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Etiology of peptic ulcer

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INDEX

INTRODUCTION

While peptic ulcer was apparently recognized as long ago as the time of Celsus and an undoubted case, described by Johann Bauhin in the sixteenth century, was related by Lebert in 1878, the post-mortem appearances and clinical manifestations of the disease were first actually described by Mathew Baillie in 1818. To Cruveillier, however, working a few years later, belongs the credit for having first thoroughly investigated the subject and describing in detail the morbid anatomy, complications, clinical history, and rational treatment.[1]

In 1853 Virchow advanced his hypothesis that the origin of peptic ulcer lay in circulatory changes; since that time it has been the subject of much clinical and experimental study. Numerous other hypotheses have been advanced, but their multiplicity demonstrates that there must be several etiological factors concerned in the formation of an ulcer, none of which can be completely eliminated.

For many years the literature has been crowded with an inflow of new theories, experimental studies, and clinical observations, all of which are written with the hope of throwing more light upon this perplexing problem. Many of the investigators have built their theories upon a sound basis and extensive experimental work, while others, however sincere they may be, have not the necessary experience, data, nor investigative work which is so essential in the promotion of a medical problem. It is with these facts in mind that

this paper is written in an attempt to give a short resume of the more plausible explanations for the cause of peptic ulcer.

BLOOD SUPPLY TO THE ULCER BEARING AREAS

The blood supply to the stomach and to the first part of the duodenum is derived, for the most part, from the celiac plexus. The celiac artery arises from the abdominal aorta and shortly after its origin it divides into three branches, the hepatic, the left gastric, and the lienal arteries. The hepatic artery in turn forms the gastro-duodenal artery which supplies vessels to the pyloric portion of the stomach and duodenum. The left gastric artery also supplies the stomach and the lienal gives off the left gastro-epiploic artery which runs along the greater curvature of the stomach and anastamosis with the same artery of the other side. The smaller vessels which are given off of these arteries run up to the base of the gastric tubules where they form a plexus of capillaries. These capillaries surround the mouth of the tubules and form meshes around the ducts. The capillaries then form veins which end in the lienal and mesenteric veins or go directly to the portal vein. In such a manner is the stomach and duodenum supplied with nutrition.[2]

PATHOLOGY OF PEPTIC ULCER

The classical description of the ulcer is that given by Cruveillier in his "Anatomia pathologique du Corps humain", published a hundred years ago. From that time to this the picture of an ulcer has been described similarly by all pathologists.

The chronic ulcer is usually single, almost always deep, and

penetrates the muscular coat to a greater or less depth. The walls may be abrupt, funnel-shaped or terraced. The edges are raised and may be overhanging. The floor is hard and indurated. In the duodenum the ulcer is almost always located in the first part above the ampulla of Vater, the part, therefore, which is most acted upon by the unneutralized acid gastric juice.

Microscopically the ulcer consists of four zones. The first is an inflammatory zone consisting of fibrin and polymorphonuclear cells. The second zone is one of necrosis, representing dead granulation tissue which provides a poor foothold for young epithelial cells growing in from the margins. The third and fourth zones are composed of living granulation tissue and scar tissue, respectively. Because of this scar tissue, which often surrounds the vessels, endarteritis is often associated with thrombosis in this region.[3]

INCIDENCE

The statements of the frequency of peptic ulcers vary according to the various investigators, but the difference is not great. One important series of autopsies reported that acute or chronic ulcers or ulcer scars were found in 6.9% of the stomachs, and 5.3% of the duodenums studied in a series of 3,058 cases. In another series of 130 cases the incidence of ulcer was equal in respect to the frequency of the lesions found in the stomach and duodenum. According to Brown[4] a conservative estimate may be made in saying that at least 10% of all persons will have a peptic ulcer sometime during their lives.

The incidence of ulcers in the stomach and duodenum vary according to the reports of the Surgeons and of the Pathologists. The Surgeons observe duodenal ulcers with greater frequency than do the Pathologists, while the latter see more stomach lesions than do the Surgeons. Such a divergence can probably be explained on the basis that duodenal ulcers more frequently cause symptoms sufficiently distressing for the patient to seek medical or surgical aid.

The incidence of peptic ulcer in respect to sex and age is generally well established. The ulcer is quite common in both male and female, but an interesting observation shows that duodenal ulcers are found three times more frequently in men than in women. Such ulcers are also more frequently found in or around the third decade of life.

TYPE, HEREDITY, AND IMMUNITY

It is common knowledge that ulcer patients usually exhibit a definite type of stature, nervous make-up, and various other predisposing factors. Many men also feel that heredity and the natural immunity of the body play a great part in either the predisposition or in the prevention of peptic ulcer. Draper,[5] after much study on the subject, found that ulcer patients usually come from families in which 70% of the fathers and 55% of the mothers have a long, thin stature. He also found, after investigating the family characteristics, that 62% of the families, in contrast to Riecher's[6] 30%, gave a history of weakness of the gastro-intestinal tract. This work corresponds with that Aschner who found that if both parents were affected with ulcers 50% of their children would be similarly troubled, and that if one parent had an ulcer 25% of the offspring would show similar lesions. He also points out that the males of the ulcer families are more susceptible to a gastro-intestinal weakness, by a ratio of 3.5 to 1, than are the females, and are, almost without exception, of the long thin type of individuals. Robinson[7], in his article, goes even further into this question and after studying a series of 70 cases describes the typical ulcer patient as being long and thin, with a broad upper jaw and a prominent pointed chin; his weight is seldom over 150 pounds, and if it is over 190 pounds the ulcer diagnosis should be questioned. The individual is usually a dynamic, hard-working, conscientious person,

who is prone to worry and to take all of the responsibility of any situation of which he is a part; an individual, in other words, who is generally found in the upper or middle strata of society.

The question of individual immunity toward peptic ulcer is constantly being brought forth. It would seem logical to assume that nature would provide some sort of protection, whether it be bile, the circulatory system, or an intestinal phenomenon as has been suggested by Bollman.[8] It has been definitely shown that short circuiting the biliary secretions to the ileum will produce ulcer, a point which will be discussed in detail later on. Turk,[9] however, feels that the immunity is not local but is derived from the circulatory system with its amboceptors, alexors or compliments, and their respective toxophores, hoptophores or receptor groups. He is undoubtedly right in his contentions, to a certain extent, but it would also seem plausible to expect some sort of a local immunity whether it be mucous, some agent of the cells, or the cells themselves. Whether one, all, or none of these theories is correct, it will be conceded by most men that some sort of an immunity to peptic ulcer exists, under normal conditions, within the human body.

CLASSIFICATION OF PEPTIC ULCER

In the August issue of the 1936 Am. Journ. Dig, Dis, and Nutr, S. C. Robinson[10] brought forth his classification of ulcers on the basis of etiology, dividing them into two classes; those of direct cause and those of indirect cause. His complete classifi-

cation is as follows:

I. Direct cause

   A. Traumatic

      1. Internal

      2. External

   B. Chemical

   C. Malignant

   D. Infection

      1. Tuberculosis

      2. Lues

      3. Intromural growth of bacteria

      4. Erosion

II. Indirect cause

   A. Psychogenic

   B. Hemorrhagic erosion caused by

      1. Nephritis with or without arteriosclerosis

      2. Acute and chronic infections

      3. Debilitating and degenerating diseases such as arteriosclerosis, amyloidosis, etc.

      4. Vascular erosions due to liver cirrhosis, gastric vessel obstruction

   C. Burns

   D. Brain trauma especially around hypothalmus

   E. Follicular ulcers - infants

   F. Melena Neonatorium

Dr. Robinson goes on to explain that most of the ulcers caused by external trauma heal very rapidly, and rarely does a chronic ulcer develop from such a cause. He also explains that it is quite possible to have a peptic ulcer associated with nephritis or with hypertension, but that this is a purely incidental finding and not associated directly with the primary difficulty.

Robinson's classification takes into account practically all of the theories of etiology, each of which has its supporters and its critics. In the following topics, discussed in this paper, the evidence for and against many of the previously mentioned causes will be described as it is seen by outstanding investigators, both in this country and in Europe.

INFECTION

For many years bacterial infection has been thought to play a great part in the etiology of peptic ulcer. Many investigators have what they claim definite proof that bacteria are the basis for a large majority of ulcers. On the other hand, some men have proven to their own satisfaction, and to the satisfaction of many others, that bacteria play a very minor part as the primary cause of the ulceration. In the early part of this century Turk[9] produced ulcers in 100% of the dogs to whom he fed B. Coli. In carrying out his experiment he continually fed the animals various quantities of the bacilli and found that he could get an agglutination of the organisms with a highly diluted serum obtained from the dogs. Micro-

scopically Turk noted cytolysis and autocytolysis of the cells of the mucus membrane of the stomach. He found no bacteremia and no reactionary inflammation and so concluded that his findings were not those of a reaction to infection nor of a local acting agent but rather that of a systemic condition and of an individual cellular change.

A year after Turk's work on B. Coli, Rosenau and Anderson[11] introduced their experimental results obtained by injecting subcutaneously, Diptheria Bacilli and their toxins. In contrast to Turk, who claimed that he could obtain merely hemorrhagic spots in the stomach by using B. Diptheria, Anderson and Rosenau reported that out of 2,882 guinea pigs so innoculated 1,897 or 66% showed definite lesions in the stomach. These lesions were produced by innoculating some of the animals with lethal doses of the toxin, and some with the toxin freed, agar cultured, organisms. In some of the animals so subjected it was found that no ulcers were present if the guinea pigs died early, but the longer the life, the higher the incidence of ulcer. As a control these scientists used tetanus toxin and numerous chemical poisons, but in no instance did they obtain lesions to those seen after B. Diphtheria injection. From this work one might be led to believe that the Diphtheria Bacillus and its toxins were somewhat specific in the etiology of ulcer, but this is not the case, as has been shown by Rosenau who, as early as 1913,[12] felt that Streptococci had an affinity for the stomach and duodenum. This belief was supported by Bolton[13] who

found that pyorrhea, tooth abscess, and other localized infections seemed to co-exist with ulcer. Moynihan[14] and Billings[15] shared this thought as is demonstrated by the fact that they found that the ulcer symptoms were more commonly aggravated during the months of upper respiratory infections and that improvement of the ulcer followed eradication of the focal infection. Rosenau, himself, found that cultures obtained from the wall of the ulcers displayed pure cultures of Streptococci in the 24 cases so examined. The colonies found varied from 1 - 5000 and the lymph glands draining the area revealed pure streptococcic strains in 4 of the 11 cases studied. Twenty-seven stomach ulcers and twenty duodenal ulcers were thoroughly studied for bacteria and in fifteen of the duodenal and twenty-one of the stomach cases diplococci or short chained streptococci were found, but the Streptococci were not specific. Rosenau did find, however, that when the Streptococcus viridans was isolated from the lesion and injected intravenously into dogs and rabbits that this similar strain of organism could later be recovered from the resultant stomach and duodenal ulcers.[16-17] From these observations Rosenau concluded, and he was strongly supported by Kennedy,[18] that the Streptococci found in the ulcers played an important part in the etiology and were not merely secondary invaders.

In spite of the findings of Rosenau, Turk, Anderson, Kennedy, and others, the large majority of the infections school feels that peptic ulcer is caused by either non-specific organisms or by the

toxic reactions of a focal infection. Deaver[19] thinks that the lesion is definitely secondary to some other infection. He mentions nervous reaction, ptosis, and mechanical irritation as possible factors, but reports that he has found sufficient evidence to cause him to feel that infection, on a non-specific or toxic basis, is the most important entity in the etiology of the disease. This theory of intoxication, as advocated by Deaver, is strongly supported by Smithies,[20-21] who cites Bolton's work of introducing sterile emulsions of appendix, gall bladder, or liver into the peritoneal cavity and forming a toxic serum. This serum, when injected into the circulation, produces necrosis and ulceration at the original site of cell emulsion. From this work and from investigations of his own, Smithies concludes that an ulcer cannot be considered a single disease entity and that the indications point to its being a self-limited disease; such a view is not taken by Alvarez,[22] however. In contrast to Smithies, he thinks that focal infection plays a small part in a majority of ulcer cases. He bases his opinion upon the fact that focal infection does not occur three times more frequently in men than in women, as does ulcer, and that it is not more common at twenty-five years of age than it is at forty-five. Such a statement, it would seem, is absolutely true, and it is also known that not infrequently ulcers recur after all focal infections have been eliminated.

In 1916 an article written by Gerdine and Helmholtz[23] called attention to the fact that an important point in ulcer etiology was

being overlooked. They stated that in infants ulcers seemed to occur in an epidemic form. In the first four months of 1908 twelve ulcer cases were diagnosed by these men, but not a single case was seen for the next twenty months. They felt that such findings, especially when supported by Holt,[24] tended to strengthen the bacterial phase of the question of etiology.

Judd and Nagel,[25] of the Mayo Clinic, made an interesting observation in citing the work of Konjetzny, Orator, and Puhl, who found that in nearly all of their ulcer cases there was an associated duodenitis or gastritis. Konjetzny discovered that in twenty-two cases of duodenal ulcer there were wart-like papillary outgrowths of epithelium, together with thinned out atrophic areas of mucosa. In some places he found the epithelium denuded and regenerating. The question which these findings brought to the minds of the authors was whether or not peptic ulcer could be an advanced stage of duodenitis or gastritis. They formed no definite conclusions on the subject but, nevertheless, such observations are interesting in spite of the fact that they are far from being conclusive.

GASTRIC, BILIARY, AND PANCREATIC JUICES

For as long a time as peptic ulcer has been recognized as a definite disease entity the factor of gastric acid has presented itself as a possible etiological cause. Devine[26] is one of those

men who have long advocated the acidic theory and in so doing he has brought forth the contentions of Matthes,[27] who believes that hyperacidity first injures the cells and is then followed by an auto-digestion of the injured cellular tissue. Devine is not as dogmatic as are many men in his ideas of ulcer etiology and, although he believes that acid is a great factor, he concedes that other causes are quite possible. He believes that acid is an influential factor in certain types of duodenal and jejunal ulcers, while circulatory, toxic, and infective disturbances may be of importance if lesions develop in the presence of low gastric acidity. The lack of alkaline juices from the duodenum will, according to Devine, allow the acid of the stomach to carry on an erosion which eventually forms an ulcer. From these facts he concludes that ulcers are formed from too much acid or from too little alkali and, consequently, that gastric ulcers may be caused by a sympathetic nervous influence while the duodenal ulcers may result from an autonomic domination.

Many experiments have been performed to show that the shunting of pancreatic and biliary secretions to a point quite distant to the pyloris will definitely cause a duodenal ulcer to appear. In one such series[28] in which three groups of dogs were used with the first group having a common bile duct fistula, the second group having a fistula followed by obstruction, and the third group having a complete biliary obstruction the following results were obtained:

Group I - 7 dogs - In three dogs anterior duodenal ulcers were found after 12-16 days, and in one dog both an anterior and posterior ulcer were found.

Group II - 11 dogs - In six dogs of this group lesions were found after 26, 29, 46, 56, 80, 99 days, respectively. In three of these animals a single chronic ulcer was discovered on the anterior wall of the duodenum, while in one dog a subacute perforating ulcer was found on the anterior wall, in another multiple erosions of the stomach and duodenum were seen, and in the sixth dog a subacute duodenal ulcer and two gastric ulcers were found.

Group III - 5 dogs - Of the five dogs in this group three of them developed ulcers after 47, 108, 109 days. In one animal multiple gastric ulcers were had, in another dog there were two perforated duodenal ulcers, and in the third canine a single chronic ulcer was seen situated on the anterior wall of the duodenum.

Such an experiment as that described in the preceding paragraph is typical of those performed by such men as F. C. Mann;[29,30,31] Bollman;[8] Grossman;[32] and Morton;[33] all of whom obtained similar results. By using the technic of ligating and cutting either the hepatic or common duct and transferring the free end to a point distant to the duodenum they obtained both gastric and duodenal ulcers in a great number of cases. The typical location for the ulcers developed by these means are, according to Morton, at a point where the acid forces converge. Morton also finds, in his experiments, that ulcers so produced will heal much more rapidly if alkalis are administered,

a fact which would lead one to believe that the biliary secretion serves as a counteracting agent in the presence of the highly acid stomach juices. None of the men mentioned above, however, will go so far as to say just what part the action of the bile plays in the production of the ulcer, but they will admit that there must be some factor present, whether it be alkalinization or not, which overcomes the autolytic actions of the other juices found in this locality.

These experiments are not above criticism, however, as has been shown by Berg,[34] Kopesnow,[35] and Dragstadt.[36-37] The former found that in his series of fourteen dogs, all of whom were deprived of their pancreatic juice, that only two developed ulcers within twenty-five days. He contends that his series is larger than many of those in which ulcers were commonly found and that the so-called ulcers of many of the investigators, principally Hartmann, were nothing more than a discontinuation of the mucosa. Berg feels, therefore, that there is no definite proof of ulcers forming in the absence of pancreatic and biliary juices. Kopesnow and Dragstadt, on the other hand, have worked more directly with the acid itself. Independent of one another, they have produced surgical ulcers in healthy dogs and both report that the lesions healed with amazing rapidity even after more acid was introduced into the ulcerated tissue. They both conclude that such results tend to disprove the theory of acid etiology and Dragstadt goes so far as to say that the acid is the result rather than the cause of the ulceration.

NERVOUS AND CIRCULATORY FACTORS

Of the many and of the varied theories for the cause of peptic ulcer the ones that point an accusing finger at the nervous system are by far the most popular. Practically every author, when writing on ulcer, mentions, in one sense or another, the possibility of nervous control as the cause of the lesion. Such opinions as have been formed on this subject are not based merely upon guess work but rather upon sound experiments and observations of such men as Robinson, Crile, Alvarez, Cushing, Schutz, and others. The accomplishments of these men are universally recognized and their opinions, while not infallible, are highly respected in this country as well as in Europe.

According to the consensus of opinion the nervous control of the blood vessels is the big factor in the formation of the lesion, and, as Gaskell[38] has pointed out, there are three groups of nervous fibers which might react to a stimulation. They are (1) the inhibitory fibers entering with the mesenteric arteries; (2) the connector fibers of the vagus which connect with the intestinal nerve cells; (3) the motor cells themselves and their motor fibers running to the musculature of the gastro-intestinal tract. Theoretically the vessels are constricted through the nervous control with a resultant ischemia, thrombosis or necrosis, and followed by a sloughing of the mucosal cells with an ultimate formation of an ulcer crater.

While these definite stages of ulcer formation are essentially speculative at the present time, the question of the nervous factor is formulated upon a more sound basis. It is commonly known that the over-worked business man who has typical symptoms of a peptic ulcer can gain relief by taking a vacation, only to have a return of symptoms when he resumes his daily work. It is also recognized that the typical ulcer patient is a tall, nervous, conscientious type of an individual who is apt to undergo emotional changes for relatively no reason. Such common findings cannot be completely ignored when the cause for the condition is being sought. In order to prove this point Alvarez, in one of his articles,[39] relates numerous incidences of nervous control to the stomach and duodenum, and he tells how disgust, fear, anxiety, anger, fatigue, or pain may inhibit peristalsis. This is well understood if one recalls that for a great number of years the means of detecting a thief in primitive India was to feed rice to the suspects and then to examine the mouths to find which one was without salivation.

Numerous experiments and observations have been reported in an attempt to ascertain just how the nervous system and the ulcer are related. In 1931 Cushing reported[40] three cases which had been operated upon for brain tumor and in which, at post mortem, peptic ulcers were found. Quoting him we find that "The interbrain has been shown to be the seat of primitive emotions which are normally under cortical control, but in experiments domesticated animals,

probably from the release of the sympathetic nucleus in the posterior hypothalmus, there occurs explosions of 'sham rage' accompanied by a mass discharge of the sympathico-adrenal system." Cushing goes on to say that the parasympathetics are also strongly affected by cortical or psychic influences and that a functional release of the vagus from paralysis of the antagonistic sympathetic fibers leads to hypersecretion, hyperchlorhydria, hypermotility, and hypertonicity of the pyloric segment. Thus by spasm of the musculature, he feels, the blood bessels are constricted which causes an ischemia or areas of hemorrhagic infarction leaving the overlying mucosa susceptible to the lytic powers of its own hyperacid juices. He is supported,to some extent, in his contention by Crile;[40-41] who believes that there is a brain-thyroid-adrenal-sympathetic combination which may be the cause of many kinetic diseases, one of which is peptic ulcer. He describes the brain as "a flame that is always glowing" and feels that certain stimuli excite this brain-thyroid-adrenal-sympathetic combination and cause the "flame" to increase. In order to prove this point Crile presents 350 clinical cases in which 53 had adrenalectomy and 297 had a denervation. The results were 93% cure for neuroasthenia, 100% cure for hyperthyroidism, and 96% improvement or cure for peptic ulcer. While such a series is large and impressive one should read the work done in 1914 by T. R. Elliott[43] if a true conception of the question is to be had.

It is commonly recognized that the gastric juice of some

nervous individuals is markedly acid, but it is not so commonly known that the secretion of pepsin may be 20-30 times greater than normal. It is this fact of continuous cellular secretion, even in the absence of food, which makes the control of ulcer such a difficult problem. Such a phenomenon may be due to the ulcer itself, as shown by Harper's experiment, or from an over-active and irritable brain as was demonstrated by Stahnke when he stimulated the vagus nerve with an electric current for 40 minutes a day and found an increase in gastric acidity, an increase in peptic activity, and the occasional formation of an ulcer. There are also reasons to believe that psychic stimuli will dry up pancreatic and biliary secretions, a condition which has been proven to produce ulcer. Alexis St. Martin showed that any great disturbance to the nervous system caused the gastric mucosa to lose its smooth, healthy appearance and to become red and dry or pale and moist.[22] Such a phenomenon has been actually observed by Robinson[7] who has seen ischemic spots appearing around the ulcer-bearing areas. These spots last for a minute or so and then the color of the mucosa returns to normal. He believes that such findings may be the answer to a patient's displaying typical ulcer symptoms in the absence of a visible ulcer crater.

Jones[44] has described investigations, carried out by the Seninitzkys Clinic, in which it has been shown that insulin tends to relieve the symptoms of peptic ulcer. This is thought to be due

to the fact that vagotonia is always accompanied by a hypersecretion of the stomach, and, as has been described by Aschoff, the fact that in such a condition there is found a cramping of the gastro-intestinal vessels with a resultant venous stasis, hyperemia, and a predisposition to ulcer formation. Such a situation will be better understood, however, after the work of Russ[45] has been read. He tells of the vagotonic and sympathetonic individuals, and claims that the latter type seldom show any signs of ulcer formation. In supporting this contention he reports that clinics in the West and in the South will have better results in ulcer treatment than will those in cities such as New York or Rome, because of the fact that the vagotonic individuals will be found in the more densely populated areas. Going further into this subject, Russ claims that he has found that the vagotonic child is usually one who shows a great amount of energy and a great amount of immunity to the average infection, but, at the same time, is not infrequently harboring a chronic ulcer.

Meyer and Karton,[46-47] working along this same line, discovered that an injection of foreign protein, in vagotonic states, would relieve the ulcer symptoms, presumably because of the relaxation of the vagus nerve and an increased blood supply around the ulcer site. They found that the same results were had even if the gastric secretions were increased during the experiment. Gray[48] is also in accordance with this work because of the results he ob-

tained when chronic smokers were taken off of tobacco and showed a marked improvement in their conditions.

Both Robinson[7] and Steigmann[49] support the neurotic theory of ulcer by quoting series of cases which show that ulcers seldom develop in races which are less subjected to worry than in the white race. In histories taken in Texas and in Chicago, of negro patients, to determine the number of ulcer cases, it was discovered that only 1/200% of those in Texas gave any symptoms of ulcer while in Chicago 12.7% of those questioned gave positive ulcer symptoms. Such results tend to show that there is probably no racial immunity to the disease but rather that the emotional status in the two parts of the country is different. Such a contention is definitely supported by McCarrison,[7] who, in nine years practice among the primitive tribes of the Himalaya Mountains, performed 3,600 operations and did not once find evidences of an ulcer. Such an astonishing finding is probably due to the fact that in the Himalaya Mountains there are no automobiles, night clubs, depressions, and financial worries.

Closely associated with the neurotic factor is that of circulatory changes. For the most part, as has been shown, the constriction of the end arteries of the gastro-intestinal tract is considered to be the activating cause of the ulcer, and this constriction is known to be caused by nervous stimulation. Such a condition is especially apt to occur on the lesser curvature of the stomach and near the duodenal cap because it is at these localities

that the circulation is largely that of end arteries. It would seem possible, therefore, that ulcers could easily form at such points and could remain present until the abnormal arterial condition was removed. In view of this fact it would seem possible, as claimed by some investigators,[22] to think of arteriosclerosis as a possible cause, but, if such were the case, ulcers would be more commonly found in the more aged persons.

The vicious cycle of ulceration in which the toxin absorbed from the ulcer irritates the nerves and causes a continued contraction of the blood vessels should also be noted at this point. Such a phenomenon has many supporters and may be of vast importance in the chronicity of the lesion in spite of the fact that Stannke does not believe that nature would make such a faulty nervous mechanism.

As long ago as 1916 Durante[50] reported ulcer formation following emboli to the small vessels of the stomach and duodenum, and he believed, at that time, that this might be the true secret to the problem of ulcer formation. His ideas were supported to a certaintain extent by Schutz[51] who had a series of thirty autopsies, performed on patients with ulcer, in which it was found that 70% had emboli and the remaining 30% had some vascular change (endocarditis, endarteritis, arteriosclerosis). These findings, however, as freely admitted by Schutz, do not answer the objection that the emboli could be secondary to the lesion itself. Schutz did find

in some cases, in answer to the objection, that the embolus was older than the ulcer, a point which would tend to support his and Durante's theory of primary embolic affection. Rosenow, on the other hand, is of the opinion that the circulatory obstruction is secondary to a localized infection. He admits that such a circulatory disturbance may prevent the ulcer from healing, but feels that it cannot be the primary cause of the lesion. He explains himself by pointing out Virchow's work[52-53] in ligating and otherwise obstructing the circulation to the stomach and failing to find any resultant ulcers.

FOODS

Research into the field of food, as a cause of peptic ulcer, will disclose the fact that many investigators have caused ulcers and have cured the same lesions by means of food control. Both the texture and the composition of the food-stuff used has been credited with being the activating factor in the formation of the lesion. The consensus of opinion upon this subject seems to be that the type of food given, or rather the lack of food given, may result in an ulcer, and that a constant irritation from harsh foods may cause an erosion which upon further development will form a definite peptic lesion. It has been shown by Beazell[54] that if a rough diet is given, along with other factors, a peptic ulcer will at times develop. In one of his experiments, Beazell, failed to

get any ulcers, even after vasotomy, when the animals were fed a soft low-residue diet. Somewhat similar results have been reported by Howes,[55] who fed rats a deficient diet and found that 70% developed peptic ulcers. He continued his work somewhat further, however, and discovered vitamin A had no effect upon the rats but that vitamin B protected the animals from ulceration, even when an inadequate diet was given.

L. P. Gay,[56] working upon the theory of anaphylaxis, as offered by Kern and Stewart in 1934, found that incompatible foods could be discerned by making a leucopenic examination shortly after the food was eaten. In the cases of incompatability the count would fall at a fast rate, and it was in this way that it was found that milk, wheat, and eggs were the most common offenders. After finding all of the foods that the patient could not correctly handle Gay removed them from the diet and was rewarded with a prompt remission of symptoms. The relief thus afforded continued as long as the incompatible foods remained out of the diet, but once they were returned the typical symptoms of peptic ulcer were again noticed. Because of these striking results Gay claims that many ulcers are upon an allergic basis and that when this condition is corrected the ulcers and their symptoms will disappear.

DRUGS

Histidine and cincophen should be given the credit for

being two of the most popular drugs used in ulcer experimentation. The use of Cincophen, in ulcer production, should be accredited to Bollman more than to any other investigators. He has found, in his numerous experiments, that Cincophen will cause an ulcer in 95% of all the animals to which it is administered.[57] The lesions begin as a diffuse gastritis, after 3-4 doses of the drug, and the mucosa becomes edematous, hemorrhagic, and covered with fine linear erosions. These erosions rapidly become acute peptic ulcers, some of which progress to chronicity. Such changes will take place regardless of whether the Cincophen is given orally, rectally, subcutaneously, or intravenously, and the lesion formation will be hastened from 10-11 days by the administration of ground bone along with the drug. This fact seems to indicate that Cincophen has a predelection for the gastro-intestinal tract, and that it will form ulcers much more rapidly if the mucosa is predisposed by some irritating agent. Histidine, on the other hand, is universally used for the relief and for the prevention of ulcers. The work done by Weiss, Bulmer, and Hessel, as described by Behneman,[58] is quite convincing evidence as to the merits of Histidine. Figures ranging from 69%-80% of definite relief of symptoms were reported, and in one series of cases, in which Histidine was used and the patient followed by X-ray studies it was found that in an average of 20 days 16 out of 20 cases showed a complete disappearance of the ulcer and the other 4 cases showed definite improvement. From

such statistics as these, Behneman may be correct in his contention that ulcer is caused by the body's failure to synthesize Cystine, lysine, Histidine, and tryptophon when these amino acids are lacking because of deficient food intake.

DIRECT TRAUMA

Both Ivy[59] and Baggio[60] have shown, by animal experimentation, that acute ulcers can be formed by constant irritation of the gastric and duodenal mucosa. In his study, Ivy, exposed the mucosa for a period of 6-8 months with no gross pathology resulting. He then caused an acute surgical ulcer to be had and found that the lesion so produced would heal of its own accord within a period of 12-18 days. After rubbing the ulcer twice a day with bread crumbs, however, he found that the healing could be delayed from 12-34 days. The delay thus occurring was not increased by an experimental infection in which streptococcus aureus and streptococcus were used. In spite of these findings it is very doubtful if Ivy, or the others, will point to such a cause as an important etiological entity in the production of peptic ulcer.

STASIS

This physiological interruption is thought by some men to be a factor in ulcer production. Goldberg and Harper,[61] Sloan,[62] Stewart,[63] and Slocumb[64] have all produced evidences which point to

this condition as being related to ulcer formation. The two former men have carried out animal experiments in which a pouch from the fundus of the stomach was placed into the bowel, and in many cases a deep perforating ulcer was found. Sloan, on the other hand, feels that adhesions around the Ligamentum Treitz will cause a decreased emptying time and that an ulcer formation will thus result. This contention is faulty, however, because the Roentgenologists report that in most cases of ulcer the emptying time of the duodenum is not decreased. It is also common knowledge that during pregnancy, when there is a great deal of back pressure in the gastro-intestinal tract, peptic ulcers seldom develop.

CONCLUSION

In all probability peptic ulcer is the result of several interacting and variable factors. Physiologists have demonstrated that the action of undiluted juices can, by erosion, produce ulcer. They produce ulcer more effectively when they impinge on tissue unaccustomed and unprotected by nature to receive them.[65] It is suggested that this factor of aggression is the more likely to cause ulceration when the resistance of the tissue exposed is in some way lowered by trauma of any kind. Thus, an infected intestinal wall or mucosa, injured by mechanical or chemical irritants, might well succumb and disintegrate, while a membrane with a normal protecting mechanism would remain intact. Systemic factors, if conducive to

dimimution of resistance of tissue or capable of producing prolonged or persistent accentuation of the factor of aggression in the acid chyme might well increase the liability to the development of ulcer and its recurrence in such cases. There seems no doubt that the factors involved in the etiology of peptic ulcer vary in different subjects at different times, consequently, every patient presents problems which must be studied carefully. Such study should reveal the particular factor or combination factors which are responsible in each case, and correction of these factors should be expected to result efficiently when applied in the treatment of the ulcer.

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