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PATHOLOGY AND CLINICAL SIGNIFICANCE OF STOMACH ULCER

From a Study of the Material from 216 Partial Gastrectomies for Ulcer, Ulcer and Carcinoma, and Carcinoma

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IN the history of the study of ulcer another period may be recorded, and that is, the observation of ulcer in the living individual as seen at operation and immediately after removal. With the improvement of legal right and individual submission to more scientific examination, trained observation, and surgical dexterity, our knowledge has increased in a systematic and orderly manner until to-day we are in a better position to confirm and add to the remarkable observations and records of Baillie, Abercrombie, Cruveilhier, Morgagni, Rokitansky, Müller, Heitler, Waldeyer, Hauser, Welch, and others in passing successively from purely autopsy findings, and autopsy and clinical findings, to the immediate examination of early ulcers during and after resection.

The cases herewith presented are a part of the material examined freshly within two minutes after removal from two hundred and sixteen resections of the stomach for ulcer, ulcer and carcinoma, or carcinoma, in the clinics of Drs. W. J. and C. H. Mayo.

The material divides itself grossly and microscopically into three groups. These groups comprise two hundred and sixteen cases, fifty-eight of which are ulcers, one hundred and twenty-five ulcer and carcinoma, and thirty-three carcinoma without any good evidence of ulcer. The last two groups will be considered in this paper. Group one comprises cases which, at operation, were ulcers which were resected for ulcer with possibly carcinomatous borders. Upon examination, grossly and microscopically, no evidence of carcinoma was found. Group two is considered here because the specimens present all the characteristics of ulcer grossly and microscopically, with the additional feature that the borders contain definite areas of carcinoma microscopically. Specimens in this group show the base of the ulcer free from carcinoma and consisting only of granulation and scar tissue. In order to show that up to the present time we cannot say absolutely that all gastric carcinomata develop on ulcer and that some ulcers do show carcinomatous remnants in the base, and may be ulcerated primary carcinomata, it may be well to show some advanced cases of ulcer and carcinoma. From the pathological standpoint during the observations the following questions arose:

What is the life history of gastric ulcers, e. g., how do they begin, progress, and terminate? What are the gross and microscopical characteristics, and how do they differ from the so-called ulcerated, gastric carcinomata?

From a clinical diagnostic standpoint: Can one be sure that one is dealing with the simple ulcer, and what are the chances for its not being a simple ulcer? From a therapeutic

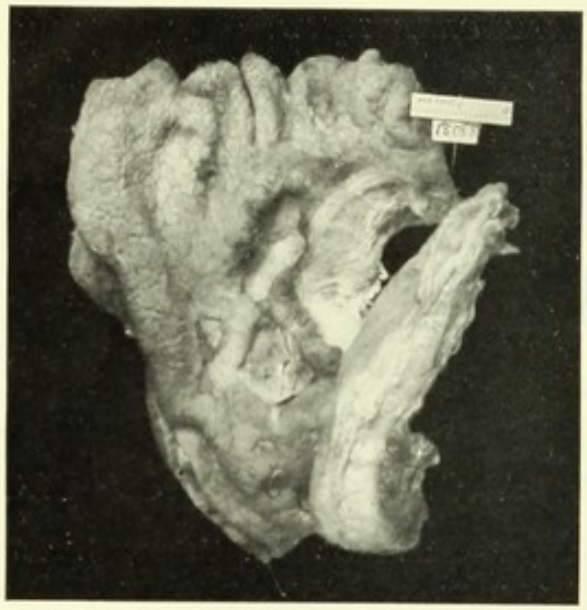

Fig. 1. (Case No. 18088.) Multiple gastric ulcers.

standpoint: In a case with a typical ulcer history what are the chances that the medical or hygienic measures are combating a condition which we know is certainly incurable by such measures? At operation what are the difficulties in making a differential diagnosis between a benign ulcer and a malignant ulcer?

Technique. Immediately after the removal of the specimens, frozen sections were made and stained with Unna's polychrome methylene blue. With this method[1] a more accurate and more beautiful picture may be had than by staining with hæmatoxylin and eosin. They contain less artifacts than would be expected, and do occur after hardening in formalin, dehydrating in alcohols, and clearing in the various clearing fluids.

Blocks were taken from every specimen and hardened in ten per cent formalin, twenty-four hours, frozen, cut, and stained with hæmatoxylin and eosin for comparison and record. The gross specimens were fixed according to Melinkow's modification of Kaiserling's method of preserving color or in ten per cent formalin.

Case No. 18088 (Figs. 1 to 8). A male, aged forty-five, who twenty years ago had three attacks of inflammation of the bowels, during a period of nine months, and was in bed about a week with each attack. He had severe pain over McBurney's point lasting three days. This was severe enough to cause vomiting. The point

[1] Wilson, Journal American Medical Association, December 2, 1905.

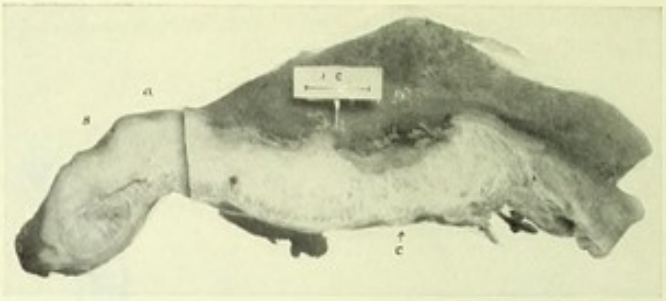

Fig. 2. (Case No. 18088.) Gross section through four of the ulcers showing various degrees of extension of the process of erosion into the coats of the stomach wall.

was tender, the soreness lasting about three days after patient was out of bed. Four years ago he had some pain and soreness, especially after exertion. About seven or eight months ago there was again tenderness over McBurney's point; it came on at eleven A. M. and four to five P. M., and continued until salty water ran out of the mouth. The patient would then vomit; the vomitus was sour and bitter, four months ago it became bloody. Three days ago a tumor was noticed in the epigastrium. His weight decreased sixty pounds. He complained of gas one to two hours after meals. Belching of this gas gave no relief. The pain often radiated to the loin. At operation three-fourths of the stomach and the lesser curvature were resected for cancer and multiple ulcers. The resected portion contains five simple ulcers and one malignant ulcer varying in size from 3 mm. to 2½ cm. in diameter. The largest of these (Fig. 1,2, c) ulcers is about one-half cm. in depth, and has a base which extends partially through the muscularis and is covered to the extent of one-half mm.with necrotic tissue. The next largest ulcer which is 2 mm. in depth, does not extend to the muscularis, but rests upon a chronically inflamed submucosa, which is composed of dense scar tissue. The ulcer

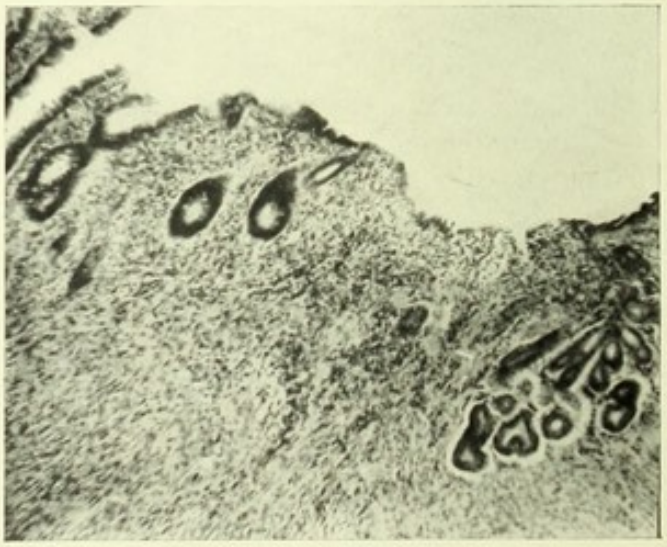

Fig. 3. (Case No. 18088.) Microphotograph through ulcer (a) Figs. 1 and 2.

(b) is 2 mm. in depth and 6 mm. in diameter and rests upon a chronically inflamed submucosa. There is no apparent hypertrophy of the mucosa, but it does project over the edge of the ulcer cavity. The bases of the two larger ulcers are composed of dense connective tissue, along the surface of which are found lymphocytes and necrotic connective tissue. Throughout this connective tissue mass and extending into the mucosa are numerous aggregations of lymphoctytes. There is no evidence in the mucosa of any irregularity in the glandular arrangement; however, a few of the cells of the individual glands show marked irregularity in size. These, however, cannot be said to be carcinoma. In no portion of the border of any of the ulcers is there any trace of epithelium dipping below the mucosa into the submucosa. The nuclei are apparently regular in shape and size in all areas examined, excepting the one small area described above. The smallest ulcer (Fig. 1, 2a, 3) does not extend below a depth greater than half that of the mucosa. Epithelial cells or remnants of glands may be seen in the base of this ulcer. The base is composed of dense connective tissue, which extends through the mucosa and submucosa. The muscularis mucosæ is almost completely intact, with narrow strands of connective tissue penetrating it. The glands in the border of this small ulcer are regular in shape, and have nuclei which show no irregularities. The mucosa is infiltrated with lymphocytes in great numbers. One centimeter from the border of the ulcer is a definite chronic gastritis.

In this specimen we have "erosions" in various stages, from a partial destruction of the mucosa to complete destruction of the mucosa and involvement of the muscularis. Whether or not the gastritis seen in the mucosa bordering the ulcers is secondary to the condition which caused the ulcer, or is primary to the erosion

Fig. 4. (Case No. 18088.) High power microphotograph through the base of ulcer (a) Figs. 1, 2, and 3.

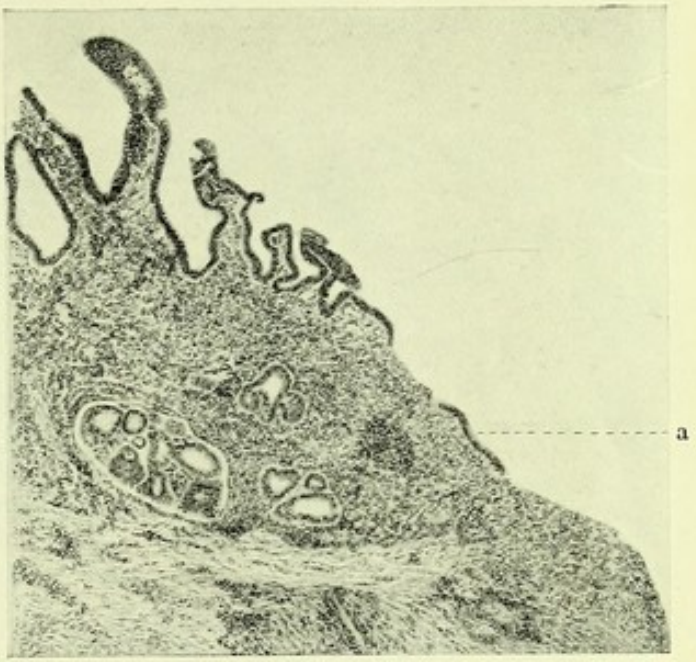

Fig. 5. (Case No. 18088.) Border of ulcer (b) in Figs. 1 and 2. (a) Apparent attempt to replace the lost epithelium.

is difficult, perhaps impossible to determine, the connective tissue elements apparently being of the same age and structure.

Case No. 28173 (Figs. 9, 11), a male aged fifty-five. Four years ago he had "stomach trouble" with distress and belching of sour fluid and gas. For one year the patient's trouble was mild and then the pain became severe in the epigastrium and extended through to the back and left shoulder, but was more severe in the back. These pains came on two to four hours after meals, and were relieved by forced vomiting. The distress was also relieved by food or soda. There was never obstructive vomiting. The condition would be improved for a few weeks and worse for a couple of months. The pains grew gradually more severe. His appetite was good, his bowels were regular, and there was no jaundice. Loss of weight 15 pounds. Gastric analysis showed a total acidity of 70, free HCl 50, and combined HCl 10. The feces contained blood. The resected portion of the stomach is about 5 cm. in diameter and contains an ulcer 8 mm. in diameter. There is no gross evidence of hypertrophy of the border. A section through the center shows a conically-shaped erosion, at the base of which there is extensive connective tissue proliferation which radiates from the base, and which was apparently adherent to some neighboring organ. Grossly there is no sign of carcinoma. The erosion penetrates the muscularis and the scar tissue extends through the whole wall. Upon microscopical examination, the base is found to consist of scar tissue, which is necrotic on its internal surface, but without new blood-vessel formation. There are extensive aggregations of lymphocytes along the necrotic border, the lymph spaces are filled with lymphocytes and radiate from the center of the ulcer.

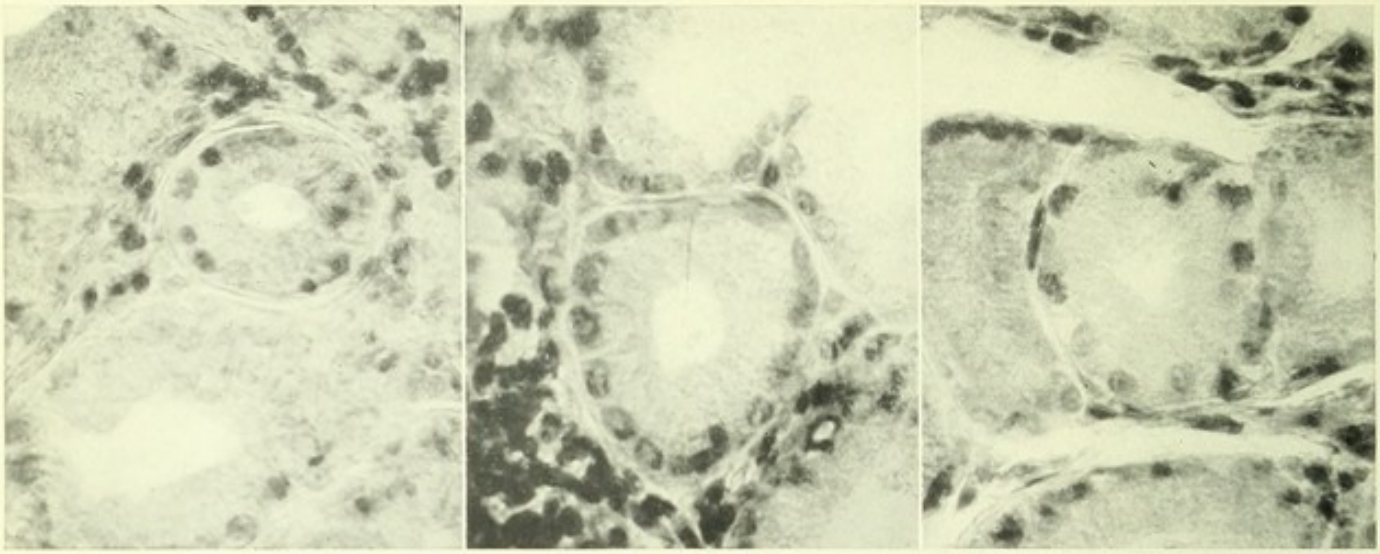

Fig. 6. Fig. 7. Fig. 8.

Figs. 6, 7, and 8. (Case No. 18088.) Microphotograph showing the regularity of the deeper glands of the mucosa in the borders of the ulcers.

The base of the ulcer shows no signs of glandular elements. The border of the mucosa is markedly infiltrated with lymphocytes. The nuclei of the glands are round and show no irregularity in form. There are no microscopical signs of carcinoma in the specimen.

Case No. 25692 (Figs. 12, 13), a male, aged sixty, who came for consultation complaining of having suffered from shortness of breath and spells of pain, associated with vomiting of sour material. This was often relieved by food for three to five hours. At times the attacks became worse; milk and hot water at night eased the pain. There was no history of acute perforation. Tenderness was present over an epigastric area the size of the hand. During the past eighteen months he has used the stomach tube practically every day, and obtained some blood at times. He has had steady pain for two to three years. Appetite good, bowels sluggish. Gastric analysis showed a total acidity 70, free hydrochloric acid 52, combined hydrochloric acid 14, and food remnants. Hæmaglobin 82 per cent. At operation the pyloric end of the stomach was resected for perforating ulcer. This specimen contains an ulcer 1 cm. in diameter and about 7 mm. in depth. The mucosa overhangs the ulcer and is composed of glands, between which is an infiltration of lymphocytes. The nuclei of the glands are regular in size and do not show mitotic figures. The mucosa is sharply marked off from the submucosa. The base of the ulcer is composed of connective tissue containing masses of lymphocytes and remnants of glands. The nuclei of these glands remnants are small, round, and do not show any mitotic figures. A gross section through this ulcer shows a perforation of all the coats of the stomach by dense connective tissue.

Case No. 27381 (Fig. 14). A male, aged thirty-four, who has had almost constant distress in stomach region for thirteen years. For four months at one time he had relief, the rest of the time distress, pain, gas, and sour vomiting occurred two to four hours after meals. Food or vomiting relieved this pain. The vomitus never contained blood. Loss of weight 45 pounds. There is a note in the history that the patient gives "a steady ulcer history." The pains were very severe but never prolonged. Gastric analysis revealed a total acidity of 42, free hydrochloric acid 25, and combined hydrochloric acid (questionable). At operation a chronic perforating ulcer of the lesser curvature, the size of a dime, was found. It had perforated into the head of the pancreas. The specimen is an ulcer of the lesser curvature 5 mm. in diameter and 5 mm. in depth. The base is composed of scar tissue and has a necrotic inner border filled with lymphocytes and leucocytes, and shows no evidence of new blood-vessel formation. There are no epithelial elements in the base. Aggregations of lymphocytes are present throughout the submucosa. The border of the mucosa is infiltrated with lymphocytes and leucocytes. There are no new formed capillaries in this border. The glands are composed of cells with round nuclei, which do not show mitotic figures, or any irregularity in size or shape. Between the cells large numbers of leucocytes are seen. No carcinoma is to be seen in the specimen.

Case No. 30163 (Fig. 15). Female, aged thirty-nine, who was in bed four weeks with "inflammation of the bowels" about nineteen years ago. About two years ago severe pain in the epigastrium and sour belching occurred one and one-half to two hours after meals. Food gave no relief. There was soreness to the left of the vertebral columns during these attacks. Later she began to vomit. This condition became gradually worse and three or four years ago she began taking hospital starvation cure, which improved her condition. Her appetite was fair, her bowels were regular, but there was some loss in weight. Soda often relieved the pain temporarily. At the time of the patient's visit the pain came on two to three hours after meals, associated with much gas and distress which was relieved by vomiting and food. Gastric analysis showed

a total acidity of 52, free hydrochloric acid 38, combined hydrochloric acid 14. At operation there was found an ulcer 1 cm. in diameter and one-half cm. in depth upon the lesser curvature of the stomach. The complete ulcer was resected and examined immediately for carcinoma. It, however, shows only a deep erosion to the muscularis and a base in which there is an extensive infiltration with lymphocytes and scar tissue. In the base there is no evidence of glandular elements. In the immediate border of the mucosa, which projects over the edge of the ulcer, is an infiltration with round cells but no apparent hypertrophy of the glands. The glands themselves are regular in contour and are composed of cells with perfectly round or oval nuclei, showing no irregular mitotic figures or signs of regular or irregular hyperplasia. There are therefore no signs of carcinoma in the border. The base shows no evidence of granulation tissue. There are no new formed blood-vessels. It is simply a necrotic base. The lymph spaces extending from the border in the submucosa and muscularis are filled with lymphocytes.

Case No. 30040 (Fig. 16), is a male, aged forty, who for ten years has had attacks of pain in the upper abdomen. At first these were not severe and were of short duration. The last three or four years these attacks became more frequent and more severe. They lasted from a month to two months, and occurred periodically with intermissions of about a month. During the periods of attack the pain was present every day, lasting one to two hours, and was severe enough to cause vomiting. The patient, at the time of consultation, was able to eat everything, but had considerable gas and had lost 30 pounds in the last three years. Food relieved pain for about an hour. He has never vomited bile or blood, but complained of sour eructations. Gastric analysis showed a total acidity of 58, free hydrochloric acid 40, combined hydrochloric acid 18, and blood present. At operation an ulcer of the posterior wall of stomach one and one-half inches below the cardia, and the size of a silver three-cent piece was resected. The ulcer is 6 cm. in diameter and 3 mm. in depth. The base is composed of scar tissue and necrotic material composed of lymphocytes and leucocytes, and shows no new blood-vessel formation, and no glandular elements. The border of the mucosa which overhangs the connective tissue border, is infiltrated with lymphoctytes,and is composed of glandular elements which show evidence of hyperplasia. The nuclei are round and oval and almost uniformly regular in shape but irregular in size. There are aggregations of lymphocytes throughout the subbasal tissue.

Case No. 27919 (Figs. 17, 18), a male, aged fifty-three, who, at his first visit to the clinic, November, 1906, for two or three months had had occasional pain and ache from two to three hours in the gall-bladder region. This was associated with some gas and distress in stomach when he ate liberally. His appetite was good. The laboratory findings were negative. Ten years ago the patient had sour eructations and pain over liver three hours after meals. October 24, 1908, appetite was good; about three hours after food was taken he began to feel distress in epigastrium with sour eructations; always has gas and occasional vomiting, less than once a week. Soda, alkalies, eating, and irrigation gave relief. He had irrigated his stomach almost daily for years past. Recently he noticed food remnants in the washings. The gastric analysis showed a total acidity of 64, free hydrochloric acid 30, combined hydrochloric acid 14, fatty acids, and food remnants. A second gastric analysis two days later showed a total acidity of 90, free hydrochloric acid 28, combined hydrochloric acid 30, fatty acids, and food rem-

Fig. 9. (Case No. 28173.) Single gastric ulcer.

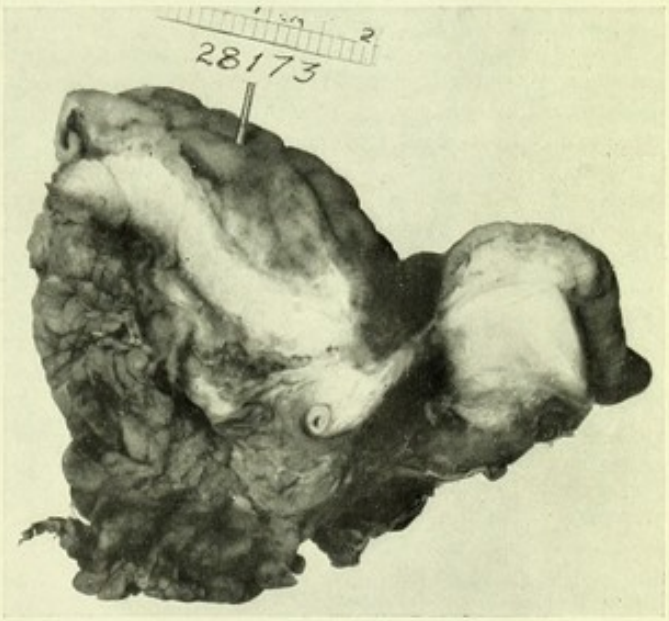

Fig. 10. (Case No. 28173.) Gross sections through the ulcer showing extension through all the coats of the stomach wall.

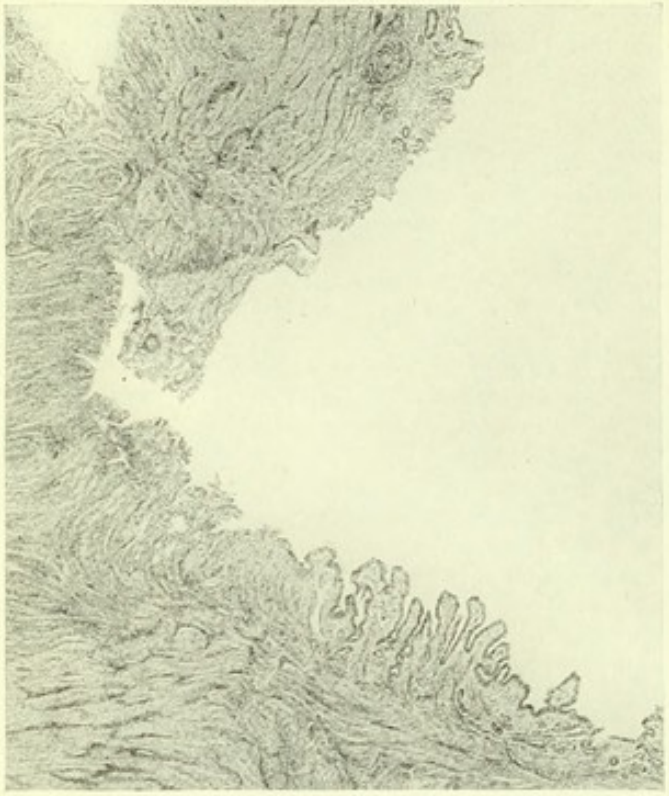

Fig. 11. (Case No. 28173.) Section through the ulcer showing the character of the border and the necrotic scar tissue base.

nants. At operation two ulcers at the pyloric end of the stomach on the posterior wall, one and one-half inches above pylorus were found. One was carcinoma. The specimen consists of a resected portion of the stomach, containing two shallow ulcers, each ulcer about 1½ cm in diameter and about 3 mm. in depth. They have not penetrated the muscularis. There is an increase in the connective tissue of the submucosa, but this increase does not extend to the muscularis. The glands of the mucosa are regular in shape and have nuclei which are round and show no irregular hyperplasia. The base of both ulcers consists of scar tissue. Beneath the mucosa in the scar tissue are islands of irregular epithelial elements. These small masses of carcinomatous tissue appear to have grown into the scar mass from the immediate edge of the ulcer below the inflammatory mucosa. The mucosa is infiltrated with lymphocytes with only occasional remnants of glands, the nuclei of which show mitosis and irregularity in size. The epithelial islands below the mucosa in this fibrous mass are typical epithelial glands, with the exception that they are irregular in form, and that the cells are irregular in size and show irregular mitosis.

Case No. 21555 (Figs. 19 to 24 inclusive). A male, aged sixty-seven, who thirty-five years ago had dyspepsia, but nothing severe, and from then until two years ago had no trouble. At this time he began to have pain, associated with gas and sourness when his stomach was empty. He became gradually worse until four months ago when he began to vomit "sour stuff" and belch gas. He complained of distress in the epigastrium. There was "coffee grounds" vomitus at this time. In two years he had lost 35 pounds in weight, and most of this has occurred during the last four months. The gastric analysis showed hyperacidity and lactic acid present. One-third of his stomach was resected. The specimen contains an oval-shaped ulcer 3 cm. in its long diameter, about 1½ cm. in the short diameter, and 1 cm. in depth. A section through the ulcer shows that the base is infiltrated with lymphocytes and composed of connective tissue, which extends through the muscularis and peritoneum. The inner surface is necrotic and contains no epithelial elements, but here and there aggregations of lymphocytes. At a point just below the border is a definite area of perverted epithelium. This area grossly is definitely marked out from the rest of the base, and is the only area which shows carcinoma. It is definitely connected with the border of the mucosa and seems to be an outgrowth from it, which is itself composed of irregular hyperthrophic glands, between which is an extensive infiltration with lymphocytes. The epithelial nuclei of this portion of the border are irregular in shape and size.

This case is of great importance because in it we have the exact picture of ulcer as seen in the foregoing cases, with the addition of a definite area of carcinoma situated below the mucosa of the border, and definitely connected with the glands of the same, showing that this area is most probably an outgrowth of the glands in the border of an ulcer, rather than a remnant of an ulcerating carcinoma.

Case No. 24527 (Figs. 25, 26). Male, aged fifty-three, who was examined on January 7, 1908, and who had complained for five months of vomiting, nearly every night for the past month, about bedtime. He

Fig. 12. (Case No. 25692.) Gross section through a single gastric ulcer.

had been eating three meals daily and felt no inconvenience through the day, but complained of gas between 8 P. M. and midnight, when he vomited a large quantity of partially digested food. He then felt comfortable until the next night. He has had no severe pain but has had some loss of appetite. There was no blood in the vomitus. He was always well until August. Hæmaglobin 67 per cent. Gastric analysis revealed a total acidity of 60, free hydrochloric acid 20, combined hydrochloric acid 20, fatty acid, but no blood. One-half of the stomach was resected. The resected portion contains a shallow ulcer about 4 or 5 cm. in diameter, and about 2 mm. in depth. The surface of the base is smooth and the mucosa gradually diminishes in thickness toward the base. A gross section shows that it has perforated all walls of the stomach and is infiltrated with carcinoma. Microscopically, one sees an eroded base containing carcinomatous tissue. The mucosa of the border is also extensively involved.

In this specimen we have an erosion of the mucosa and an involvement of all the coats of the stomach under the ulcer by carcinoma. It is impossible to say whether this ulceration was due primarily to carcinoma, or whether the carcinoma was due to an ulceration.

Case No. 16651 (Figs. 27, 28). Female, aged forty-two, who sixteen years ago, five days after a confinement, was washing clothes, at which time she had a severe cramp in "stomach." During that summer she had cramps, which lasted from one hour to a day. Toward fall of the same year she began to vomit immediately or about two hours after meals. This vomitus was not sour, there was no blood and no pain. She had no gas from stomach until this last summer. Bowels usually regular. These same spells lasted until four or five years ago and then began to be less severe. For two years previous to last July she was perfectly well, ate everything, was hearty, strong, and worked steadily, weighed 142 pounds. Then she began to lose her appetite and felt weak and tired.

There was no pain. In August she began to belch as soon as food was taken; often the vomitus contained a previous meal. A tumor was palpable in the epigastrium. Hæmaglobin 27 per cent. Gastric analysis showed a total acidity of 50, no free hydrochloric acid, combined hydrochloric acid 5, lactic acid, blood, and fatty acids. At operation about three-fourths of the stomach were resected. The specimen contains an ulcer about 2 cm. in diameter and one-half cm. in depth, with a border which overhangs about 3 mm. Upon gross section, there is a connective tissue proliferation extending from the base to the peritoneum. The former rests upon the lower half of the musculature, through which it has almost completely eroded. In the base one sees grossly and microscopically carcinomatous areas, some of which have become partially eroded.

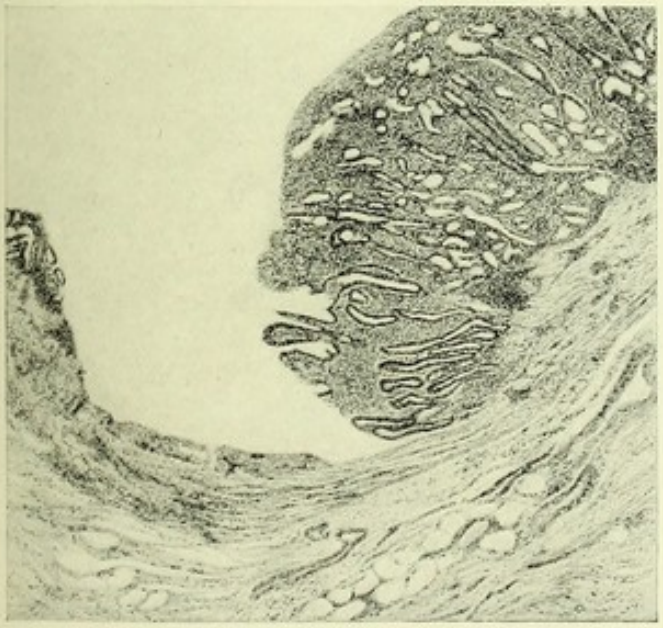

Fig. 13. (Case No. 25692.) Section through the border of the ulcer showing the overhanging hypertrophic border.

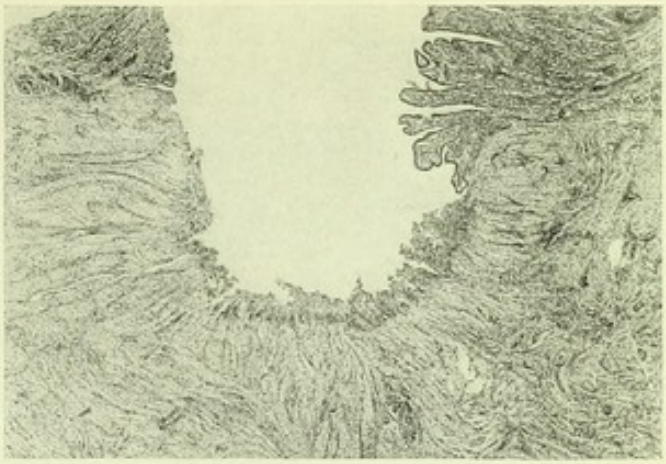

Fig. 14. (Case No. 27381.) Section through an ulcer showing the infiltration, destruction of the mucosa and the necrotic base.

Fig. 15. (Case No. 30163.) Section through an ulcer with an extensively infiltrated base.

Fig. 16. (Case No. 30040.) Section showing the hyperplasia in the mucosa in an ulcer border.

In the overhanging border there is an extensive carcinomatous change with an hyperplasia of the glands and an infiltration with lymphocytes. The carcinomatous areas extend completely through the wall and the scar tissue of the perforation.

Case No. 21882 (Figs. 29, 30). Female, aged thirty-eight. Eight years ago she was weak, tired, and worn out; four to five years ago she became weaker. About one and one-half to two years ago she had her first sickening pain. There was no nausea, no vomiting, but occasional sour eructations. About two weeks ago there was a severe pain in the back and left costal arch. A tumor in epigastrium has been noticed for about seven or eight months; epigastric pain, gas, nervousness, weakness, and loss of flesh. Gastric analysis (second test) showed a total acidity of 50, free hydrochloric acid 30, combined hydrochloric acid 14. At operation two-thirds of the stomach were removed for carcinoma associated with ulcer. The specimen contains an ulcer from 3½ to 4 cm. in diameter and from 1½ cm. to 2 cm. in depth. There is a perforation of all the coats of the stomach, which has become adherent to neighboring organs. There is an extensive carcinomatous involvement of the ulcer base

The specimen shows that the ulceration, although it might have started as a simple ulcer, has become deeper through the process of erosion of tissue composed of carcinoma. Such specimens have undoubtedly led to the belief that all ulcers which show carcinoma were developed in this manner. It is impossible to say whether or not this originally was an ulcer, or carcinoma with secondary ulceration.

Macroscopic description. Ulcers of the stomach vary in size from 1 mm. (Figs. 1, 2, 3) to several centimeters in diameter and from 1 mm. to 2–3 cm. (Fig. 30) in depth. They may be single or multiple (Fig 1). The base may be ragged or smooth. All of the ulcers in my series have rough bases because they were removed soon after an acute attack or in the stage in which mild inflammatory symptoms were present. The base contains elements of the mucosa, muscularis mucosæ, submucosa, or muscularis, depending upon the extent of the necrosis, as may be seen in Fig. 3, in which the smallest ulcer (Figs. 1, 2, 3) has eroded about half of the mucosa forming a base containing glands and infiltrated interglandular stroma. The largest ulcer in case No. 18088 (Fig. 2) involves the muscularis. On section through the specimen, the immediate base is seen always to be composed of connective tissue, which speaks perhaps for the gradual development of the ulcer instead of a rapid destruction below the muscularis mucosa. The initial erosion or necrosis of the mucosa may be of rapid formation, but the connective tissue base seems to show that the process is sufficently slow below the muscularis mucosæ for the formation of a temporary, if not permanent, barrier of scar tissue. Hæmorrhagic areas in the base are present in many ulcers in this series. The border of the mucosa which has the color of congested normal mucosa, does not always show evidence of hypertrophy, especially in small ulcers. In

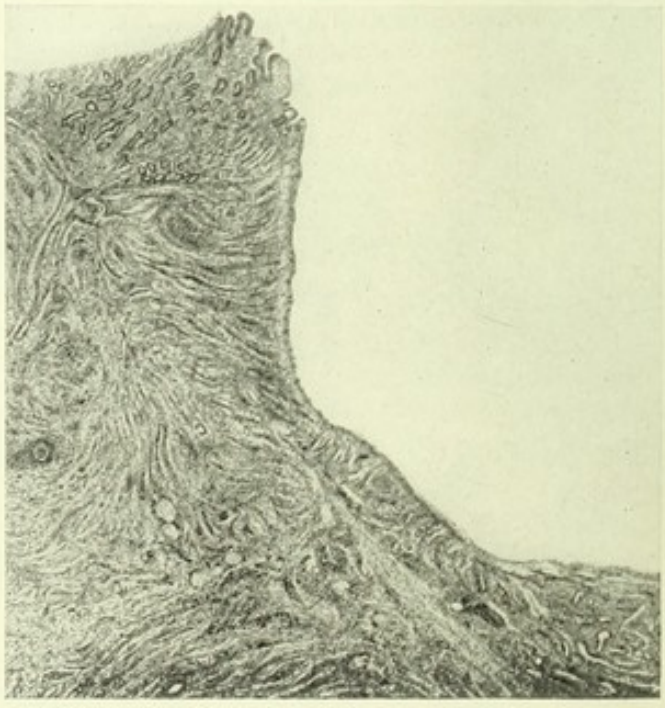

Fig. 17. (Case No. 27919.) Section through a portion of the border of a benign ulcer.

the larger ones, which appear to be of long standing, the border of the mucosa projects or hangs over the edge and is almost always hypertrophic. When one examines a fresh ulcer in gross section there are four distinct coats visible: the mucosa, submucosa, muscularis, and subserosa. These are either eroded in the base of the ulcer or infiltrated with scar tissue (Figs. 1, 2). It is difficult and often impossible to detect epithelial growths in the wall of early ulcers (Figs. 18, 20). In many of such cases which, grossly, one is justified in calling an ulcer, early microscopic carcinomatous invasions from the mucosa exist (Figs. 18, 20).

Microscopic description (low power). The mucosa of an ulcer border rests on or is marked off from the submucosa by the muscularis mucosa, which is composed of two or three rows of muscle cells. The glands which are regular in shape in the border of some ulcers may be seen cut longitudinally or transversely (Figs. 3, 4). The demarkation between the glands and the interglandular tissue is sharp. There is a regularity in the arrangement of the component parts of the mucosa, which is best seen with low power. An infiltration with leucocytes or lymphocytes, or both, destruction of the glands, and invasion of the submucosa, may be readily seen with this power. The base is composed of dense connective tissue, the general growth of which is perpendicular, or nearly so, to the base (Figs. 2, 11). The base which extends to the border of the mucosa is infiltrated and necrotic (Figs. 14, 15). If there are remnants of irregular glands and the muscularis mucosæ has been destroyed or penetrated by perverted epithelium, one may be sure that carcinoma is present (Figs. 26, 28). If the base does not show these elements a careful search should be made for epithelial structures in the rest of the submucosa (Fig. 21). If such be present they should be studied for any irregularity in architecture, as seen in Figs. 22, 23. If perfectly regular (Figs. 16, 24) one may be dealing with an adenoma. If irregular (Figs. 22, 23) one is surely dealing with carcinoma. In the mucosa the differentiation between infiltrated tissue, inflammatory hyperplastic tissue, adenoma, and carcinoma is not always possible with a low power. The submucosa and mus-

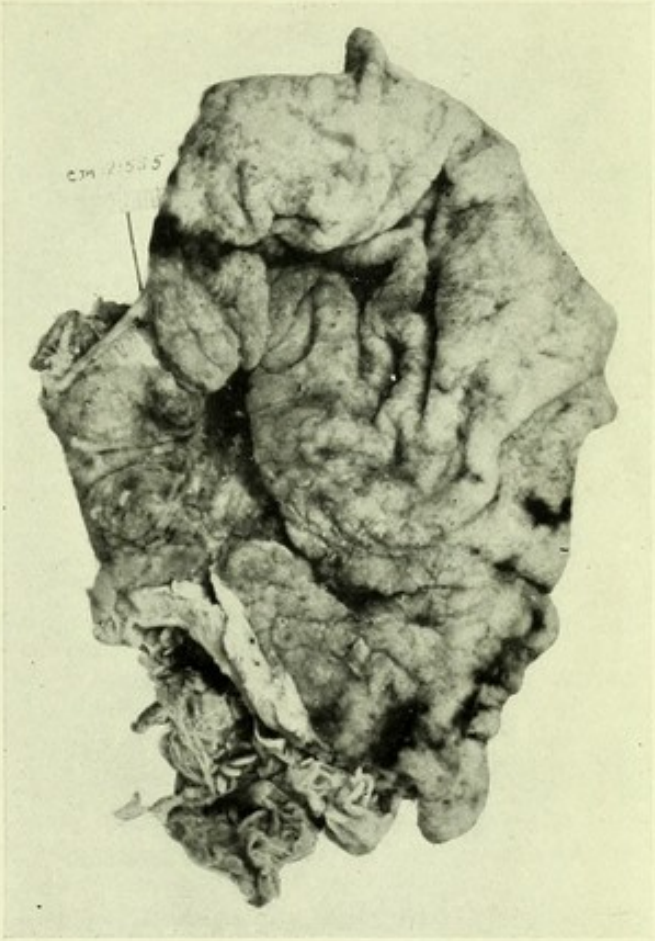

Fig. 19. (Case No. 21555.) Single gastric ulcer with a carcinomatous border.

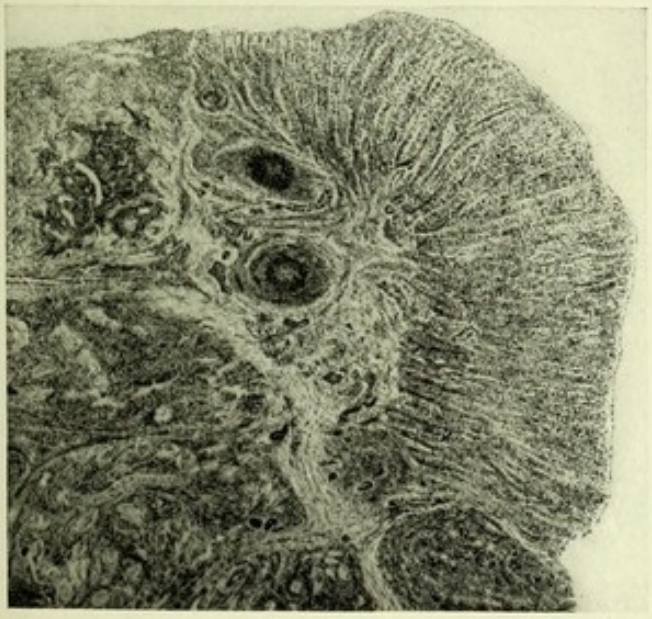

Fig. 18. (Case No. 27919.) Section through a portion of the border of a malignant ulcer, showing islands of carcinoma in the submucosa.

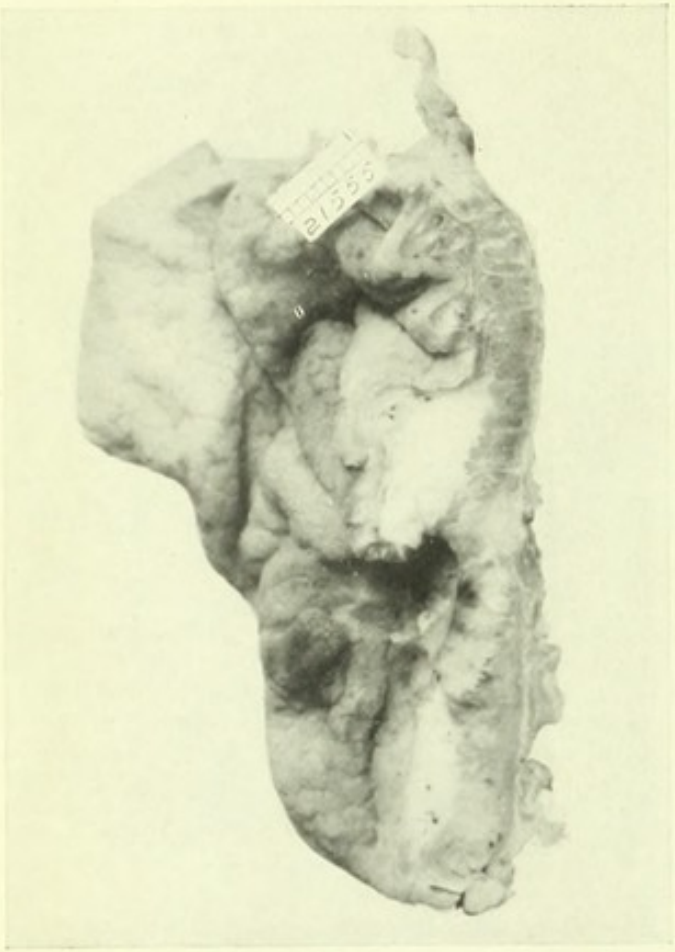

Fig. 20. (Case No. 21555.) Gross section through the ulcer.

cularis in ulcers and ulcers associated with carcinoma in the immediate vicinity of the lesion are infiltrated with scar tissue, and usually the lymph spaces are filled with lymphocytes (Fig. 15). Not infrequently aggregations of lymphocytes may be seen throughout the wall, especially in the mucosa and submucosa.

Microscopic description (high power). Groups of cells (Figs. 16, 22, 23) such as may be seen in a section through one gland should be studied with the high power to determine whether or not the border of an ulcer has passed beyond the stage of inflammatory hyperplasia. A study of the glands in this manner reveals the following conditions: In the smallest ulcer seen in Fig. 3, the bases of the cells rest regularly on a basement membrane and do not penetrate it. The relative proportion between the nucleus and the protoplasm is that of a differentiated cell and is about 1:3 or 1:4. The surrounding stroma is infiltrated with lymphocytes. The nuclei take the stain (Unna's polychrome methylene blue or hematoxylin) densely, and are either oval or round and vary in size and shape within the normal limits of normal gastric gland nuclei, depending on the plane in which they are cut. They are regular in shape and size. In the border of an ulcer which shows a more marked reaction to the irritant the same picture may be seen accompanied by more extensive hyperplasia (Fig. 16) and increase in the relative proportion of the size of the nucleus to protoplasm. The nuclei stain less densely. In this condition the line of demarkation between the stroma and the gland is usually not so regular. The glands may be and often are distended and distorted. In the same specimen in which such an hyperplasia occurs one may frequently see glands which are more irregular and possess all the characteristics of hyperplasia, with the addition that the nuclei are irregular in size and shape beyond the normal limits (Figs. 22, 23). Indeed some may be two or three times the size of the nuclei lying next to them. Such irregularity is seen

Fig. 21. (Case No. 21555.) Section through the hypertrophic border showing the ulcer characteristics and the invasion of the submucosa by hyperplastic epithelium of the border.

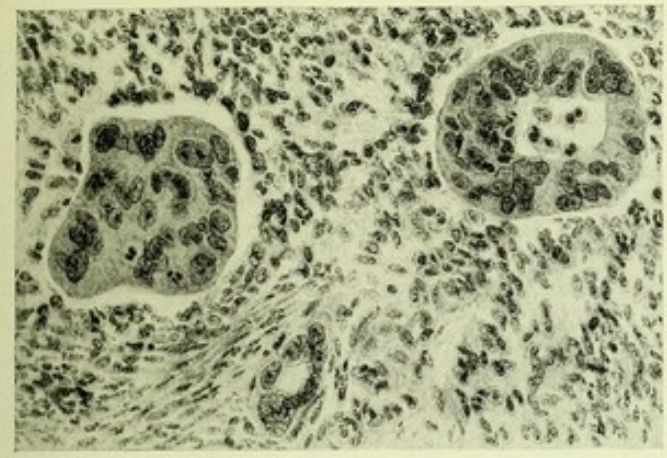

Fig. 22. (Case No. 21555.) Islands of carcinoma in the submucosa.

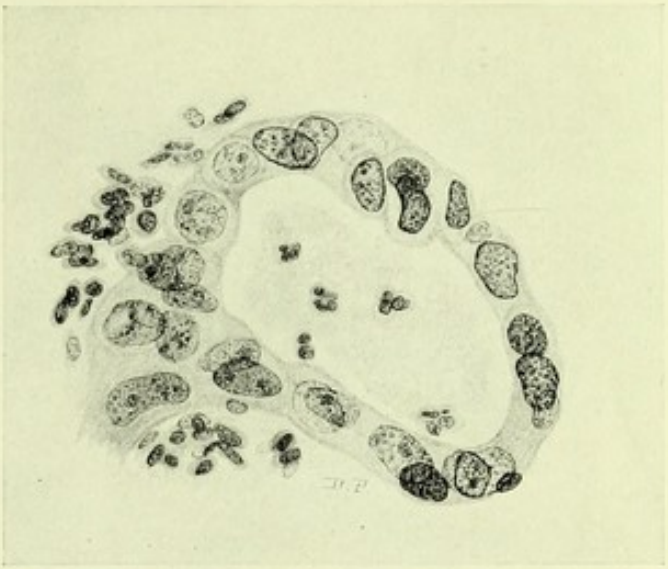

Fig. 23. (Case No. 21555.) Irregularly shaped epithelial cells in the border of the mucosa near the muscularis mucosæ.

in more extensive carcinomata and no hesitation occurs in making a diagnosis. Such a picture occurs in very early cases in the mucosa, before the submucosa has been invaded, and should be also considered carcinoma. One need not always wait for the basement membrane to be ruptured or invasion of tissue in which normally there is no epithelial tissue. There are many cases, however, in which the differentiation between hyperplasia and malignant hyperplasia is impossible at present on account of the apparent lack of demarkation between simple inflammatory hyperplasia and malignant hyperplasia. We are beginning to have it strongly impressed upon us that hyperplasia is a forerunner of malignancy, that hyperplasia varies in degree, and that carcinoma is a malignant hyperplasia which also varies in degree, and that some of the degrees, so far as the morphology is concerned, are indistinguishable, if not identical.

Ulcer and malignancy. The question, do ulcers become malignant as one of their sequelæ, seems, from my material at least, to be answered in the affirmative. What percentage heal, perforate, or become malignant is impossible to determine. The close association of carcinoma with ulcer may be strikingly seen in the fact that seventy-one per cent of all our resected specimens of the stomach for carcinoma were associated with definite ulcers (Wilson and MacCarty)[1] and that sixty-eight per cent of the resected ulcers of the stomach, including the duodenal ulcer, which rarely becomes malignant, were associated with carcinoma.

Ulcer process and life history of gastric ulcer. From a study of the morphology of ulcers it would seem that the process of ulceration, erosion, or necrosis manifests itself in single or multiple lesions, and that the initial lesion, at least in many cases, is a destruction of the mucosa itself, and that the reaction to this destruction is a connective tissue proliferation, and an attempt on the part of the epithelium of the mucosa to replace that which was lost (Fig. 5). The architecture of the connective

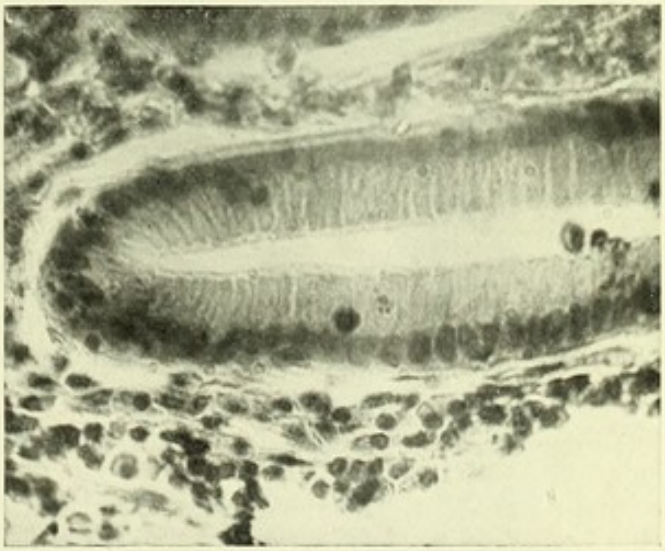

Fig. 24. (Case No. 21555.) Microphotograph of regularly shaped glands in the mucosa near the ulcer border.

[1] American Journal of the Medical Sciences, December, 1909.

Fig. 25. (Case No. 24527.) Gastric carcinoma.

tissue proliferation in the underlying tissue forming the base of all the ulcers studied in this series is such as to form an attempted barrier against further destruction. This barrier undergoes necrosis in the ulcer crater, thus increasing gradually the depth. If the base contains carcinomatous tissue, it too shares in the destruction (Figs. 26, 28). Perforation occurs by extension of the inflammatory process through the lymphatics, or by direct erosion, as may be seen in some acute cases. One may state the life history of gastric ulcer after the initial necrosis, the nature of which we do not know, as a gradual necrosis of the mucosa, muscularis mucosæ, submucosa, and subserosa. Ulcers heal, as may be seen at autopsy; they deepen and perforate as seen at autopsy and operation, or become malignant, as seen especially at operation. The last condition is often the sequel of ulcer, because we find ulcers which show no carcinoma, and ulcers which, grossly and microscopically, are exactly similar to the ulcers without carcinoma, but which contain small areas of irregular gland structures, with irregular nuclei, which show irregular mitosis. These islands of perverted epithelium may be seen in the dense scar tissue of the submucosa, just under and connected with the mucosa of the border (Fig. 21). Such ulcers do not present any epithelial elements in the base, and are therefore not ulcerated carcinomata.

CLINICAL DIAGNOSIS

The details of the clinical diagnosis will not be considered in this paper. While there has been a vague feeling from the pathological standpoint that carcinoma frequently occurs upon gastric ulcer, strong pathological evidence has been wanting. The clinician has for years noticed that carcinoma of the stomach often follows a prolonged history of gastric ulcer, and has believed that such was a forerunner of malignancy. The evidence, however, was only circumstantial. The fact established allows and demands a stronger admonition to the diagnostician who, as soon as he has diagnosed ulcer of the stomach, must consider the strong possibility of its becoming malignant. The chances of this occurrence may be readily seen, as stated above, in the fact that seventy-one per cent of our resected specimens of gastric carcinoma were associated with ulcer, and that sixty-eight per cent of our resected gastric ulcers were associated with carcinoma. It must be granted that gastric ulcers do sometimes heal with or without treatment, when seen early, or when not seen at all until autopsy, but unfortunately the early stage of ulcer cannot be so easily recognized,

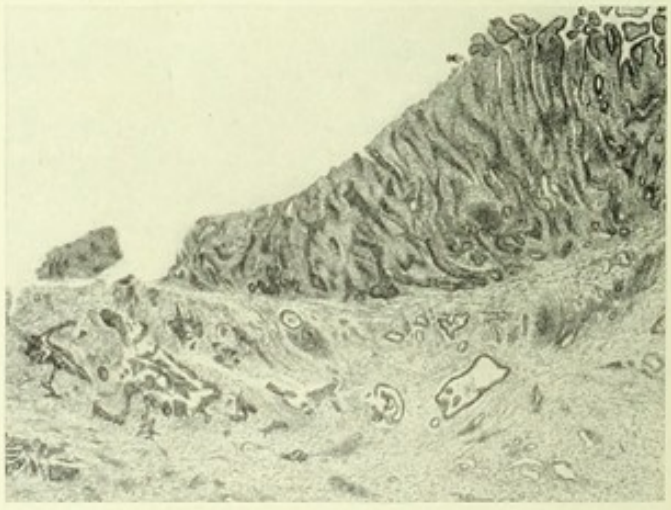

Fig. 26. (Case No. 24527.) Section through the border of the ulceration showing carcinoma in the border, submucosa, and the base.

and when recognized at the first definite sign or symptom it is impossible to determine whether the ulcer is a small one or a large one, or whether it has been present for weeks or months without having given rise to definite symptoms or even symptoms other than slight discomfort. Many cases with ulcers do not give a history of vomiting blood. As may be seen in cases 30163, 28173, 27381, 27919, 21882, 16651, 24527, many cases give a history of hyperacidity and do not show hyperacidity at the time of gastric analysis, and therefore absence of hyperacidity is of no value in a case which otherwise gives gastric symptoms. Lactic acid and fatty acids are not to be expected until there is mechanical or motor obstruction, which may occur associated with a small or a large ulcer, depending upon its location. The length of the history of epigastric discomfort or distress varies within wide limits, and the case with a short history often has a more extensive lesion than one with a long history. The lesion occurs most often, and practically always in early adult life or middle life. Our cases have occurred oftener in males than in females. A few, as may be seen in cases 18088 and 30163, give previous histories which appear

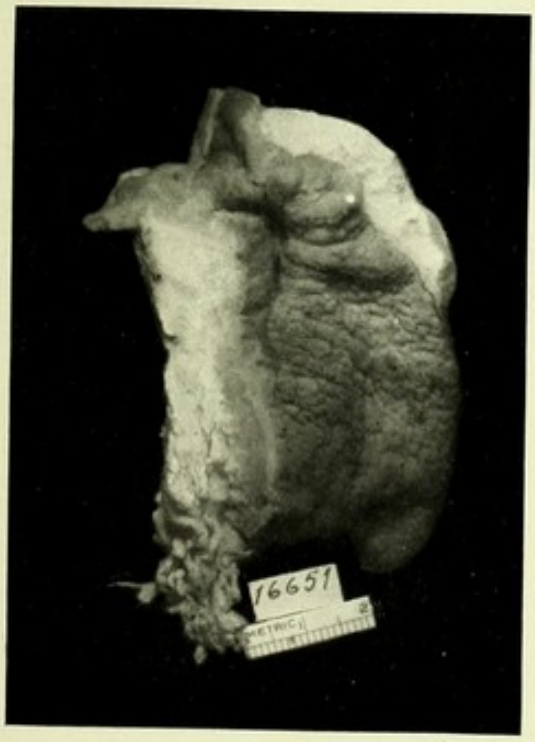

Fig. 27. (Case No. 16651.) Gastric carcinoma

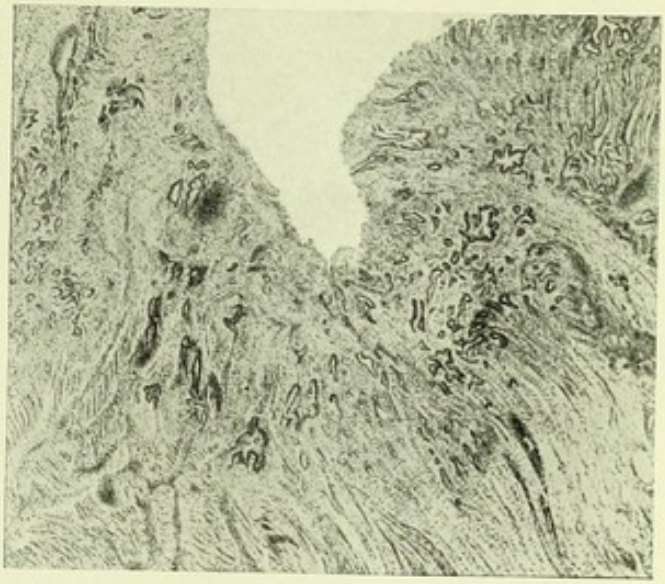

Fig. 28. (Case No. 16651.) Section through the border of an ulcer in which the mucosa, submucosa, and base are extensively infiltrated by carcinoma.

to be appendicitis. This coincident, if it be a coincident, is well worth considering however, as a possible etiological factor in view of some experimental and clinical experiences. Cannon has, by the injection of irritants into the large intestine, produced a retardation of the gastric discharge. Roger has shown that the injection of betanaphthol into the cæcum produces erosions of the mucosa. Litthauer has produced ulcers, which do not heal, by the production of localized anæmia and destruction of the mucosa. Clinically, many cases of appendicitis, especially chronic appendicitis, present symptoms of gastric disturbance which predominate those in the appendix region. Such cases, after the removal of the appendix are relieved and recover from the gastric symptoms. In these cases the stomach and duodenum present no lesion recognizable on exploration. These clinical and laboratory experiences are sufficiently striking to warrant further study and experimentation in regard to the possible production of pyloric spasm, gastric anæmia, hyperacidity, and necrosis or ulceration of the mucosa.

RESUME

1. Ulcers may be single or multiple and in different degrees of extension in the same specimen.

2. After the initial destruction of the mucosa,

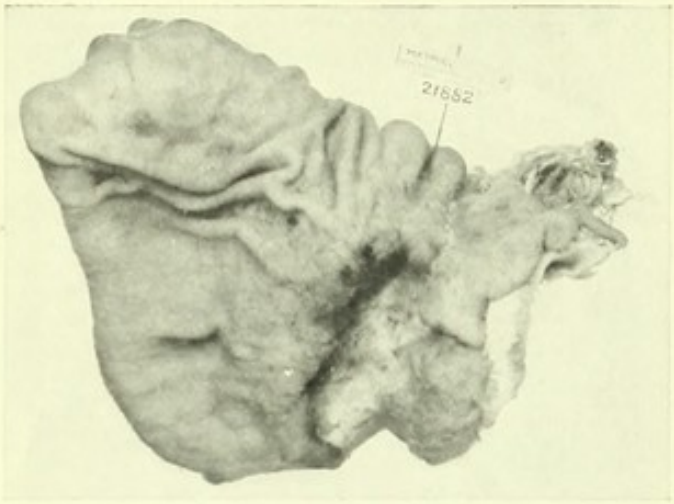

Fig. 29. (Case No. 21882.) Gastric carcinoma.

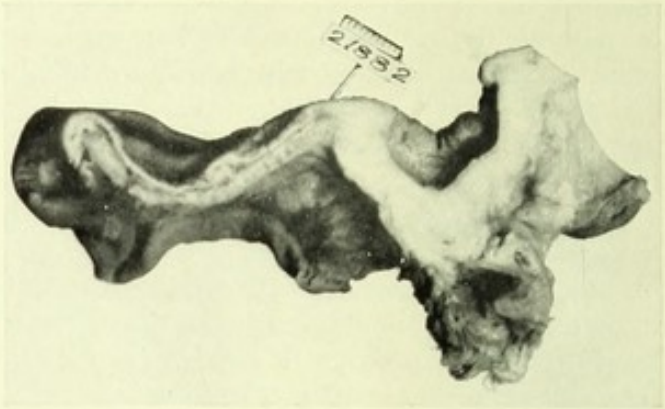

Fig. 30. (Case No. 21882.) Gross section showing the great depth produced by the process of erosion.

there is definite deepening of the ulcer by necrosis.

3. This deepening is sufficiently slow to allow a dense connective tissue barrier against perforation to be formed.

4. Ulcers heal, perforate, and become malignant.

5. Perversion of the glandular elements occurs in the mucosa, and the cells then invade submucosa.

6. One cannot say positively that all carcinomata of the stomach have developed on ulcer, because carcinomatous tissue in the base of an ulcer may be an ulcerated primary carcinoma.

7. The length of the clinical history is no positive index of the extent of the lesion.

8. The absence of blood in the vomitus or gastric contents at the time of laboratory analysis when associated with gastric symptoms is not evidence against the presence of ulcer.

9. Absence of hyperacidity at the time of gastric analysis is also no evidence against the presence of ulcer.

10. Clinically, with our present means of diagnosis, it is impossible to say that a gastric ulcer is not malignant.

11. The intimate relationship between irritation in the appendix or cæcum and gastric disturbance may have some bearing in the etiology of ulcer.

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