THE MECHANISM OF PEPTIC ULCERATION A REVIEW OF THE RESULTS OF EXPERIMENTAL INVESTIGATION*

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I wish to present some of the more important results obtained by my associates and myself from our investigations of the experimentally produced peptic ulcerations. I should have liked to include the development of the current ideas concerning the experimentally produced ulcer since the pioneer work of Bolton (1913), but because of lack of space I shall confine my discussion to the mechanisms of production of the lesion. Since this is a review of the results of investigation pursued over a period of many years, I shall draw freely on our previous publications for subject material. No attempt will be made to correlate the facts that have been learned about peptic ulceration from experimental studies with those that are known from clinical studies of the lesion in man, as knowledge concerning the life history of both the experimentally produced gastro-intestinal ulceration in animals and the spontaneously occurring lesions of man is as yet too incomplete.

Types of Peptic Ulceration produced Experimentally

In general the ulcerations of the gastric and intestinal mucosa which are considered as the so-called peptic lesions, and which we have produced and studied experimentally, can be classified into one of three groups on the basis of character of lesion, site of lesion, and mechanism of development. While the individual lesions in these groups have many characteristics in common, and while there are some experimentally produced ulcerations that do not correspond exactly to the major criteria for any group, on the whole the marks of delineation between the three groups of lesions are about as definite as obtains in most pathological conditions.

The first type of peptic ulceration I wish to describe is the one most often formed experimentally. It can be readily produced by a variety of methods. It appears to be similar in most respects to the lesion as seen at necropsy in man following death in uraemia and other conditions in which there existed a terminal toxic condition. This type of ulceration has usually only been seen as an acute lesion. There is as a rule more than one ulceration; the individual lesions are often but shallow erosions of the mucosa, irregular in outline and covering relatively large areas; and the mucosa of the fundus is more often involved than other regions of the stomach or the intestine. The exact site of occurrence

of the lesions is never definite or constant; they usually begin as a haemorrhage in the submucosa, and the ulceration of the mucosa appears secondarily to the vascular injury. The lesions rarely extend deeper than the submucosa; very infrequently do they become chronic or perforate.

The second type of lesion produced experimentally more nearly resembles the chronic peptic ulcer as seen in man. The conditions under which it develops are definite and limited. It is usually single, although two or rarely three, hardly ever more, ulcers may be present at one time. The site of the lesion is in the pathway of the outflow of gastric content, never in the fundus. The exact site of its development is definite and constant. It starts on the surface of the mucosa as a greyish circumscribed membrane. At first it is saucer-shaped, and later the usual appearance of peptic ulcer as seen in man develops. In the beginning the lesion is acute, but if perforation with peritonitis or fatal haemorrhage does not occur it quickly becomes chronic. Grossly and microscopically this type of lesion resembles the chronic peptic ulcer as found in man.

The third type of lesion studied experimentally appears to begin as gastritis, which involves both the fundic and pyloric mucosa. The fundic lesions heal very quickly, but those in the pyloric mucosa persist as chronic lesions so long as the exciting agent is permitted to act. The pyloric lesions resemble the gastric peptic ulceration as seen in man, except that the experimentally produced lesions are more often multiple.

There are a few conditions in which ulceration of the gastro-intestinal tract occurs where the lesion does not quite correspond to any one of the types mentioned. For instance, peptic ulceration may arise in the animal with an Eck fistula. Here the lesion corresponds to the second type of ulceration described, except that it usually remains acute in appearance and is often accompanied by erosion of the fundic mucosa as a terminal condition. The lesion also often occurs following obstruction to the biliary outflow. Such ulcerations correspond in general to the first type of lesion except that they are prone to perforate. Peptic ulceration also occasionally follows partial removal of the liver, in the condition of cirrhosis of the liver, after the removal of the pancreas or evulsion of the pancreatic ducts, and quite frequently after draining the pancreatic secretion externally. The lesions found in all these instances resemble the second type of ulceration except that they rarely become chronic.

* A special lecture delivered before the Royal College of Surgeons of England, London, July 14, 1938.

Peptic Ulceration of the First Type

The methods whereby ulceration of the first type can be produced are too numerous to mention, but the characteristics of the resulting lesions appear to be quite similar regardless of their method of production. Peptic ulcerations of this type are found mainly in the gastric mucosa, and very rarely in the duodenal mucosa involved. The lesions can be separated into two subgroups: one is a widespread superficial erosion; the other is a punched-out ulcer formation. For convenience they will be described as gastric erosions and as ulcers, but the fundamental mechanism of their development appears to be the same. The gastric erosions, which are the usual type of lesion encountered, practically always occur in the fundic division of the stomach, and in most instances the pyloric mucosa is normal. The lesion begins as a widespread haemorrhagic region in the mucosa and develops along the rugae, thus presenting an irregular appearance. The denuded surface is haemorrhagic and the fluid in the stomach usually contains blood. The gastric ulcers are round or oval in shape and vary in size, but rarely exceed 3 mm. in diameter. They are almost always multiple. They vary in position, being found in the fundic and pyloric regions on both curvatures of the stomach, but usually they occur in the prepyloric region. At the onset the ulcers appear as small haemorrhagic regions; when fully formed they penetrate to the muscularis mucosae, with complete loss of epithelium. The walls are smooth, causing the punched-out appearance.

Microscopically the gastric erosions show a loss of surface epithelium of different degrees. Only the surface of the mucosa is affected, the loss of epithelium rarely extending through to the submucosa. Usually the epithelium beneath the ulceration is infiltrated with blood. The ulcers are cone-shaped, with the base of the cone at the surface of the mucosa and the apex at the muscularis mucosae. A small eroded blood vessel can almost always be found at the centre of the base of the ulcer.

The mechanism of the formation of this type of peptic ulceration appears to be as follows. The primary injury is a vascular one. In the gastric erosion form of lesion the vascular injury occurs in the capillaries or small blood vessels in the mucosa; in the ulcers it occurs in an arteriole located in the submucosa. Following the vascular injury and infiltration of the mucosa with blood there is a destruction of the epithelium in the region where the blood supply is affected.

Second Type of Ulcer

We have studied the second type of peptic ulceration in greater detail, both because it appears similar to the chronic lesion of man and because the development of successful methods for its experimental production and healing made possible the study of the complete life history of the lesion. The ulcer has been observed through the various stages of its development from the time it could just be recognized as a pathological process up to several months after it had the characteristic appearance of the chronic lesion. Then, in turn, the healing process of the chronic lesion has been observed in detail until restoration was so complete that it was impossible to recognize grossly that an ulcer had existed.

METHODS OF PRODUCING THE ULCER

The fundamental procedure necessary to produce this type of peptic ulceration is to expose the mucosa of the intestine to the acid gastric content by the elimination of the mechanism which normally produces the necessary

diluting, neutralizing, and buffering secretions. This can be accomplished by (1) removal of the duodenum, (2) draining a fundic pouch with an isolated loop of intestine, or (3) transplantation of the common bile duct and pancreatic ducts to the terminal segment of the ileum. Peptic ulcer will develop in a high proportion of instances, following the above procedures, in the intestinal mucosa adjacent to the site of emergence of the gastric content. However, the most successful method of producing chronic peptic ulcer is as follows. The pylorus is sectioned and the distal end closed, and the jejunum is transected a few centimetres distal to the ligament of Treitz. The distal end of the jejunum is anastomosed to the pylorus and the proximal end anastomosed to the ileum within 40 cm. of the termination of the latter. These procedures cause the gastric content to be expelled from the stomach into the intestine, without becoming mixed with the secretions normally poured into the duodenum—the bile, the pancreatic juice, and the duodenal secretion, which are now drained into the ileum. If this procedure is carried out correctly, peptic ulceration will occur in more than 90 per cent. of the cases.

GENERAL CHARACTERISTICS OF THE ULCER

The ulcer thus produced is grossly and microscopically similar to the lesion as seen in man. The ulceration usually develops within two to three weeks after exposure of the mucosa to the gastric content. The site of development of the ulcer is very constant. The lesion forms a few millimetres distant to the pyloric mucosa and usually on the postero-lateral aspect of the intestine. The site of formation of the ulcer is always just distal to the point of emergence and in the direct pathway of the gastric content. Usually only one ulcer occurs, but sometimes a contact ulcer is present, and rarely three ulcers are found. The ulcer usually develops rapidly, and the interval from the time of the first visible signs of mucosal injury to the time a lesion is well formed may be but a day or so. When fully formed the ulcer varies from 4 to 15 mm. in diameter and is round or elliptic in shape. The ulcer exhibits a punched-out appearance with overhanging edges. The lesion always progresses until it involves the entire thickness of the mucosa, and usually penetrates considerably deeper into the intestinal wall. The base of the ulcer is hard on palpation, and on section thick and sometimes oedematous. Microscopically there is destruction of the mucosa and of the intestinal wall down to the base of the ulcer, with leucocytic infiltration and initial proliferation of connective tissue.

DEVELOPMENT OF THE ULCER

The ulcerating process always begins at the surface of the mucosa. At first all that can be seen is an oval or circular area covered with a homogeneous grey membrane. Microscopical examination of the lesion at this stage shows that this membrane is very thin, involving only the surface cells, and that it is composed of mucosal cells in various stages of necrosis, leucocytes, and erythrocytes. With the exception of small regions of haemorrhage between the tubules just beneath the membrane, the rest of the tissue appears normal. If the membranous layer is gently sponged and rubbed off, a slight depression is uncovered, where the surface of the mucosa has disappeared and which bleeds profusely. This formation of grey membrane composed of cell debris is constantly occurring, and the surface of the membrane, which is older and consists of the more severely injured cells, is constantly being eroded by the gastric content passing over it. The ulcer is saucer-shaped until the muscularis is reached. The muscularis is at first penetrated by the

pathological process to a slightly greater extent peripherally than the mucosa, undermining the latter and causing the characteristic punched-out appearance of the fully developed lesion. In association with penetration of the mucosa, infiltration of leucocytes and proliferation of fibroblasts and mucosal cells occur at the periphery of the injured region. Shortly after the ulcerating process has started, bacteria in varying numbers can be found at the periphery of the lesion, and the amount of fibroblastic proliferation appears to depend to a considerable extent on the degree of secondary infection.

While it has been necessary to describe the development of the ulcer by stages, it really is a continuous process, the essential features of which are identical in all lesions. This same statement also applies to the process of healing. This occurs simultaneously with the developing process, but the lesion does not heal unless it has been partially or completely protected from the gastric content. In the unprotected ulcer the delicate growing edge of granulation tissue covered with a single layer of mucosal cells, which is the initial stage of the healing process, is injured and swept away by the gastric content as soon as it has progressed beyond the protecting edge of the periphery of the lesion.

METHODS OF CAUSING THE ULCER TO HEAL

The ulcer can be made to heal very quickly by completely protecting it from the gastric content. This is accomplished by closing the opening of the intestine proximal to the ulcer at the pylorus and draining the stomach by gastro-enterostomy. However, often before the ulcer has healed another ulcer develops in the efferent loop of the jejunum draining the stomach, perforates, and causes death. This latter occurrence can be avoided if at the time the gastro-enterostomy is performed the duodenum is drained back into the jejunum just distal to the gastro-enteric stoma. The ulcer can also be made to heal by draining the duodenum back into the jejunum in the region of the lesion; but under this condition the healing process is not orderly, as when the lesion is completely protected from the gastric content. The healing of the ulcer will also follow simple gastro-enterostomy; but here, also, the healing process is complicated and retarded by injury resulting from the gastric content passing over the lesion.

HEALING OF THE ULCER

The process of healing of the protected ulcer is very characteristic, and occurs in a uniform and progressive manner until the lesion is completely healed. Within just a few hours after the ulcer has been protected from gastric content flowing over it, the base of the ulcer becomes covered with a thin fibrinous membrane; the leucocytes and bacteria begin to disappear beneath the protection of this membrane, and the growing granulation tissue and mucosa are able to advance from the periphery over this supporting structure covering the base. The granulation tissue grows faster than the mucosa, and eventually fills the whole ulcer and usually extends over the edge of the lesion. Concomitant with the proliferation of the granulation tissue, the periphery of the lesion moves inward, the diameter of the lesion becoming thereby greatly decreased.

The growing edge of mucosa consists of a single-celled layer of flat cells, which are not at first attached to the supporting granulation tissue. While proliferation of the mucosal cells appears to occur throughout the growing surface, it is fastest at the periphery of the ulcer, so that the advancing edge of mucosa seems to be pushed over the surface of granulation tissue. Sufficient pressure is

soon developed in this most rapidly proliferating region to cause simple folds of mucosa to appear adjacent to the normal mucosa at the periphery of the ulcer. The first fold at the growing edge of the ulcer and nearest the centre of the lesion usually has an elongated slope on the side of the advancing edge that is very characteristic.

As previously stated, the growing edge of granulation tissue usually overflows the sides of the ulcer, giving a mushroom appearance. When the growing edge of mucosa, which is protected by overhanging granulation tissue, reaches the stalk of this mushroom, it passes upwards and may cover the whole surface of the granulation tissue, even that portion which is beyond the edge of the ulcer. Eventually, however, the stalk of the mushroom of granulation tissue with its covering of mucosa is squeezed off and discarded, leaving the whole surface of the lesion covered with the mucosa which has been developing under the protection of the granulation tissue. When the granulation tissue has filled the base of the ulcer completely, the lesion can be recognized by the raised pearly white appearance of the newly formed tissue. The healing tissue is very delicate at this stage, and can be washed out by dropping water on it with a medicine dropper, leaving the appearance of the ulcer almost identical with that before the lesion was protected. The whole healing process occurs in a very orderly fashion, and, when completed, the site of the ulcer, as has been said, usually cannot be distinguished grossly. Microscopically the site can be recognized because the restored surface of the mucosa is thinner than normal, contains atypical villi, and, since smooth muscle does not regenerate, the mucosa over the ulcerated area rests on a connective-tissue base instead of the muscularis mucosae.

THE CHRONICITY OF THE ULCER

Studies of the processes of development and healing of the experimentally produced peptic ulceration have indicated the mechanism causing the lesion to become chronic. The same agencies that are responsible for producing the ulcer prevent its healing. The same cellular changes that constitute the essential elements of the healing process can be found to a varying degree in all ulcers. An ulcer begins to heal as soon as the initial injury occurs. The processes of tissue destruction and tissue repair take place simultaneously from the incipiency of the lesion; but the former, in the developing lesion, always predominates, because the new cells formed in the process of healing are destroyed by the acid or swept away by the passage of the gastric content before they have had an opportunity to establish themselves as an integral part of the tissue. The destructive processes which produce the ulceration and the reparative processes which cause the lesion to heal go on at the same time constantly throughout the life cycle of the ulcer, except when it is completely protected from the gastric content. In the unprotected ulcer, exposed to the gastric content, each protective covering of granulation tissue formed over the base of the ulcer is destroyed before healing can take place beneath. The delicate cells of the mucosa developing in the edge of the ulcer are killed or swept away by the gastric content passing over them. Only when the ulcer is protected from the gastric content to such a degree that the ever-present reparative processes can take place faster than the destructive processes does healing occur.

COMPLICATIONS OF THE ULCER

All the complications of peptic ulcerations as seen in man have been observed in experimentally produced lesions of this type. The more important complications have been perforation of the lesion and haemorrhage from

the ulcer. A very high percentage of experimentally produced ulcers perforate. The perforation may occur very quickly, with resultant leakage of intestinal content and peritonitis. Another viscus may be pierced, such as the gall-bladder, colon, or a loop of intestine. The perforation usually is closed by the surface of an adjacent organ, or, especially, the omentum. In some instances the perforated ulcer shows one or two terraces, indicating that there has been more than one active onslaught in its creation. A few ulcers have even perforated through the abdominal wall, producing a fistula.

Haemorrhage from the experimentally produced ulcer is a frequent occurrence, and death of the animal from loss of blood at the site of the lesion is not uncommon. The haemorrhage occurs from one of two sources. Rarely, the pathological process involves an artery, producing necrosis of the arterial wall with a resulting loss of blood. Usually the bleeding occurs from an injured surface of the granulation tissue in a healing lesion. As previously described, in the healing process the base of the ulcer is filled with a very vascular granulation tissue. Injury to this newly formed vascular bed easily occurs, and may be followed by a haemorrhage of sufficient magnitude and continued for a long enough time to cause death. The ulcers more prone to bleed are those healing under a condition of partial protection. For instance, if gastro-enterostomy is carried out on an animal with ulcer, thus diverting a portion of the gastric content from passage over the lesion, the ulcer will slowly heal. While the ulcer is in the process of healing, the gastric content that does pass over the lesion frequently injures the delicate growing and developing granulation tissue in the base, and a haemorrhage often ensues. A coarse diet is more prone to cause bleeding than a liquid one. The fully protected healing ulcer—that is, a lesion from which gastric content is completely excluded—has never been the site of a demonstrable haemorrhage in our experiments.

The Third Type of Ulceration

The third type of peptic ulceration we have studied comprises those lesions produced by a single agent, cinchophen. The entire life history of the gastro-intestinal lesions produced by the administration of cinchophen has not as yet been fully observed, but enough is known to warrant a consideration of these lesions separately. The lesions produced by cinchophen appear to be a combination of the two types of lesions previously discussed.

The administration of a sufficient amount of cinchophen over a sufficient period to dogs that eat their daily ration produces gastro-intestinal ulcerations in a high proportion of animals. The lesions are mainly gastric; rarely is the duodenum involved. Shortly after the administration of an effective amount of cinchophen an acute gastritis develops, with multiple erosions, involving both the fundic and pyloric lesions. The gastric lesions at this stage appear similar to those described in the first type, but usually are more severe and widespread. An accompanying haemorrhage is a very prominent feature of these lesions. The multiple acute ulcerations throughout the fundic mucosa and in most of the pyloric mucosa heal rapidly, usually leaving a single chronic ulcer in the pyloric mucosa. The chronic lesion is situated from 2 to 3 cm. from the pyloric ring on the lesser curvature and posterior wall of the stomach.

The chronic ulcer is large and punched out, with overhanging edges and a necrotic indurated base. The lesion has a great tendency to perforate, and often penetrates the entire thickness of the gastric wall. The chronic

ulcer produced by cinchophen heals after the administration of the drug is discontinued. The healing process, which is active during the entire life of the ulceration, begins to be effective within three days of the withdrawal of cinchophen, and the lesion is completely healed within three weeks. The healing process is similar in all respects to that described for the ulceration of Type 2. As previously stated, the life history of the cinchophen ulcer has not been observed completely. The mechanism of development appears to be similar to that described for the ulceration of Type 1, in that the initial lesion seems to be a vascular one, involving a very large region of the gastric mucosa. The cinchophen ulceration differs from those of Type 1 in that some of the lesions in the pyloric region become chronic and will perforate.

Summary

There are at least two mechanisms of development of the experimentally produced peptic ulcerations. One mechanism involves initially the blood supply to the ulcerated region. The life history of the lesions produced by this mechanism is not completely known, because the methods for producing them usually result in death to the animal. The other mechanism has been summarized in a previous paper as follows (Mann, 1937):

The site, character, extent, processes of development, and healing of the ulcer depend to a very large degree on an anatomical and physiological basis. The important factors in the development of the lesion are chemical and mechanical. The typical lesion of peptic ulcer occurs in a mucosa exposed to acid gastric content which is not protected by the mechanism for diluting, buffering, and neutralizing the acidity of the gastric content. It never occurs in a mucosa not exposed to acid gastric content. The ulcer begins with injury and destruction chemically of the surface cells of the mucosa with which the acid gastric content comes in contact. The site of the ulcer is determined by the mechanical factor of expulsion of the gastric content—that is, it occurs in the region where the gastric content first strikes after emergence from the stomach. Progression of the lesion is due to the mechanical erosion of succeeding layers of the injured surface cells and chemical injury to the living cells previously protected by the dead cells above. Limitation of the lesion is determined by the area over which an effective degree of acidity for cellular injury can be maintained. Chronicity of the lesion is brought about by the same two important factors producing the lesion—by destroying chemically and washing away mechanically the delicate newly formed proliferating cells as soon as the healing edge has progressed beyond the periphery of the ulcer. Healing of the lesion always occurs immediately after it is protected from the acid gastric content.

REFERENCES

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A. Biemond (*Nederl. Tijds. Geneesk.*, 1939, 83, 1234), who records his observations on 250 cases of disseminated sclerosis treated at the Neurological Clinic of the Wilhelmina Hospital at Amsterdam between January, 1928, and December, 1937, maintains that drug treatment of this condition has hitherto proved entirely ineffective. The type which offered an apparently favourable response to treatment was just that which tended to show spontaneous remissions. Operative treatment by bilateral stellate ganglionectomy is inadvisable as it is theoretically unsound and not free from danger.