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The Pathological Relationships of Gastric Ulcer and Gastric Carcinoma.

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THE PATHOLOGICAL RELATIONSHIPS OF GASTRIC ULCER AND GASTRIC CARCINOMA.

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The following report is based on the study of specimens from gastric and duodenal resections and excisions for ulcer and carcinoma, by Drs. W. J. and C. H. Mayo, from January 1, 1905, to April 1, 1909. In five of the cases the material was obtained at autopsy from patients on whom gastro-enterostomies had been done for ulcer or carcinoma, and from whom no material had been removed at the operation. These autopsies, however, were all made within one hour after the death of the patient; consequently all the material was quite fresh when placed in fixatives. The routine examination consisted of the study of fresh material, sectioned and stained by the method of one of the writers[1]. Blocks of tissue were then fixed in Zenker's fluid and Flemming's chromo-osmo-acetic fluid and in 10 per cent. formaldehyde. In some instances additional blocks were fixed also in absolute alcohol. The gross specimen was then prepared by Melnikow's modification of Kaiserling's method. The gross specimens were photographed by the method of Wilson and Andrews,[2] either fresh or after fixation. The photomicrographs of sections herewith shown were made from hematoxylin-stained specimens. In these no attempt has been made to show fine detail, which has been sacrificed to a study of the distribution of the cells.

The total amount of material studied comprised specimens from 218 cases. Eight of these were from the duodenum, and were all simple ulcers. The remaining 210 were from the stomach. Of these, 47 were ulcers without suspicion of carcinoma; 2 were sarcomas, 2 adenomas, and 1 a diverticulum. Of the remaining 158 cases from the stomach, 5 were ulcers with enough microscopic appear-

[1] Wilson, L. B., A Method for the Rapid Preparation of Fresh Tissues for the Microscope, Jour. Amer. Med. Assoc., 1905, xlv, 1737.

[2] Stereophotography of Pathological Specimens: Some Improvements in Technique and New Apparatus, Jour. Med. Research, 1908, xvii, 487 to 494.

ance of aberrant epithelial proliferation to place them in the doubtful class as possible transition cases. Of the remaining 153 cases, which were undoubted carcinoma, 109 (71 per cent.) presented sufficient gross and microscopic evidence of previous ulcer to warrant placing them in a group labelled "carcinoma developing on preceding ulcer." Eleven other cases (7 per cent.) showed considerable evidence of precedent ulcer, but not sufficient to warrant placing them in the previous group. In 33 cases (22 per cent.) there was relatively small or no pathological evidence of precedent ulcer.

It is unnecessary to review the enormous literature of this much discussed subject. For years the pendulum of opinion swung back and forth, and it has been only within the last decade that sufficient material from early cases has been collected to give a clear understanding of the facts. The reports on specimens removed at operation during that period have practically settled the question as to the very frequent occurrence of gastric carcinoma on the site of previous ulcer. Our excuse for offering these cases at present is to place them on record as one more bit of evidence to clear up a misconception which has done much harm in the past, and which still exists, as is shown by the attitude of the author of the most exhaustive recent work on cancer.[3]

Protocols. Case No. 22,826 (Fig. 1). This specimen is from a woman, aged twenty-six years, who for nine years had had some stomach distress, some gas, occasional vomiting, and eructations. For the last eight weeks she had had some loss of strength, had lost in weight (20 pounds), and had vomited occasionally. Stomach analysis showed a total acidity of 65, free hydrochloric acid 50, lactic acid absent, and blood absent. Operation revealed a chronic ulcer of the lesser curvature. Fig. 2 shows the scar tissue and the eroding base of the ulcer within which are no epithelial inclusions. The character of the lesion deep down below the overhanging border, just where the mucosa comes in contact with the basement membrane, is shown in Fig. 3. Here are numerous groups of epithelial cells cut off by the products of inflammation.

Case No. 22,020. The specimen in this case is through the pylorus of a man, aged fifty-one years, who for three years had had some stomach distress with gas, vomiting, etc. For three months he had had some loss of strength and loss of weight (15 pounds), with severe pain. The stomach analysis showed a total acidity of 56, free hydrocloric acid 30, lactic acid absent, blood absent. This case much resembled the preceding one. Fig. 5 shows the eroding mucosa with swollen epithelial cells in the overhanging border of the ulcer. Fig. 6 from near the base of the mucosa shows several small groups of epithelial cells which are segregated from the rest of the mucosa, as in Case 1.

[3] Williams' Natural History of Cancer, Wm. Wood & Co., 1908, pp. 279 to 280.

These two cases show how in chronic gastric ulcers in which no carcinoma is demonstrable there already exist isolated areas of epithelium which is under conditions favorable to its aberrant proliferation.

Case No. 18,088 (Fig. 7). This specimen is from the pyloric half of the stomach from a man, aged forty-five years, who had only mild symptoms of so-called dyspepsia until nine months ago, when he began to have marked gastric distress, vomiting blood, gas, eructations, loss of appetite, loss of strength, and loss in weight (60 pounds). The stomach analysis showed a total acidity of 50, free hydrochloric acid 12, lactic acid absent, blood present. Operation showed multiple ulcers of the lesser curvature. Three of these were carcinomatous. Fig. 8 is a section from the overhanging border of the ulcer showing the least amount of carcinoma. Fig. 9 is a section from deeper down in the tissues showing the isolated groups of epithelial cells proliferating and infiltrating.

Case No. 18,867 (Fig. 10). This specimen is from a woman, aged sixty years, who for twenty-five years had had more or less severe stomach symptoms, distress, vomiting, gas, etc. For the last six months she had had considerable loss of strength, loss of weight, and severe persistent pain. Analysis of the stomach contents showed a total acidity of 60, free hydrocloric acid 45, lactic acid absent, blood absent. Operation revealed a carcinoma on an ulcer of the lesser curvature. Fig. 11 is from the ulcerating portion of the stomach lesion. Fig. 12 is of a section showing the proliferation of the epithelium without infiltration. Fig. 13 is from a section showing the true carcinomatous character of the lesion.

Case No. 16,525 (Fig. 14). This specimen is from a male, aged forty-six years, who for seven years had had considerable stomach distress with vomiting and eructations of gas. For the last seven months he had had loss of strength and appetite and had lost 45 pounds in weight, being now quite emaciated. The stomach analysis showed a total acidity of 42, with a free hydrocloric acid content of 37, lactic acid present, and blood present. On operation there was found a carcinoma on the border of an ulcer covering a greater portion of the lesser curvature. Fig. 15 is of a section from the ulcerating border showing cross sections of distended glands with round cells between. Fig. 16 shows the bases of glands clipped off by scar tissue. Fig. 17 shows active proliferation in segregated epithelium. Though strongly suggestive of carcinoma, one would hesitate to diagnosticate this section, since the field is obscured by the round cell infiltration. Fig. 18, however, shows typical scirrhous cancer, that is, the inflammation has here subsided and the fibrous tissue has increased around the islands of proliferating epithelium. These four sections are all from the border of the ulcer, but in successive microscopic steps away from its centre.

Case No. 15,681 (Fig. 19). This specimen is from a man, aged

thirty years, who has suffered from gastric distress, nausea, vomiting, and gaseous eructations for five years. During the last seven months he had had marked loss of strength, with a loss of thirty pounds in weight. Stomach analysis showed a total acidity of 62, free hydrochloric acid 32, lactic acid absent, and blood present. Operation revealed a carcinoma on an extensive ulcer of the lesser curvature, involving also the pylorus. Fig. 20 is from a section from the base of the ulcer. Fig. 21 is of the overhanging border nearest the ulcerating area, showing segregated proliferating epithelial masses. Fig. 22 is of an area a little farther removed from the ulcerating area than the preceding section.

Case No. 16,651 (Fig. 23). This is a specimen from a woman, aged forty-two years, who for sixteen years had had intermittent stomach distress with vomiting, etc. For the last four months she had had considerable loss of strength, weight, and appetite. Stomach analysis showed a total acidity of 50, with free hydrochloric acid absent, lactic acid absent, and blood present. The gross specimen shows a lesion of the lesser curvature. Fig. 24 is of a section from the edge of the ulcer showing at the right side the old scar tissue in the border of the ulcer, and at the left side the carcinoma advancing into the scar.

Case No. 21,555 (Fig. 25). This specimen is from a man, aged sixty-seven years, who for twelve years had had considerable stomach distress, including vomiting, eructations, gas, etc. During the last few months he had grown considerably worse, had lost strength, appetite, and 35 pounds in weight. The stomach analysis showed a total acidity of 30, free hydrochloric acid 15, lactic acid absent, and blood present. The gross specimen showed a large ulcer of the lesser curvature, which is further shown in gross section in Fig. 26, in which the character of the ulcer can be more clearly made out. Fig. 27 shows the carcinoma advancing into the scar tissue at the edge of the ulcer. Fig. 28 is from material at the base of the overhanging mass, and shows scirrhous carcinoma change.

Case No. 19,322 (Fig. 29). This specimen is from a man aged thirty-three years, who for ten years had had symptoms of gastric ulcer, that is, distress, vomiting, gas, eructations, etc. During the last eight months he had had considerable loss of appetite with a loss of 50 pounds in weight. The stomach analysis showed a total acidity of 35, free hydrochloric acid 14, lactic acid absent, and blood absent. The gross specimen closely resembles a simple ulcerated pylorus. In one area, near the greater curvature, however, a nodular mass may be seen which suggests carcinoma. The character of the isolated islands of mucosa at this point is shown in Fig. 30; in Fig. 31 is shown the carcinomatous invasion of the scar tissue in the edge of the ulcer.

Case No. 16,636 (Fig. 32). This specimen is from a man, aged forty-six years, who for ten years had shown marked stomach symp-

toms, distress, gas, eructations, etc., and for the past eight months had loss of strength, appetite, and 70 pounds in weight. The stomach analysis showed a total acidity of 35, free hydrochloric acid absent, lactic acid present, and blood present. The specimen shows an enormous thickening of the muscularis and submucosa. On this mass of scar tissue is developing a carcinoma. Fig. 33 is of a section from the lesser curvature area, showing a group of partially segregated tubular glands and near the lower edge of the figure a nest of aberrant proliferating epithelium. Fig. 34 shows the development of the carcinoma in the scar tissue.

Case No. 14,857 (Fig. 35). This specimen is from a man, aged fifty-one years, with a history of chronic stomach trouble for ten years, nausea, vomiting, gas, distress, etc. During the last six months these symptoms have been markedly increased and the patient has suffered a loss of 30 pounds in weight. The gross specimen shows the site of an old perforating ulcer, the muscularis being completely broken through, and the adhesions from the old perforation being quite evident. The carcinoma fills the site of the ulcer. Fig. 36 shows a carcinoma developing within the scar tissue. Judging from the microscopic appearance alone, one might hesitate to decide that this was a case of precedent ulcer, although the bands of scar tissue with masses of epithelium included are quite suggestive. The gross specimen with the history, however, is sufficient to warrant a positive diagnosis.

Case No. 15,351 (Fig. 37). This specimen is from a man, aged forty-one years, who for many years (fifteen or more) had had gastric distress, vomiting, and eructations of gas. In the last six months he had had a loss of strength, and a loss in weight of 30 pounds. The stomach analysis showed a total acidity of 25, free hydrochloric acid absent, lactic acid present, and blood present. The gross specimen shows a large ulcer of the lesser curvature and a small carcinoma developing in a raised island of tissue in the base of the ulcer near one edge. It is the only instance of the kind in our series.[4]

Case No. 18,514 (Fig. 38). This specimen is from a female, aged forty-one years, who had for three years suffered gastric distress, vomiting, gas, eructations, etc. In the last six months she had had marked loss of appetite, loss of strength, and loss in weight (60 pounds). The stomach analysis showed a total acidity of 100, free hydrochloric acid absent, lactic acid present in large amounts, and blood present. The specimen showed a widely diffused cancer on a large ulcer of the lesser curvature.

Case No. 14,949 (Fig. 39). This specimen is from a man, aged thirty-one years, from whom no history of any stomach trouble could be elicited prior to that beginning one year ago, when he began to

[4] The microscopic details in this and most of the succeeding cases are omitted for lack of space. They were closely parallel with those already shown.

have nausea, vomiting, loss of strength, and loss of 65 pounds in weight. Stomach analysis showed a total acidity of 10, free hydrochloric acid absent, lactic acid present, and blood present. A gross section through the lesser curvature of the stomach is here shown. The stomach wall at this point was from 2.5 to 4 cm. thick. The lesion was purely of an ulcerous character for the lower 8 cm. of the lesser curvature; about 2 cm. of the upper portion of the lesser curvature showed a rapidly growing carcinoma, which had formed metastases in the adjacent glands.

This case is presented to show the unreliability of ever so well taken clinical histories, particularly in the young male, who is not accustomed to give much attention to slight stomach trouble. There can be no question that this patient had stomach ulcer for years preceding the onset of cancer.

The preceding nine cases are fair representatives of those gastric resections for carcinoma in which we consider the pathological evidence of preceding ulcer sufficient to warrant such a diagnosis.

Case No. 16,824 (Fig. 40). This specimen is from a man, aged forty-three years, who was apparently well until one year ago, when he began to show stomach distress, with gas, loss of strength, and loss of weight (40 pounds). The stomach analysis showed a total acidity of 25, with free hydrochloric acid 8, lactic acid present, and blood present. The specimen shows a small carcinoma of the pylorus, without gross evidence of previous ulcer. Fig. 41 is from a deep level of a section and shows adenocarcinoma. We would not seem to be warranted in making any diagnosis of preceding ulcer in this case of carcinoma, either from the history or the pathological evidence.

Case No. 16,806 (Fig. 42). This is a specimen from a man, aged sixty-eight years, who during the last thirty years had had three prolonged attacks of stomach trouble, marked distress, gas, vomiting, eructations, etc. During the last eight months he had had loss of strength, loss of appetite, and a loss of 30 pounds in weight, and there was also severe persistent pain. Stomach analysis showed a total acidity of 30, free hydrochloric acid absent, lactic acid present, and blood present. Two-thirds of the stomach was removed. Only a small portion of the specimen is here shown—a section through the wall of the lesser curvature, which was about 3 cm. thick. Colloid degeneration with deposition of lime salts had occurred throughout the wall of the removed portion of the stomach. In this case there is absolutely no pathological evidence of the occurrence of previous ulcer, although the thirty-year history is very strong clinical evidence.

These last two cases represent the group of 33 (22 per cent.) of our cases, in which we could find insufficient pathological evidence to warrant a diagnosis of preceding ulcer. The latter case also is a fair example of the type of case which frequently comes to autopsy and shows no evidence of preceding ulcer.

The preceding cases are fair representatives of our series. The 109 cases (71 per cent.) which present pathological evidence, gross and microscopic, parallel with that shown in detail herewith, that is, large ulcers with scar tissue centres and overhanging borders, deep in the bases of which cancer is present, in almost every instance have unmistakably originated on the lesser curvature of the stomach, the usual site of gastric ulcer. Further, almost every case gives a clinical history suggesting gastric ulcer for a long period of years preceding the relatively short period when the history became that of gastric cancer.

That carcinomas should develop in the edges of gastric ulcers is only what we should expect; the wonder is that the facts should have been so long in being recognized. This has been due to: (*a*) Failure to recognize clinically the frequency of gastric ulcer; (*b*) failure to recognize that gastric cancers are not initially pyloric tumors, but extensions thereto from the lesser curvature; and (*c*) giving undue weight to observations at autopsies. When the patient has died of gastric cancer, the neoplasm has usually obliterated all gross and microscopic evidence of previous ulcer.

As the pathologist examines stomach specimens from the surgical clinic he constantly observes the various steps in the following sequence:

1. Chronic ulcers from the centres of which the mucosa has disappeared leaving a scar tissue base.
2. In the overhanging broders of the ulcers the mucosa is proliferating.
3. Deep in the borders many groups of epithelial cells have been nipped off by scar tissue and are exhibiting all stages of aberrant proliferation with infiltration of the surrounding tissues.
4. Metastases are forming in the lymphatics of the stomach wall and adnexa.

A small percentage of cases operated upon are too far advanced to show these steps, and a very small percentage—probably not over 2 per cent.—give evidence of rapid aberrant epithelial proliferation and infiltration without any sign of previous ulcer.

Adopting Adami's[5] classification we may therefore correctly desig-designate most gastric carcinomas as "blastomas originating from unipotential cells of postnatal displacement," although it is probable that a very small number are "blastomas originating from unipotential cells that assume neoplastic characters without displacement and rapidly assume malignancy."

[5] Principles of Pathology, 1908 i, 770.

Fig. 1

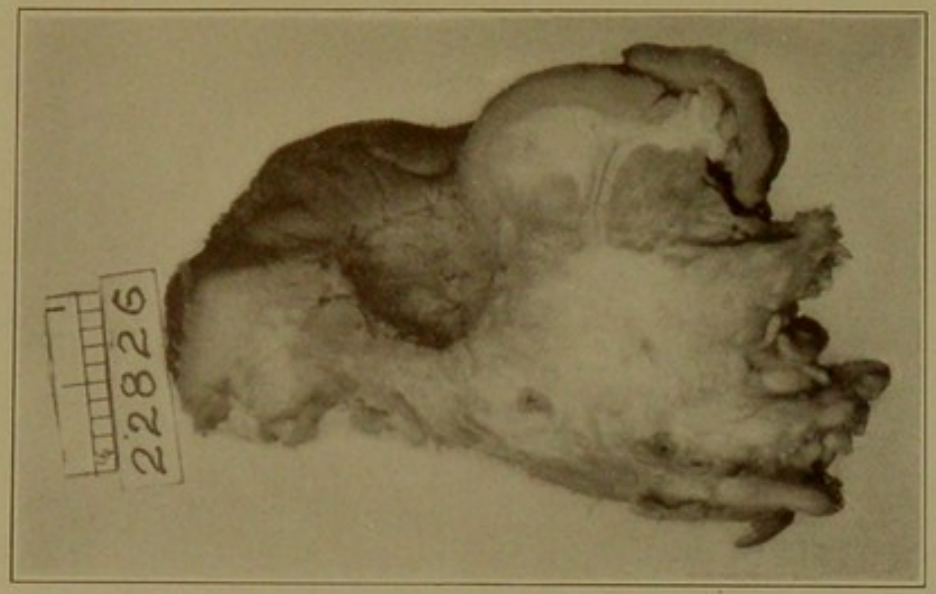

Fig. 2

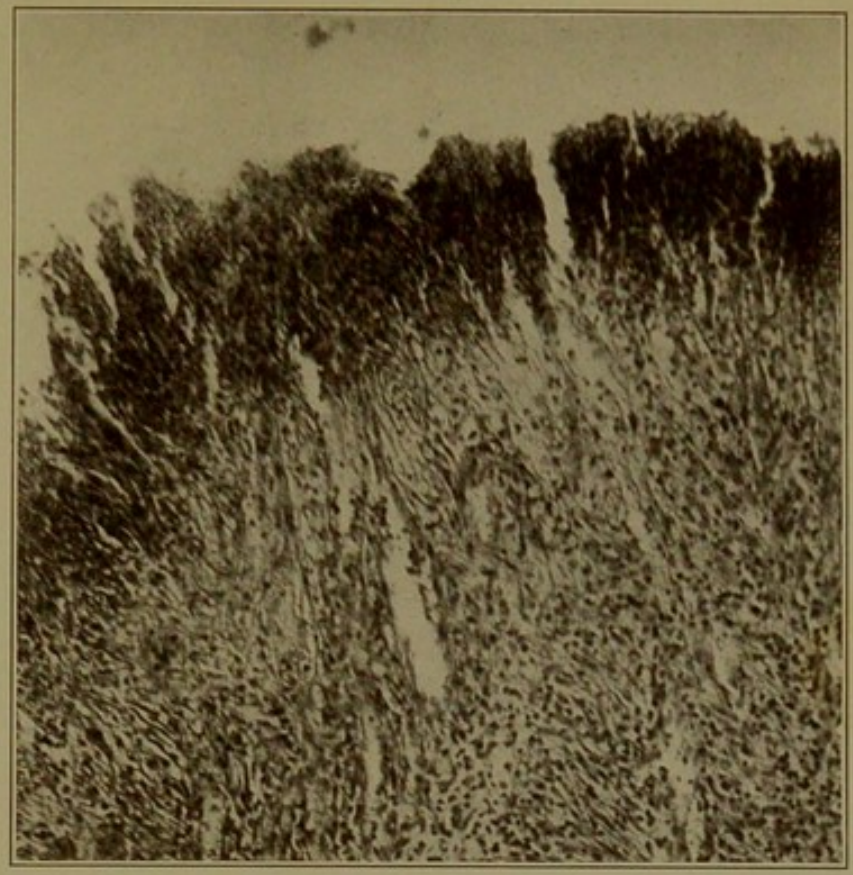

Fig. 1 (Case No. 22,826).—*Stereogram of a chronic ulcer of the lesser curvature of the stomach. Note the overhanging mucosa, the perforation of the muscularis, and the large mass of adhesions.

Fig. 2 (Case No. 22,826).—Photomicrograph of the base of the ulcer. (× 100)

* These pictures were originally shown as stereograms but are here reproduced as single pictures only.

Fig. 3

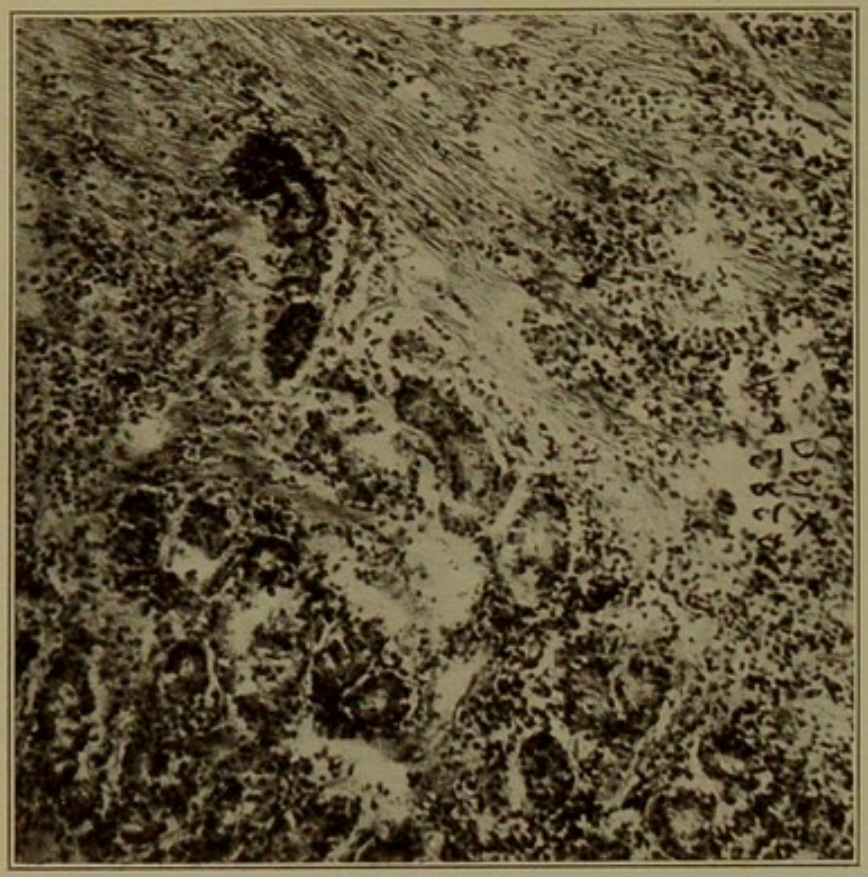

Fig. 4

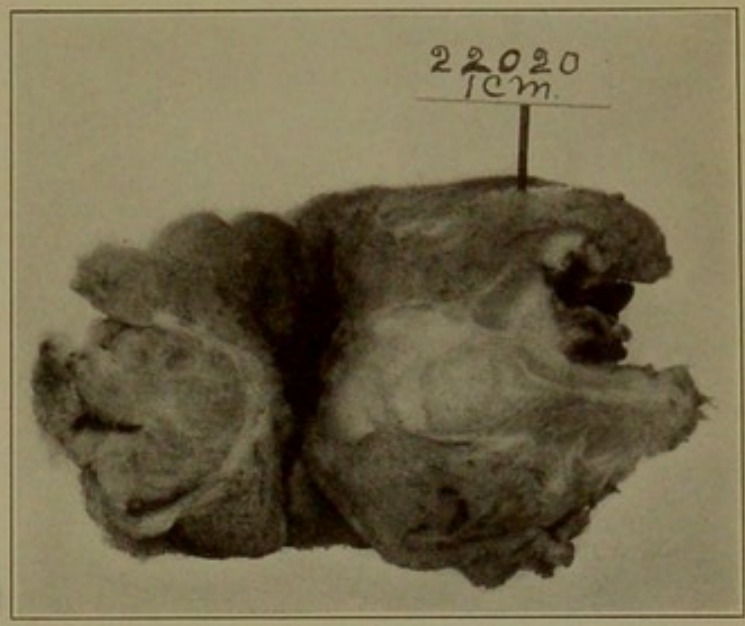

Fig. 3 (Case No. 22,826).—Photomicrograph showing groups of normal epithelium (bases of glands) cut off by products of inflammation deep under the overhanging border of the ulcer. (× 100)

Fig. 4 (Case No. 22,020).—Stereogram of a section through the pylorus, showing the eroded mucosa of a chronic ulcer.

Fig. 5

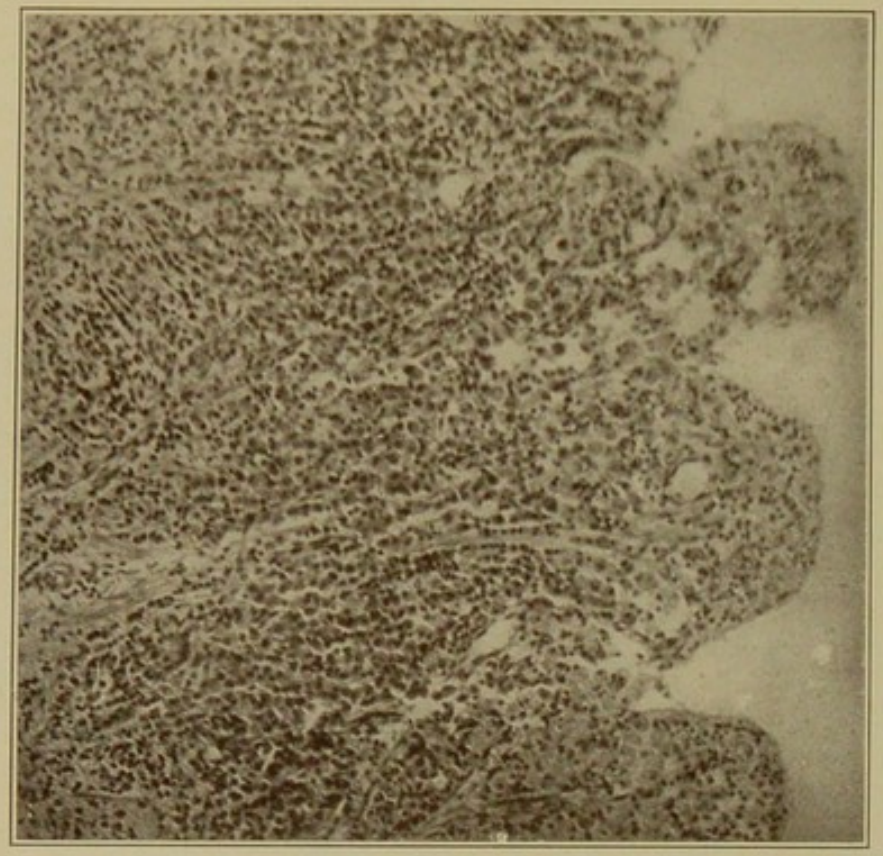

Fig. 6

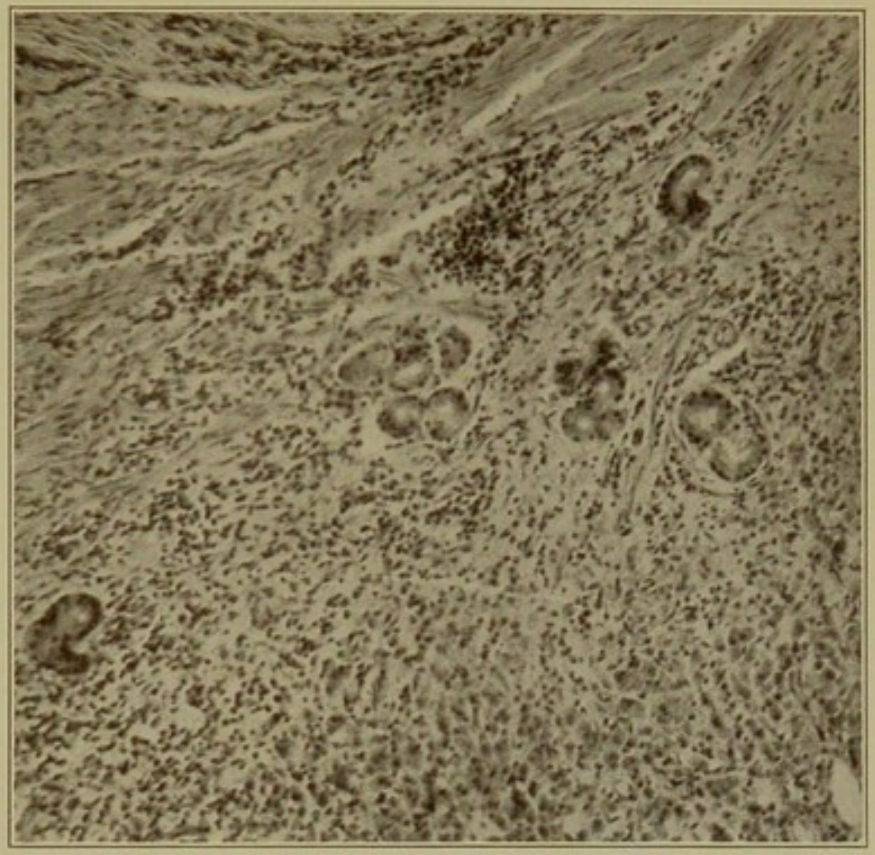

Fig. 5 (Case No. 22,020).—Photomicrograph of the eroding border of the ulcer. (× 100)
Fig. 6 (Case No. 22,020).—Photomicrograph of the base of the ulcerating mucosa, showing isolated groups of epithelium. (× 100)

Fig. 7

Fig. 8

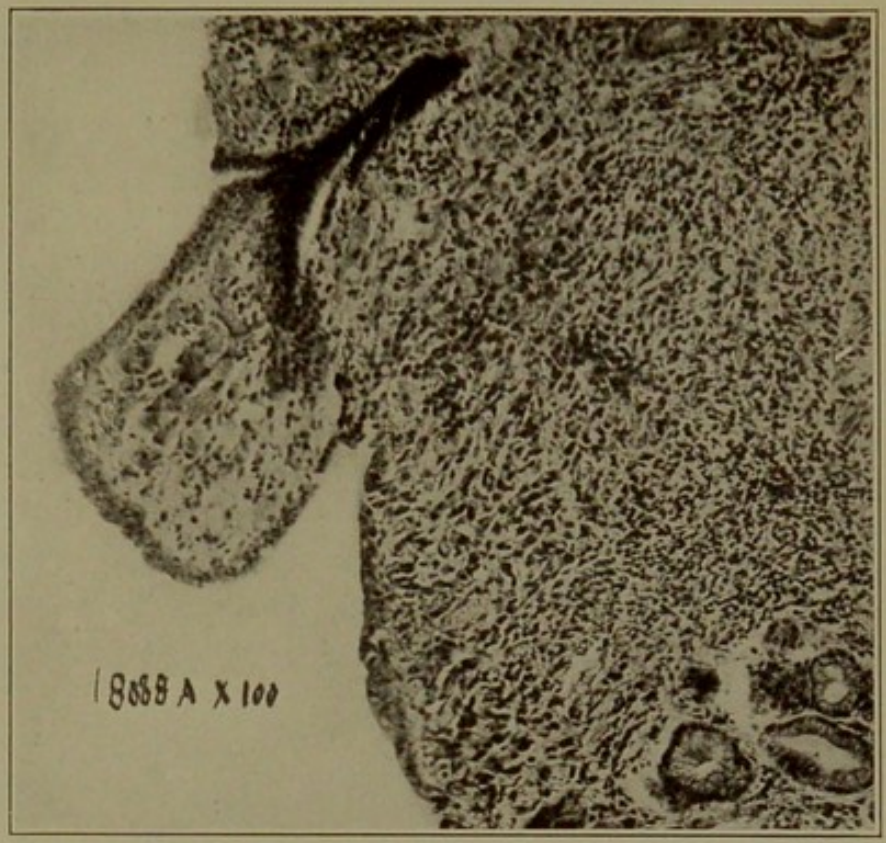

Fig. 7 (Case No. 18,088).—Stereogram of the pyloric one-third of the stomach, looking at the lesser curvature; multiple ulcers; a mass of cancerous tissue was removed from the area near the number needle.

Fig. 8 (Case No. 18,088).—Photomicrograph from the overhanging border of the ulcer. (× 100)

Fig. 9

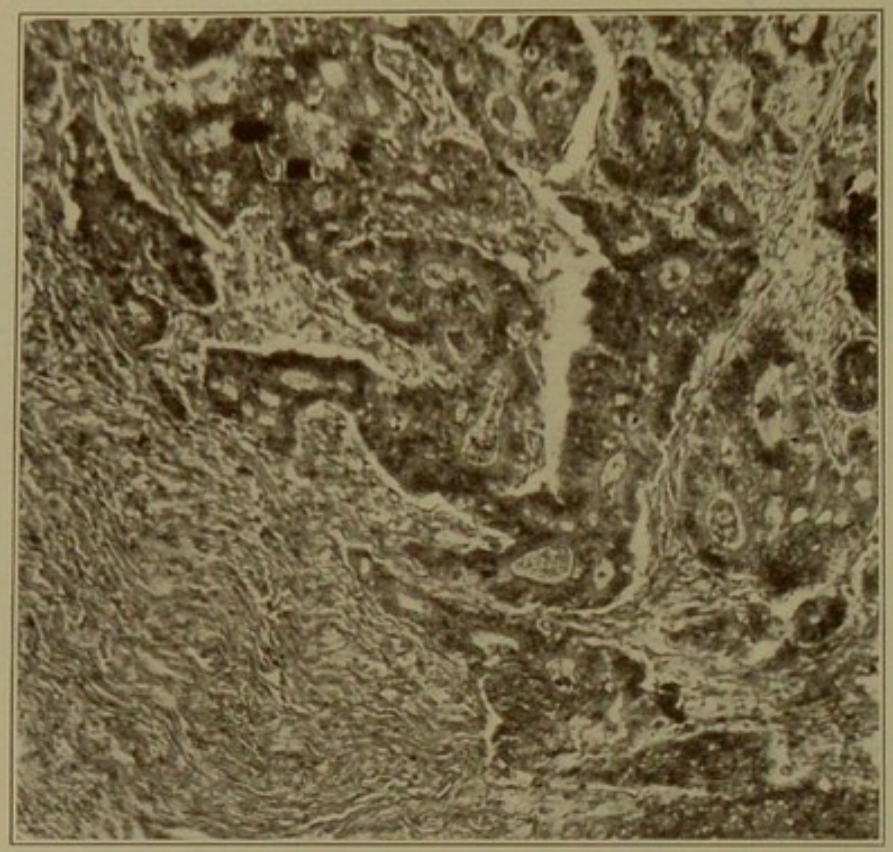

Fig. 10

Fig. 9 (Case No. 18,088).—Photomicrograph from an area deeper than that shown in Fig. 8. The epithelium shows aberrant proliferation and infiltration. (× 100)
Fig. 10 (Case No. 18,867).—Stereogram of the lesser curvature, showing proliferation of the muscularis by an ulcer with carcinoma in the border.

Fig. 11

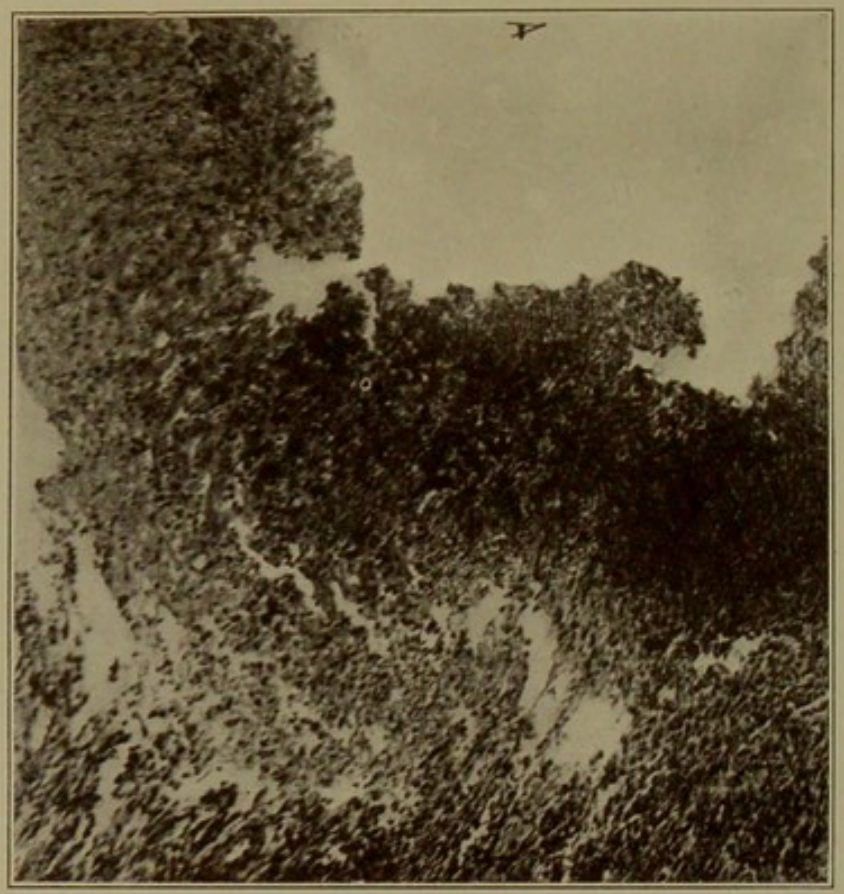

Fig. 12

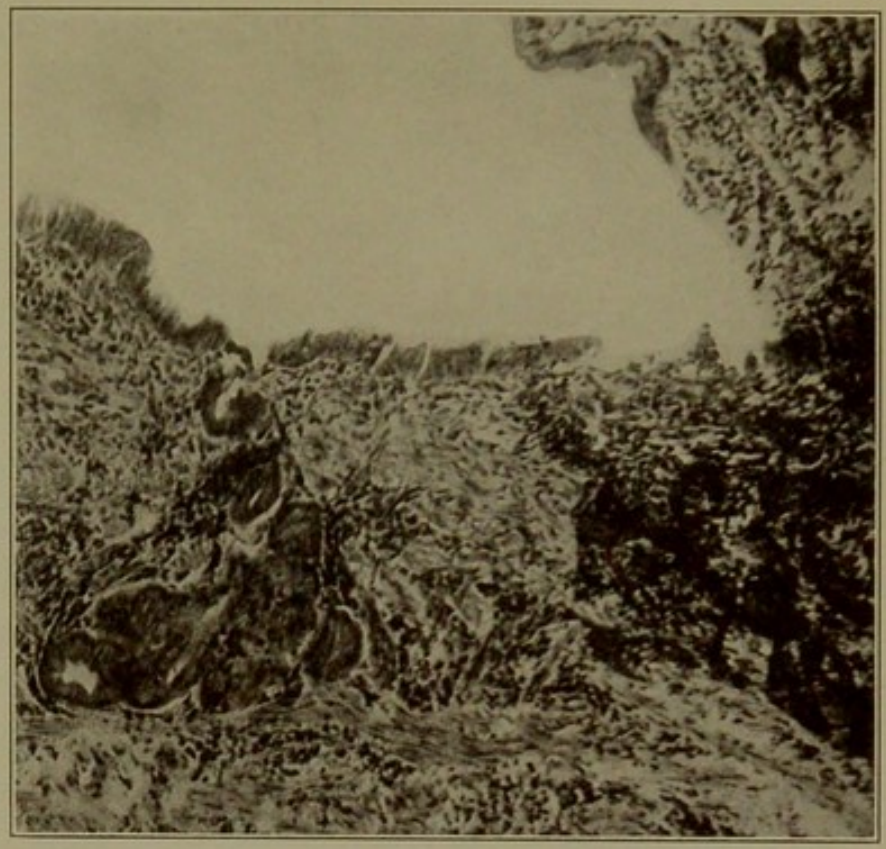

Fig. 11 (Case No. 18,867).—Photomicrograph of the base of the ulcer. (× 100)

Fig. 12 (Case No. 18,867).—Photomicrograph showing groups of epithelial cells partially cut off from the surface, actively proliferating but not infiltrating the surrounding tissues. (× 100)

Fig. 13

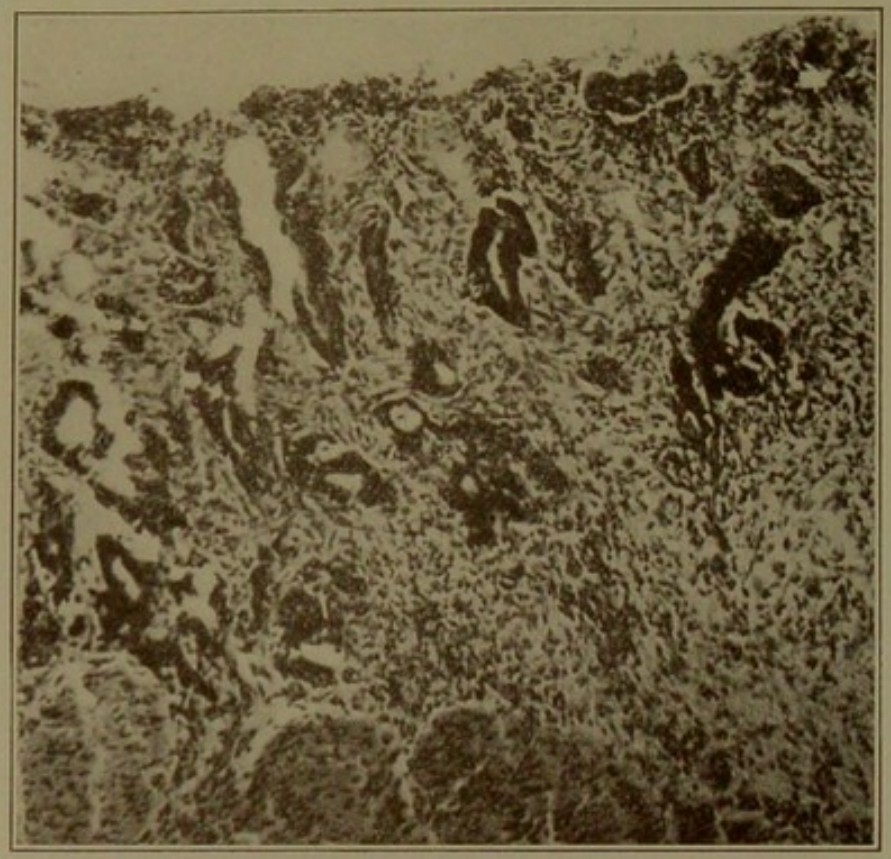

Fig. 14

Fig. 13 (Case No. 18,867).—Photomicrograph showing typical carcinoma. (× 100)
Fig. 14 (Case No. 16,525).—Stereogram of the pyloric two-thirds of the stomach; carcinoma on a large ulcer beginning in the lesser curvature.

Fig. 15

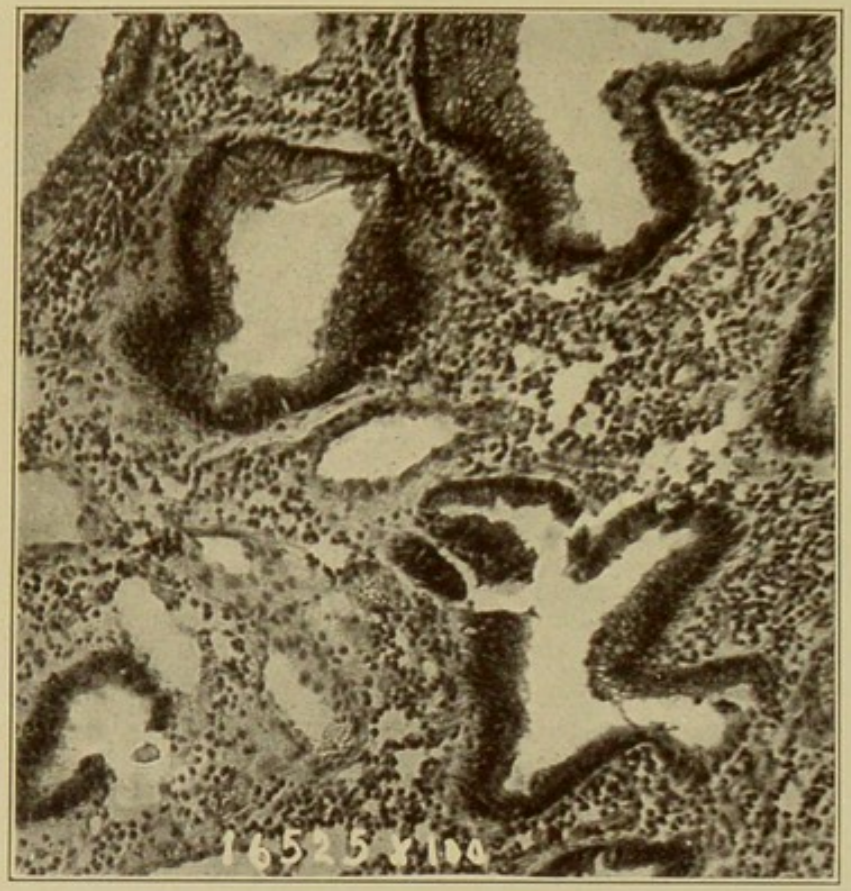

Fig. 16

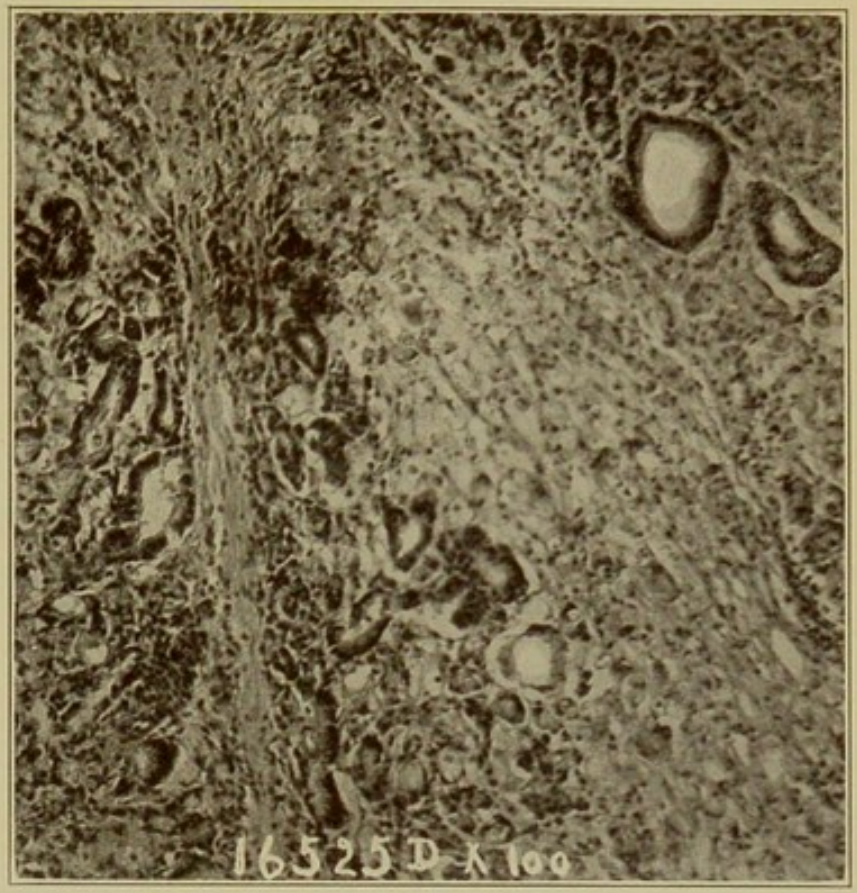

Fig. 15 (Case No. 16,525).—Photomicrograph showing a cross-section of the swollen glands with round-cell infiltration between the glands. (× 100)
Fig. 16 (Case No. 16,525).—Photomicrograph showing the bases of the glands clipped off by scar tissue. (× 100)

Fig. 17

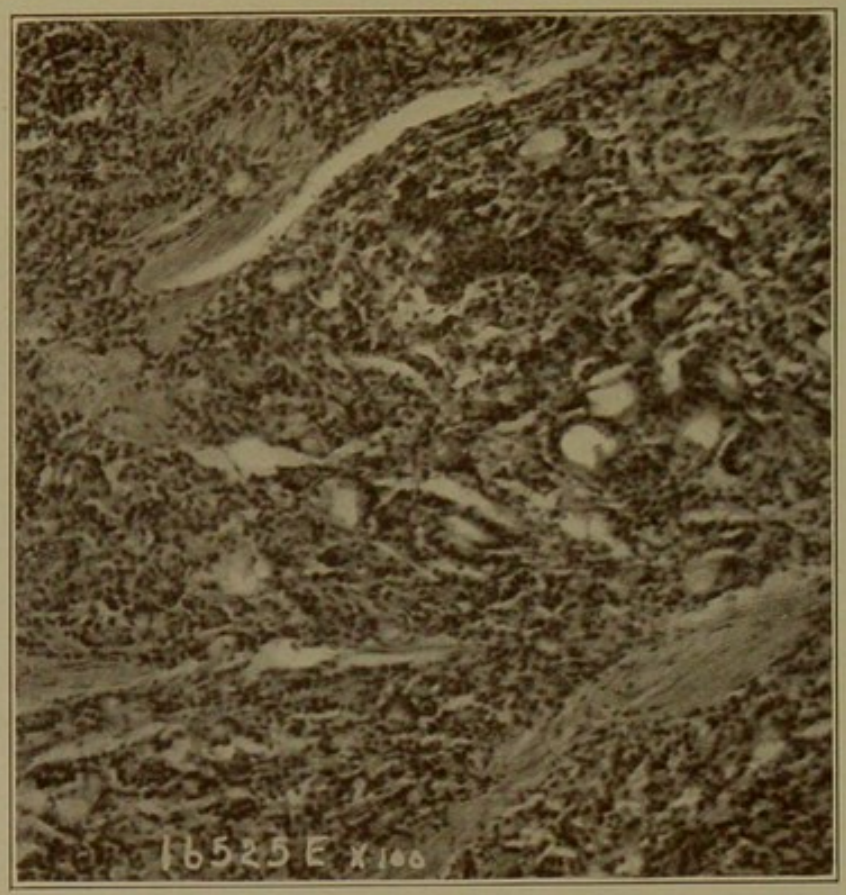

Fig. 18

Fig. 17 (Case No. 16,525).—Photomicrograph showing active proliferation and much round-cell infiltration. (× 100)

Fig. 18 (Case No. 16,525).—Photomicrograph showing typical scirrhous cancer. Figs. 15–18 are from the border of the ulcer, but in successive microscopic steps away from its centre. (× 100)

Fig. 19

Fig. 20

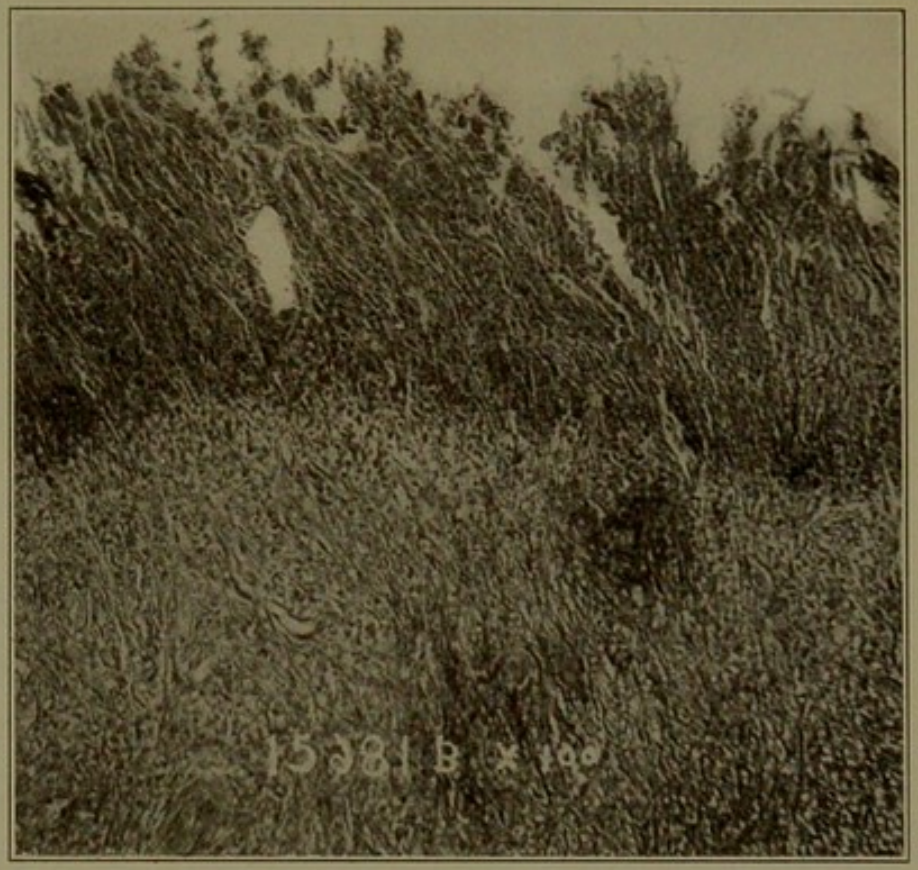

Fig. 19 (Case No. 15,681).—Stereogram of a portion of the pyloric one-half of the stomach, showing carcinoma of the lesser curvature involving also the pylorus.
Fig. 20 (Case No. 15,681).—Photomicrograph from the base of the ulcer. (× 100)

Fig. 21

Fig. 22

Fig. 21 (Case No. 15,681).—Photomicrograph showing proliferating epithelial masses at the base of the swollen mucosa; edge of the ulcer. (× 100)
Fig. 22 (Case No. 15,681).—Photomicrograph showing an area a little farther removed from the ulcerating area than the preceding section (Fig. 21). (× 100)

Fig. 23

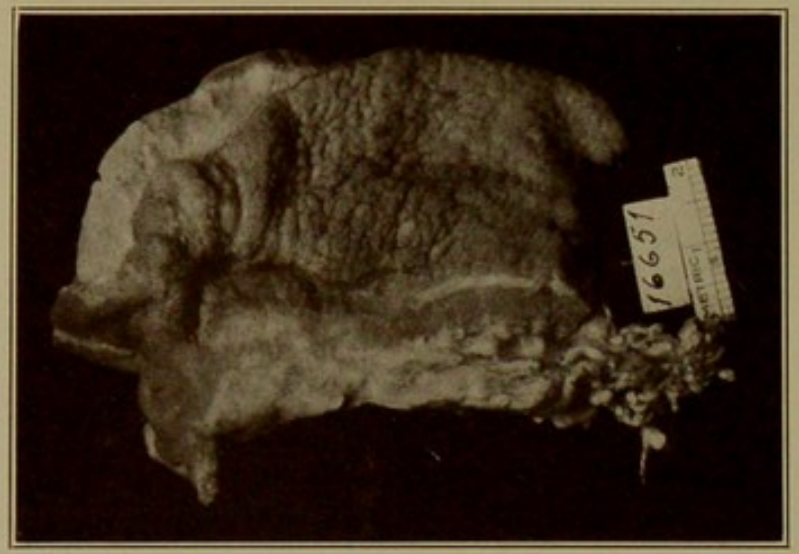

Fig. 24

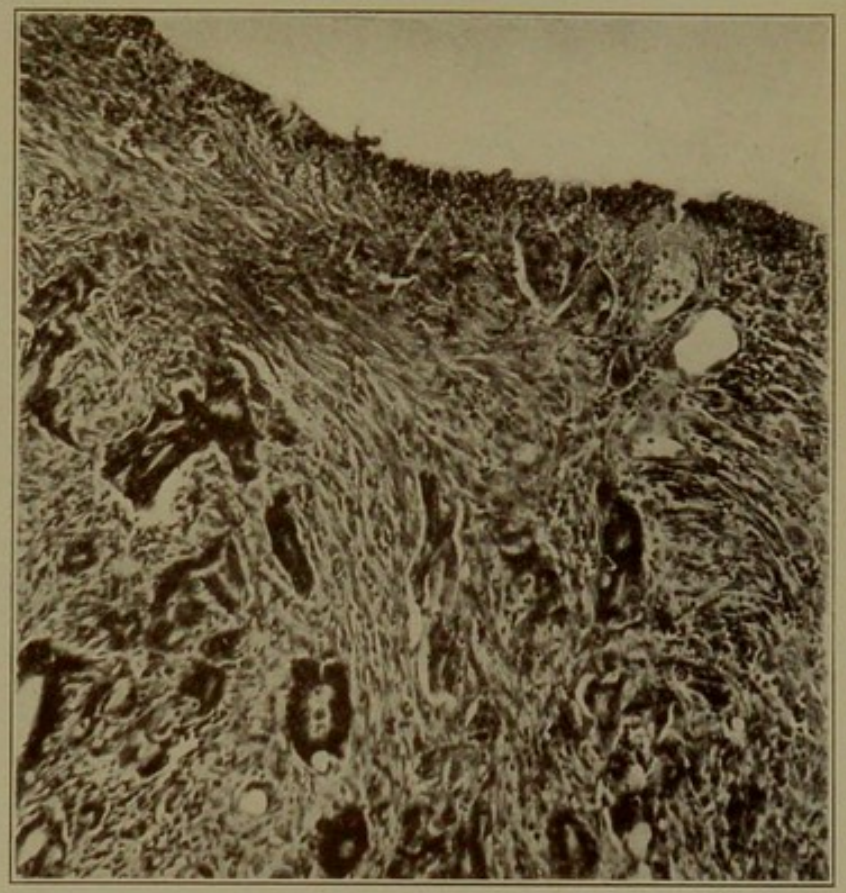

Fig. 23 (Case No. 16,651).—Stereogram of a portion of the pyloric one-third of the stomach showing carcinoma involving the lower lesser curvature and pylorus.

Fig. 24 (Case No. 16,651).—Photomicrograph of a section from the ulcer border, showing at the right side the ulcer base and at the left the developing carcinoma. (× 100)

Fig. 25

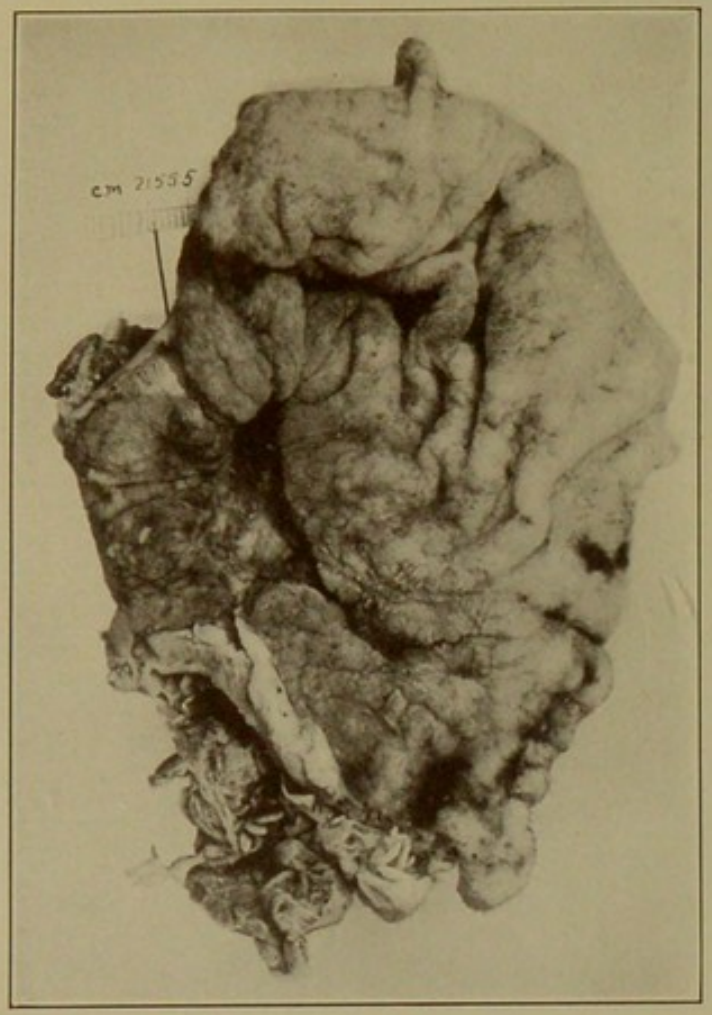

Fig. 26

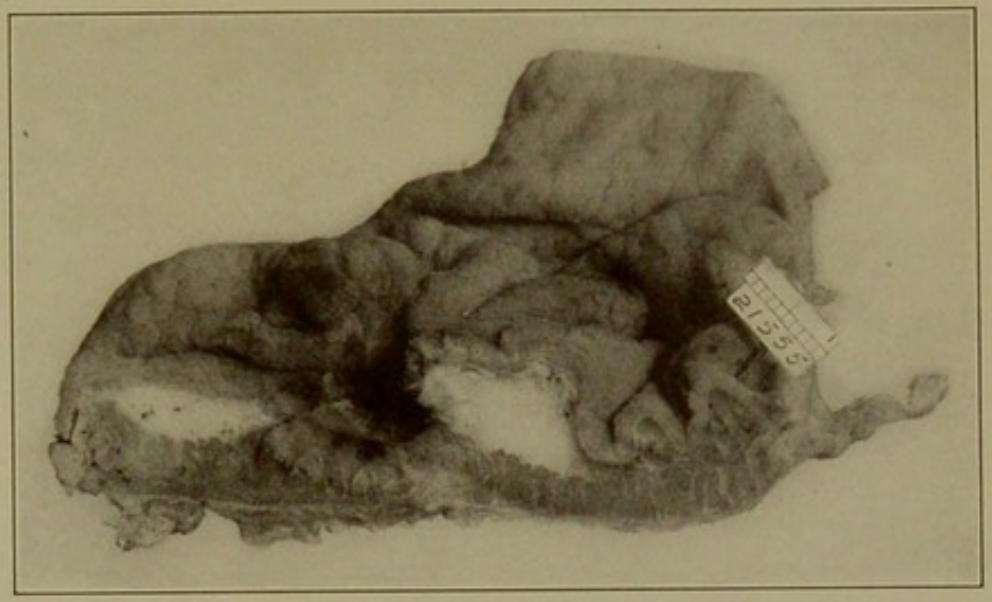

Fig. 25 (Case No. 21,555).—Stereogram showing carcinoma on a large ulcer of the lesser curvature of the stomach.
Fig. 26 (Case No. 21,555).—Stereogram of a gross section through a carcinoma and ulcer.

Fig. 27

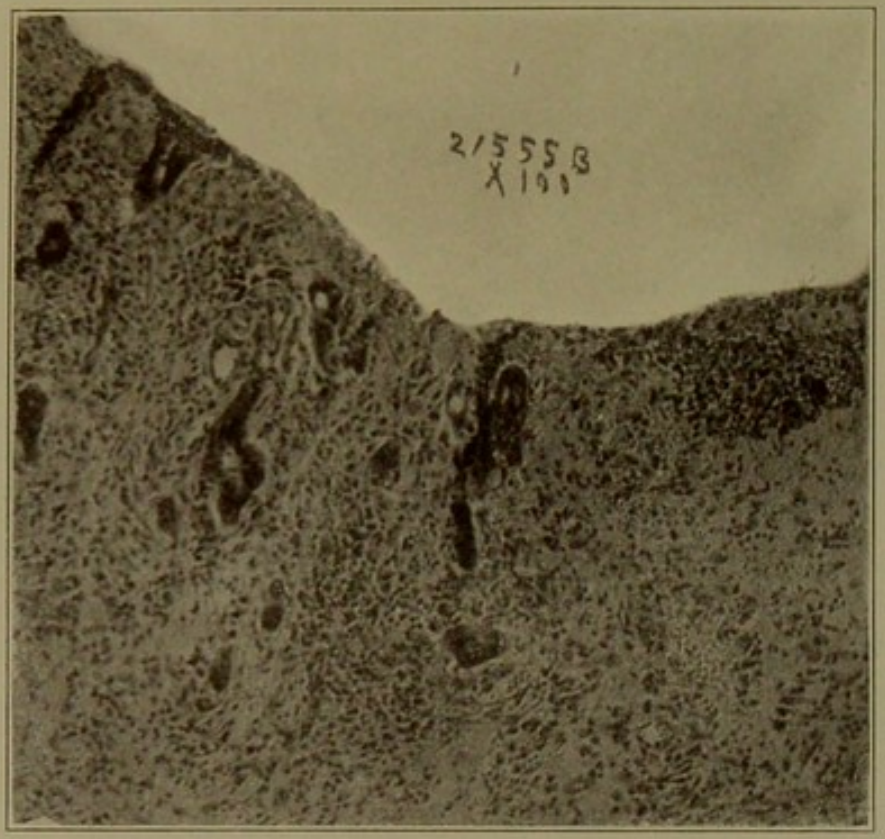

Fig. 28

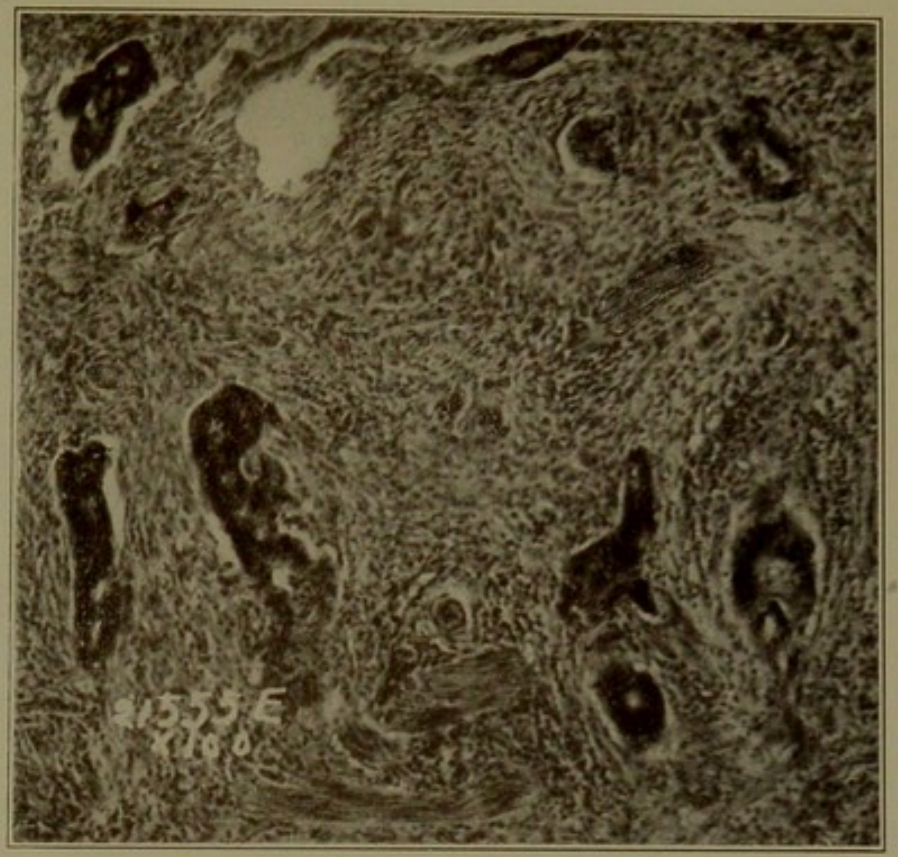

Fig. 27 (Case No. 21,555).—Photomicrograph from the edge of an ulcer; base of the ulcer at the right; separated bases of tubular glands showing early carcinomatous changes at the left. (× 100)

Fig. 28 (Case No. 21,555).—Photomicrograph of a section from under the base of the overhanging edge, showing scirrhous cancer. (× 100)

Fig. 29

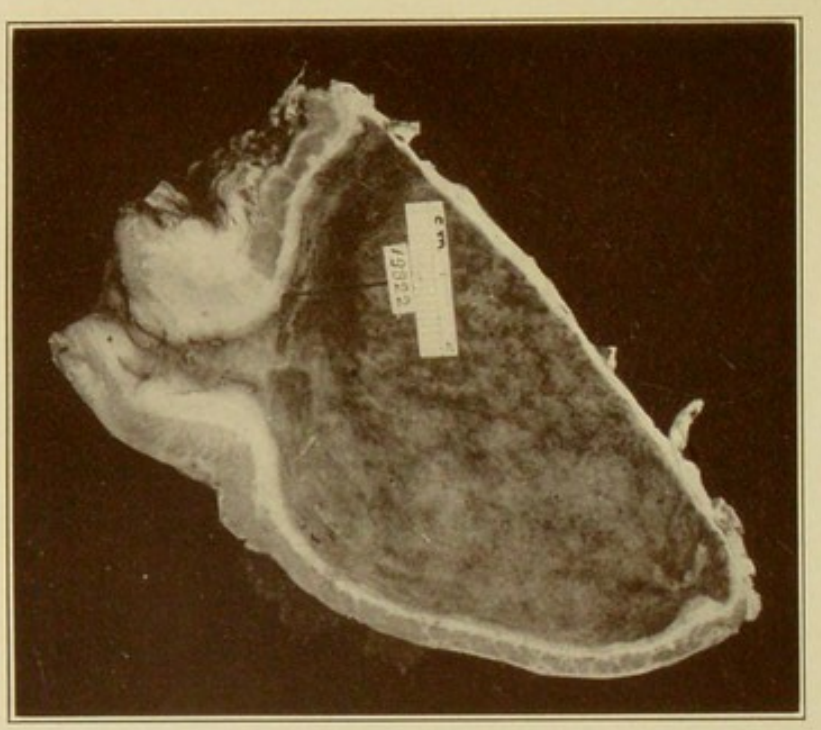

Fig. 30

Fig. 29 (Case No. 19,322).—Stereogram showing a "ring cancer" of the pylorus (originated in an ulcer of the lesser curvature).
Fig. 30 (Case No. 19,322).—Photomicrograph showing islands of proliferating epithelium at the base of the mucosa of the overhanging border of an ulcer. (×100)

Fig. 31

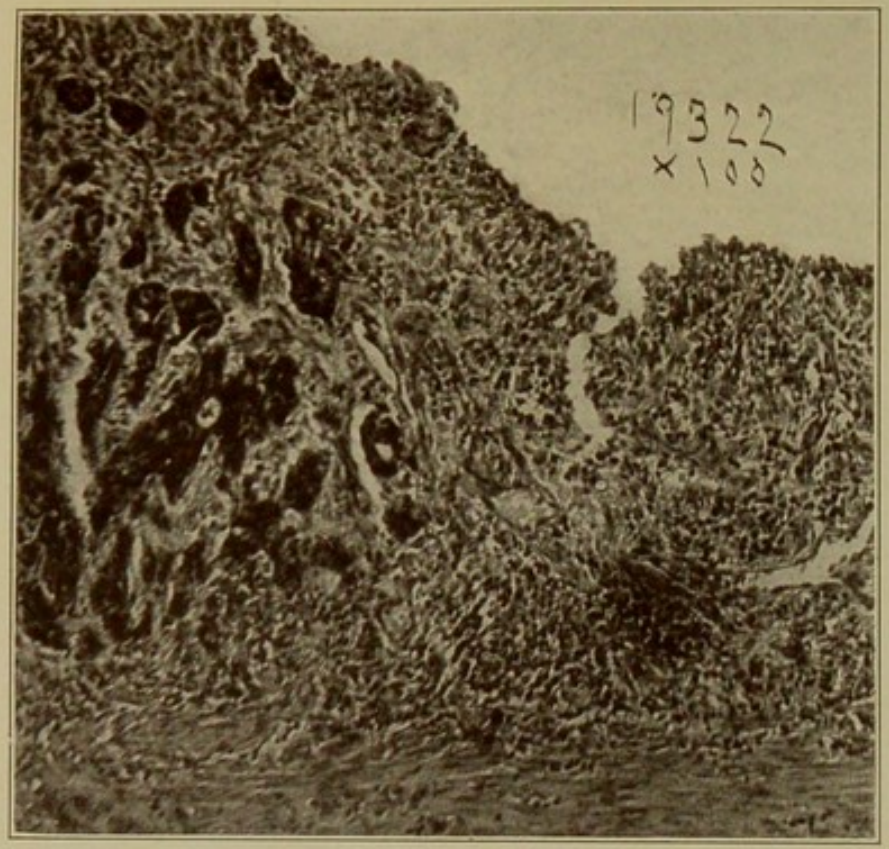

Fig. 32

Fig. 31 (Case No. 19,322).—Photomicrograph showing the base of the ulcer at the right, and carcinoma in the border at the left. (× 100)
Fig. 32 (Case No. 16,636).—Stereogram showing a large ulcer of the lesser curvature with carcinoma in the border.

Fig. 33

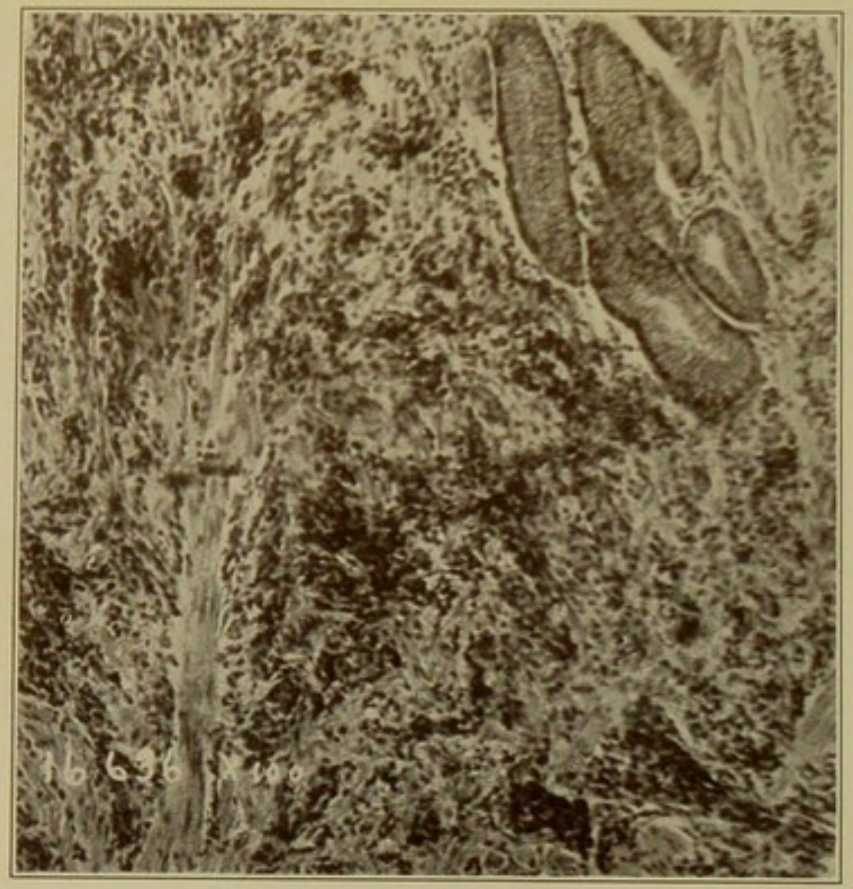

Fig. 34

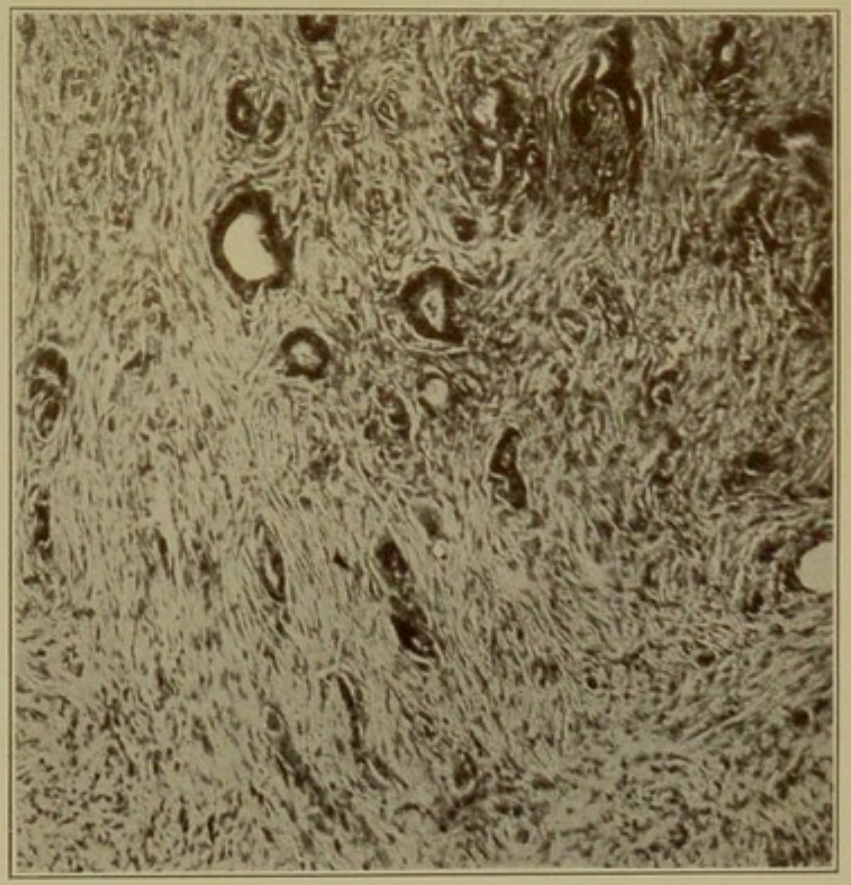

Fig. 33 (Case No. 16,636).—Photomicrograph showing a group of partially segregated tubular glands, and, at the lower right hand corner, one nest of aberrant proliferating epithelium. (× 100)

Fig. 34 (Case No. 16,636).—Photomicrograph showing the development of carcinoma in the scar tissue in the edge of an ulcer. (× 100)

Fig. 35

Fig. 36

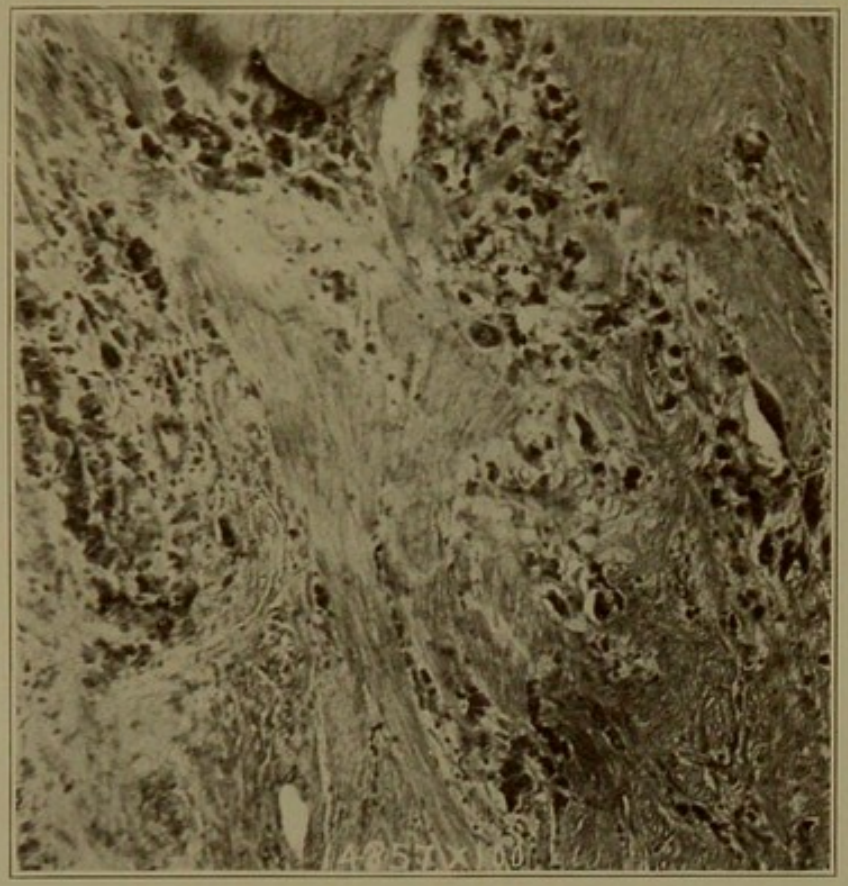

Fig. 37

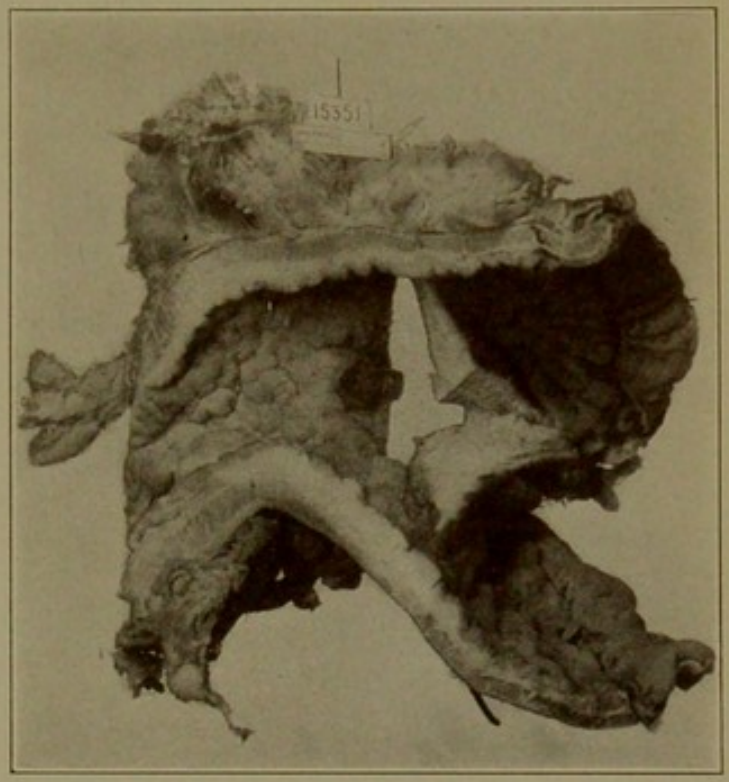

Fig. 35 (Case No. 14,857).—Stereogram showing a carcinoma filling the site of an old perforating ulcer of the stomach.
Fig. 36 (Case No. 14,857).—Photomicrograph showing a carcinoma with scar tissue. (× 100)
Fig. 37 (Case No. 15,351).—Stereogram showing a carcinoma in a small raised island of tissue in the base but near the edge of a large ulcer of the lesser curvature.

Fig. 38

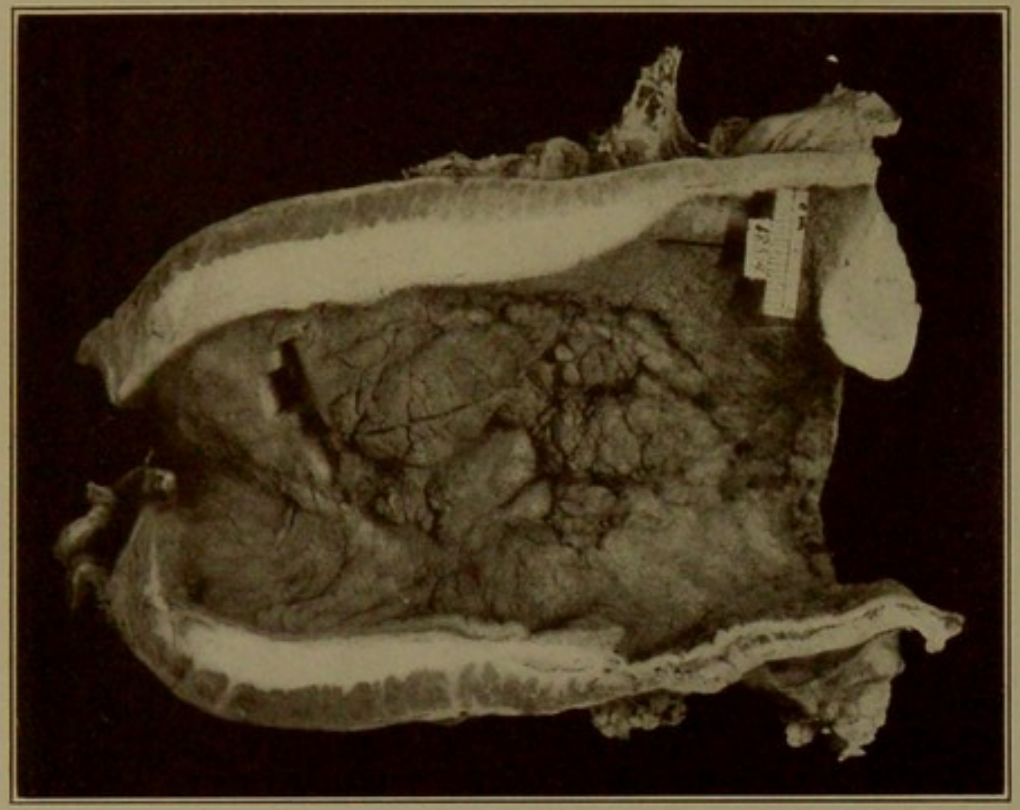

Fig. 39

Fig. 38 (Case No. 18,514).—Stereogram showing an extensive carcinoma on a large ulcer of the lesser curvature.

Fig. 39 (Case No. 14,949).—Stereogram of a gross section through the pylorus and the lesser curvature showing an ulcer of the lower 8 cm. of the lesser curvature and carcinoma about 2 cm. above; metastasis in the glands.

Fig. 40

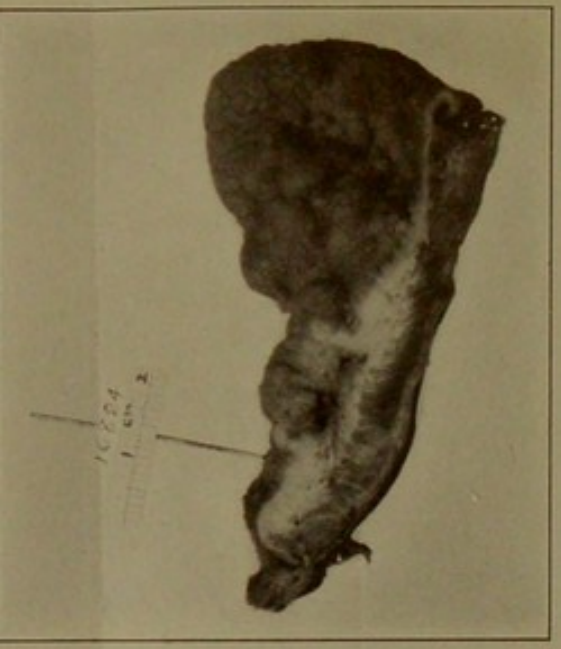

Fig. 41

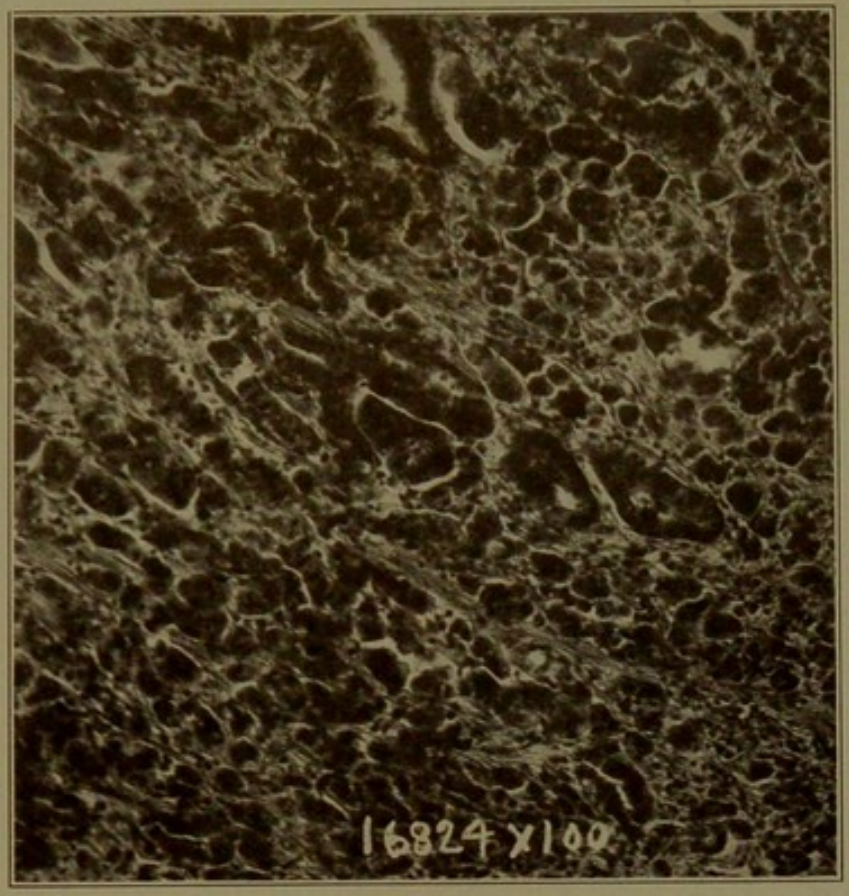

Fig. 42

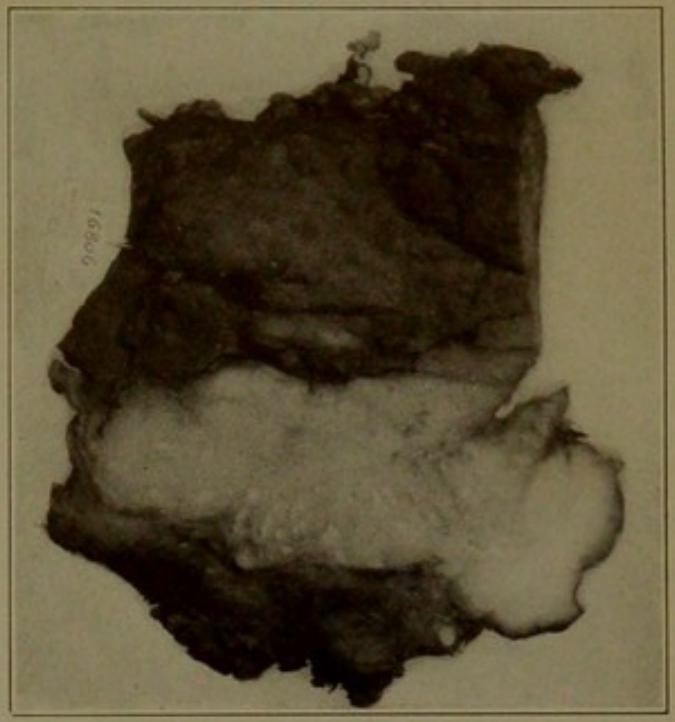

Fig. 40 (Case No. 16,824).—Stereogram showing a small early carcinoma of the pylorus without pathological evidence of previous ulcer.
Fig. 41 (Case No. 16,824).—Photomicrograph showing an early adenocarcinoma. (× 100)
Fig. 42 (Case No. 16,806).—Stereogram of a portion of the stomach wall showing carcinoma with colloid degeneration and deposition of lime salts; no pathological evidence previous ulcer.