THE RELATION OF GASTRIC ULCER TO CANCER

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The relation of peptic ulcer to cancer of the stomach is a matter of first importance in the pathology of this organ, and, since gastric cancer is the most frequent form of malignant disease, it is a matter of considerable economic importance. If a high proportion of peptic ulcers, 50 per cent., become transferred into cancer, then the excision of two gastric ulcers prevents the development of one cancer, which is practically a fatal condition. Moreover, if gastric ulcer is a strongly predisposing condition to cancer, since it usually gives pronounced symptoms before reaching an inoperable stage of malignant change, ulcerocancer is the only type of gastric carcinoma which offers a favorable prognosis. On the other hand, if ulcers seldom result in cancer, it is unwise to spread the belief that by excising ulcers we are seriously attacking the problem of gastric carcinoma.

On the relation of ulcer to cancer, there are the widest variations of opinion. Rokitansky, in 1840, recognized that cancer might develop from ulcer. Dietrich, 1848, among 160 cancers found 6 developing near ulcers, and two in which the carcinoma was limited to portions of ulcers. Lebert, 1878, calculated that 9 per cent. of cancers arise from ulcers, while Zenker, 1882, went so far as to say that all gastric cancers are secondary to some form of ulceration. In 1890, Hauser described five cases of cancer of characteristic anatomical form following ulcer and at the same time 33 cases of other types. He pointed out the frequent persistence of free HCl in these cases. G. Futterer, 1902, concluded that ulcers in the pyloric region frequently give rise to cancer, especially in those portions of the ulcer most exposed to irritation. Mayo-Robson is quoted as finding a history suggestive of ulcer in 59.3 per cent. of his cases of gastric cancer, but he reports (1904) only one case in which a carcinomatous change in an ulcer was actually demonstrated. Payr distinguishes between simple and callous ulcers and by serial sections finds cancerous changes in 26 per cent. of the latter. Kuttner found them by serial sections in 40 per cent. of 30 cases. The Mayo clinic reports that 71 per cent. of their gastric cancers were associated with ulcer, and 68 per cent. of ulcers were complicated by carcinoma.

On the other hand, more recently, Kuttner expresses himself in quite a different way, stating explicitly that "transformation of ulcer into cancer we have not observed." The majority of callous ulcers he regards as originally cancerous and says that only exact pathological study can determine this question. Duplant (1898) described eight supposed cancerous ulcers and concluded that they were all originally cancers. He supported with numerous arguments the view that all previous cases of ulcerocancer were

misinterpreted, and concludes that cancer never develops on peptic ulcer. Hirschfeld places the proportion of ulcers that become cancerous at 5 to 6 per cent., and he summarizes clinical and statistical data indicating that the proportion is small. Among 500 ulcers reported by Stall, Greenfeld and Berthold, only 13 showed cancer and in three of these the cancer was not connected with the ulcer. Boekelmann collects a series of estimates varying from 3 to 50 per cent.

From the surgical side, the following proportions of cancerous transformation of ulcers are reported: Rubritius, 8 per cent.; Mayer, 1.9 per cent.; Busch, 2 per cent.; Spriggs, 2.1 per cent.; Bamberger, 2 per cent. in 1589 cases; Drummond, none in 72 cases long observed. Borrmann reports that among 63 gastric resections by Mikulicz for cancer none showed an origin from ulcer. In France opinions are widely at variance. Moutier in 35 cases from operation and autopsy found 19 simple ulcers, 15 distinctly cancerous, and 1 cancerous duodenal ulcer.

Thus, among acceptable authorities it is possible to choose between 2 and 68 per cent. of ulcers becoming cancerous, and between none and 71 per cent. as representing the proportion of gastric cancers that arise from ulcers. It is therefore evident that the criteria upon which one may assert that an ulcer is cancerous or that a cancer has arisen from peptic ulcer have never been clearly established or have not been respected.

It is the object of this paper to offer a contribution in this direction.

The evidence bearing on the relation of cancer to ulcer may be derived from several sources: statistical, clinical, gross anatomical, and microscopical.

Statistical.—The statistical evidence relates to the sex and age of the patient with simple ulcer and cancer, to the locations of the lesions, to the fate of ulcers under treatment, and to the occurrence of healed ulcers.

Hirschfeld has shown that in Berlin and Hamburg, ulcer is more than twice as frequent as in Zurich, Munich and Vienna (7 per cent. *vs.* 3 per cent.) while gastric cancer is rather less common. Yet autopsies show the same rates for gastric cancer in both Berlin and Vienna (3.3 to 3.5 per cent.). Gastric ulcer may have been a more popular diagnosis in the Berlin hospitals than in Vienna. These comparisons do not appear to be very impressive. Gastric ulcer in these cities was about four times as frequent in women as in men, but gastric cancer about equally or more frequent in men.

Williams finds in England a cancer mortality from gastric cancer among males of 21.4 per cent., females 13.2 per cent., but he found 60 gastric ulcers among 32,505 male patients and 117 among 28,175 females. The sex divergence is therefore rather striking. Bulstrode reports that in the London Hospital 402 cases of gastric ulcer were in females, 98 in males. Fiedler in 2200 bodies found ulcers or scars in 20 per cent. of female, 1.5 per cent. of male bodies. On the other hand, not a few recent observers have found ulcer quite as frequent in men as in women. Since the older view was rather substantially supported, one must conclude that some recent observers have encountered a selected material, or that they have not carefully

excluded ulcerating cancers, or else that the proportions have actually changed. It seems at present difficult to state whether there is a great preponderance of ulcers in women.

Half the gastric ulcers occur between the ages of twenty and thirty years, and nearly all before thirty-eight, while most cancers occur in the decade of fifty to sixty years (Williams). Yet the age incidence is not always so uniform. Riegel shows that the maximum frequency for ulcers is between twenty and thirty years for women (62 cases), and between forty and fifty for men (36 cases), while isolated cases occur in advanced years. Greenough and Joslin in 187 cases found gastric ulcer five times as often in females as in males. The average in men was thirty-seven years, in women twenty-seven years. Yet Hauser's 5 cancers which were rather clear sequels of ulcer occurred between the years fifty-five and eighty-three. It is possible that the transformation of ulcer into cancer is limited chiefly to subjects well advanced in years.

The seats of election of cancer and ulcer do not favor the frequent origin of one from the other. The commonest seat of ulcer is the lesser curvature (36.3 per cent., Welch, Fenwick), whereas only 12 per cent. of cancers occur in this situation (Brinton, Welch). The commonest seat of gastric cancer is the pylorus, 60 per cent. of 4574 cases collected by Williams occurring there, while only 12 per cent. of Welch's 793 cases of gastric ulcer were thus located.

Williams regards the statistical evidence as incompatible with the frequent origin of cancer from ulcer, but it does not preclude the possibility that it occurs in a considerable number of cases. The theory of the cancerous transformation of peptic ulcer would be more acceptable if there were parallels in other organs, but in the lip, tongue, tonsil, œsophagus, rectum, larynx, cervix uteri, and in X-ray dermatitis there is first carcinoma and then ulceration. In the few instances where carcinoma follows ulcer, the malignant process develops as a rule only after many years, as in varicose ulcers of the leg. Lupus carcinoma never appears before the fifth and usually toward the thirtieth year of the disease and in the scar tissue. The cervical erosion is often associated with carcinoma, but these lesions are not originally ulcers, but rather extrusions of the mucosa which are long the seat of irritation and glandular overgrowth. On the other hand, the peptic ulcer is an exceptional condition and may be followed by exceptional results.

Clinical Evidence.—Since the development of cancer in a peptic ulcer must require considerable time, a history of gastric ulcer should be available in all cases so interpreted. Although gastric ulcer may occasionally fail to give symptoms, this situation must be extremely rare in any long continued case, and so long as the question is open to debate it would seem that no case should be accepted as an ulcerocarcinoma unless a long history of peptic ulcer is provided. The gastric ulcers that fail to give symptoms and furnish the healed scars found at autopsy are usually small or superficial. Latent cases of fully developed peptic ulcer are very rare.

Mayo-Robson is said to have found a history suggestive of ulcer in 60 per cent. of his cases of cancer, but suggestive symptoms are not sufficient. More convincing is the very definite report of pain, vomiting, and hæmatemesis of ten years' duration in one of Hauser's cases. Bamberger reports a history of recurrent ulcer for thirty-two years before death from ulcerocancer, and Mayo-Robson one of twenty-one years' duration. Greenough and Joslin observed a characteristic history of ulcer for two years before death from a secondary cancer. Riegel states that he is able to recognize clinically the cases of ulcerocarcinoma. They first show a long period of hyperacidity and symptoms of ulcer, then a tumor appears, the cachexia changes, and free acid diminishes or disappears. Hauser claimed that the long persistence of free HCl indicated an origin of the cancer from ulcer, but this feature is not invariable. Lockwood found a history of ulcer suggestive in 7 per cent., definite in 3 per cent., of 174 cases of gastric cancer.

An important phase of the clinical evidence relates to the fate of ulcers long observed and treated, which shows that while ulcer is permanently cured by medical measures in only about 40 per cent., it very rarely develops into cancer while under observation. Greenough and Joslin followed for five years 114 cases of ulcer treated medically. Of these 41 recurred, 27 died, 4 from unknown causes, but only 1 from the subsequent development of cancer. Hemmeter, who is one of the few authors who have adequately considered the complexities of the diagnosis, observed only three cases of cancer developing in the course of 232 peptic ulcers.

The results of gastro-enterostomy for ulcer reveal a small percentage of recurrences in the form of carcinoma (Galpern Lit.). In 1025 gastro-enterostomies for ulcer, traced for some time, Bamberg collected 22 cases developing cancer, 2.1 per cent. In 152 ulcers treated by resection, cancer developed in 1.9 per cent. Since the carcinoma usually developed within two years of the gastro-enterostomy, there is some reason to assume that some of the ulcers were originally cancerous. Gressot from an elaborate study of the literature concludes that ulcers become cancerous in 2.3 per cent. of cases treated by gastro-enterostomy. Billeter observed the course of 116 cases of ulcer treated by gastro-enterostomy. Eighty-seven patients were well after four to twenty-six years and only one developed cancer. Von Eiselsberg reports that of 269 cases of ulcer treated by gastro-enterostomy, 13 died from cancer (5 per cent.), while among 41 cases in which the ulcer was excised 2 died from cancer (also 5 per cent.). Sherren saw no cases develop cancer among 200 gastro-enterostomies for ulcer.

From the clinical evidence it may be concluded that a great number of ulcers have been treated medically for some years without developing cancer, that among the many ulcers so treated which persist or recur not more than 2 per cent. develop cancer and some of these may have been originally cancerous; that the number of cases developing cancer from ulcer after gastro-enterostomy is not appreciably larger than after resection of the ulcer; that a diagnosis of cancer following ulcer to be acceptable should carry

with it a previous history of ulcer; that this history covers a period of ten to thirty years in certain well attested cases, while in less satisfactory but possibly genuine cases the history of ulcer covers only two years.

Gross Anatomy.—The gross anatomy of cancer engrafted upon ulcer is usually characteristic, and hence if the case is to be accepted as such, this characteristic appearance should be demanded. On the other hand, it has repeatedly been shown that grossly typical peptic ulcers may form on a mucosa which is the seat of carcinoma. Failure to realize this fact has often led to the excision of ulcers under the impression that they were benign. A microscopic study in every case is called for.

Hauser clearly depicts the rather specific appearance of cancer grafted upon ulcer (Fig. 1). The deep, sharply cut excavation, overhanging proximal edge, firm fibrous base, and often the extension of the cicatrix to surrounding organs are satisfactory evidences of the long existence of a typical peptic ulcer. The carcinoma has usually appeared at one or more points, usually distal, sometimes becoming fused, and causing induration and fixation of the edge. Outlying islands of polypoid adenoma or adenocarcinoma are not infrequently observed. Menetrier states that carcinoma develops on ulcer only after a preliminary stage of polypoid adenomatoid growth.

The necessity of insisting upon a dense indurated base free from cancer seems to me essential. A. Schmidt finds it impossible to conceive how large flat ulcers, 3 to 4 cm. in diameter with extensive cancerous infiltration of the periphery, can be derived from the malignant transformation of an ulcer. The opposite relation seems to him more probable.

That an original cancer may be stripped of epithelial tissue over a central area and the base converted into dense cicatricial tissue resembling peptic ulcer is shown by Verse, in the report of his case No. 34.

The early stages of many carcinomas of the stomach reveal the important rôle of ulceration in the course of these lesions. Verse has described 12 very early carcinomas of the stomach. They consisted of circumscribed thickenings of the mucosa, 1 to 2 cm. in diameter, in which the glands presented the changes of adenocarcinoma or fully developed carcinoma. In some, the surface was unbroken, but the stroma was infiltrated by polynuclear leucocytes. I have studied such a lesion covering an area of 2 cm. in the cardiac region. Usually ulceration had become established with more or less complete excavation of the central portion. These early and rarely observed lesions reveal the close connection between ulceration and cancerous proliferation in carcinoma of the stomach and they emphasize the necessity of great caution in assuming that an ulcerating and carcinomatous process is anything else than an ulcerating cancer. Especially in the pyloric region where mechanical erosion is constantly at work, early and sometimes deep ulceration may be expected as a natural sequence in the growth of carcinoma.

In certain cases of peptic ulcer followed by carcinoma the latter process has appeared to be disconnected from the former (Hauser, Verse, Galpern). This occurrence has been sufficiently frequent, as after excision of ulcers,

to lead to the conclusion that when carcinoma does follow ulcer the relation may be accidental. Galpern and Bamberger state that the stomach with peptic ulcer is as likely to become cancerous as the normal stomach and no more. Yet this conclusion ignores the undoubted development of cancer in the inflamed edges of certain ulcers.

From the anatomical data one may conclude that the gross appearance of cancer grafted on ulcer is usually characteristic; that this evidence is the most direct and convincing in regard to the relation of the two processes and should be demanded in acceptable cases; that ulcerating cancers may closely simulate peptic ulcers with secondary malignant changes; and that cancer and ulcer may occur independently in the same stomach.

Microscopical Evidence.—The development of carcinoma in the edges of chronic ulcers has been minutely described by Hauser, Verse, Menetrier, Wilson and McCarthy and others. In this field it is necessary to emphasize the difficulty of recognizing all the structural variations which carcinoma may exhibit. When one compares the fading remnants of carcinoma cells in the leather-bottle stomach (linitis plastica) with the bulky masses of adenocarcinoma, and contrasts these in turn with the diffuse round-cell carcinomas and the curious forms arising in wide areas of glands with intact membrana propria, one realizes that in carcinoma of the stomach there are unusual hazards in histological diagnosis. Perhaps the active movements of the pyloric antrum account for some of these structural peculiarities. When such an experienced observer as Krompecher, after years of study of pyloric stenosis, is forced to change his opinion and to accept these lesions as carcinomas which he had long failed to recognize, it becomes apparent that this is no field for hasty interpretation.

In Hauser's cases the edges of the ulcers were markedly hypertrophic, the carcinomatous changes were most marked at the line of ulceration and extended with diminishing intensity for a distance of ½ to 1 cm. over the outlying mucosa, the infiltration involved the peripheral submucosa and the muscularis, while the indurated base of the ulcer was free from infiltration. The various stages of transformation of the normal into carcinomatous glands were traced in detail, ending usually in an adenocarcinomatous structure. Lesions presenting these features and this series of changes in portions only of the edges of indurated ulcers must be accepted as satisfactory examples of the development of carcinoma on peptic ulcer. I do not find, however, that all authors have observed these criteria in the diagnosis of ulcerocarcinoma. Verse describes three typical cases and then ventures with some hesitation to include a fourth, a broad ulcer in a woman of twenty-eight years in which projecting islands of carcinoma of rather diffuse type occurred over the base of the ulcer. I cannot regard this lesion as anything else than an ulcerating cancer. It would seem extremely unlikely that a secondary carcinoma can ever invade the indurated base of a peptic ulcer. These tissues are usually very dense and fibrous and when they are invaded by carcinoma it would be much safer to assume that the infiltration existed before the ulceration.

McCarthy evidently includes among the evidences of carcinoma a variety of inflammatory hyperplasias and misplacements of gastric glands some of which result from inflammation about the ulcer and at other times probably precede the formation of the ulcer. These changes may well be grouped in the class of precancerous processes. Yet it is one of the dangers of the dissemination of the doctrine of precancerous lesions that their presence may too readily be assumed to mean that carcinoma already exists or soon will appear, whereas there can be no certainty that any given precancerous lesion would, if undisturbed, go on to develop cancer. In the case of gastric ulcers Galpern's and Bamberger's observations on the fate of gastric ulcer after gastro-enterostomy seem to prove that these lesions seldom go on to produce cancer.

In my own material I have had much difficulty in deciding how to interpret some ulcerating and cancerous lesions. Certain conclusions, however, have been drawn from the study of material from autopsy and operation which bear upon the relation of cancer to ulcer.

(1) The great majority of ulcerating lesions of the stomach fall clearly in the classes of ulcerating cancers or simple peptic ulcers. The cancers are usually broad, widely and uniformly infiltrating, and the ulceration is merely an erosion or an irregular excavation beginning in the centre and extending over much of the surface. Pyloric cancers are especially prone to suffer excavation. The peptic ulcers are sharply cut, the edges flat but overhanging, the base is indurated and free from any signs of cancer. The surrounding mucosa shows much or little glandular overgrowth. This material does not support the view that peptic ulcer tends strongly to atypical glandular proliferation.

(2) With certain peptic ulcers a large part of the gastric mucosa is the seat of glandular hypertrophy with atypical changes in isolated glands and interstitial growth of connective tissue which causes some disarrangement of the glands. This condition is not secondary to the ulcer but may well predispose to ulcer. It may serve as a source of error in interpreting atypical overgrowth on the edges of ulcers (5584, 5715) (Fig. 2).

(3) Deep excavations may occur in portions of established carcinoma especially in the pyloric region where powerful muscular contractions tend to cause hernias of infiltrated and weakened muscular tissue. This condition appears clearly in three of my cases. In case 5296 the entire pyloric region for a length of 6 cm. is the seat of a broad, dense carcinoma of uniform texture. It is considerably excavated and at a point 2 cm. from pylorus the excavation descends abruptly in a cavity ½ cm. deep which lies upon pancreas. All portions of the ulcer, edges, base, and adjoining pancreas are uniformly infiltrated with large alveolar adenocarcinoma. Some would interpret this case as carcinoma grafted upon ulcer, but I am unable to conceive how carcinoma could have infiltrated so uniformly all portions of the base of this lesion if it arose on the edges of an ulcer and had to attack old dense connective tissue. This same type of adenocarcinoma covered the

mucosa uniformly for a distance of 3 cm. about the ulcer. There was no history of an old ulcer (Fig. 3).

In case 5099, a very similar gross lesion with deep central excavation proved to be a rapidly growing diffuse round-cell carcinoma. The tumor cells infiltrated the entire base of the ulcer, splitting up the muscular coat and invading the subserous fat and the pyloric lymph-nodes. This type of carcinoma is not readily derived from atypical proliferation on the edges of an ulcer (Fig. 4).

Case 8253, placed at my disposal by Doctor Elser of New York Hospital, is highly instructive, illustrating the formation of peptic ulcers on a diffuse carcinoma of the stomach. The patient, a male, fifty years, moderately alcoholic, enjoyed good health until four months before death, when he began to suffer from gastric disturbance soon followed by sharp pains after eating. He died after laparotomy. At autopsy there was extensive miliary carcinosis of peritoneum. The whole pyloric region of stomach showed moderate thickening of mucosa increasing toward the pyloric orifice, and this region was irregularly adherent. There were three typical peptic ulcers. One was a slit-like excavation at the pyloric orifice looking into the duodenum. The others lay on posterior surface 6 and 9 cm. from the pylorus. They measure 1½ cm. in long diameter, edges overhanging but not indurated, bases cleanly excavated and smooth, extending into muscularis. On microscopical examination the entire pyloric region was the seat of diffuse carcinoma infiltrating all coats. The bases of the ulcers were formed throughout by carcinoma tissue infiltrating the muscle. The remnants of glands on the edges showed no change (Figs. 5 and 6).

(4) Gastric digestion may strip a primary carcinoma down to the muscularis or deeper, leaving no trace of carcinoma over most of the base but only a peripheral ring of tumor tissue which is protected by the mucosa. This event is indicated in some of Verse's cases which ulcerated early and it appears in one of mine.

This case, 5397, presented the usual appearance of peptic ulcer of rather broad dimensions and was excised as such and at first passed the laboratory as simple ulcer. On section it was found that the entire ulcer was surrounded by a continuous narrow ring of carcinoma partly protected by the intact mucosa (Fig. 7). Glandular proliferation of the peripheral mucosa was missing, the tumor ending abruptly. The structural type was that observed in many early carcinomas, strongly atypical small alveolar adenocarcinoma. The lymph-nodes were not involved. The central two-thirds of the base was free from carcinoma. Wilensky and Thalhimer seem to have encountered a notable case in which all traces of an original carcinoma were completely excavated, leaving a simple peptic ulcer in the stomach wall, while the adjoining lymph-nodes were the seat of carcinoma.

(5) When the base of an ulcer is uniformly infiltrated with carcinoma, especially of diffuse or atypical small alveolar type, the condition is difficult to reconcile with an origin from the edges of the ulcer (Fig. 8). When

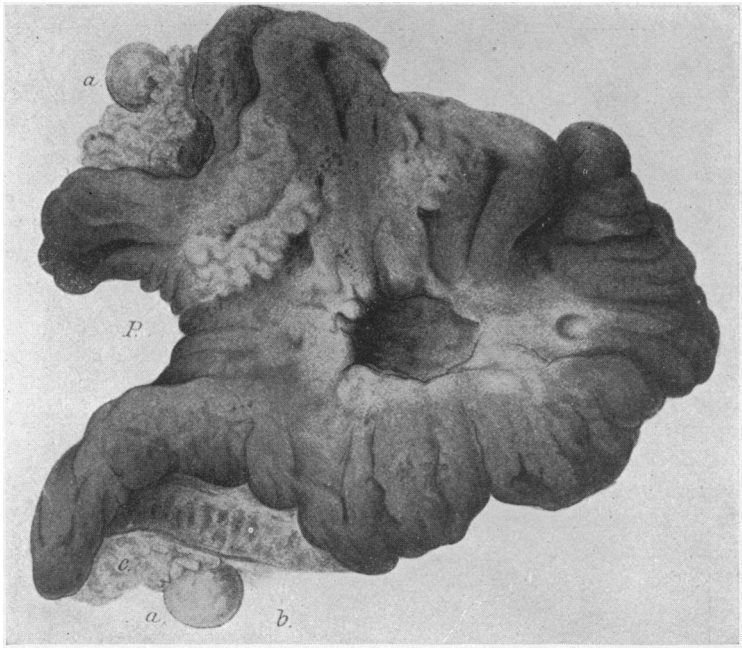

FIG. 1.—Hauser's drawing showing the gross anatomy of carcinoma grafted upon ulcer. Note the polypoid projections and the irregular distribution of the opaque carcinomatous tissue.

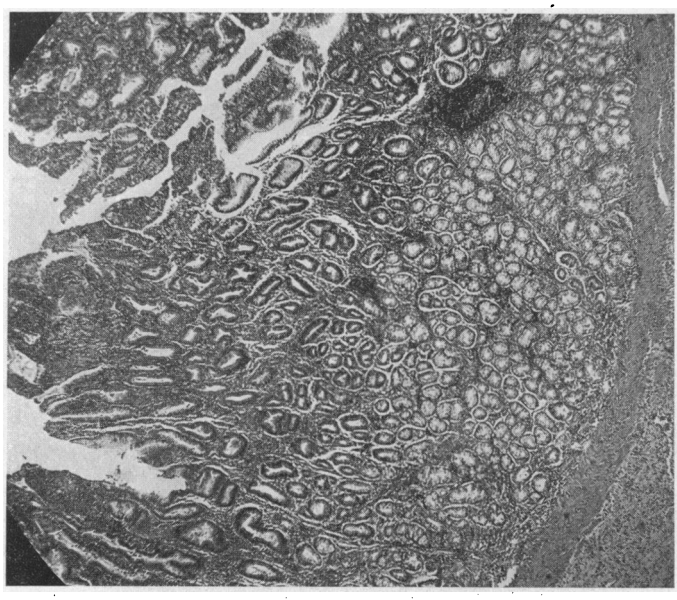

FIG. 2.—Atypical changes in glands in diffuse hypertrophic gastritis involving most of the mucous membrane in a case of peptic ulcer. The hypertrophy is not a result of the ulcer.

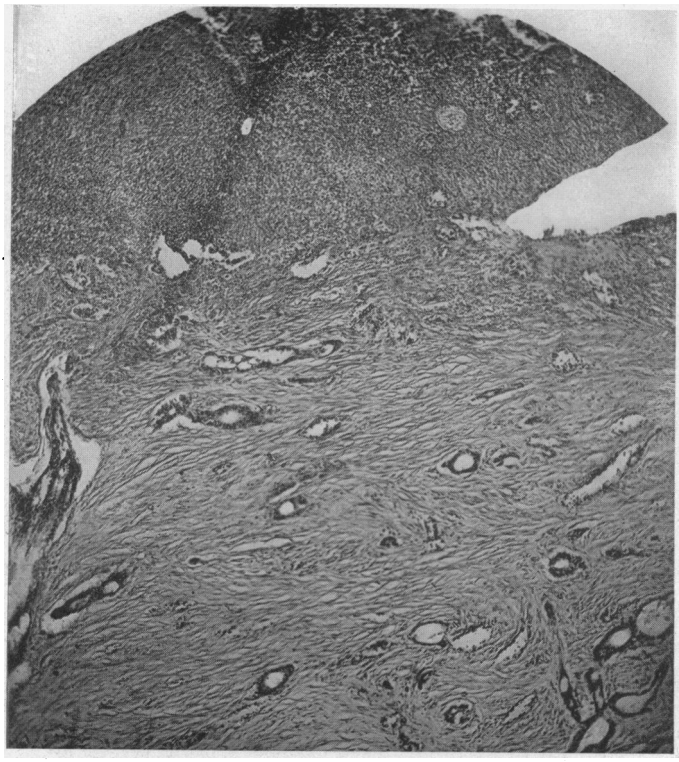

FIG. 3.—Case 5296. Fibrosing adenocarcinoma involving 6 cm. of the pyloric region. The section comes from the edge and base of a deep ulcer reaching almost to pancreas.

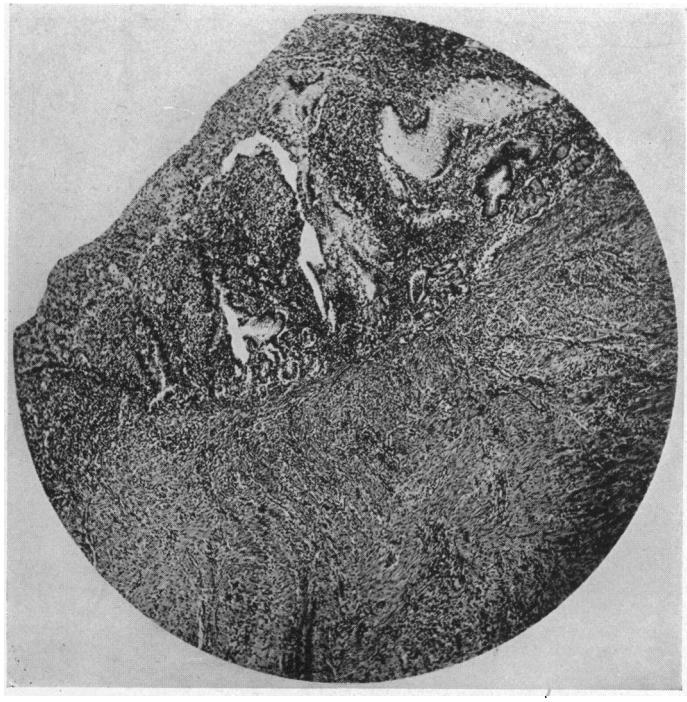

FIG. 4.—Case 5099. Inflammatory changes in the mucosa on the edge of a peptic ulcer grafted on diffuse round-cell carcinoma of pylorus. The carcinomatous process is invisible in this magnification.

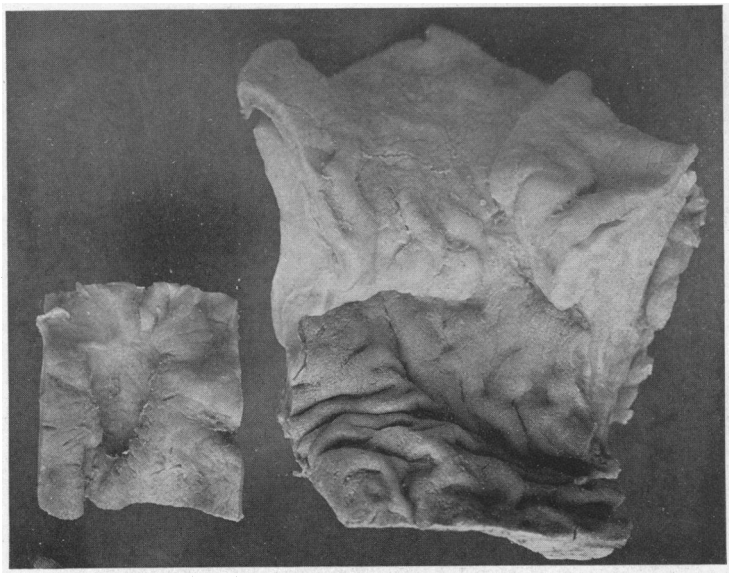

FIG. 5.—Case 8253. Multiple peptic ulcers grafted upon diffuse carcinoma of pyloric region.

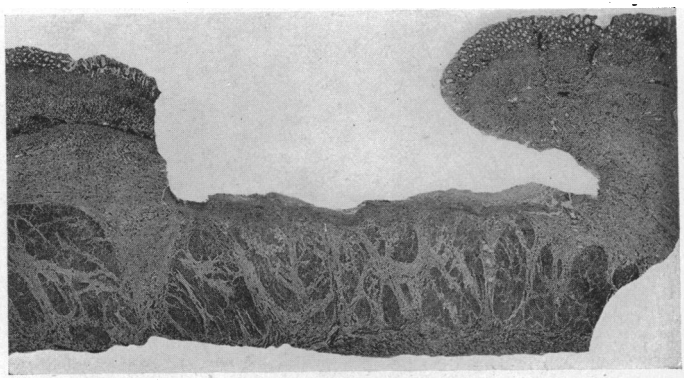

FIG. 6.—Cross-section of one of the ulcers in Case 8253. The muscularis is split up by diffuse carcinoma. The glands in the overhanging edges are unchanged.

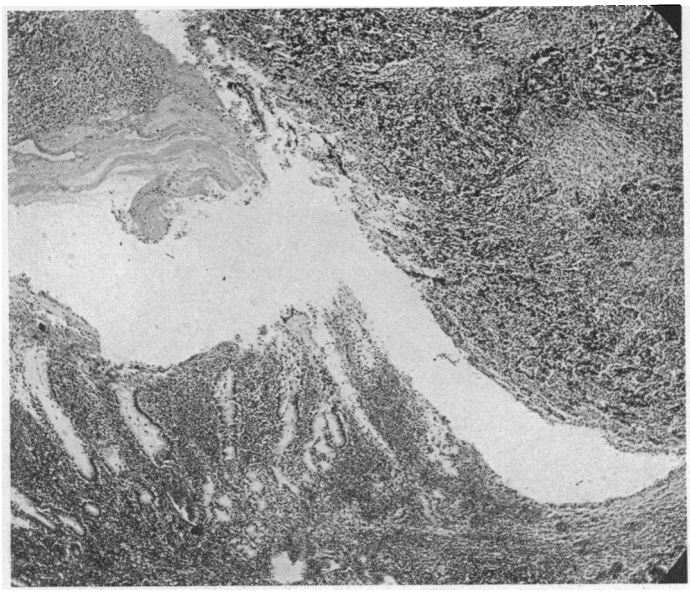

FIG. 7.—Edge of an ulcerating adenocarcinoma. The carcinoma (in upper right corner) is limited to a narrow peripheral ring protected by the overhanging edge of inflamed mucosa. The base of the ulcer is free from carcinoma. There are no atypical changes in the glands. The lesion is an early adenocarcinoma extensively excavated by the digestive action of the gastric juice.

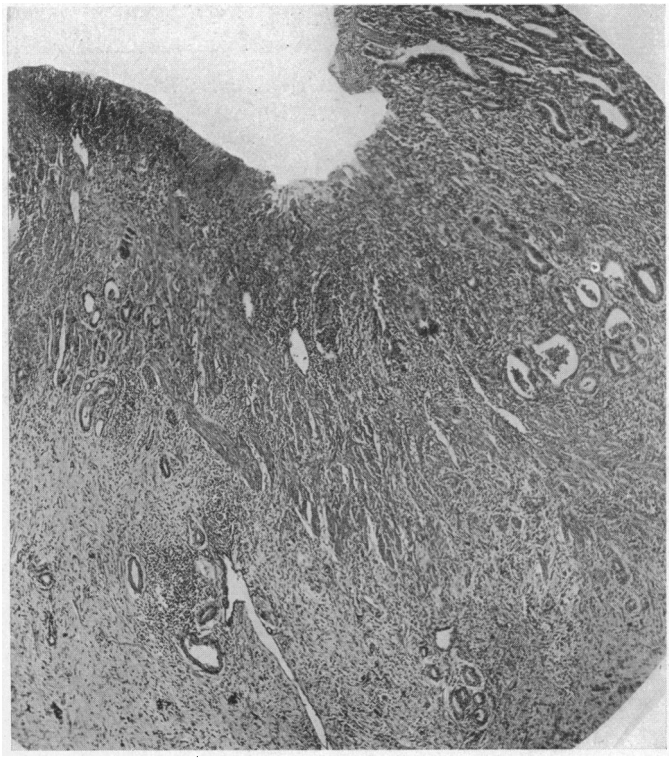

FIG. 8.—Atypical proliferation and misplacement of glands on edge of an ulcer grafted upon diffuse carcinoma. The structure of the carcinoma is greatly altered by inflammation and cicatrization. The visible glands do not constitute the carcinoma.

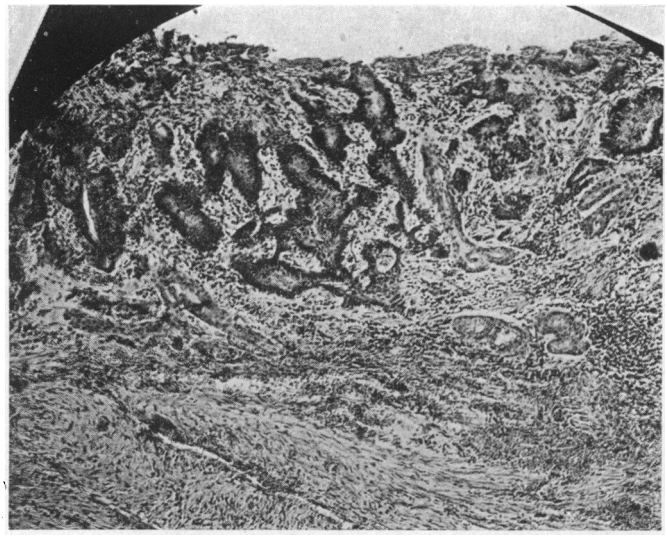

FIG. 9.—Atypical proliferation of glands on edge of a simple peptic ulcer. This lesion is not cancer.

one visualizes the conditions which must exist for the development of cancer by atypical proliferation on the edges of an ulcer, it is clear that the process must take considerable time, probably months, certainly in the best attested cases many years, and the base of the ulcer must become indurated, fibrosed and infiltrated by leucocytes which are antagonistic to tumor growth. Close to the surface of such a lesion it may safely be said to be impossible for cancer to advance. The natural paths of extension of such a secondary carcinoma will be those of least resistance which are outward, and such was evidently the course in Hauser's cases. Hence great importance would seem to attach to the condition of the base of the ulcer in the diagnosis between primary and secondary carcinoma.

(6) The occurrence of atypical epithelial proliferation in the glands on the edge of an ulcer is not sufficient evidence that the lesion is going on to cancer (Fig. 9). A safe application of the doctrine of precancerous lesions recognizes that the suspicious lesions may never pass beyond the stage observed. This rule is especially patent in the breast and prostate, where atypical changes are very frequently seen in chronic mastitis and prostatitis, but the disease terminates in cancer at most in only 15 to 25 per cent. of the cases. The same rule doubtless applies to the stomach, in which I find atypical proliferation on the edges of peptic ulcers is rather uncommon.

From the above considerations the writer is forced to conclude that the cancerous transformation of peptic ulcer is rather infrequent and probably does not exceed the incidence of 5 per cent. originally established. This proportion would be much smaller if only those cases were included in which the evidence is demonstrative, viz.: a long history of gastric ulcer, the limitation of the tumor to isolated foci or one portion only of the ulcer, and freedom of the base from infiltration.

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