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PATHOGENESIS OF PEPTIC ULCER

SENIOR THESIS

UNIVERSITY OF NEBRASKA

COLLEGE OF MEDICINE

THEODORE LOKEN

1932
PATHOGENESIS OF PEPTIC ULCER

The definite history of Peptic ulcer dates back about one hundred years, when the French pathologist Cruveilhier, described ulcers of the stomach, accurately, for the first time, as a pathologic entity, definitely distinguishing it from carcinoma of the stomach. The German pathologist, Rokitansky, later presented the subject fully. These men emphasized the importance of the corroding or digestive action of the gastric juice in the etiology of the condition and later Queeneke, who coined the term "Peptic Ulcer", emphasized this fact.

Some of the other early men, who attempted to explain the etiology, were Virchow, who catered to the anemic theory, and Lebert, who experimented with the injection of pus, intravenously and produced acute ulcers of the stomach. In 1840, Long published his observation of burns as a cause.

A few general statements before entering on the definite etiology. The term "Peptic Ulcer" includes not only gastric but Duodenal and peptic ulcers of the lower end of the esophagus and post-operative marginal and jejunal ulcers.

Peptic ulcer, according to A.D. Devon, occurs in at least 10 to 12% of the population. More than ninety percent of the gastric ulcers occur in that portion of the stomach, which Waldeyer first described as the Magenstrasse or the stomach street, the portion that extends from the esophagus along the lesser curvature to the pyloris. It is the most
vulnerable part of the stomach. Its mucus membrane differs from that of the rest of the stomach. It is laid down in longitudinal folds. Its blood vessels are more like end-arteries. It is significant that gastric and duodenal ulcers occur only where the tissues of these structures are exposed to the digestive action of the gastric juice. In approximately 95% of all cases of ulcers of the duodenum, the lesions are located in the first inch and a half. The majority of these are about one-half inch beyond the pyloric ring. Only 50% of the clinical ulcers of the duodenum develop beyond the first two and one-half inches of the duodenum. The farther away from the pyloris, the less frequent is the lesion. The anterior wall of the duodenum is the most common location of the ulcer, but any portion of the duodenum or its entire lumen may be involved. Ulcers of the duodenum or stomach are usually single; however, post-mortem records show that in more than 20% of the cases, two or more ulcers are present. Old ulcers are found side by side or in different locations, likewise, healed scars and open ulcers are found co-existing. The size of the ulcer may vary from that of a pin-head to an ulcerated surface involving the greater part of the organ. Ulcers may be superficial, involving the mucosa and sub-mucosa or extend to a greater depth, through the muscular layer and eventually the peritoneal coat may be involved.

The anatomy of the stomach, gross structure: The first
coat is the peritoneal or Tunica serosa, which forms the outer layer. Then, the muscular coat or Tunica muscularis, which progressively increases in thickness between the cardia and the pyloris. All three muscular layers are found at the pyloris. The next layer is the submucosum, a loose, areolar tissue, which becomes thick or thin, depending upon the amount of distension of the organ. The last layer or the mucosa is a single layer of columnar epithelium.

The blood supply of the stomach: There are two arterial anastomotic circles, which form along the lesser and greater curvatures. The arch about the smaller curvature is formed by the anastomosis between the right gastric (branch of the hepatic artery) and the left gastric (branch of the celiac axis) arteries, which anastomose in the region of the incisura angularis. The large circle or arch, along the greater curvature is formed by the right gastro-epiploic (branch of the gastro-duodenal) and the left gastro-epiploic (branch of the splenic artery) arteries, which anastomose near the pyloric area. We note that the upper part of the stomach has the best blood supply as it has the more and larger branches, namely, the left gastric and the left gastro-epiploic arteries and the vasa brevia (branches from the splenic artery direct to the greater curvature), while the pyloric area is supplied by two branches, only, the right gastric and the right gastro-epiploic. The left gastric arises from the celiac
axis as a main artery, also the left gastro-epiploic and the vasa brevia are large branches of the splenic. So we see, the upper stomach has a blood supply directly from the celiac axis. The pyloric area has only the two arteries and both of these are smaller branches of the hepatic artery, therefore we may say that the pyloric area is somewhat anemic as compared with the rest of the stomach. Ralph W. Elston relates in his article that in the lesser curvature the finer branches which pierce the submucosa are scarce in number and tortuous in character as proved by the injection of dyes. They anastomose infrequently and are essentially terminal vessels as far as the function is concerened.

The various theories of etiology will now be considered. The aim of this paper is to review the various stated causes of peptic ulcer and to arrive at the most logical factor if possible and wherever possible, contradictory facts and statements will be given so as to exclude that theory or to prove that the theory is still contested.

The first etiological theory that we wish to consider is that of local anemia or malnutrition as presented largely by Ralph W. Elston. Anatomically, there is as has been stated, an anemic area about the pyloric end of the stomach on its anterior border as compared with other portions of the stomach. Elston goes on to state that the pyloric area is subject to frequent deep, muscular contractions, which reach the maximum intensity as the pyloris is approached and will
naturally compress these small and scarce vessels. Refilling will then take some time, allowing for a period when a large area has temporary anemia. Furthermore, the tortuosity of the vessels and the frequent trauma by contraction and the more or less mechanical injury to their walls by these contractions all favor interference to the circulation by reason of easy blocking and are very liable to favor foci of anemia due to the terminal nature of these vessels. Praevol, as quoted by Elston, is of the opinion that there is a familial tendency toward anomalous scarcity of small vessels in the pyloric area. A further factor is that the stomach tends to sag and put tension on the vessels, thus reducing their lumen when the individual is in an upright position. This has been shown by hardened specimens. The thickness of the muscular coats in the various parts of the stomach is another factor to be considered. The fundus is relatively thin-walled, with oblique fibers while the pyloric area has thick longitudinal and circular fibers, which are necessary for the firm contraction, but which may work havoc on the small vessels by compressing them. The other layer, submucosa, is also thicker and firmer in texture. The mucosa of the pyloric area is thicker and more closely attached to the submucosa, with numerous convolutions than at the fundus. The longitudinal mucous folds in the lesser curvature are on tension, while they are relaxed in the fundus along the greater curvature.
It is not very probable that there is sufficient anemia in this area, if there is no damage as thrombosis or embolus or spasm of the vessels. These factors will be considered now under the vascular theory. This theory originated with Virchow and Cohnheim, who advanced the theory that peptic ulcer is due to an embolus or a thrombus interfering with the local circulation, leading to infarction of the gastric area supplied by the vessels and exposing it to digestion by the acid secretions. Some of Virchow's pupils, notably Houser and Cralin, are still of the opinion that in almost every case of peptic ulcer, the chief causative factor is a localized blood vessel disease producing nutritional disturbance. Cralin obtained his experimental evidence to prove that in most cases the arterio-sclerotic vessels in the vicinity of the ulcer is the primary cause, from individuals who died of intercurrent disease at an age when general arterio-sclerosis is common. It is also likely that the arterio-sclerotic changes in the blood vessels in the vicinity of the peptic ulcer may be secondary to the ulcer, and not its cause. Pathologists very seldom find arterio-sclerotic changes in the gastric vessels even in cases of general arterio-sclerosis. Diseases where the changes in the vascular system are rather common such as Lues, Thrombo-Angitis-Obliterans &c, gastric ulcer is not a very common accompaniment with the exception of the so called purely
Syphilitic ulcer. Syphilitic gastritis plays little if any role as an etiologic factor in peptic ulcer. The reason is that the anacidity or achylia that is generally present in these cases prevents their development. The corroding action of the Hydrochloric acid may play the secondary role in digesting the malnourished tissue thus eventuating in a ulcer. The vascular theory is not generally accepted, yet it cannot be abandoned because, without disturbance of local nutrition, the occurrence of ulcer cannot be conceived. The existence of a definite pathological change in the blood vessels such as arteriosclerosis or an embolus need not be present. A purely functional disturbance of localized nature, may so spastically close the vessels as to interfere with blood circulation. These functional disturbances are favored by a number of factors, very important among which are, the anatomical position of the vessels and the nature of their nerve supply. The anatomical location of the vessels is alone, insufficient to explain why emboli should lodge in them, in only certain individuals and not in others. The embolus is certainly not carried there from some distant gland or infected thrombus as is the case in multiple erosions of the stomach in severe infections and sometimes after operation. There is also no reason to assume that a local disease of the blood vessel wall or some chemical change in the blood, exists locally, which would cause the formation of thrombi. There is left only one possible or
probable explanation of the impediment of circulation in these localized blood vessels and that is spasm. Spasm is a highly probable factor in the emotionally unstable patient.

The most universally accepted theory is that of hyperacidity or hypersecretion. Considering the distribution of the secreting glands of the stomach, we note that the pylorus is essentially an alkaline secreting area, while the fundus is essentially acid. Pepsin secreting cells are also in the fundus. The acid secreting glands in the lesser curvature extend only about 60% of the distance down from the cardiac orifice to the pylorus, as compared with the greater curvature where the acid glands extend at least 80% of the distance. The acid would therefore strike the demarcating cells, the alkaline cells, earlier on the lesser curvature than on the greater curvature as the distance to travel is less. Likewise the regurgitated alkaline duodenal juice will strike the acid cells on the greater curvature before those on the lesser curvature for the same reason. Thus, theoretically, these demarcating type, alkaline mucus secreting cells, are the first to receive acid and the last to be alkalinized by regurgitation. Boldyoff in his experiments has proven exclusively that the hydrochloric acid concentration is always secreted at a constant of 4.4 to 5%, and if it varies, it is because of reduction by other substances. He thinks and alleges that the alkaline duodenal juice normally
regurgitates back through the pylorus and neutralises the acid back to the normal level. Experimentation on dogs seemed to prove this to be the normal physiological method of controlling the excessive acidity of the stomach. This view is also held by J.B. Muclin, Alvarez and others. We shall make further mention of this in considering Alvarez’s views on the mechanism of the digestive tract. In Oxford Medicine it is stated that it is believed that the local defects resulting from malnutrition or necrosis, would practically always undergo rapid repair and be without serious clinical symptoms in absence of gastric corrosion. It is significant as already stated that the duodenal ulcers are located within the first one and one-half inches of the pyloric orifice. The duodenal bulb retains the gastric content longer than any other portion of the duodenum. There is definite experimental evidence to support the role that hydrochloric acid plays in the production of ulcer. C.B. Morton produced experimental ulcers in dogs which substantiate acidity as a definite cause of the lesion. He first produced experimental ulcers in dogs that were normal and then in dogs in which the alkaline duodenal secretion had been sidetracked so that it could in no way enter the stomach. He did the so-called surgical duodenal drainage which entailed the isolation of the duodenum from the stomach and the upper jejunum is cut
across and put into the terminal Ilium, while at the same time, below where it was cut, it is anastomosed to the pyloris. In this case, the gastric contents pass into and directly against the jejunal wall, while the alkaline duodenal content passes directly into the ilium close to the caecum. Results of the experiment reveal that in the dogs in which the above operation had not been performed, allowing regurgitation of the duodenal fluid back into the stomach, the experimental ulcers healed spontaneously, whereas in dogs on which the operation was performed, so that the alkaline duodenal secretion could not enter the stomach, the ulcers on the lesser curvatures of these dogs did not heal but became chronic just like those in the human. These healed by re-introducing the alkaline duodenal juice by gastro-jejunalostomy and pyloric exclusion, protecting the ulcer from the acid chyme. In 100% of cases, a chronic jejunal ulcer was formed where the stream of acid stomach content struck against the intestinal wall. Further evidence is that the jejunal ulcer in man does not occur until the gastro-jejunal enterostomy has been formed, allowing acid chyme to pass directly into the jejunum instead normally being neutralised by the bile, pancreatic and duodenal juices. These facts support the theory of the importance of acid in the production of ulcer and likewise the importance of the regurgitation of the alkaline duodenal secretion in their
prevention. The experimental work on dogs was originally done by Mann and Williams.

It is now assumed that the opening and closing of the pyloris is accomplished by the contractions of the stomach and the chyme, which forces the pyloris to open also allows the alkaline duodenal secretion to regurgitate back into the stomach. It is stated by Devine and Kline that if the acidity becomes high due to lack of duodenal regurgitation, ulcer is apt to result. A stricture or spasm of the pyloric orifice would hinder regurgitation. Any factor which increases acidity, certainly must be considered as a contributing cause.

Smoking, according to Gray, produces increased acidity and is therefore an etiological factor. In his study of 1000 cases, he found that smoking caused hyperacidity in one third of the series with clinical improvement after reduction to normal acidity after cessation of smoking.

B.W. Saunders has noted that ulcer patients are invariably of the asthenic type with narrow costal angle and similar shapp duodenal angle, which anatomically, should limit bile regurgitation in the first portion of the duodenum. This may be of importance.

The relation of hyperacidity to the production of erosion and even ulcer is exemplified in those rare cases in which Mickel's diverticulum is present and has gastric
mucosa. In a Mickel's diverticulum, lined with gastric mucosa, acid secretion results when the gastric secretion is stimulated. This acid secretion, erodes and eventually digests the mucus membrane and leads to deep ulceration and perforation. Living tissue can therefore be digested by acid secretion and a thrombi in the vessels with resulting infarction of surrounding areas need not be present.

The question arises as to why these erosions do not occur in all parts of the stomach. Aschoff and his pupils say that the lesser in the lesser curvature, on the anterior and posterior walls, the mucus membrane appears in large folds as an anatomic protection against erosion. Furthermore, the mucus secretion is here more pronounced, tending to neutralize the acid. In the areas where erosion and eventual ulcer formation do occur, the mucus membrane is not in folds and has therefore less mucus secreting surface thus being less protected and more disposed to erosion.

Aschoff and his pupils as quoted by Held and Goldbloom, injected Histamine into fasting rats and caused an increase in the gastric secretion and hyperacidity. They were able to produce peptic ulcer of varying depths.

The question arises: Why does the erosion and eventual ulcer formation occur in some and not in others? Buchver answers that so long as the secretion in the corpus of the stomach and in the pyloric glands and in the Brunner glands is normal, no ill effect of acidity can result. When,
however, abnormal psychic influences disturb the gastric secretion or there is abuse by food or by some other factor erosion and eventual ulcer formation will result.

Now, there arises the question as to whether there is a hypersecretion in cases of ulcer. E.S. Emery, R.T. Monroe in their gastric analysis of 414 patients suffering from ulcer, found that 50% of the patients had free acid of 50 points or more and that 25% of the total had a free acidity of 70 points or more. These findings have been corroborated by other workers. The majority of the patients may be said therefore to have hyperacidity. It is true that ulcer may occur in achylia gastrica but the ulcer may have been present before the achylia developed. It is also probable that an ulcer in achylia may have been caused by an infection, which occurred because of the achylia.

G.W. Crile strongly supports the acid theory but approaches it in a little different light. He says that a peptic ulcer is never found among the lower animals, is rare in the lower races of men and in the higher races, select the highly organized, active individual. He points to the incidence of ulcer among medical men as illustrating his point. He goes on to say that ulcer is a unique lesion, which, with due regard to the exceptions to the rule, in the last analysis is caused by hyperacidity. Methods of treatment, medical and surgical, are directed at controlling acidity. The treatment that maintains the lowest acidity is the one which yields the best results. Crile feels
that the central nervous system and the endocrines control the motility and secretion of the stomach and that a disturbance in their relations and function is responsible for the lesion. Personality and temperament are the products of the interaction of the nervous system, the thyroid and the adrenal glands. Since this is true, one would expect an increased acidity in hyperthyroidism. That this is the case is well known. One would expect low acidity or anacidity in Myxedema and this is the case. In addition, the incidence of peptic ulcer in cases of hyperthyroidism is higher than the average incidence, moreover, of equal significance is the fact that in hypothyroidism, peptic ulcer does not occur. The thyroid gland then, has the power of controlling gastric acidity. It follows that the influences that are known to cause changes in the activity of the thyroid gland would be expected to modify the incidence of peptic ulcer. In the winter season, thyroid activity is increased and therefore peptic ulcers are more active in the fall winter and spring. The activity of the thyroid gland is increased by infection especially focal infections. Peptic ulcer is effected by focal infections. The emotions, worry, anxiety, etc., increase the activity of the thyroid gland and they aggravate peptic ulcer. Crile, in conjunction with several other investigators tested the relations between the thyroid and adrenal glands and peptic ulcer.
It appears that the adrenals have considerable influence on the motility and secretion of the stomach. The principal does not stop with the thyroid and adrenals but extends to the great driving master of the organism, the brain and nervous tissues. Thus ulcer may be attacked by control of the mental and emotional processes. In this direction, experimental results were impressive. The gastric function of the dogs gave a most striking relation to the mental and emotional stages. The emotional state of the animal, completely dominated the formation of gastric juice as did the injection of adrenalin. Crile’s hypothesis, therefore, is: 1. Hyperacidity is the actual cause of peptic ulcer. 2. The thyroid, the adrenals and the nervous system completely dominate gastric activity. His argument is therefore, in short, that hypermotility, hyperacidity are essential factors in the development of ulcer and that this hypermotility and hyperacidity are in turn controlled by the nervous system, the thyroid, suprarenals, and that these exhibit a reciprocal relation. Crile reports five cases that underwent partial thyroidectomy and suprarenalectomy for intractable recurrent ulcers of the stomach, followed in each case by decreased gastric motility and disappearance of gastric symptoms and gastric secretion. Among other interesting things, he found by experimentation that thyroid feeding caused an increase
in the total quantity of gastric juice. From observations made by others, the author learned that in cases of hyperthyroidism there is an increased motility of the stomach, an increased intestinal peristalsis, while after thyroidectomy, the gastro-intestinal motility returns to normal. Emotional states are frequently associated with hyperacidity and hypermotility and these two are associated with ulcer. This is a possible mechanism by which the gastric ulcer may be produced.

The thyroid gland of itself does not initiate increased activity. It waits at its station to be stimulated. The stimulus comes through the sympathetic system and the most powerful control of the sympathetic system is in the adrenal glands. One would suppose therefore that if the adrenal factor could be controlled, the thyroid would in turn remain inactive to a certain degree. It would follow, therefore that division of the nerve supply of the adrenals on both sides should lead to immediate improvement. In Crile's experiments on animals, it was found that removal of one adrenal gland did not produce as definite results as were secured in the thyroid experiment.

Another widely accepted theory as to the cause of ulcer is that of infection. E.C. Rosenau is probably the greatest exponent of this view. He has shown that streptococci can be demonstrated in the ulcer area of the stomach, that streptococcus infection of the teeth tonsils and nose, favor
streptococccic stomach ulcers, and that the organisms isolated from the ulcer and from demonstrated foci (teeth and tonsils) each have an affinity for the stomach mucosa and produce ulcers on the lesser curvature, when injected into the blood stream. The ulcers produced by the injection of streptococci, resemble those in man, in location, growth and microscopic appearance and in that they tend to become chronic and perforate, causing severe or fatal hemorrhage. Streptococci, having a characteristic affinity for the stomach and duodenum have repeatedly been isolated from foci of infection in patients with ulcer and from the ulcer themselves. They have been isolated from ulcers in animals and the ulcers have again been produced on their reinjection. Filtrations of these cultures show no specific tendency to produce ulcers. So Rosenow feels that the necessary requirements have been fulfilled to warrant the conclusion that the usual ulcer of the stomach and duodenum in man is primarily due to localized hematogenous infection of the mucous membrane by streptococci. Rosenow feels that the ulcer is due to localized infection and secondary digestion.

ElW. Saunders has also done some fine work along this line. A summary of his facts, which favor the infectious etiology of ulcers of the stomach are: 1. Streptococci have been isolated from 19 gastric, duodenal and gastro-jejunal ulcers and proved to be identical and specific by
differential culture tests and by agglutination and cross agglutination and agglutinin absorption. 2. Patients suffering from ulcer, have this organisms specific agglutinins in their blood stream in 100% of cases, while those suffering from any other streptococcus infection fail to agglutinate it or only in low titre. 3. Organisms are apparently present in lesions in immediately prepared Levalatis tissue sections. 4. Organisms undergo dissociation from S (virulent form) to R (non-virulent form) under artificial cultivation and the possibility of them doing likewise in vivo has been demonstrated. 6. The S form will not grow in bile of low dilutions and the U (intermediate form) rapidly become R. under bile cultivation. 6. Surgical treatments which turn bile to ulcer areas give the best results. It is possible that the protective substance in the bile, whatever it is has been been removed and that the normally, non-virulent organisms become virulent. This same thought is stressed by Alvarez. Attempts are now being made to maintain the stability of the S type and to convert the R type back to S. E.W. Saunders says that one can only surmise that in ulcer patients, there is some deficiency in the bile or that there is not enough bile for protection or there may be failure of regurgitation of bile into the first portion of the duodenum and stomach.

There are over 100 reported cases of perforated duodenal ulcers in marasmic babies, from one to six months
of age. Helmholtz has demonstrated the infectious origin of many of them but the babies certainly do not have any foci of infection at this early age. But there could be a deficiency in the physiology of the bile which would permit the growth of gastric streptococci.

Another able worker in this field is Makamura. He also says the organs in which the primary foci are usually found are the tonsils, teeth, sinuses, bladder, intestine, seminal vessels, and prostate. He studied the bacteriology of extirpated tonsils and the localizing power of bacteria isolated in a series of selected cases of arthritis and ulcers of the stomach, observed in the Mayo Clinic from May 1, 1922 to June 30, 1923. The cases for animal experimentation were carefully selected. Only those were studied in which tonsils were septic and in which active symptoms of ulcers of the stomach had developed a short time before or cases with recent exacerbations of symptoms. One of his illustrative cases of ulcer of the stomach follows.

A man, aged 40, came to the clinic, November 4, 1922 for stomach trouble, of twenty-five years duration, symptoms, intermittent, were indigestion, gas, dull pain, occurring about one hour after meals, nausea, vomiting, belching, occasionally hemoptysis and tarry stools. The teeth were found septic. In June, 1921, the patient came to the clinic and a posterior gastro-enterostomy and appendectomy were performed and special diet prescribed. The patient
remained well until October, 1922 (16 months) when the old symptoms recurred. Roentgenograms revealed ulcers along the lesser curvature of the stomach and infected teeth. In January, 1923, the teeth were removed. On Feb 3, 1923, tonsilectomy was performed. By Feb, 12, 1923, nine days after tonsilectomy, and 34 days after removal of the teeth, symptoms referable to the stomach had disappeared and roentgenograms of the stomach were negative. This case strongly suggests the importance of focal infection as a cause of ulcer.

His animal experiments and results reveal hemorrhage and ulcer or both of the stomach with no lesions elsewhere, in two rabbits injected with pus from tonsils, in the two injected with primary culture in glucose brain broth and two injected with sodium chloride solution, washings of apices of two infected teeth. Four controls, two injected with sodium chloride and two with glucose brain broth did not have lesions.

A summary of results in the ulcer experiments: Of the nine patients with gastric symptoms, selected for animal tests, five had undoubted ulcer findings and four had severe hemorrhages, presumably due to acute ulcer. Gross evidence of tonsil infection was found in all. Streptococcus viridens predominated in cultures injected into seven of the animals and slightly hemolyzing streptococci in the two others. Elective localization occurred in all but one of the former and in one of the latter.
Strains from nine patients with ulcers of the stomach were studied experimentally. Seventy three rabbits were used of which seven were controls, sixty-six rabbits injected with strains from tonsils, 46 (70%) had hemorrhage or ulcer or both in the mucous membrane of the stomach. Only one of the nine strains gave negative results. Lesions occurred in the pyloris in 30 (34%) of the positive rabbits, along the lesser curvature in 18 (27%), along the greater curvature in 10, and in the fundus in 13. This incidence corresponds in general to the incidence of ulcer in these regions in man. Streptococci, similar to those found in pus from the tonsils and in extirpated tonsils were isolated from both hemorrhage and ulcerated areas in the stomachs of the rabbits. In three of the animals, streptococcus and micrococcus tetragenus also were found. Cultures from normal mucous membrane, if thoroughly washed were generally free from streptococcus and only occasionally showed bacillus Coli and bacillus subtilis.

Besides lesions of the stomach, hemorrhages and vegetations in the right tricuspid valve in four rabbits, hemorrhages in the lungs in five, turbid joint fluid in nineteen (from ten of which streptococci were isolated), hemorrhagic lesions of the kidneys in three, hemorrhage in the skeletal muscles in one were found. These ulcers were about .25 cm wide and varied from .25 to 5 cm in length. They were usually superficial and covered with blood.
Some occurred in groups of from three to five and when the blood clot was rubbed off, only slight defect in the epithelium could be detected.

The exceptionally large number of punctate hemorrhages in the mucous membrane in animals injected with strain from patients with recurring gastric hemorrhage, without demonstrable ulcer and prompt disappearance of attacks following removal of the patients tonsils, indicate that focal infection and elective localization may be the cause of this somewhat obscure condition.

Conclusion: The tonsils of patients, suffering from ulcers of the stomach and joint arthritis, commonly harbor streptococci, which tend to localize in the mucous membrane of the stomach and joints of animals producing ulcers and arthritis in them. This is not true of the tonsils of normal persons. Hence, it may be concluded that foci of infection harbor streptococci having elective localizing power are important factors in the primary cause and persistence of ulcers of the stomach and arthritis.

The theory does not meet with universal concord. J.W. Held and A.A. Goldbloom say that a specific bacteriological cause cannot be simultaneously claimed for peptic ulcer. It is our belief that even streptococci with elective affinity for the stomach, are not the true cause of ulcer and that Rosenow's work is of the greatest value from the standpoint
of prophylaxis. If an ulcer exists, streptococci can prevent its healing or be the cause of more extensive ulceration.

Next, we will consider a debated causitive theory, that of imbalance between the vagus and sympathetic nervous system. Most of the material will be taken from El Simpson (9) and from experimental work by Slohnke. Also from some controversial work by Alvarez (2).

The vagus supplies the entire digestive tract to the level of the splenic flexure. The remainder is supplied by the sacral branch of the vagus autonomic system which functions similar to the main branch of the vagus. It is commonly called the nervi erigentis. The stomach musculature and secretory structures are activated by the vagus and are inhibited by the sympathetic. The actions of these two groups are antagonistic. The overtone of the vagus multiplies the physiologic action and is known as vagotonia, while overactivity of the sympathetic group is termed sympathetico-

(9) E. Simpson alleges that overactivity of the vagus is the cause of ulcer, through the development of: 1. hyperperistalsis, which may cause direct mechanical damage to the mucosa or by causing spasm of the pyloris with retention. This will allow the gastric juice to corrode the mucosa. 2. Hypersecretion. The increased acid is a factor as it digests the already mechanically damaged mucosa or a trophically damaged mucosa or by its direct action on the normal mucous membrane. In short, a vagotonia supposedly manifests itself in increased peristalsis, gastric spasm and increased
secretion with its resultant damage to the mucosa.

Simpson's trophic theory is based on the analogous function of the gastric mucosa, its physiological and particularly its anatomical construction with that of the buccal cavity and lips, as here it is common to have herpes which supposedly is a result of trophic disturbance. He thinks that it is reasonable to assume that herpetic eruptions may occur on the gastric mucosa and when once formed they may conceivably pass into well developed ulcers through the action of the gastric juice (acid) as this is increased secondarily by delayed emptying of the stomach, because of spasm of the pyloris which is hyperirritable due to hyperactivity of the vagus.

The experimental work by Slohnke is very interesting. He studied the effect of prolonged stimulation of the vagus on peristalsis and secretion of the stomach in dogs. The vagus was stimulated directly by Faradic current and observations were made through gastric fistulae and necropsy examinations. He found marked increase in secretion and blood supply to the stomach. Post-mortem examination demonstrated no pathology in the nerves but definite gastritis with superficial defects in the mucosa. He is not satisfied, however that he has found the cause as he feels that the beginning of an ulcer must be considered merely as a local damage to local cells. This pathological process need not
be specific. A variety of agencies, each effecting the physiological processes may be capable of producing damage, as bacteria, their toxins, toxic materials from faulty metabolism. This research thus confirms the possibility of hypersecretion and gastritis and not purely nervous influence as the factor in the production of ulcer. It cannot be said to be a factor in all cases.

A peptic ulcer syndrome is often found in young folks and young adults who have appendicitis and cholecystitis. These wrongly diagnosed cases comprise and indeterminate percentage of reported treated ulcers. Extra gastric disease may cause muscular spasm and tenderness that is found on examination as it is in ulcer cases. These symptoms and findings are due to pyloric spasm, retention and increased hydrochloric acid content. In Simpson's group of vagotonias, he found 87% who showed retention. This can be overcome by check study under the action of belladonnae. He feels that the pyloris is the most sensitive and therefore the first to show overtone. These pylorospasms may be transient when due to a mere overtone depending upon vagal overstimulation, or they may be persistent when due to some intra-gastric disease such as ulcer near the pyloris in either the stomach or duodenum. Pyloric spasm is usually found regardless of the site of the ulcer.

The vagotonic state persists after the healing of the initial ulcer and the neurogenic, secretory and motor disturbance
continues, which may account for the many recurrences of ulcer.

W. C. Alvarez is not so sympathetic toward this view. He says that men are satisfied that the two magic words "Vagotonia and Sympathectonia" explain everything. But he himself is not satisfied with this explanation. He emphasizes strongly the autonomy of the gastric tract and the importance of the local muscular mechanism. He has experimentally shown that the intestinal musculature has an inherent gradient of irritability, of rhythmic contractility, of metabolism and of tonus. This gradient of irritability decreases from above downward.

His experimental work demonstrated that after the preliminary shock wears off, digestion goes quite well after section of the vagi and splanchnic nerves. Excised stomach and intestine either perfused or placed in oxygenated Locke's solution will show a peristalsis and strong rhythmic contractions. In short segments of the bowel or even in bits of muscle from the wall, these movements are seen. It is clear then that the gastro-intestinal tract is largely autonomous, that is, it carries within itself, the mechanism essential to peristalsis and digestion. Extrinsic nerves undoubtedly have something to do with peristalsis both in health and disease but but the tract can get along without any outside help or interference. Function of the Auerbach's plexus possibly serves for conduction of stimuli and coordination of movements and probably to make muscles respond properly to stimuli coming
from the underlying mucous membrane. These stimuli are collected by Meissner's plexus and transmitted to Aurbach's by connecting fibers. Cannon, as quoted by Alvarez has remarked that peristaltic movements seem to be modified continually by the chemical nature of the intestinal content and we know that inflammation of the mucous membrane and the irritation of certain drugs will give a hyperperistalsis.

Other possible functions of the plexus may be to keep muscles from becoming too active or from contracting down into a hard knot, that it serves to bring about reflexes in the intestinal wall is unlikely, according to Alvarez because neither the anatomists or physiologists have been able to demonstrate the requisite nervous arc. Its principle function like nerves elsewhere is to expedite conduction.

In order to establish the autonomy of the gastric tract, it would be necessary to consider the properties of and peculiarities of smooth muscle but I shall not take time for that here. Suffice to mention one or two of the more important properties. Namely, 1. Smooth muscle in hollow organs responds to tension. Most of the motor activity of the stomach and bowel is brought about and regulated largely by internal pressure caused by food or gas. Cannon has shown that rhythmic segmentation in the small intestine is due simply to the presence of food and that those muscle fibers which are stretched, tend to contract. When contractions increase, the pressure in the neighboring segments is increased so that the process goes on. This reaction, according to Cannon
is purely local and does not depend on nervous control. 2. Smooth muscle shortens also under direct irritation, therefore we find spasmodic contraction of the cardia, pyloris, ilio-cecal sphincter and anus, when there is ulceration or inflammation, near by. We find hourglass contraction of the stomach opposite an ulcer. Some of the sphincter spasm that one sees with inflammations or ulcers in various parts of the gastric tract may be due to simply a greater irritability of sphincter as compared with the rest of the gut. The muscle fibers in the pyloric sphincter actually are more irritable than fibers of the rest of the tract (Alvarez).

Reversed peristalsis is probably pathological except toward the close of gastric digestion, when the duodenal content normally regurgitates into the stomach. Reversed peristalsis is physiological in the large bowel.

Presenting some of Alvarez views on the gradient theory. The contraction wave spreads out from muscle fiber to muscle fiber and there is little need for any assistance from nervous ganglia or centers. Animals open under salt solution demonstrate that the rate of rhythmic contraction varies from about 20 per minute in the duodenum to 10 in the lower ilium. Also short segments of the bowel will present a variation of rhythmic contraction inversely as the distance from the pyloris. The same is true of strips excised from the stomach. The fastest rate is found in strips from the lesser curvature near the cardia. The waves probably have their origin in the most highly rhythmic and sensitive area which is possibly
about the cardia on the lesser curvature, which may call the pacemaker for the stomach. Factors that alter the gradient are: 1. Irritable lesions in the muscle lining the tract, in the mucous membrane, in the serous coat, in the neighboring organs connected with the tract, as appendix, gall bladder, liver pancreas and Mickel's diverticulum. There may also be a relationship with inflammation and overactivity with vascular engorgement of organs lying close to the digestive tract, such as the uterus, urinary bladder, prostate, spleen and perhaps kidneys. As these lesions may effect metabolism and an increased metabolic rate will raise the rate of rhythmic contractions. 2. Ingestion of food with distention of the bowel by increasing the contraction which in turn increases metabolism. 3. Nervous stimuli: we have no data to show that the extrinsic nerves effect the metabolism, rate of rhythmic contraction. They probably depress the irritability so that the muscle will not respond to every stimuli. 4. Toxic depressions, the exact mechanism of which we do not know. 5. Drugs, of which little is known of the definite mode of action.

Most of the symptoms of the gastro-intestinal diseases can be shown to be due to disturbance in the mechanical function. Reverse peristalsis and its symptoms may be responsible for vomiting, regurgitation, heartburn, belching, nausea, coated tongue, foul breath, feeling of fullness after beginning to eat, globus, hiccoughs and biliousness.
After this introduction, we are ready to have Alvarez reaction toward the vagotonic and sympathecotonic theory. He begins by attacking the belief that the autonomic, vagi and sacral nerves, stimulate and the sympathetic fibers inhibit the intestines and that an imbalance of these is supposed to result in disease and that this imbalance can be diagnosed and corrected by the use of certain drugs, which are supposed to be elective in their action. He says that the whole foundation of these statements is very shakey and predicts the downfall of the theory in time to come. Although, he says, that in the main the vagus tends to stimulate and the sympathetic to inhibit the stomach and bowel, these effects are often transient and indecisive and not infrequently reversed. They vary with the strength of the stimulus and with the condition of the stomach. The first effect of vagus stimulation is generally a lowering of the tone. After from 15 to 60 minutes, there may be an increase of tone and activity which lasts for a few seconds or minutes and then disappears. Opposite effects can be obtained in different parts of the gut from one and the same stimulus. Weak currents tend to inhibit, which strong ones stimulate.

Another difficulty with the vagotonic theory is that the vagus is not a simple nerve like the motor root supplying the voluntary muscles of the frog. It is a plexus, a bundles of nerves of all sorts and sizes, medulated and un-medulated, most of the fibers are probably connecting neurones
running from the brain to the motor ganglia in Aurbach's plexus but there are also afferent and sensory neurones and even some sympathetic fibers. Similarly, a sympathetic nerve in the abdomen may consist of pre and post-ganglionic fibers, fibers to muscles, blood vessels, glands and even sensory fibers belonging to the central nervous system. The strongest objection to the vagotonic theory is that the expounders of this theory make it appear that the sympathetic nervous system with the celiac ganglion constitute a separate and distinct brain which can be antagonistic to or out of harmony with the central nervous system. This view is entirely out of harmony with the facts as discussed by Gaskett, quoted by Alvarez, where he shows that involuntary nerves and ganglia are a part of the central nervous system. That they are connected with it just as the voluntary nerves are and that they are developed from the same embryonic cells. Alvarez feels that the part played by the extrinsic nerves is to coordinate and act as communication paths between different parts of the tract and between the body and the tract as there are times when the animal as a whole needs to communicate with its digestive tract. There are times when the tract needs to communicate with the body and there are many times when one end of the tract must communicate with the other and on all of these occasions, the extrinsic nerves come into play. The vagi carry feelings of hunger and satiety from the stomach
to the brain. They help adjust the tone of the stomach wall to the food coming down the esophagus and they carry the stimulus that gives rise to the psychic secretion of gastric juice. If the food must be rejected, they carry the impulse that brings the abdominal muscles to aid the stomach. The splanchnics serve largely to quiet the stomach and stop digestion when the body is distressed or injured (Cannon). Alvarez states that the extrinsic nerves probably have much to do with digestive upset and disease elsewhere but these changes can be accounted for by actual damage to the gastro-intestinal muscle.

Insufficient anti-pepsin theory is of long standing and has able supporters. J. Hunter has found it as early as 1772 by stating that there is some vital principle in all living tissue which discourages digestion. In 1556 Heinoid found some exceptions to this. Levine alleges that only the first portion of the stomach and duodenum possess this resistance to the digestive action of gastric juice. Katzenstein quoted by Held and Goldblom feels that it is possible for pepsin to digest the gastric mucosa, to cause ulcer in some individuals and not in others because of the marked diminution or absence of anti-pepsin in such individuals.

Alvarez approaches it a little differently and has shown experimentally that there may be hypersecretion of pepsin in ulcer patients (Sioux Valley Medical Society, 1932)
It has long been known that ulcers often follow severe burns. Definitive data, dates back to Long's time in 1840.

E. Simpson believes that the explanation of ulcers following burns rests on the occurrences of septic processes in the burned area with subsequent infection of gastric mucosa.

Kaufman quoted by Held and Goldman seems to have proven that burns cause hypersecretion, which is the cause of the ulcer. He caused extensive skin burns in animals, setting free histamine, which he states stimulated gastric acidity.

Held and Goldbloom explain that duodenal as well and gastric erosion secondary to severe burns may be due to loss of detoxification function of the liver.

The toxic theory developed as lesions of the stomach resembling peptic ulcer when toxic drugs and chemicals were injected locally or generally and it is found that similar lesions develop when biological toxins, foreign protein, dead bacteria, filtrate of living bacteria, gastro-toxins, serums, hepato-toxins, anthrotoxins and extracts of burned tissue are injected. This led to the conception that similar toxins in humans, as result of absorbed end products of digestion may cause peptic ulcer. This theory
gained impetus by the work of Bolton in London, who experimentally produced a substance from the titurate of gastric mucosa, which he called gastro-toxin and which when injected into the blood of animals produced lesions of the stomach. The application of this theory to human peptic ulcer is of questionable clinical value.

Some, including Gunderman, have advanced the theory that toxins arising from organs other than the stomach particularly the liver may be the cause of peptic ulcer. Gunderman, ligated the main left branch of the portal vein of one rabbit and caused atrophy of the liver. In one of the animals, acute ulcer of the stomach resulted. The animal lived 48 days. He concluded that normally toxic substances are found in the liver which, when the function is normal are non-poisonous but which may cause gastric ulcer when the liver is diseased.

Occupation as a factor had great weight at one time but according to G.H. Gaither, this factor is no longer looked upon as likely. Close study of cases has usually led to the discovery that other factors play the predominate role.

Gaither also disagrees with the thermic theory. He says that it has not been proven that excesses of very hot or very cold foods produce ulcers. Diet undoubtedly acts as an accessory factor rather than as a primary one.

Not infrequently ulcers are met in diseases of the kidneys,
heart and liver and it is thought that in the majority of such cases, gastric pathology is brought about by the circulation of bacterial toxins. In cardiac failure, the starting point may be due to hemorrhage into the mucous membrane because of passive congestion of the organ.

Excessive proportion of pepsin as a factor as suggested already by Alvarez and by Gunzberg, who investigated the gastric juice of fasting stomachs which contained pepsin by absorption on mucus. The tests on 350 patients revealed fully 66% of the group had extra potent pepsin and these proved to be ulcer cases. Hyperpepsinia was noted in 48 patients out of 55 with ulcer of the stomach. In his opinion the excess of pepsin creates a predisposition to ulcer. Alvarez feels that this may be a valuable supposition worthy of extensive study.

Kaiser holds that fatigue hypotonia is the most frequent but not the only cause of gastric ulcer. Stretching of the vessels from various causes, narrows their lumen and reduces to a dangerous level the blood supply of the gastric mucosa. The necrotic mucosa is attached by the gastric juice and the beginning of an ulcer is set up.

Mechanical theory: as presented by Aschoff, quoted by Held and Goldsboom, ulcers are in the majority of cases situated in those parts of the stomach that have physiological narrowings and are subject to pressure by the surrounding
organs. He advances the theory that if an erosion of the
mucous membrane, whatever the cause, begins in the locality of
these physiological narrowings, healing is mechanically
interfered with and a chronic ulcer results. These
narrowings are caused at the antrum cardia by the diaphragmatic pressure, at the lesser
curvature by the pressure of the abdominal aorta, at the
pyloris by the spine and at the duodenum by the head of the
pancreas. The flow of chyme forcing itself, mechanically
through these narrowings may cause the early erosion. This
theory is not without fault because in many cases the ulcer
occurs in part of the stomach not subject to such pressure
influences. Moreover, it occurs in individuals in which the
stomach is placed so that even the areas of the narrowings
are not placed so that pressure from surrounding organs
effects them. Consequently the passage of chyme in a certain
direction cannot be the sole cause of production of the
ulcer and the further pathological changes determining its
shape. It does explain chronicity in some individuals in
which there is persistent pressure from neighboring organs
as in the hypersthenic individual or the extremely asthenic.

The final theory that I will consider is that of consti-
tutional influence as presented very logically by Held
and Goldbloom. These men feel that all the advanced theories
do not solve all the problems in the pathogenesis of ulcer.
For the solution, they seek a factor of constitutional makeup. Some nationalities and races are more affected by certain diseases than others. Ulcer is very infrequent in Russian and Norweijgans, living in their home environment. It appears oftener in the England, the U.S. and central Europe and is almost unknown in the negroid races. Such an anomaly may be explained only, if we apply to disease, particularly the chronic, non-bacterial the element of constitutional predisposition.

B. Mathis and Baker have observed the tendency of ulcer to occur in families and they definitely state that the family tendency is an indisputably fact. Held and Goldbloom have found four brothers in the same family afflicted with duodenal ulcer, three of whom were operated and the other had a serious hemorrhage. In another family, the father and his son were ulcer victims and in still another there were three brothers with the disease. The constitutional status may run in some families because of a similar mode of living. The constitutional factor is of two type: the born characteristic (truly constitutional) and conditioned characteristics (conditional constitution). The constitutional factor need not be, and in most cases is not evidenced by external appearances. It resides chiefly in the response of the stomach proper to endogenous and exogenous influences. Such influences are more apt to cause pathology in a stomach that has been altered in status by constitutional
influences rather than in a stomach of constitutionally abnormal status. An organ that is constitutionally inferior is spared by necessity or some compensatory mechanism prepared in the body by nature to make up for the defective organ. However when the organ is altered by circumstances, accommodation is at best very slow. Repeated irritation may cause disturbed accommodation to the point of permanent injury.

The reason why the ulcer is confined to certain locations on the lesser curvature may be found in the anatomical architecture (musculature, blood supply and innervation) of the area involved. This has been stressed throughout the paper.

Conclusion: 1. A specific etiological factor cannot be stated. 2. Multiplicity of factors may be responsible.
The six case reports to follow will not serve to substantiate or disprove any of the theories that have been considered in this paper. There are, however, some common factors present in each case report, which are of significance. They are: Presence of free HCl in all but one case and in some instances a high total acid and all but one case responded to the Sippy regime. All of the cases were taken from the University Hospital and I have interviewed the first four. #1.

**Man, aged forty, #37877, a painter and decorator, came to the university hospital, 2/11/32 for stomach trouble of ten years duration.** The symptoms were intermittent indigestion, dull pain in the epigastrium, occurring about one hour after meals, nausea, vomiting and belching. There was no hemoptysis or tarry stools. Teeth were bad. X-ray findings showed chronic osteomyelitis of the jaw. The family history gave the father as having had stomach trouble and the mother an abdominal tumor. Gastric analysis: Free HCl 20 and total HCl 30. Roentgenogram of the stomach showed ulcer on the lesser curvature near the pylorus about eight millimeters in diameter. Spasms of the pylorus and some pyloric obstruction. Treatment: Partial alvolectomy, 2/15/32. Sippy diet with powders. Progress: The pain and distress disappeared as soon as the Sippy treatment was started and have not recurred. He had a slight attack of appendicitis on 3/20/32. This was
transient and no treatment was instituted. Discharged after 7 weeks, relieved of all distress. Advised to continue diet and alkalis for one month.

#2

E.B., forty-five year old laborer, white, came to the hospital on 2/12/32, with the chief complaint of intermittent pain in the epigastrium, coming on at 10 A.M. and lasting until lunch then free until 4 P.M. and lasting until dinner time. It appeared occasionally at 12 P.M. He was absolutely free of pain before breakfast. Gas and belching were another complaint. The duration of the above symptoms was eighteen months. Examination demonstrated tenderness midway between the umbilicus and the xeciform and a little to the right. Gastric analysis: No free HCl, total 13. Stools were positive for occult blood. X-ray showed ulcer on the medial border, about 1/2 inch beyond the pyloris. Treatment: Sippy diet and powders. Progress: On the fourth day after the beginning of treatment, he became pain free and there has been no recurrence. Dismissed after six weeks free of all distress. He was given dietary instructions.

#3

G.T., male, #30148, a barber, white, aged 25, admitted to the hospital 3/5/32, for stomach trouble of two years duration. Symptoms which were intermittent, were belching, epigastric pain of dull character and a sensation of fullness after meals. The pain had been getting more severe prior to entrance.
The pain was temporarily relieved by eating small amounts of food or taking soda and milk. Milk gave the most relief. He was free of pain before breakfast, it coming on one half hour after breakfast and remaining until lunch and reappearing one half hour after lunch. The patient would take milk for relief between meals. These symptoms were present for from one to three months at a time followed by remissions of three months periods, when no symptoms were present and the patient could eat everything. Attacks were more severe during the summer. There was no history of tarry stools. Previous illnesses, Nephritis about seven years ago and sinusitis. The antral and frontal sinuses had been operated three times. Tonsillectomy was also done. Examination: Tall, slender, slightly undernourished, white man, abdomen soft and flat with slight tenderness in the epigastrium. Gastric analysis: Free HCl 46 and total 56. X-ray: revealed a duodenal ulcer. Treatment: Sippy regime. Progress: Pain and distress was relieved on treatment and he was dismissed after five weeks.

#4.

J.R., Male, aged 48, white laborer, admitted 12/17/31., with complaints of stomach trouble of six months duration. Symptoms, intermittent, were vomiting, belching after meals, sharp colicky pains in the abdomen, beginning in the epigastrium and radiating down over the entire abdomen and over the lower thoracic region of the back and into the lumbar and both inguinal regions. It was more severe immediately after meals. For the past six weeks he had vomited following meals and an increase of pain, so severe at times that he was unable to eat.
Weakness had prevented his working for the two weeks prior to entrance. Gastric analysis: Free HCl 32, total 52. Occult blood in large amounts. X-ray showed a penetrating ulcer on the lesser curvature, about an inch in diameter and a half inch in depth, about three inches below the cardia. The bottom of the crater was irregular. Treatment: modified Sippy diet, which immediately relieved the patient of all pain and discomfort. X-ray check up on 1/22/32, revealed presence of an ulcer crater at the site of the former lesion and it was decided best to operate at that time. Therefore on 2/20/32, a partial gastrectomy was performed. Postoperative diagnosis and pathological diagnosis confirmed the clinical diagnosis of a penetrating ulcer. Progress: Has been rapid.

5.

J.H., male, 41, admitted on 9/23/30, with the chief complaint of pain in the epigastrium for past eighteen years. The pain would come on about two to three hours after meals and was relieved by taking food. Up until four years ago, the patient depended upon short periods of milk diet to rid himself of the pain. However, he found that upon returning to an ordinary diet, the pain usually recurred. Bloody stools were noticed for the first time the preceding spring and had been frequent since. The last hemorrhage amounted to a quart of blood per rectum. Examination: Abdomen was tender to palpation in the epigastrium. Gastric analysis: Free HCl 26
and total 75. Stools were positive for blood. Fluorescopic examination showed a duodenal ulcer, just beyond the pyloris. 10% of the barium remained in the stomach after 6 hours. Treatment: syrup regime. Dismissed on 10/28/30 after 35 days, free of abdominal pain. Advised to continue diet and alkalk for one month.

Fix #6.

F.K., male, 30 years of age, bricklayer, admitted to the hospital, for the second time on 2/16/31, with the chief complaints of, pain in the pit of the stomach and in the back. In the winter of 1922, the patient had obstipation for 17 days. After three days of hospitalization and cure the bowels were opened. Three months after this, severe pain in the stomach developed, coming on during the day and lasting two hours. Five to nine, similar attacks occurred during the day and occasionally at night. The pain was not relieved by eating. The appetite was very good. The pain came on at any time and had no relation to meals. Soda relieved it. He vomited for the first time, two weeks before entrance and experienced marked relief afterwards. Physical examination showed tenderness along the entire colon and especially in the epigastrium, below the tip of the xyphoid. Gastric analysis: free HCl of 96 and total 120. Stool was positive for occult blood. Fluoroscopic examination revealed a duodenal ulcer. Treatment: syrup regime. Dismissed after seven days, free of pain and advised to continue the treatment.
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