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## Study of the etiology of peptic ulcers especially in regard to infection, physiological changes and innervation

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A STUDY  
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W . T . N Y G R E N .

Ulcers of the stomach and duodenum is one of the most important pathological problems engaging the attention of scientific workers. Ulcers have been known to exist for many years before being recognized clinically. In the 16th century the condition was recognized by Stahl, but the condition was not described clinically until between the years 1829 and 1835 by Cruveilhier. He gave the first anatomical description and many therapeutic measures, and was the first to recognize ulcers as a typical disease form. Following him came Rokitansky and Jaksch. After the 4th decade of the eighteenth century, Panum, C. I. Bernard, Cohnheim, Selebermain, and others, contributed much to our knowledge.

Clinically, peptic ulcers have led to investigations of the numerous conditions with which it is directly or indirectly associated, such as pain, hemorrhage and perforation, together with the secondary results, such as obstructions, adhesions and contractions, which carry a high mortality rate in medicine. Within recent years, due to the rapid progress in surgery, ulcers have been studied in association with carcinoma of the stomach, due to the fact that ulcers and carcinoma are often found together. R. H. Miller, in 1928, after careful study of the literature and his own cases, concluded that duodenal ulcers are never malignant, while gastric ulcers frequently cannot be distinguished from early carcinoma. W. L. Wellbrock, of the Mayo clinic, found that in one hundred cases of ulcers, resection of the stomach showed suspicion of beginning malignancy. Therefore it may be easily understood why so much literature has been written about the etiology of peptic ulcers.

Peptic ulcers vary in size from a pin point area to ulcers which may cover the greater part of the stomach or duodenum, and vary in depth from a mere superficial lesion to deep lesions involving the peritoneal surface.

The location of ulcers has been studied by various scientists, who have found that a greater percentage of ulcers of the stomach occur in the lesser curvature. Sippy, who has made a comprehensive study of ulcers, found 35% in the lesser curvature, 30% in the posterior wall, 12% in the pylorus, 9% in the anterior wall, 6.5% in the cardiac portion, 3.5% in the greater curvature, 3% in the fundus, and 1% in the cardia orifices. In grouping these percentages, one finds approximately 85% in or about the pyloric orifice.

The frequency of ulcers varies according to different men in different localities. Riegel made a comprehensive study of the literature and reports that 362 cases of ulcers were found in Berlin Charité Pathological laboratory from 1868 to 1882, being present in 2.7% of all post mortem examinations. Nole reported ulcers present in 1.23% of all autopsies; Ziemse in Erlangen, in 4.5%; Stoll in Zurich, in 2.16%; and Stark in Copenhagen, in as many as 13%. Grunfield found larger percentages. He succeeded in demonstrating the presence of ulcer scars in 92 out of 450 autopsies (241 women and 299 men), approximately 20%. Of the 92 cases, 77 were found in women and 15 in men. B. W. Sippy stated that 5% of all autopsies showed evidence of either open or healed ulcers. Robertson and Hargis of the Mayo clinic stated that 19% of all autopsies showed ulcers, 65% of the duodenum and 35% of the stomach. Eleston found that 25% of all cases autopsied showed

two or more ulcers, and as many as 5 and 6 have been recorded especially in infectious diseases.

Little is known of the geographical distribution. Early in the 18th century Gerhardt called attention to a few cases in Russia and attributed this cause due to the Russians eating more vegetables than meat, and that consequently more potassium was introduced with the food, and more potassium was in the blood of the people. This was later disregarded, as studies revealed a large percentage of ulcers were present with hyperacidity as one of the symptoms.

The most common age of affliction has been stated to be from 20 to 30 years in women, and from 20 to 40 years in men, but cases of ulcers have been found in infants at birth and in young children. Therefore one must consider ulcers in all ages. R. B. Shannon demonstrated ulcers in an infant 6 months old, and based the etiology on a probable syphyletic basis.

Many investigators have been able to produce peptic ulcers by various methods which I will attempt to discuss. The literature is so full of such experiments, that I will only be able to touch upon the subject. I have concentrated most of my time to a discussion of the etiology in regard to infection, physiological changes and innervation, since these seem to be the outstanding theories today.

Acute ulcers have been produced by many methods, but to produce a chronic ulcer, as is present in human, has as yet not been possible. The question naturally arises as to the initial cause of the acute ulcer, and to the chronicity of the ulcer after being present.

The role that cytolysis and autocytolysis in the form-

ation and persistence of ulcers must be regarded as an important factor. It points back to the fundamental problem--what prevents the self digestion of the stomach, and what prevents the autolysis of all the tissue of the body? That some sort of protection existed to prevent self-destruction of the stomach was recognized by the ancients, who thought that it was due to some supernatural power.

Stahl regarded our protection to be the "sensitive soul." He states, "This very prevention of a thing essentially destructible by which its destruction through its own activity is prevented, is exactly what we ought to understand by the common word 'vital.'" In any case, the fermentation which takes place in the alimentary canal is not an ordinary fermentation such as occurs in a merely compound not living body, but a most special character is impressed on the change by "energy of the soul."

Hunter believed that a certain "vital principle" inherent in the parts, protected the wall from autodigestion, and claimed that a living hand, if put in a stomach while digestion was going on, would not be digested, but if the hand was cut off and placed in the stomach, it would be digested. As cellular pathology developed, the word tissue was added to the same "vital power" of Hunter's, and as Reigel expresses it "the main reason why the stomach does not digest itself is unquestionably the vital resisting power of the tissue."

Seeing that the normal stomach did not digest itself, various ideas of local resistance or protection came into view. Whether it was a local vital power residing in the cell or a secretion acting as a protection was not known. Thus Vaughan Harley thought "the mucous acted as a protection coat of mail to the

mucosa of the stomach," and thus prevented self-destruction. From Turck (1) "the modern idea of this local protection is shown in Weiland's work, who holds that an anti-pepsin ferment residing in and as a part of the gland cell, protects them from destruction." Hunter's theory was robbed by C. Bernard, who showed that a living frog's leg was partly digested in a stomach during digestion. He claimed that life itself did not prevent the digestion of the stomach, but that the superficial layer of the mucous was destroyed and that deeper layers were protected by the rapid growth of the epithelium. Pavy repeated Bernard's experiment and concluded that regeneration of the mucosa did not protect the stomach from autodigestion, but that the blood was alkaline in the stomach and neutralized the hydrochloric acid in the deeper layers, and he attributed the digestion of the frog's foot due to the small amount of blood supply present in the foot.

About the middle of the 18th century, chlorosis and anemia was thought to be an etiological factor, but Riegal did not uphold this theory and stated, "Naturally an old chronic ulcer leads to anemia and would naturally be a secondary factor." Experiments were performed by Riegal, and he found that ulcers healed more slowly in dogs who were made anemic than in those that were not anemic. He found in chlorosis a hyperacidity in the stomach, and after collecting a large amount of literature on this disease, concluded that hyperacidity did not lead to the development of ulcers, "but that it played an important role in preventing its cure, and that hyperacidity is present in the majority of cases of chlorosis. This alone may explain why ulcers of the stomach and chlorosis are so frequently found together." It was

found that after death the stomach digests itself, but that during life normally the stomach did not digest itself. According to Riegel, the latter condition does not occur because during life the walls are continually flooded with alkaline blood, and that consequently the gastric juice is always neutralized, and when the secretion is impended, autodigestion of this portion will occur due to lack of alkaline blood getting in to neutralize the acids.

Many attempts have been made to evaluate acids as a primary or secondary factor in the cause of peptic ulcers. The results have lead to demetrically opposite conclusions. Certain observers believe that acid is a primary cause and others believe it has no casual relationship.. Some believe the ulcer develops in association with an over-production of acid, or an increase in the degree of acidity, and others, that ulcer develops where there is a decrease in the acidity. Numerous experimental investigations have been made to determine the relation of acid to ulcers, by administration of alkaline or acids by mouth with or without operative procedures, with negative and positive results. We find from our physiology books that the acid secreted by the gastric mucosa must be neutralized before the pancreatic enzyme can be effective. The neutralization not affected by food must be taken care of by the intestinal secretion, bile and pancreatic juice. Enough alkaline must be produced from these secretions to neutralize the acids that pass the pylorus. Mann and Williams performed some interesting experiments upon dogs in regard to intestinal and stomach secretions. They worked on the theory that if the upper portion of the intestinal tract was subject to an acid median by damaging the alkaline mechanism, that ulcers would result. They



produced this by removing the duodenum, by transplanting the bile duct and pancreatic duct to the terminal ilium. The duodenum was functionally resected and made to drain its own secretion and that of the pancreas into the lower ilium. It is interesting to note the large percentage of dogs that developed ulcers. In the first series, 2 out of 10 developed ulcers; in the second series, 10 ulcers out of 31 dogs; in the third series, 8 dogs out of 10; and in the fourth series, 14 dogs out of 16 developed ulcers. They found that all but two dogs coming to necropsy, less than two weeks after operation, did not have ulcers. The usual time for development was during the third or fourth week. The ulcer was usually located in the intestine, a few millimeters distal to the pyloric mucosa. Many showed lesions in the pyloric mucosa. The ulcers were relatively large, usually only one, and appeared grossly, like the peptic ulcer in man. In conclusion they stated "that the acid or lack of alkali was an important etiological factor." The procedure produced ulcers by breaking up the normal mechanism of digestion, which normally is not the case in human. Therefore I believe, while the methods used produced ulcers, I cannot say that this is the case in human ulcer patients, unless it is produced through innervation, which as yet has not been proven. Rosenow disregarded the theories of digestive action of gastric juice and hyperacidity as the cause of ulcers. He acknowledged that some ulcers are made to heal by the use of alkaline, such as Sippy diet, but regards this due to neutralizing the acid in the stomach so the ulcer can heal, as the digestive action of the hyperacid gastric juice on the floor of the ulcer prevents healing. Rosenow states "that if this is true, chronic ulcers should be found where this action proceeds for the longest time and is most direct; that is, in the

acid secreting portion of the stomach." This is not the case, as the corrosive action must be less in the duodenum than in the stomach, and probably is much less in the pylorus and in the lesser curvature, where according to statistics the greater percentages of ulcers are found. Rosenow considered that ulcers due to something with greater penetrating power than the gastric juice, and considers the primary factor due to localized hematogenous infection of the mucous membrane by the streptococci.

Burge (W. F. & E. L.) believed that the ulcers were due to a decreased resistance in the walls of the stomach, followed by digestion of these areas by the unrestricted action of the pepsin. It has been shown that ulcers can be formed by cutting off the blood supply to certain areas of the stomach, thus causing anemia to this area and ulcers result, which Burge explained was due to deprived oxygen resulting in lessened oxidative processes. Araki showed that the oxidative processes are decreased in rabbits rendered anemic and in certain poisons the oxidative processes of the body are decreased, which renders the tissue more susceptible to autolysis. Schlesinger found that in diseases of the circulatory and respiratory system, where the amount of oxygen was decreased, the oxidative processes were decreased, and there was great tendency of all the tissues to undergo self-destruction. Burge considered that these facts seemed to point to some relation between the oxidative process of the body and the resistance of the tissue to the digestive action of the proteolytic enzymes. Burge (2) showed that pepsin, as well as trypsin, is easily destroyed by oxidation. Lillie showed that the cells of the gastric mucosa possessed intense oxidative properties. Burge (1) worked on the

theory that since pepsin is easily destroyed by oxidation, and that the cells of the mucosa possess ~~#####~~ oxidative properties; that these cells easily become digested when these properties are decreased; and that under normal conditions are not destroyed because the pepsin is in contact with the walls of the stomach, and rendered inert by the oxidative process. He assumed "that normally a balance existed between the oxidative process of the cells of the mucosa, and the digestive action of the pepsin in the stomach. If this balance be destroyed ~~ed~~ by cutting off the blood supply, thereby decreasing the oxidative process of the area, this area should be digested by the pepsin and an ulcer result." We know, for a ulcer to form in any part of the body, there must be a break in the continuity of the tissues, followed by necrosis and an ulcer. Sippy believed that an area of the stomach mucosa loses its resistance "thorough malnutrition, injury or necrosis, to the peptic action of the gastric juice, and that this area becomes digested with a resulting defect--the ulcer." This theory follows along with the early theories advocated by the pioneers, and is accepted at large. How this resistance is lost, and the cause of such loss, is still open for investigation.

Many theories have been advocated to explain the etiology of peptic ulcers on an anatomical basis. Elston believed that there was a deficient blood supply in the region of the pylorus. The upper part of the stomach receives its blood supply from three different branches--the left gastric, the left gastroepiploic and from the vasa brevis, while the pyloric area is supplied by two branches only--right gastric and right gastroepiploic, which are smaller than the upper three. The vessels to the pyloric area are smaller

than the upper three. The vessels to the pyloric area are also longer and smaller, the distance being greater, the blood flow per volume is less in the pyloric area. Elston believed "that during a contraction of the stomach, the wave of contraction is at its height when it reaches the pylorus, and there elapses a period of time when there is most complete anemia of the pyloric region, due to the vessels in this region being smaller, and acting as terminal vessels and predisposed to circulatory disturbances, and are deficient in ability to develop collateral circulation. Therefore this area is prone to become more anemic than any other part of the stomach." While Elston's theory is not accepted as the single cause of ulcers, it is a theory which fits into the ulcer picture, especially in regard to the location, since 80% of ulcers are found in and about the lesser curvature of the stomach and the pylorus.

Many other methods have been used to produce acute ulcers, such as injecting acids and caustics into the stomach. Ulcers have also been found following severe burns, and also following trauma. Roberts published a paper in 1908 which stated that during his experience in surgery he noted that after trauma to the bladder and kidneys, many of his patients later died from ulcers of the stomach or duodenum. He also sighted cases where the patients had kidney stones removed, and later developed ulcers. He thought the cause was due to toxemia in the first series, and to uremia in the second series.

A vast amount of literature may be found in regard to infection as a cause of peptic ulcers. Some investigators have been able to produce ulcers by various pathogenic bacteria, while others have met with opposite results. Turck (2) believed that

ulcers were due to B. Coli, and gave several reports regarding his findings. He found that feeding animals (dogs) with B. Coli Communis for several months, spontaneous or induced, genuine peptic ulcers of the stomach and duodenum were found in every animal experimented upon, the ulcer causing death either by perforation or hemorrhage. Controls were necessary and he examined 271 dogs from the street (post mortem) and no ulcers were found, showing the percentage of ulcers in healthy dogs is at least most exceedingly small. Turck stated that in his experiments in production of ulcers "that the factors concerned seemed to indicate a dual condition. Some toxic condition produced overcame nature's resistance, resulting in cytolysis, and possibly some chemical substance formed within the alimentary **tract**, which when absorbed may neutralize the protective bodies in the blood and tissue, resulting in autocytolysis." He further stated that "we now have a **firm** basis by which to solve the problem of the finer or underlying etiology of ulcer." Turck (3) also injected toxins, such as diphtheria, into the stomach of animals, and reported that ulcers were **not** produced, but found pin head hemorrhagic spots and areas of necrosis near the pylorus. In all his experiments with bacteria, toxins, etc., he only found ulcers typical to human after feeding B. Coli as reported above. He was unable to produce typical ulcers by any other method. While Rosenow and Anderson were experimenting on guinea pigs in the Chicago public health laboratory, they discovered that 65% of the guinea pigs injected with diphtheria toxins for public health work showed gastric lesions. It is interesting to note that Turck did not produce ulcers by injecting diphtheria toxins. On the other hand, Rosenow and Anderson did produce ulcers by

injecting the toxin subcutaneously in doses to cause acute death of the animal.

About the same time that Rosenow and Anderson made their discovery, M. E. Rehfuse found that after the injection of the heloderma into guinea pigs, gastric ulcers and hemorrhagic erosions were found in 85% of all the animals used. He also found the ulcers were agglutinated by atropine and pilocarpine, and also found that various poison substances, such as magnesium chloride, paraldehyde, phenol and chloroform all produced similar changes in the mucosa. He assumed the effect of these substances not specific for the cause of ulcers, but probably an indirect one, acting either through a weakened influence on the circulation, or through a direct injurious effect on the cells of the mucosa. He also found that when an alkali was injected into the stomach, it prevented ulceration in most of the cases, and from these observations rendered it most certain that usually digestion is primary and in many cases hemorrhage is merely the result of secondary erosions of the vessels, thrombi forming also as a secondary factor due to the fact that he was unable to prevent the occurrence of ulcers by first making the blood incoagulable, and he states "that thrombi are not the cause of ulceration, but that secondary thrombosis must be considered as a beneficial process in that it prevents fatal hemorrhage."

F. Billings did not attempt to regard the etiology of peptic ulcers due to any one specific cause, but believed that the gastric juice was the active agent in its production in a limited area, and that this occurred because of nutritional disturbances in a circumscribed region of the mucosa. That the

nutritional disturbance was brought about by bacterial infections associated with local trauma, and that vascular disease, local areas of muscular spasm, gastric stagnation and anemia were all factors in certain instances. His theories were far fetched and covered numerous etiological probabilities, which has previously been discussed by many other investigators.

Rosenow (2) demonstrated that streptococcus injected into the veins of rabbits and dogs produced ulcers of the stomach and duodenum. The streptococcus was cultured directly from human ulcers, infected teeth, infected sinuses, nose and tonsils. He found that certain strains of streptococcus had a tendency to produce ulcers more often in the duodenum than in the stomach. He demonstrated this by taking streptococcus directly from the duodenal ulcer and injecting it directly into the veins of healthy dogs, and found that a greater percentage of ulcers formed in the duodenum than in the stomach. He also found that the location of the ulcers produced were in accordance to ulcers found in human. In 25 dogs used, he found that 12 ulcers were in the pyloric portion, 4 being along the lesser curvature, 2 in the fundus and 7 in the duodenum. He concluded by stating "that the chief differences between lesions lesions in the stomach and duodenum following injections of the strains from ulcers, and those from strains of other sources, are one of total incidence and degree, rather than of kind, the strain from ulcer showing by far the greater affinity for the stomach and duodenum." Wilensky, working along this same line, isolated streptococcus from a human ulcer and injected this directly into the stomach of 9 dogs. Surgical procedures were used and controls. He incised the stomach along the

greater curvature under asepsis, and then injected the streptococcus. At various intervals he opened the stomach and inspected it for a chronic ulcer, and found in all nine animals used, irrespective of the size and depth of the defect or of the virulence or number of the organism injected, that the surgical defects healed as promptly as those observed in the controls. He concluded by stating "that the series of experiments demonstrated that the presence of organism found in the human ulcer had no appreciable effect, either in giving the experimentally produced defects the characteristics of the chronic endured ulcer, or in retarding the healing." Nakamura also demonstrated that ulcers were produced by streptococcus when injected into rabbits. He found that streptococcus from infected tonsils in ulcer patients, when injected into rabbits, developed ulcers. He used 66 rabbits and found that 70% developed ulcers or hemorrhages in the stomach. He found that the tonsils of patients suffering from ulcers of the stomach commonly harbor streptococcus which tend to localize in the stomach and produce ulcers, which he found was not true of streptococcus in the tonsils of normal persons. Hence he concluded "that foci of infection harboring streptococcus having elective localizing power are important factors in the primary cause and the persistence of ulcer of the stomach."

The bacteriology of peptic ulcers is rather interesting, since so much work and confusion has arisen in regard to infection as an etiological factor. Saunders did some interesting work along the bacteriological side of this question of ulcers. He found by a careful bacteriological study, streptococcus present in 19 resected gastric and duodenal ulcers, and proved them to be



identical and specific by agglutination, cross agglutination and agglutinin absorption. His work covered the bacteriological side of the ulcer question, and I believe quite conclusively proved that streptococcus infection is of utmost importance, and must be considered as an important etiological factor, and that it is probably the primary cause in some instances, but one must not lose sight of the probability of the ulcer being present before the infection.

A. D. Bevan disregarded the theory that peptic ulcers were due to infection from teeth, tonsils, sinuses, etc. He said "that so much attention was being placed on such infections that the scientists were losing sight of other possible conditions. He acknowledged the fact that if a patient with peptic ulcers had a foci of infection that the infection should be removed, not that they were the cause of ulcer, but that removing the foci of infection would better the general health of the patient." He further stated "that there was little scientific evidence supporting such a theory of infection." He disregarded all the work of his profession without presenting any scientific data of his own, and I do not believe that he can disregard foci of infection under those conditions.

C. S. Judd of the Mayo clinic did not make such a radical statement in regard to infection as the cause of ulcer. Judd, although not disregarding foci of infection, stated "that realizing the importance of Rosenow's work, we have for many years paid particular attention, in the clinic at Mayo's, to foci of infection in gastroduodenal cases. While undoubtedly something has been accomplished in curing and preventing the recurrence of ulcers

by routine treatment of foci of infection, the clinical results are not as promising as we had hoped." He regarded the Mann and Williams experiments, which I have already discussed, as a more probable cause, and attributed this due to a break in the normal physiology. I believe, from the above experiments and many others on foci of infection, that we must consider, or assume, that infection plays a part in the etiology of ulcers. Whether it is an active factor early in producing ulcers, or is a secondary phenomena, is as yet not definitely known. It seems probable that infection plays a part in chronicity of ulcers in many cases.

Much investigating and experimental work has been done in regard to the relation of peptic ulcers to the neuromotor and neuro secretory mechanism of the stomach. Various investigators have endeavored to produce ulcers by damaging the neuromotor system. Some have been able to produce ulcers and others have met with opposite results, which makes the subject very difficult to understand.

Ulcers of the stomach have been produced experimentally by section of both the sympathetic and the vagi. Ulcer lesions have also been produced in the stomach by experimental pathology of the pons, bulb, cervical spine and the vagus nerve. Simpson considered trophic disturbances of greater importance than the literature indicated, and sighted cases where patients have pylorospasm and hyperacidity with presence of ulcers. Eusterman states "an imbalance of the parasympathetic nervous system provoking physiological disfunction, particularly, regional spasm, combined with the irritant action of the hydrochloric, is one

important factor in the production of ulcer." He points out, however, that there are other factors necessary, because such embalance is seen in many individuals who do not develop ulcers. Deaver and Burden also considered the cause of ulcers as due to acidity, and more especially the chronisity of ulcers. They also believed that infection, either within the abdomen or without, was probably the origin of the initial lesion in the way of preparing the soil for the destructive action of the acid. They considered that the food in the stomach stimulated the vagus nerve, which in turn stimulated gastric secretion, hydrochloric acid, pepsin, etc. Thus under normal conditions, during digestion, there is just enough hydrochloric acid secreted to care for the food in the stomach. If this nervous mechanism is thrown out of tune by higher stimuli, such as from anxiety, worry, fear, and und<sup>er</sup> pressure, there will be an excess of hydrochloric acid secreted, and spasm of the pyloric sphincter, resulting in hyperacidity and retention of food. Monsarrat did not believe that chronic gastric or duodenal ulcers were caused by specific organisms or alteration in the chemistry of the gastric secretions. He believed it was due to alteration in the gastric **rhythm** being the primary morbid condition, which if persisted would lead to the development of ulcers. Further, that the fundamental condition on which these morbid changes in gastric motility and rhythm depended, was doubtless a disorder of gastric innervation, which may have its origin in toxic influences, or psychic influences, or in **reflax** influence from disease elsewhere.

Wolfer produced ulcers by X-Rays, and then studied how ulcers affected the gastric secretion and emptying of the stomach.

He found that ulcers, located from one to two inches proximal to the pyloric sphincter, did not cause any change in the gastric secretion of dogs. But when the ulcer was within the pyloric sphincter or near, there was a delay in the emptying time of dogs. In other words, Wolfer expressed that the ulcer had only a very local and quite narrowly circumscribed effect on the intrinsic nervous mechanism. In man, however, in whom psychic factors play an important part, long reflexes from pain, he considered, may cause a change in gastric motility.

Durant, after experimenting with dogs over a long period of time in regard to ulcers, considered that under normal conditions, the vitality of the gastric mucosa is directly dependent on three factors: secretion, circulation and innervation. The latter is the result of the two former, inasmuch as the secretory glands are stimulated by nerve impulse and food supply. He succeeded in producing ulcers by resection of the vagus and the splanchnic nerves. He based his theory on the vaso-motor problem, and regards that "excessive psychic stimuli were capable of changing the normal vaso-motor tonus, that vascular disturbances culminating in rupture of the small arterial walls, may be caused in any part of the body, a fact which may be explained by the close association, both in anatomy and function, of the sympathetic nervous system and cerebrospinal tract." In other words, ulcer may be produced by any agent capable of damaging the sympathetic nervous system, "as it is on the integrity of this system, which controls circulation, secretion and profound sensibility in the stomach, that the very life of the gastric cells may be said to depend." Thus the theory of trophic

ulcers may be said to depend."

Crile, while studying the thyroid gland in relation to hyperthyroidism and gastric secretion, worked upon the theory that since hyperthyroidism was often associated with hyperacidity and hyperacidity with ulcers, that one might consider hyperthyroidism as a causative factor of peptic ulcer. He considered six ways of precipitating a crisis, through the influence of adrenalin, emotion, pain and injury, infection and foreign protein, inhalation of anesthesia, hemorrhage and asphyxia and adrenalin. Since the control of acidity of the stomach is under the control of the thyroid, adrenals and nervous system, he stated, "we might venture to attack the ulcer from one of the organs governing it." Crile reported several cases of chronic ulcers where he removed the adrenals, and found that the symptoms of ulcers disappeared, as well as hyperacidity, and based his theory on these observations.

Singer found peptic ulcers frequently enough in pulmonary tuberculosis where mediastinal involvement was marked to lead him to believe that the vagus nerve had been affected, resulting in stomach ulceration. He also reported cases of vagus neuritis in lead poisoning, where peptic ulceration had been found. Oberling and Kalló claim to have produced peptic ulcers following experimental lesions of various central gray nuclei. Finzi and Kippch, among others, have reported atrophic ulcerations following resection of the vagus. Alvarez, while experimenting on gastro intestinal movements in rabbits, noticed that a large percentage of ulcers were found in the animals, and he noticed changes of the nerves in the stomach following such pro-

cedures, and concluded "that the gastro intestinal tube possesses a large degree of autonomy, and the neuor muscular mechanism responsible for orderly diastalsis must be looked for in the bowel itself." Manenkow produced peritonitis in rabbits followed by section of the vagi. He found that if he performed a bilateral vagotomy and then waited a few weeks before subjecting the rabbit to peritonitis, that the rabbit with a bilateral vagotomy outlived and even survived in many cases, while rabbits that had no previous vagotomy all died within nine to twelve hours. He further proved that a local severe inflammation of the stomach wall of a rabbit was always fatal, while the production of local peritonitis in organs such as the large intestine, uterus, etc., which are not directly associated with the vagus, did not give fatal results.

From the latter series of experiments, Best assumed that possibly the presence of a neuro-lymphatic connection between the stomach, vagi nerves and medulla might explain the chronicity of certain lesions of the stomach. He assumed that a primary traumatic ulceration or inflammation beginning in the stomach wall would result in pathological changes of the vagi nerves or various nuclei in the medulla oblongata. To confirm this assumption he injected the stomach wall of ten rabbits with a suspension of staphylococcus aureus, and after death an autopsy was performed and sections taken from the medulla, cervical vagi, theracic vagi and stomach for microscopic examination. Sections were also taken from the sciatic nerves as controls. At post-mortem examination there was no evidence of general peritonitis, but a marked inflammation of the stomach wall at the sight of the injection. Serial sections were made from the medulla. There was no definite path-

ological changes found. The same was noted of the vagi and sciatic nerves. Section of the stomach showed varying degrees of inflammation, and there was no definite relationship between the degree of inflammation of the stomach wall and the degree of slight changes in the nervous tissue. He regarded the slight changes in the nervous tissue as due to toxins, since the sciatic nerves showed the same changes. Being unable to demonstrate any nerve changes with the primary lesion in the stomach, Best's next procedure was to produce a chronic irritation of the vagus and note the pathological changes that might occur in the stomach. This was done by exposing the vagi in the neck of ten dogs, and wrapping magnesium strips about the nerves. The first two dogs died on the fourth day. The autopsy findings were negative, both vagi and stomach showed no changes. The experiments were repeated using only one vagi nerve. At various intervals, ranging from for to six months, the dogs were killed. Autopsy findings were again negative as to ulcers or changes present in the stomach and duodenum. No ulcers were present on examination. Best concluded by stating that "the results are rather convincing that lesions of the stomach do not result in organic changes of the vagi and medulla through a direct neuro-lymphatic connection, and that continued irritation of the vagus with magnesium strips does not produce chronic gastric or duodenal ulcer and does not prolong healing."

#### C O N C L U S I O N

From all of these observations on experimental production of peptic ulcers, and to the numerous theories in regard to ulcers, one must assume that the etiology of peptic ulcer is not known.

The ulcers which have been produced experimentally, have been accomplished by damaging the gastric mucosa directly or indirectly, either by surgical procedures, or by subjecting the gastric mucosa to poisons, trauma, toxins, or infections over a long period of time, under non-physiological conditions.

Another factor must be considered, and that is, that the experimentors, with all the material at their command, can sight facts and apparently prove their own conceptions to be true, while others can repeat these same experiments and prove, according to their findings, opposite results. Since no one experiment can be performed by all the investigators and get the same results, one must assume that there is no one factor to date that may be said to be the specific cause of peptic ulcers.

I believe that peptic ulcers are due to an embryological defect within the tissues of the stomach and duodenum before birth, That is, that active ulcers are either present at birth, or appear later in life due to some embryological development within the tissues, so as to lower the vitality and function of this area, and so that it loses its resistance to protect itself from digestion. In other words, all ulcer patients are born with apparent ulcerations of these areas in the stomach, which have lost their protection by anomalies in tissue development in the embryonic stage.

I have based this theory on the facts, that peptic ulcers have been reported in infants at birth, who have died from perforation and hemorrhage. Autopsies on these infants have demonstrated genuine ulcerations, characteristic of ulcers in the adult. Surely these cases could not have developed



ulcers in such a period as to cause death from hemorrhage and perforation, but must have developed in utero.

Normally there is no active digestion going on in the stomach of a foetus until after the fifth month of foetal life, since before the fifth month the glands of the stomach are inactive. After the fifth month, pepsin, rennin and hydrochloric acid is present in small quantities, which indicates a certain amount of glandular activity. The meconium found in the intestinal tract of a new born is composed of bile, lanugo hair, epidermal cells and water. The bile demonstrates that the liver is also functioning before birth, and the rest of the contents of the meconium is thought due to the foetus swallowing amniotic fluid. It was found by Hoppe-Seyler and others, that the amniotic fluid was alkaline in reaction, and contained 98.48% water, 0.19 % albuminoid material, and the balance in soluble and insoluble salts. Since the foetus is thought to swallow amniotic fluid in large amounts which contains albuminoid material, this might account for the slight amount of glandular activity of the stomach after the fifth month of foetal life. Assuming this to be a fact, and that the tissue in the stomach is normal, then an ulcer should not form in the stomach of the foetus, since there is nothing in the amniotic fluid itself which would produce an ulcer. Then the ulcer must be due to some defect within the stomach itself, either in the gastric mucosa or in the glandular tissue, or both. After the fifth foetal month, the gastric secretions are more active, and there is a possibility that a certain concentration of hydrochloric acid is present normally without any effect on the gastric

mucosa. But with an area of mal development present, whether it be the acid secreting parietal cells or to the gastric mucosa, the hydrochloric acid would naturally attack this lowered resistant tissue and precipitate more active digestion, with an increase of hydrochloric acid and pepsin, which would soon break down this area, producing necrosis and ulceration. If this ulcer appears early after the fifth foetal month, then it will tend to become larger and probably be so extensive that there will be immediate hemorrhage or ~~perforation~~ shortly after the child is born. On the other hand, the erosion may be only slight, and the child will be born without any apparent gastric pathology. In the last case, the ulcer would probably not cause any noticeable symptoms, as the child diet would prevent further erosion, since milk is the chief diet furnished during the first year of life, with only easily digested foods added the next two or three years. In many cases, the ulcers are no doubt healed completely by this diet, which could account for all the ulcer scars found at autopsy in adults who have died from other diseases than ulcers, and who have never complained of any gastric distress, or of any symptoms pertaining to peptic ulcers. On the other hand, the ulcer may be kept at a quiescent stage by such a diet and be carried to early adult life before any symptoms of gastric pathology appears. It seems more probable that the patients who carry ulcers are troubled with their stomach over a longer period than they realize, due to the vague mild symptoms an ulcer produces in the early stage, and the patient does not seek medical aid until the symptoms drive them to such courses. In other cases, the patient may carry the ulcer, which was present

at birth, throughout life without any discomfort. Others may carry the ulcer along without trouble until an extra load is thrown onto him which weakens his general vitality and throws his nervous mechanism out of balance. Infection would come into play here by lowering the resistance of the patient, and if there were an active or chronic infection from the nose or throat, a certain amount would be swallowed and could be found in the ulcer which was present before the infection. The same could be said about trophic disturbances, as ulcers being due to such changes has not as yet been proven, but I believe that these nervous manifestations are primary factors in disturbing the ulcer which was present, by causing increased gastric motility and secretions, which in turn will produce hyper-acidity which will attack the ulcerated area, and produce symptoms of peptic ulcers.

In conclusion, I believe that peptic ulcers, or their equivalent, are present at birth through an embryologic defect in the development of the tissues of the stomach. Many of these ulcers are carried throughout life without presenting any gastric pathology, while others are aggravated and stimulated at various times during life by abuse of the stomach, nervous manifestations, infections and anything which will lower the vitality of these weakened areas, or the body in general, with resulting symptoms such as distress, hyperacidity and gastric disturbances in general. In other words, peptic ulcers are congenital.

The following cases demonstrate how difficult it is to state the etiology of ulcers as being due to any one specific cause. If the etiology was known, it would be difficult in most cases to trace such causes in the early stages, due to the fact that most ulcer patients cannot give an accurate account of the very early symptoms, due to the apparent little distress in the early stages of development.

CASE NO. I. HOSPITAL NO. 36519.

Mr. F. W. C., American, white, married, conductor, age 61, was admitted to the University Hospital on October 7th, 1931. Complaining of pain in the right hyperchondrium, nausea and vomiting after eating, constipation, difficulty in voiding and palpitation. The onset of his trouble dated back ten years, at which time he noticed pain just below the costal cartilage. He would get relief after taking soda at this time. The pain would last only a few days and then disappear, to reappear again every two or three months. Seven years ago he had an attack which lasted for over two months. Since then the attacks have been coming more frequently, and more severely. About September 1st, 1931, he had another bad attack of pain, was nauseated and vomited. Since then he has had a continued knowing, burning sensation in his epigastrium.

Past diseases: measles, mumps, chicken pox, and influenza ten years ago, and stated that up to the time he had influenza he was never bothered with his stomach.

The physical examination was negative with the exception of rigidity and tenderness in the upper abdomen.

The family history reveals that one sister and one brother died from carcinoma, the brother from carcinoma of the stomach and the sister from carcinoma of the uterus. The father dies from anemia and the mother from senility.

Urine examination was negative. Blood Hb 95%; R. B. C. 4,620,000; W. B. C. 8,000; Poly. 75%; Lymph 25%. Gastric analysis showed:

Free	Total
2	22
5	31
15	55
26	76
39	71
50	77

X-ray showed an obstructed lesion in the pylorus, and was diagnosed as a probable ulcer.

On October 28th an operation was performed. The stomach was viewed and it was noticed that on the duodenal side of the pylorus there was an indurated area about two inches in length by one centimeter in width, which gave the impression of an old chronic ulcer. A gastro-enterostomy was performed, and the wound closed. The patient made an uneventful recovery, and was dismissed in fourteen days, free from any symptoms.

DISCUSSION: An outstanding feature of this history is the influenza, which he stated left him with stomach trouble. It is possible that the stomach was damaged at this time and precipitated an ulcer. The cause of the chronicity may be attributed to a nervous manifestation which acted upon the gastric secretions, causing hyperacidity as a secondary reaction in the chronicity. It is also possible that the ulcer was present in an inactive stage before he had influenza and that the disease stimulated the ulcer into activity.

C A S E N O . II. HOSPITAL NO. 32822.

Mr. W. A., American, white, auditor, age 34, entered the hospital for the first time on August 27th, 1930, complaining of sever abdominal cramps and pain, and of generalized weakness.

Early in the morning on August 27th, on the way to Omaha by car, he was seized with very severe cramps which doubled him up, for a few minutes. This was the first attack of its kind he ever had. He had complained at times of not feeling well and of some abdominal discomfort, but no sever cramps or pain. At times he would have a slight aching sensation in his stomach, but this had been going on# for several years previous. About one hour after this sever attack, he was seized by another similar attack, which left him with a burning sensation in his stomach. He returned to his home about eight in the morning, and while standing in the kitchen he was seized by severe abdominal apins, and he fell to the floor. He got up and walked to the bed room and went to bed. He noticed that after this last attack his whole abdomen was rigid and hard as a rock. A county doctor was called in at this time. He pumped his stomach and gave him a quarter of a grain of morphine. No blood was found in the stomach at this time.

On physical examination, the abdomen was falt but the bodies of all the abdominal muscles were protruding in a state of extreme contraction. On palpation, the stomach was rigid and board-like, and produced pain to the patient when pressure was exerted on the abdomen. Over the right rectus, definite tympany could be made out. The eyes, ears, nose, chest, heart and ex-

tremities were all normal. His teeth were in very poor shape, many being missing, many decayed roots present. Before he left the hospital he was advised to have a complete alveolectomy, which was to be done at the hospital, but the patient refused.

The family history was negative. All were living except his mother, who had died from brain hemorrhage.

On entrance, his urine showed a two plus albumin. No casts or blood was present. On dismissal his urine was negative. Blood count, 90% hemoglobin; R. B. C. 4,200,000; W. B. C. 10,700; Polys 55%; Staff 20%; Young 14%; Lymph 7%; Mono 4%. The Wasserman was negative.

An X-ray study of the chest and sub-diaphragmatic region in setting up posture, showed air between the diaphragm and the liver on the right side consistent with a rupture of the bowel. The costo-phrenic angles were clear. From the X-ray findings with the clinical symptoms, a diagnosis of perforation was made.

The patient was rushed to the operating room, where a high midline incision was made, extending from from the ensiform cartilage to the right of the umbilicus. On exposing the stomach, a small perforation was seen on the anterior wall of the pre-pyloric end of the stomach, from which little bubbles of air were escaping. The peritoneal cavity contained a straw colored fluid, which appeared slightly cloudy. No other pathology was noted. The perforation was closed, and the omentum placed in such a position that it would act as a protection for further seepage from the site of operation. Four rubber dams were placed in the region of the peritoneal fluid, and the wound

closed in the usual procedure.

The patient made an uneventful recovery, and was dismissed from the hospital in good condition, and free from any of the presenting symptoms.

DISCUSSION: In this case, again the initial cause of the ulcer cannot be traced to any one factor. It would fit best under a physiological condition, which may be anything causing disordered gastric secretions. It may also be classed under a nervous origin, since in going further into his personal history, it was found that he had left his wife on several occasions, and was chasing other women, and leading a high-strung life. The chronicity may also be assumed as due to infection from his teeth, since he had carried a mouth full of bad teeth for many years, which Rosenow and others have found will cause ulcers of the stomach in dogs and other animals experimented upon. It is also very probable that this ulcer was present at birth and was irritated by the above causes, and made active, producing ulcer symptoms.

CASE NO. III. HOSPITAL NO. 36804.

Mr. W. C., male, American, white, farmer, age 68, was admitted to the University Hospital on November 1st, 1931. Complaining of pain and distress in the epigastrium, chronic constipation, weakness, nausea and vomiting. He stated that he had suffered intermittent attacks of epigastric pain for the past thirty years, being more marked the last 20 years. The attacks occurred at irregular intervals and lasted two or three



days. The pain was not related to meals, but was relieved at times by eating food, and was always relieved by drinking soda water. For the past seven months his attacks have been more frequent, and have not at all times been relieved by drinking soda. On October 28th, 1931, he had the most severe attack he ever had, followed by very severe epigastric pains, nausea and vomiting. The vomited material contained partially digested blood. He stated that his bowels had not moved since October 28th. The stools were not tarry at any time during his attacks.

Previous diseases: Mumps, measles, and scarlet fever about four years ago.

Family history: Mother and father dead, cause-senility; wife dead, cause-pneumonia. Two brothers living and well. One sister died from carcinoma of the breast; another sister died from scarlet fever.

Upon physical examination, the abdomen showed marked rigidity and tenderness in the epigastrium; eyes reacted to light and accommodation; ears, throat, chest and reflexes were normal. All the teeth were extracted except two lower premolars, which were not in good condition.

On laboratory examination the urine was negative. The blood examination showed 86% hemoglobin; R. B. C. 4,600,000; W. B. C. 8,000; P 64%; L 33%; Eos. 2%; Bas. 1%. There was no gastric analysis run. An X-ray examination revealed an ulcer in the lesser curvature of the stomach. X-ray revealed a saccular out pouching from the lesser curvature of the stomach adjacent to the esophageal orifice, about four cm in diameter, and suggested an ulcer of very large size.

The patient was placed on a Sippy diet which completely relieved him of his symptoms, and he made a very satisfactory recovery while in the hospital. A check-up X-ray was made before he was dismissed from the hospital, which showed a decrease in the size of the lesion. Dismissed on Nov. 29, 1931.

Diagnosis: Gastric Ulcer.

DISCUSSION: The cause of the ulcer in this case is unknown. The only severe illness the patient had had was scarlet fever, ten years before he noticed any gastric symptoms. According to infection as a cause of ulcer, one might assume the scarlet fever as one of the causes, which produced enough toxin to cause a necrosis and ulceration of the stomach. Again assuming the ulcer was present at birth, one could as well see how the infection and lowered resistance could precipitate this ulcer and give symptoms of distress, such as he complained of.

CASE NO. IV. HOSPITAL NO. 34491

Mr. F. C., American, white, married, carpenter, age 57, entered the University Hospital for the first time on March 3, 1931, complaining of pain in the pit of his stomach, nausea and weakness.

He stated that he had been bothered with his stomach for the past 20 years. Eighteen years ago he had a sharp pain in his stomach and stated that at that time he felt sick to his stomach and went to bed. He ate eggs and drank milk for a few days and then went back to work. These attacks seemed to come in the fall of the year, and sometimes in the spring. Nine years later he had a very severe attack which required morphine. The

pains were severe in his upper abdomen, so much so that he vomited, but no blood. His stools were never black, but dark after each attack. Three years later he had another attack, but this time stated that he vomited blood. Since then he has been careful with his diet, eating a soft diet of eggs, milk, etc. He had poor teeth and had them removed as they decayed and gave him trouble; otherwise his throat was negative. Seventeen days prior to entrance, he was awakened at midnight with sharp shooting pains in his abdomen hyperchondriac region. The next day he went to see a doctor who gave him some medicine. Since this attack, he has had a burning, aching sensation in his stomach.

No previous illness, except diphtheria 22 years ago, at which time he was very sick.

His family history is negative.

The physical examination was negative, with the exception of his tonsils, which were enlarged and inflamed, and for the remainder of his teeth, which were decayed and in poor condition.

Laboratory: Urine negative; Blood, W. B. C. 1,2000; R. B. C. 4,400,000; Poly. 57%; Lymon, 13%; Eos. 4%; Mono, 6%.

Spec.	1.	2.	3.	4.	5.	6.
Free	0	0	0	0	0	0
Total	54.	55.	37.5	33.	0	32.0
Occult B.	(-)	(-)	(-)	(-)	(-)	(-)

Vomit contained bile, no blood or free acid. Wasserman was negative. Stool was negative for blood. The X-ray picture revealed an ulcer in the duodenum cap.

A sippy diet was given with some relief. On March 16th he was operated upon and a gastro-enterostomy performed. The pylorus was infected and there was an area of fat necrosis about the pancreas. The diagnosis of duodenal ulcer was confirmed at this time.

The patient made an uneventful recovery. He was given the Sippy treatment and was dismissed on April 4th feeling well, and relieved of all symptoms of pain and distress.

**CONCLUSION:** From the history of diphtheria about a year before his stomach complaints, one might consider diphtheria as a cause of his ulcer, that is, assuming that infection plays a part in the production of gastric lesions, which Rosenow and others have found in animals experimented upon.

#### CASE NO. V.

Mr. E. W. B., American, white, painter, male, age 45; farm hand, entered the University Hospital for the first time on February 12th, 1931. Complaining of a steady burning pain in the epigastrium. The onset of his trouble started nine years ago, at which time he stated that he ate some fried liver which poisoned him. He was in bed at this time for three weeks, and incompatiated for work about four months. During these four months he stated that he could not eat heavy foods because he would feel sick to his stomach. Three years ago he had another attack of vomiting and pain in his stomach which he stated was due to food poisoning, but upon questioning him as to his food, he was unable to recall what he had eaten at this time. Since this last attack he has complained of epigastric distress more

or less, which came on about two or three hours after meals. This distress became more often and more severe, being of a burning sensation. A year ago last July 4th, while he was visiting in a town with friends, he had a sever attack of abdominal pain. He vomited up his dinner and was put to bed. He continued to vomit all that day. The next day he started home and stated that he had another vomiting spell while on the train. Since that attack, he has had a continued burning distressful feeling in his stomach, and would have expulsive attacks of vomiting at any time. He did not know if he had vomited blood, but thought he did at times. I asked him if he had ever had any stomach trouble previous to the time he was poisoned by liver. He stated that he never had, and that he never knew he had a stomach.

On entrance, the physical examination was negative, other than distress in the upper abdomen on palpation. His teeth, throat, chest and reflexes were normal.

Laboratory examination revealed the urine to be normal, and the blood count was within normal limits. Gastric analysis showed no free hydrochloric acid, and total acid 13. Occult blood was present in the gastric contents of four different tests. The stool showed positive blood on three tests. On X-ray examination, an ulcer was diagnosed within the pyloric area.

The patient was placed on a Sippy diet, which has relieved him of his gastric distress. He stated that he was feeling fine and was ready to go home at any time.

DISCUSSION: It seems probable that in this case, the

onset of his ulcer may be traced to his attack of poisoning that he had nine years ago. At that time he probably had a severe gastritis with erosion of the stomach mucosa, followed by necrosis and ulceration. He stated that he was a nervous, high strung man, and that when he had a job painting, he would hustle and worry until the job was done. This nervous condition, and the fumes from paint and handling lead, may account for the chronicity of the ulcer.

CASE NO. VI. HOSPITAL NO. 35109

Mr. F. H., American, white, farm hand, age 50, entered the University Hospital for the first time on May 18, 1931, complaining of nausea, vomiting, constipation and soreness in the abdomen. He stated that he was well until eight years ago, at which time he began to have attacks of pain in the epigastrium, which was followed by vomiting. He continued to have these attacks for a year. He consulted a physician and was taken to the St. Joe hospital, where he had a gall bladder drainage. He was discharged in fair health, but one year later he had a recurrence of his symptoms, but added jaundice, which he did not have before. He was again operated upon at Yankton, S. D., and had his appendix removed this time, which was said to have been adherent to the liver. Numerous adhesions were present about the liver, which were removed. He was well for a time following the operation, but because of some complication, he was operated upon again by the same surgeon, who loosened some adhesions in the left lower quadrant. He remained quite well, except for occasional attacks

of distress followed by jaundice. One year ago he became worse, vomited as before, and had pain in his stomach. He continued to get worse, vomiting every day before entrance. He lost about twenty-five pounds in the last year, and was unable to work. The vomiting occurred about three hours after meals. The pain was described as a soreness made worse by exercise. No particular food caused the distress. He never had a gastric hemorrhage that he could remember. The ph

The physical examination was apparently negative. His upper abdomen was tender upon pressure, especially over the gall bladder area. The throat, chest, and reflexes were normal. Eyes reacted to light and accommodation? His teeth were negative.

Laboratory: Urine was negative. Blood count was within the normal range. Gastric analysis showed a low free and combined acidity. The Wasserman was negative. An X-ray showed a deformity of the duodenal bulb, and a gall bladder dysfunction.

On account of his persistent vomiting, he was operated upon. A routine upper rectus incision was made. The stomach delivered readily, and upon examination a large white scar was seen, apparently well healed, on the posterior superior aspect of the junction of the pylorus and duodenum. The gall bladder was adherent to the liver, stomach and large bowel, and showed considerable scarring in the wall of the bladder and the liver. A gastro-enterostomy and a cholecystectomy was performed at this time.

The patient made an uneventful recovery, and was dismissed from the hospital on June 19th, with no symptoms of

vomiting or distress,

DISCUSSION: From the history of first a gall bladder disease and later an appendicitis, one could assume that the cause of the ulcer was due to an infection, which caused a peritoneal irritation resulting in pylorospas, through irritation of the vagus and sympathetic nerves. This case well fits the theory of Deaver, J. B., who believed that peritoneal irritation may cause spasm of the pylorus, accompanied by gastric hypersecretion, favoring the development of ulcers of the stomach and duodenum. This same condition could also irritate an old ulcer which may have been present at birth, and produce symptoms of ulcers due to the ulcer again becoming active.

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