalkalinity and that the specific toxin of burns is similar to histamin and that the combination of hyperacidity and the devitalizing effect of the toxin on the mucous membrane favors the development of the ulcer. Localization he believed is due to the tortuosity of the vessels of the lesser curvature of the stomach and first part of the duodenum and the relative poor anastomosis rendering them more liable to thrombosis.

Acute ulcers have been found to develop very rapidly - in some cases as early as nineteen hours following a severe burn. By killing dogs at various intervals after an ulcer-producing toxin has been injected, the different stages of their formation can be traced. It has been conclusively proved that an area of necrosis forms first and that the necrotic tissue is then digested by the gastric juice with the production of an acute ulcer.

Liver dysfunction has been thought by some to be a cause of ulcer. This may account for the frequent association of ulcer to Gall-bladder disease, in which there is an interference
with the normal flow of bile or where the liver as a detoxifying agent failed to act following burns.
Inflammatory Theory

The theory of inflammatory ulcer is based upon the fact that evidence of inflammation is always found on examining the mucous membrane of the stomach and duodenum in fresh specimens obtained in the surgical treatment of ulcer by resection of the duodenal bulb and more or less of the stomach.

Konjetzny and Puhl, quoted from Held and Goldbloom, advanced the theory that gastric catarrh is present in practically all cases of ulcer and that gastritis is always a fore-runner of ulcer. This gastritis is usually located in the prepyloric and pyloric regions. A catarrhal inflammation has been confirmed by Ashoff (20).

The work of Wellbrock (18) and Berg (19) in this country deserves especial prominence. Berg was able to study a large amount of fresh pathological material from sub-total gastrectomies. He claims that there is a specific ulcer gastritis. In the early stage of this gastritis, the mucous membrane is studded with small polypoid elevations - the size varying from 1-2 mm. Their tops at times are abraded or eroded, or the seat of small superficial ulcerations. This polypoid infiltration of the mucosa involves not only the pyloric and prepyloric areas but extends up on the lesser curvature, on the body of the stomach and occasionally even up on the cardia. These polypoid infiltrations consist of lymphoid cells which frequently compress the gastric glands until they, the glands, disappear. Lymphoid cells sometimes break through into the muscularis and to the peritoneal layer. These polypoid
elevations persist for a time, their tops erode, give rise to hemorrhage and the erosion may develop into an ulcer. In healing, fibrous tissue replaces these polypoid infiltrations and the gastric glands do not fully recover.

The causes of this specific ulcer gastritis, Berg states, are faulty metabolism and an inherited constitutional tendency to ulcer. This is the reason why so many cases of gastritis do not develop into ulcer. He mentions two other factors important in ulcer formation, the acid factor and the infective factor.

Wellbrock suggests a definite relationship between duodenitis and duodenal ulcer. He showed the pathological changes to be the same and the duodenitis the forerunner of the ulcer in many instances. The causes of this duodenitis he states may be single or a combination of factors, as trauma from within or from without, high temperature, strong acid or alkalies, vascular disease, functional disturbances and allergic reactions. Stasis also plays an important part, as the chyme causes an irritation and an excellent media for the development of infection.

Nassau states that in every case of ulcer, he has found the ulcer the result of a definitely inflammatory destruction of the mucosa.

The difficulty in accepting chronic gastritis or chronic duodenitis as the forerunner of ulcer is apparent. There are many cases in which ulcer never develops. The usual excess of mucus found in each fraction of a test-meal in chronic gastritis
is not often observed in cases of ulcer and hyperchlorhydria would rarely if ever be present with ulcer. Achlorhydria is the usual finding in gastritis and duodenitis, while the opposite is true for ulcer.
Glandular and Neurogenic Theories

The effect of glandular activity on the formation of ulcer may be received as associated with some type of nervous instability.

Durante (22) noted that ulcers following median splanchnic nerve resections were associated with lesions of the suprarenals. Other investigators have reported ulcers associated with a thickening of the suprarenal capsule, hypertrophy, fatty degeneration, congestion, and multiple hemorrhages in the glands.

Mann (23) observed acute ulcerations in ninety per cent of animals following the removal of both glands. These ulcers did not develop when sodium bicarbonate was given suggesting the acid factor.

One of the factors which influences gastric secretion are the impulses which reach the stomach over the vagus. Klein (24) working with this physiology in mind conceived the idea that sectioning the vagus would eliminate the continuous secretion. This sectioning was done at the level of the cardia on the left vagus which presumably influences the acid cells on the anterior half of the body of the stomach. All of the patients operated upon showed a gastric anacidity.

It is common knowledge that the action of the vagi is to accelerate peristalsis and that the sympathetics are inhibitors. The two are normally in balance. It can easily be seen then that by a destruction of the sympathetics the vagal preponderance would lead to hyper-peristalsis and even a tonic spasm of the musculature leading to ischemia, passing of acid chyme and
undigested food particles into the duodenum. This should only be for a short interval however as it is an accepted fact that the intrinsic nerve supply of the gastro-intestinal tract soon acts as a moderator, Kuntz (25).
Autolysis of the Stomach.

Gastromalacia or self digestion of the stomach is an issue which has been much disputed by pathologists. Katzenstein advanced the theory that it is possible for pepsin to digest the gastric mucosa and cause ulceration in some individuals and not in others because of a marked diminution or absence of anti-pepsin in such individuals.

If this auto-indigestion were possible it could be considered as related to the formation of ulcer. It being that the process is attributed to an abnormal acidity of the digestive enzymes or to a deficiency of the tissues for natural self protection against enzymatic activity.

Pathologists have shown that soon after death, especially if the stomach is at the height of digestion, that there rapidly is a digestion of the stomach. Virchow and Cohnheim, quoted from McCann, agreed that this was a cadaverous process. Bernard (26) attributed the immunity of the stomach against auto-digestion to the fact that pepsin was not absorbed by the gastric mucosa and because any destroyed cells were rapidly regenerated.

Dragstedt and Vaughan (26), in a study of the resistance of various tissues to gastric digestion, emphasized the intrinsic resistance of the exposed living cells to digestion, ruling out any protective function by the mucosal coat by implanting other living tissue in the lumen with the raw surface exposed without digestion.

This latter work is quite conclusive and has been accepted by most investigators at the present time.
Experimental Operative Ulcers

This work was done in an endeavor to explain the recurrences of ulcer following a gastroenterostomy. Mann (28) operating on dogs caused the gastric contents to be expelled from the stomach into the jejunum without becoming mixed with the secretions poured into the duodenum, the bile, pancreatic juice and duodenal juice being poured into the ileum. He found that peptic ulcers developed in almost every animal in which the operation was performed. The time of the production varied. The operative trauma and blood supply were not factors because the ulcers were always found at the same site in the intestinal mucosa just distal to the suture line, lateral and posterior to the central axis of the intestine.

McCann experimenting similarly, studied the effects produced by drainage of the duodenal secretions back into the stomach. Despite the volume of alkalies drained into the stomach, ulcers still formed in the anastomosed jejunum in eighty per cent of cases. Both agree that there are two factors which are significant in regard to the process of the development of experimentally produced ulcers, a mechanical and a chemical.

The mechanical factors being the action of coarse cellulose foods and the force of the stream ejected through the pylorus against the mucosa of the pyloric segment, the mucose is closely attached here and does not form protective rugae such as found in the fundic portion and peristalsis is more active in the pyloric portion.
The chemical factor is the action of acid chyme. Fractional gastric analysis showed a normal acid which was independent of regurgitation of the duodenal alkalies. There was no essential alteration in the character of the curves in response to the test meal whether the alkalies on the distal side of the pylorus were present or not. The ulcers produced exhibited the highly destructive action of the acid chyme. They emphasized a gradient immunity of the mucosa of the intestinal tract to ulceration which they consider the deciding factor in determining the greater frequency of duodenal ulcer as compared to gastric ulcer and the tendency for jejunal ulcer to develop following gastroenterostomy.
Intestinal Infection

It is apparent from the many theories put forth that the problem is still unsolved. Perhaps some light may be thrown on the cause of peptic ulcer if we consider the relation of the appendix and the gall bladder to the duodenum and stomach.

In reviewing the literature, it is surprising to find such a high frequency of the co-existence of appendicitis, cholecystitis and duodenal ulcer. No one has experimentally tried to prove that appendicitis and infection of the remainder of the intestinal tract are predisposing or etiological factors in duodenal ulcer although many point to the appendix as primary to duodenal ulcer. Several large clinics have made it a routine procedure in surgery of one of these organs to always examine the others, especially in chronic cases.

Hinricksen (29) calls attention to the fact that post operative complaints are often due to the affection of an organ other than that which has been operated upon. Many appendectomized patients later suffer with a disease of the biliary system or with gastric and duodenal ulcers, and the complaints made it necessary for a second operation. In the combinations of affections of the gastrointestinal tract and appendicitis, he believes that there is little doubt but that the appendix was primary as the appendix always showed complete processes. He also believes that in many cases of co-existances of cholecystitis and appendicitis, the appendix was also primary.
If we should accept this as true, in what way would the stomach and duodenum become affected. The possible routes are, septic emboli which are carried by the portal system to the liver and then to the gall bladder and duodenum; by direct extension into the duodenal cap and into the ampulla of vater; and by the lymphatics. I shall only consider the role of the lymphatics. As was pointed out, the lymphatic drainage of the abdominal viscera is toward the coeliac group of glands. This triad of organs, the appendix, gall bladder and duodenum are considered to be in a very intimate association by the lymphatic chain. Infection of the appendix, gall bladder and any part of the intestinal tract can readily be carried to the coeliac glands and then by retrograde emboli to the duodenum or by the lymphatics direct to the duodenum before arriving at the coeliac glands. Very little is known about lymph drainage but it is considered not to be constantly in one direction.

Normally the duodenum would not be involved but with a lowered resistance and by the additional action of the acid chyme and mechanical trauma, the lymphatic tissue in submucosa and mucosa has set up an inflammatory reaction, becomes necrosed and ulceration takes place in exactly the same manner in which Rosenau has produced ulcers by injection of streptococci into the peritoneal cavity.
Hyperacidity Theory

In view of the fact that peptic ulcer is so frequently accompanied by hyperacidity, it was natural to associate both conditions and to regard hyperacidity as the precursor and even the cause of the ulcer.

The older methods of gastric analysis failed to show a constant hyperchlorhydria in gastric and duodenal ulcer. Using the Ewald and Rehfue's test meals, Hurst has found at the New Lodge Clinic a hyperchlorhydria in 61 per cent of cases of duodenal ulcer and a high normal in 29 per cent and in gastric ulcer hyperchlorhydria present in 32.1 per cent, a high normal curve in 26.3 per cent and subnormal acidity in 9.5 per cent. If these figures are true values, it would be difficult to explain why those with a normal or subnormal acidity develop ulcers.

Cheney (30) using a newer method injected a small amount of histamine, a powerful stimulant to gastric secretion, subcutaneously. In his series of 88 cases with an unquestionable diagnosis of duodenal ulcer, he found 96.5 per cent with high acidity and in a series of 33 cases of gastric ulcer a high acidity in 96 per cent, whereas by the Ewald test meal only 46 per cent of this same group showed hyperacidity.

Bálint (31) has investigated in particular the reaction of the blood and tissues in cases of peptic ulcer. He believes in an ulcer diathesis in which the acidity of these tissues is higher than normal. In 77 cases in which no ulcer was present, he found the H-ion concentration of the blood to vary between
7.54 and 7.64 with an average of 7.59 and in 89 cases of gastric or duodenal ulcer it varied between 7.46 and 7.60 with an average of 7.55. In this latter group only 7 per cent showed the blood to be more alkaline than the average individual. He states that this abnormal acidity affects the tissues as well as the blood.

If the results of Bálint's observations were true, there would be good reason in accepting this theory. However, as yet, other investigators have not confirmed his observations.

If we are to accept the theory that an abnormal acidity is the cause of ulcer, we must explain the cause of this abnormal acidity. An attempt to explain this has been on a glandular and neurogenic basis. These were considered under their appropriate headings.

No one has conclusively proven that hyperacidity is the cause because the cases have not been carefully examined prior to the development of the ulcer. It may be that the ulcer itself has caused this hypersecretion of acid and having once formed, the acid secretions inhibit the healing process and the ulcer develops into a chronic state.
Conclusions

At the present there is no conclusive evidence that gastric and duodenal ulcer are caused by any one agent. But as has been suggested there may be a dual etiology.

Modern medicine has accepted abnormal acidity, autonomic imbalance and infection as factors and physicians have been highly successful in treating those individuals with ulcer by agents which combat these abnormal conditions.

In as much as ulcer formation is most frequently found in a certain segment of the gastrointestinal tract, the anatomical characteristics must be considered as playing a big part in the ulcer pathogenesis.

We must also consider the physiology of the organ. It was shown that the proximal part of the duodenum and distal part of the stomach have a very similar function, that of digestion and evacuation, in contrast to the storage and secreting functions of the body of the stomach.

As shown by operative experimentation, there is a very constant formation of ulcer at a definite site — just distal to the suture line. The factors suggested, mechanical trauma and an abnormal acidity, must be accepted as agents in the process. The intrinsic immunity of the mucosa to ulcer being a predisposing factor — important in determining the site and the reactive ability of the lesion to heal.

There is little doubt but that the infective factor plays a big role. The experiments of Rosenaw and Nickel are quite conclusive and clinical experience has shown that following the
removal of foci of infection the probability of a cure is greater.

Hyperacidity although a nearly constant feature in ulcer has not been conclusively proven to be the cause - it may be a result. A result which must be removed before healing can take place.

It is highly probable that there is a vicious cycle present in the persistence of an ulcer, initiated by some factor not yet discovered and carried on by a deficient blood supply, an infection, a muscular spasm and a hypersecretion. By breaking such a cycle of events, healing is possible.
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