ETIOLOGY OF CANCER OF THE STOMACH*

A REVIEW OF ONE HUNDRED SIXTEEN CONSECUTIVE CASES OF CANCER OF THE STOMACH WITH PARTICULAR RELATION TO ETIOLOGY

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The first known reference to carcinoma of the stomach developing on a preëxisting ulcer was made by Cruvielhier in 1839, when he said that a simple ulcer of the stomach in people suffering from "diathise cancereuse" might change into cancer. This was followed three years later by the statement of Rokitansky in which he observes that ulcer appears together with cancer and in that case as a rule it is easy to see that the carcinoma had its origin in ulcer. Dittrich, in 1848, examined 160 cases of gastric carcinoma and only in one case did he find carcinoma in the margin of an ulcer, and even this he regarded as a coincidence. Steiner and Wollman in 1868, Meyer in 1874 and Lebert in 1878, all agreed with Cruvielhier that carcinoma developing on an ulcer only rarely exists. A sudden transition to exactly the opposite view was made in 1882 by Zenker, who proposed the idea that all gastric carcinoma originated in ulcer. During the following year, Hauser, a pupil of Zenker's, published an extensive investigation on the subject. From his morphological description, Hauser maintained that the atypical epithelial changes in ulcer of the stomach were prestages of cancer. However, Friedlander and Cohnheim have shown that the morphology of epithelial proliferation is not limited to the stomach and ulcer, but that, at any place where chronic irritation causes the formation of granulation tissue and where epithelial tissue is present, an epithelial proliferation may appear, which frequently results in an atypical and to a certain degree, cancer-like appearance.

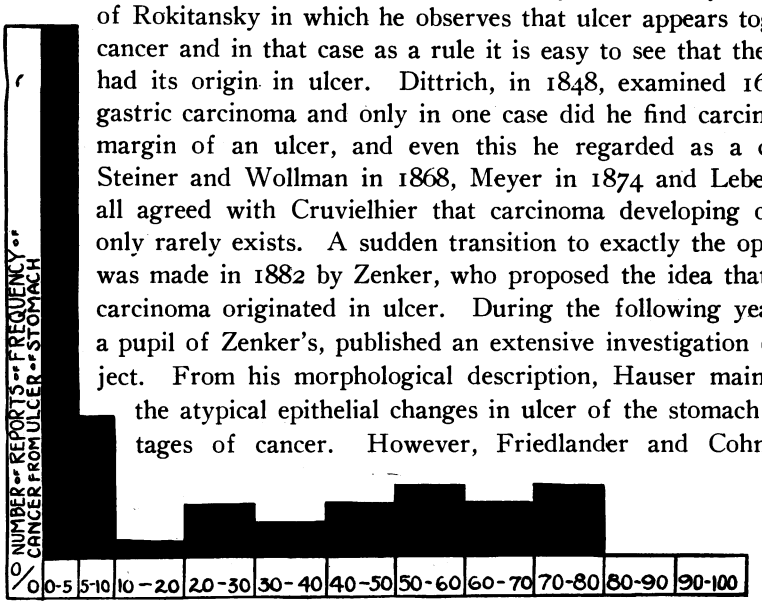

Fig. 1.—1906 to 1915.

Tripier and his pupils, Duplant and Saneroth, in 1900, from morphological and clinical observations, advanced the theory that the ulcero-cancer was not a simple gastric ulcer with carcinomatous degeneration, but a cancer, which in many respects bears a resemblance to the ulcus rodens of the skin. The growth of a gastric carcinoma is so slow and its tendency to ulcerate so

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pronounced, that it is often difficult to find carcinoma cells in the lesion. Tripier did not produce any scientific evidence to support this view, merely stated it as a theory. It was not regarded very highly in France because of the opinions of such men as Bouvert, Dieulafoy, Mathieu, Hayem and Audistere, who all stood for the cancer *ex ulcus* theory.

Without doubt, the theory that has caused the most discussion and led to a great deal of work on the subject, is the one claiming the development of carcinoma in a preëxisting ulcer of the stomach. From a fairly comprehensive review of the literature there are found at least 82 writers who are willing to commit themselves to figures estimating the frequency of this occurrence. The percentages of frequency vary from 0 to 100 per cent. These reports extend over a period of 77 years, the first one being given by Dittrich in 1848. He placed the estimate at 5 per cent. During the next 34 years there are only four estimates, two of which are below 10 per cent., one at 40 per cent., and one at 100 per cent., which was given by Zenker. The last is the only 100 per cent. which appears in the literature. Within the next 18 years there were six more reports, all of which were under 15 per cent. This brings the reports up to 1900, making a total of eleven in all. The

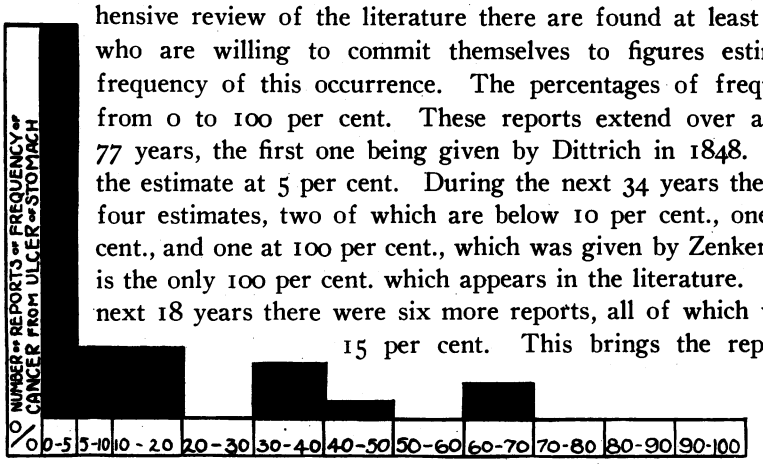

FIG. 2.—1916 to 1925.

majority of the work has been done since that time with perhaps the greatest amount in the decade between 1905 and 1915. Since 1900, there appear in the literature 71 articles in which an estimate is given, varying from 0 per cent. to 90 per cent. It is interesting to note that between 1905 and 1915 there are 38 articles, while between 1915 and 1925 there are 22 articles. (Fig. 1.) To analyze briefly the figures quoted in the former decade, we have of those under 5 per cent. fifteen, or 39 per cent., under 10 per cent. 19, or 50 per cent.; from 10 to 15 per cent. one and from 15 to 20 per cent. none, or under 20 per cent. twenty, or 52 per cent.; from 20 to 30 per cent. three; from 30 to 50 per cent. four, or under 50 per cent. twenty-seven, or 71 per cent. From 50 to 80 per cent. eleven, or 28 per cent. (Fig. 2.) In other words, there are approximately twice as many men believe that the development of carcinoma from ulcer is below the small number of 10 per cent. as there are those who believe the frequency is between the high percentages of 50 and 80. To analyze the whole number of reports found, which is 82, we find 39 per cent. of men estimating the frequency under 5 per cent., 50.6 per cent. under 10 per cent., as compared to 18 per cent. of men who estimate the frequency to be over 50 per cent. (Fig. 3.) Figures, in this case, of course, do not prove that the occurrence is necessarily low, but in the face of such strong evidence it is very difficult to believe that the frequency is anywhere near as high as some reputable authorities would have us believe.

The crucial point in the whole question of the frequency of occurrence of cancer from ulcer lies in the individual differences in the determination of the pathology. This involves the criteria upon which the diagnosis is made. Examination of about 150 articles shows a surprising lack of harmony in the criteria. Until pathologists and surgeons adopt a uniform standard for the interpretation of the microscopic picture, there will always be a wide diversity of opinion, and furthermore, until such an agreement is reached we shall not be in a position to say with approximate accuracy the frequency of development of carcinoma on an ulcer basis.

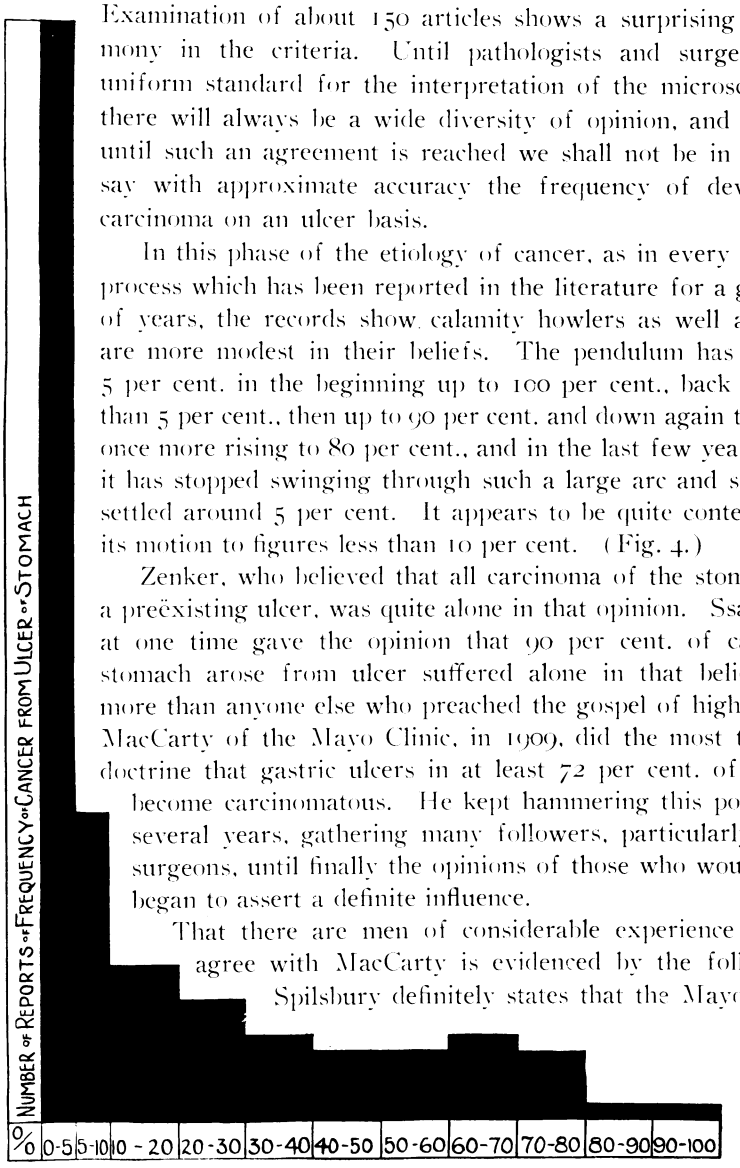

FIG. 3.—1843 to 1925.

In this phase of the etiology of cancer, as in every other disease process which has been reported in the literature for a great number of years, the records show calamity howlers as well as those who are more modest in their beliefs. The pendulum has swung from 5 per cent. in the beginning up to 100 per cent., back again to less than 5 per cent., then up to 90 per cent. and down again to 0 per cent., once more rising to 80 per cent., and in the last few years apparently it has stopped swinging through such a large arc and seems to have settled around 5 per cent. It appears to be quite content to confine its motion to figures less than 10 per cent. (Fig. 4.)

Zenker, who believed that all carcinoma of the stomach arose in a preëxisting ulcer, was quite alone in that opinion. Ssapeshka, who at one time gave the opinion that 90 per cent. of cancer of the stomach arose from ulcer suffered alone in that belief. Perhaps more than anyone else who preached the gospel of high percentages, MacCarty of the Mayo Clinic, in 1909, did the most to spread the doctrine that gastric ulcers in at least 72 per cent. of cases would become carcinomatous. He kept hammering this point home for several years, gathering many followers, particularly among the surgeons, until finally the opinions of those who would not be led began to assert a definite influence.

That there are men of considerable experience who do not agree with MacCarty is evidenced by the following facts. Spilsbury definitely states that the Mayo criterion of isolated cells detached from the regenerating epithelium and buried in the fibrous tissue is not necessarily correct. He goes further even, in pointing out that processes of irregular regeneration are mistaken for malignant transformation by many.

Aschoff, whose opinion is extremely valuable, does not state definitely the

percentage of occurrence, but does say, in 1911, that the transformation of a simple ulcer into cancer is not as frequent as it has been variously assumed.

Anschutz, in 1912, said that the Mayo group lay great stress on the history of preëxisting ulcer which in his opinion was of little value. MacCarty shows very pretty pictures and gives exact histological descriptions, but even then he cannot be convinced in this important question. He is not able to join in opinion with MacCarty that 70 to 80 per cent. of carcinoma develops on known ulcer basis, but gives as his own opinion that the number of cases that one can say with precision developed from an ulcer basis is very small. As late as 1920 he believes that the highest percentage of carcinoma from ulcer is from 3 per cent. to 5 per cent.

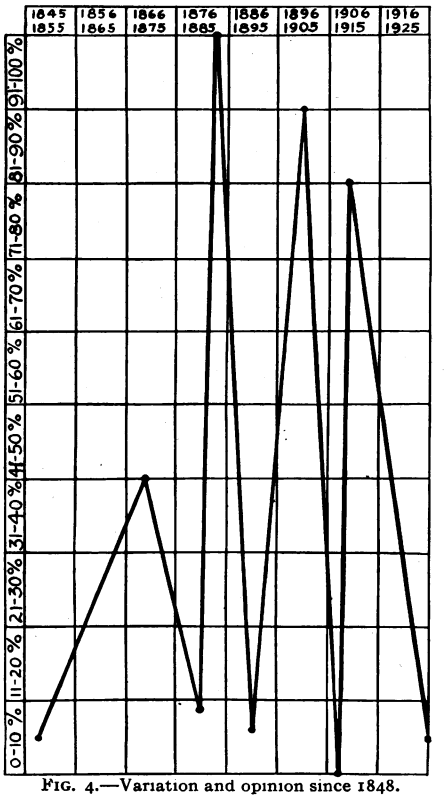

FIG. 4.—Variation and opinion since 1848.

Aaron, in discussing carcinoma of the stomach, quotes Wilson and MacCarty as concluding that practically all carcinomata develop on the site of a previous ulcerative lesion of the gastric mucosa and adds that this report is not in accord with his clinical experience. Aaron also quotes A. Kocher, who says that he has personally examined the Mayo specimens and is convinced that much of what they labeled cancerous degeneration of ulcers was in reality merely atypical proliferation of epithelium, or only epithelial changes in the progress of the ulcer and have nothing to do with carcinoma.

Ewing, in 1918, says that MacCarty uses as evidence of carcinoma, inflammatory hyperplasias and misplacement of gastric glands, which may well be grouped under precancerous conditions, but that is no evidence that they develop carcinoma.

Spilsbury and Ewing have both emphasized the observation that if the base of the ulcer is infiltrated with carcinoma the lesion has been carcinoma from the start.

Bartlett adds another observation which may well be included in the criteria. It is that in gastric ulcer the muscle coat is completely destroyed in the base while with carcinoma this but rarely happens; hence if there were well-defined portions of muscle in the base of a carcinomatous lesion, it is strong evidence that the neoplasm did not arise in the edge of an ulcer.

Konjetzny, in 1913, in speaking of MacCarty's work of 1909, says the description is so fragmentary and scanty, so purely subjective, that not in

a single instance does it suffice or satisfy even a moderate claim. As to the question how frequently does carcinoma develop from an ulcer, the work of MacCarty and Wilson is worthless.

As has already been pointed out, the percentage of frequency of carcinoma from ulcer varies from 0 to 100 per cent., according to the pathologists who have reported on this subject for the last 75 years. That there is such wide divergence of opinion is only evidence of the lack of standardization of criteria. In addition to the microscopic evidence we must examine the clinical aspects and attempt to bring them nearer together. The most important feature of the clinical side of the question according to some authorities seems to be the history of the patient, that is the evidence by symptoms that a gastric ulcer has existed for a certain period of time, usually more than five years, previous to the appearance of the typical gastric carcinoma picture. This particular point also seems to be somewhat in doubt. There are those who lay great stress upon the ulcer history and others who claim that it is very difficult to make a diagnosis of ulcer from the history, some who say even that any patient with gastric symptoms may be made to give practically an ulcer history by the clever presentation of leading questions. Then there is always the possibility of a typical gastric ulcer history really being that of duodenal ulcer.

Lockwood, in speaking of the 70 per cent. frequency of cancer from ulcer which is claimed by some, maintains that the pathological findings are at variance with the clinical observations, namely, that the history of preëxisting ulcer is not present in 70 per cent. of carcinoma cases. He finds 7 per cent. of cases with a suspicious history, while only 3 per cent. have a positive history. Lockwood also points out the change in the ideas of Mayo-Robson who in 1901 wrote, " It is, however, rare to elicit a history of very old standing stomach disorder. The first evidences of local disease appear suddenly in persons of perfectly sound health and robust digestion." In 1907, only six years later, Mayo-Robson writes, " In no less than 59.3 per cent. of carcinoma of the stomach on which I have performed gastro-enterostomy for the relief of symptoms, the disease having advanced too far for gastrectomy, the long history of painful dyspepsia suggests the possibility of ulcer preceding the onset of the malignant disease." Lockwood comments on the pretty rapid and radical change of ideas.

Moynihan, in 1909, says that two out of three cases of carcinoma operated by him had a history of previous ulcer. In 1906, he found in one group of 22 patients, 72.1 per cent. of ulcer preceding cancer. McDowell, in 1919, says that it seems probable that gastric cancer rarely develops except at the site of a previous ulcerative lesion of the mucosa and that the clinical and pathologic data of the development of gastric cancer on gastric ulcer are in close agreement with regard to, one, the average age of the patient at operation; two, the average period of previous history of ulcer; three, the average number of months of acute symptoms.

Taylor and Miller find a history of preëxisting ulcer in 17 per cent. of a group of 182 cases.

Osler in 150 cases found ulcer history in 2.6 per cent. and in not a single instance could it be positively diagnosed. Fenwick found 3 per cent. ulcer history in his cancer cases, Haberlin 2.3 per cent. and Eichhorst 2 per cent.

As evidence tending to show that cancer does not develop from ulcer with great frequency, we may briefly review those cases in which a gastro-enterostomy has been done for simple ulcer and the patients observed for

TABLE I.

Age Incidence.

Age	Cases	Per cent.	40 to 60	50 to 70	40 to 70
15–19	1	0.86			
20–29	4	3.44			
30–39	13	11.2			
40–49	18	15.5			
50–59	42	36.2	51.7		81.0
60–69	34	29.3		65.5	
70–79	3	2.5			
80–89	1	0.86			
Total...	116				

several years after. Paterson finds that death from carcinoma after gastro-enterostomy for simple ulcer is rare, in his own cases 1 per cent. Kocher in 50 cases of gastro-enterostomy for simple ulcer one to twelve years after found no cases of malignancy. He later adds 30 cases to the already published 50, making 80 in all, and still finds no case of carcinoma developing after operation for ulcer. Billeter, in reporting 122 cases of ulcer, had 6 deaths, 4 resections in which no malignancy was found, 112 gastro-enterostomies in which only one carcinoma developed after operation. Greenough and Joslin had one carcinoma out of 114 gastro-enterostomies, Hemmeter had three out of 232 gastro-enterostomies. Bamberg, in 1909, reported 1025 gastro-enterostomies for ulcer and found that 2.1 per cent. developed cancer subsequent to the operation for ulcer. Of 152 cases of gastric ulcer in which resection was done, 1.9 per cent. subsequently developed carcinoma. Gressot reports a percentage of 2.3 of carcinoma developing after operation for ulcer, presumably gastro-enterostomy. Sherren operated 200 cases of gastric ulcer, performing gastro-enterostomy, and in no instance did he find carcinoma developing after operation. Rehfus, in 1924, reports his percentage as one to two. Exalto, in 1918, found two out of 208 cases.

The group of cases here considered is that coming to the Surgical Service of the University of Michigan Hospital from 1916 to 1925. They include

only cases in which the facts have been demonstrated by operation and many of them checked by the pathological report. We are quite aware that this is not a large series of cases, but we think it justifiable to consider them particularly in their bearing upon the question of relation of ulcer to cancer.

Table I shows the age incidence and does not importantly depart from the figures of other observers. It shows, as have others, that the condition is most common at or after middle life, 51 per cent. of the cases falling between the ages of forty and sixty and 81 per cent. between the ages of forty and

TABLE II.

Duration of Symptoms According to Age of Patient.

	2 mo.	4 mo.	6 mo.	9 mo.	12 mo.	18 mo.	2 yr.	4 yr.	5 yr.	8 yr.	10 yr.&over		Not mentioned
Age	Duration of Time and Number of Cases.												
20–25				1	1			1					
26–30	1		1			1			1				
31–35	1		1		2								
36–40	1	1	3	1	5								
41–45	1	1	1	1	2				1				
46–50	3	1	2	1	1	1	2						
51–55	1	2	1	2	7	2	1	1		1			
56–60	3	4	4	4	4		2			1	1		
61–65	4	6	4	1	2	1	2				1		
66–70	2	2	2					1					
71–75			1										
76–80			2										
Total.	17	17	22	11	24	5	7	3	2	2	2		4-116

seventy. It is perhaps also worth while to point to the relatively large number of cases between thirty and forty, 11 per cent.

Table II shows the duration of symptoms and again departs in no important way from the accepted views upon the subject, namely, that the symptoms in cancer are notoriously of short duration as compared with the cases of non-malignant ulcer. The vast majority of these patients had symptoms for less than one year and a very considerable proportion had symptoms for six months or less.

History of Ulcer.—Some discussion might readily arise over what constitutes a history justifying the diagnosis of peptic ulcer. Some observers would take the view that any history showing pain in the upper abdomen, whether or not related to food, whether or not coming in attacks, might be regarded as evidence of ulcer. It has seemed to us that we were required to

at least attempt to be a little more critical and we have regarded the phrase "a history of ulcer" as requiring us to show pain referred to the upper abdomen bearing some demonstrable relation to the taking of food and continuing over a reasonable period of time. Judged in this way there are only nine cases in this series which could be regarded as having a history of ulcer. (Table III.)

Of these some had a surprisingly long history, one of them extending over thirteen years, though only acute during the final twelve months. One lasted

TABLE III

History of Previous Ulcer in 112 Cases

Cases with History of Previous Gastric Disturbance..... 9—8.3 per cent. of 112.

Number of Cases	Duration
1	3½ years
2	4 years
2	5 years
1	7 years
1	8 years
1	10 years
1	13 years
9	

Cases without History of Previous Gastric Disturbance....103—91.7 per cent. of 112
Cases in which Duration of symptoms were not mentioned. 4

116

ten years; one, eight years; one, seven years; two, five years; two, four years, and one, three years and a half. Here is a group of roughly 8 per cent. of our cases in which the history strongly suggested ulcer of the stomach and in which cancer was ultimately found. It is unfortunate that in this group we have only fifty-six cases in which the complete pathological study was made.

Various writers have put forward the view that the history was an important part of the evidence leading to the opinion that cancer was a relatively frequent result of ulcer. We confess that this does not appear to us logical. The short duration of the history in most cases of cancer cannot, we think, be properly held to bear any known relation to the disease itself. It is notorious that in other parts of the body at least, cancer, particularly in elderly people, is a relatively slow-growing process and it does not seem to us likely that the massive tumors which occur in some of these patients with a very short history of discomfort could have been produced in that short period. We doubt whether the duration of symptoms in the cases of cancer has any relation to the duration of the growth. It is of course possible that the symptoms are chiefly produced by surface loss of substance and that a malignant process developing in the stomach wall which does not result in loss of substance might go on for a considerable period without producing symptoms. There is another reason for skepticism in regard to the value of

so-called history of ulcer, namely, that it is not uncommon to see patients with an almost classical history of ulcer in whom no ulcer can be demonstrated to exist. It is certainly true that other conditions may produce symptoms which at least, as interpreted by the patient, would suggest ulcer. We are inclined to take the view that the history is a relatively unreliable basis for judging the relationship between ulcer and cancer.

Location of the Growth.—Some interest attaches to the position of the growth, particularly in relation to the discussion of etiology. In our series

TABLE IV.

Location of growth	Number cases	Per cent.	
Pylorus	55	56.1	of 98 cases
Diffuse	16	13.8	of 114 cases
Lesser curvature	15	11.7	of 98 cases
Cardia	9	9.0	of 98 cases
Both walls	8	7.1	of 98 cases
Posterior wall	5	5.1	of 98 cases
Greater curvature	4	4.0	of 98 cases
Anterior wall	2	2.0	of 98 cases
Not mentioned	2		
	116		

sixteen cases should be excluded since the growth was so diffuse as to make it impossible to say where it had begun, and two should be excluded since location is not mentioned. Of the remaining ninety-eight, fifty-five occurred at the pylorus, fifteen upon the lesser curvature, nine at the cardiac end, eight on both walls, five upon the posterior wall, four upon the greater curvature, and two upon the anterior wall. These figures are somewhat less striking than those of many observers reporting larger series. In general, the common figures show that 60 per cent. of the cases of carcinoma occur at the pylorus and about 12 per cent. of the cases of ulcer, while 60 per cent. of the ulcers occur upon the lesser curvature and only 12 per cent. of the cases of carcinoma. In general our figures agree with other observers and tend to show that from this view there is no very striking ground for the assumption that cancer commonly or generally originates on the basis of ulcer. (Table IV.)

In our series the type of cancer is known in fifty-six cases. Of these twenty-five were adenocarcinoma, nineteen were scirrhous carcinoma, seven were mucoid carcinoma, three were medullary carcinoma and two were colloid carcinoma.

Evidence of Preëxistent Ulcer as Shown by the Pathological Report.—It may perhaps be suggested that no clinician ought to venture into the dis-

cussion of the pathological evidence of previous ulcer and certainly any clinician so venturing takes his life in his hands. As we have already shown, opinion in regard to the frequency of ulcer as a forerunner of cancer has varied through very wide limits and this variation of opinion has occurred both among the clinicians and the pathologists. It seems to us that the question turns largely upon the criteria which are laid down as diagnostic. It is obviously possible to lay down criteria by the result of which the vast majority of cases of chronic ulcer, whether of the stomach or elsewhere, may be adjudged to be showing precancerous tendencies. MacCarty has perhaps taken the broadest view of the evidences which should be adjudged to indicate either the presence or the imminence of cancer. He has had at his disposal an immense material and his opinions are clearly entitled to weight not only on this account, but on account of his very careful and thorough study of the subject. He has been the outstanding advocate of the view that a large proportion of cases of cancer had as their cause a preëxisting ulcer. From his many contributions to this subject it is difficult to pick out excerpts which will fairly represent his criteria. The following quotation from his publication in 1909 shows his views at that time:

Infiltration after Proliferation:

In scirrhous type—fibrous tissue forms around epithelial cells which are proliferating.

Cancer develops in scar tissue in some cases.

Bands of scar tissue with epithelial cells included suggest early cancer.

Ulcer usually exists for years before cancer develops—in a group of cases.

Large ulcers with scar tissue centres and overhanging borders deep in the bases of which cancer is present, in almost every instance have originated on the lesser curvature, the usual site of gastric ulcer. Further, history of ulcer extends years back before relatively short period when history became that of cancer.

In 1910:

Inflammatory hyperplasia and malignant hyperplasia are indistinguishable.

Hyperplasia is forerunner of malignancy.

Cancer is a malignant hyperplasia which also varies in degree, and some of the degrees so far as morphology is concerned are indistinguishable if not identical.

In 1915:

The epithelial cells of the glands in some ulcers lose their cuboidal or columnar shape and regularity of size and arrangement. They become oval or round and the nuclei larger and more distinct. The exact origin is unknown since in gastric glands there are not two distinct rows of cells normally present as in breast, prostate, skin, etc.

Various degrees of intraglandular morphological changes are found in the borders until the cells become indistinguishable from cancer cells. When such a condition is found, careful search frequently demonstrates a lack of demarcation between gland and stroma, and epithelial cells may be seen in the stroma, the latter condition being accepted by general pathologists to be the histological criteria of cancer.

When cancer is definitely present the intraglandular cells always present what is described as secondary hyperplasia in other organs.

In the production of this epithelial hyperplasia, there is an attempt on the part of nature to reproduce the epithelial lining of the glands. In this attempt there is failure to completely differentiate the cells with the coincidental picture of secondary hyperplasia, the cells of which differ from cancer only in position.

From these facts one may clearly see that the gastric cancer cell arises from intraglandular hyperplastic cells of the mucosa, and represents a malignant end-stage of a process of hyperplasia of normal cells.

MacCarty in 1909 gives cancer ex ulcero as 71 per cent.

MacCarty in 1914 gives cancer ex ulcero as 69 per cent.

HAUSER is commonly thought of as having early dealt with this question of criteria and has been much quoted in these discussions. He has the following to say on this subject:

Deep, sharply cut excavation, overhanging proximal edge, firm, fibrous base and often the extension of 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 fused and causing induration and fixation of the edge. Outlying islands of polypoid adenoma or adenocarcinoma are not infrequently observed.

The edges are markedly hypertrophic. Cancer changes are most marked at the line of the ulcer and extend with diminishing intensity for a distance of one-half to one cm. over the outlying mucosa, the infiltration involving the peripheral submucosa and muscularis, while the indurated base is free from infiltration.

EWING lays down the following criteria and also states his conclusions in regard to the relation of ulcer to cancer.

1. The great majority of ulcerative lesions of the stomach fall into two classes:
   A. Ulcerating cancers.
   B. Simple peptic ulcers.

2. In 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 causing some derangement of glands. This is not secondary to ulcer, but may well predispose to ulcer. This may serve as a source of error in interpreting atypical overgrowth on ulcer edge.

3. Deep excavations may occur in portions of established carcinoma, especially in the pylorus, where powerful muscular contractions tend to cause hernias of the infiltrated and weakened muscle tissue.

4. Gastric digestion may strip a primary carcinoma down to muscularis or deeper, leaving no trace of carcinoma over base, but only peripheral ring of tumor tissue which is protected by mucosa.

5. When ulcer base is uniformly infiltrated with carcinoma, the condition is difficult to reconcile with an origin from the edge. 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 the ulcer is not sufficient evidence that the lesion is going on to cancer.

CONCLUSIONS

Carcinomatous transformation of a peptic ulcer does not exceed 5 per cent. The proportion would be smaller if only the cases were included where the evidence is demonstrable, *viz.*, a long history of ulcer—the limitation of the tumor to isolated foci or one portion only of the ulcer—freedom of the base from infiltration.

SPILSBURY, 1922, has the following to say:

Discusses the diagnosis of gastric ulcer under two heads:

1. Destruction.
2. Regeneration.

At this stage there are commonly found at the edge of the ulcer, gland cells which

have penetrated deeply into the scar tissue and are cut off from the regenerating glands. They may show a typical glandular arrangement, or may form narrow solid columns of cells. Isolated cells are also seen. It is these *cells* detached from the regenerating epithelium and buried in the fibrous tissue of the ulcer which are referred to as precancerous, and from position and irregular arrangement regarded by *others* as indicating a malignant transformation in the ulcer.

This is the Mayo criterion—not necessarily correct.

Displaced and buried epithelial cells are not peculiar to healing peptic ulcer. Found anywhere in skin or mucous membrane, ex. varicose ulcer of leg.

If cancer develops in a peptic ulcer, it must do so from actively growing and regenerating mucous membrane at the margin of a healing ulcer or from buried cells mentioned above. Such might spread from margin into tissue at base or might spread into normal stomach wall, spreads here more rapidly, hence ulcer will exhibit structure of peptic ulcer, but with a more pronounced thickening of margin on one side. There may be superficial ulceration of indurated area, growth may fungate, forming polypoid or large, soft, irregular tumors; beyond the apparent margin of the tumor separate nodules may be found in the stomach wall. On microscopic examination the bulk of the original peptic ulcer will be found to consist only of fibrous tissue and to be free from cancer. These have been encountered occasionally and described as malignant transformation in a peptic ulcer.

Processes of irregular regeneration mistaken for malignant transformation by many.

Estimate from above criteria (same as Ewing) certainly not more than 5 per cent. of peptic ulcers of the stomach, probably not more than 1 to 2 per cent. develop secondary malignant disease.

When dense fibrous tissue of base is infiltrated everywhere with cancer cells regard such a tumor as a primary cancer with secondary ulceration.

Malignant transformation of a peptic ulcer must be an uncommon event.

At our request PROFESSOR A. S. WARTHIN has set down for us the following as the criteria which influence him in coming to an opinion:

Criteria for diagnosis of carcinoma arising in a chronic peptic ulcer: There must be convincing evidence of the existence of an older ulcer in the presence of an induration or cicatricial fibrosis extending through the stomach wall with characteristic sclerosis of the blood-vessels—the greater part of this cicatrix being entirely free from carcinomatous infiltration—the latter being limited to the borders or surface of the ulcer—the carcinoma must be a relatively early development, infiltrating the ulcer-scar to but a slight extent, so that there can be no doubt that the fibrosis is the result of the healing of an older ulcerative process and not secondary to the carcinoma. If the induration is the result of a primary carcinomatous ulcer, it will be infiltrated throughout with cancer-cell nests. It is important, however, that no errors be made in the interpretation of regenerative gland-formations and proliferations at the sides or base of an ulcer. These have undoubtedly been mistaken by some pathologists for evidences of malignancy. No diagnosis of cancerous or pre-cancerous states can be made from the characteristics of individual cells of such regenerative conditions, either in size, form or staining qualities of nuclei or cytoplasm. The diagnosis of carcinoma depends wholly upon the presence of free-growing cells in the tissue-spaces, infiltrating the scar tissue, producing a secondary inflammatory reaction in the latter and presenting the appearances of mature cancer nests, and not connected (in serial sections) with the normal glands at the border of the ulcer. In serial sections the continuity of regenerative proliferations with the bordering epithelium can always be demonstrated; in the cancer no continuity between normal gland epithelium and the carcinoma can be shown. A destructive infiltration of the mucosa at the border of the ulcer with cords and masses of epithelial cells more or less atypical, growing without relationship to a basement membrane, should be interpreted as carcinoma.

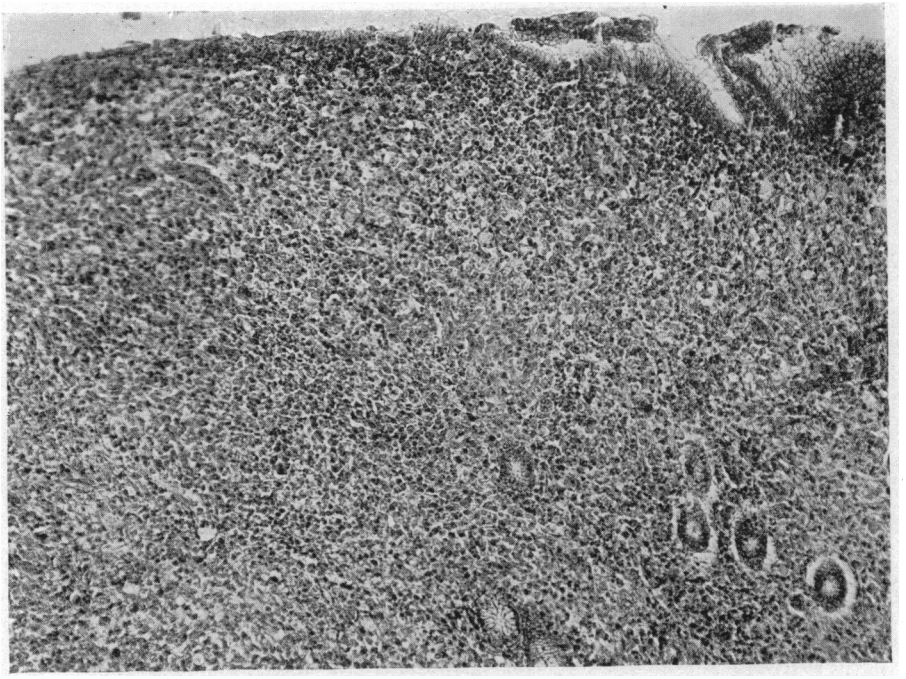

FIG. 5.—Case I, 1329-4, J. G. Scirrhous ("signet-ring" celled) carcinoma infiltrating mucosa at border of chronic peptic ulcer.

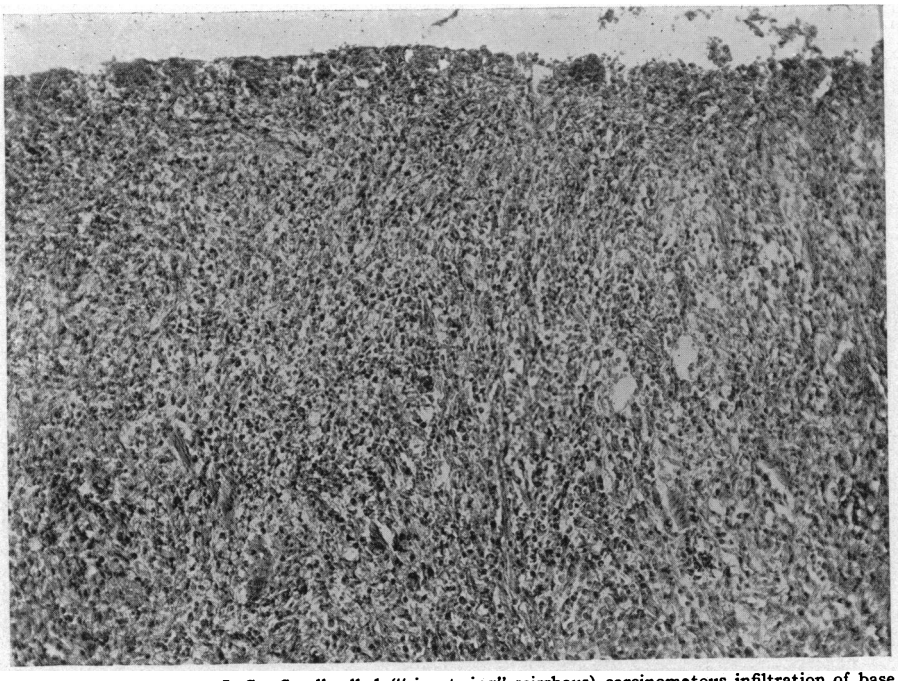

FIG. 6.—Case I, 1329-7, J. G. Small-celled ("signet-ring" scirrhous) carcinomatous infiltration of base of chronic peptic ulcer, near border

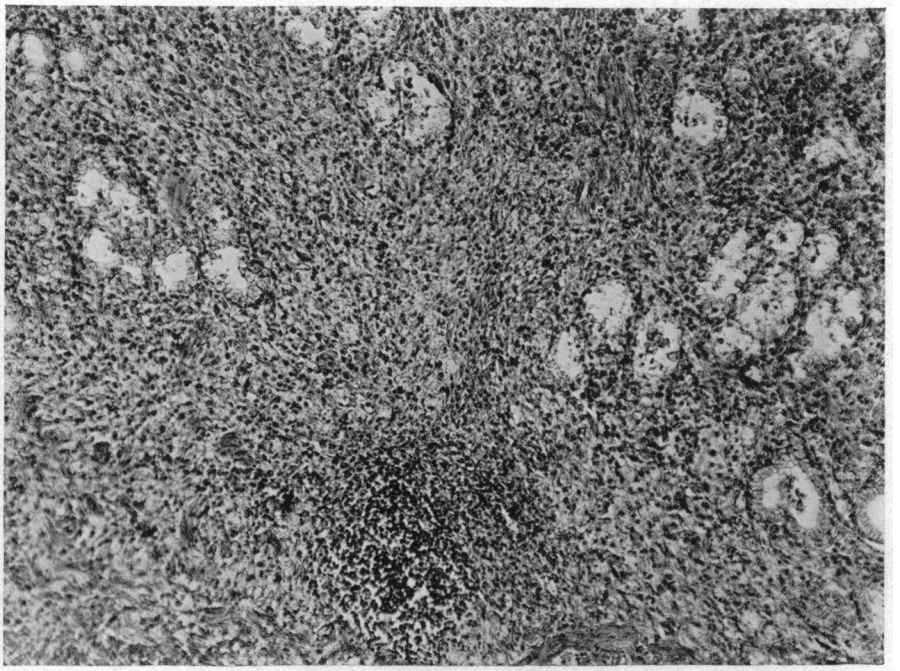

FIG. 7.—Case I, 1329-7, J. G. "Signet-ring" scirrhous carcinomatous infiltration of mucosa near border of chronic peptic ulcer. Remains of older glands showing mucoid degeneration.

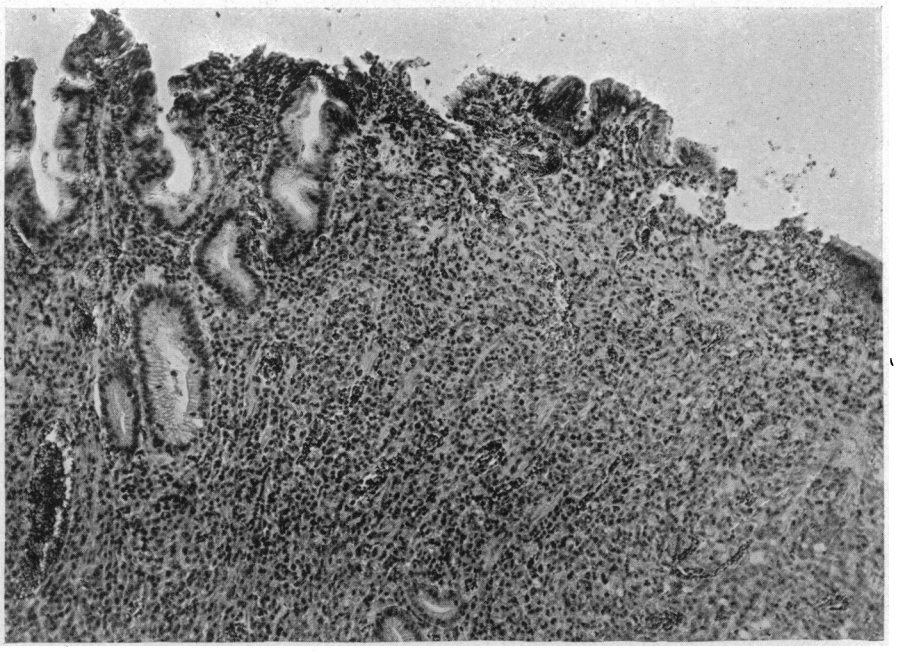

FIG. 8.—Case II, 1607-AA, C. C. Edge of chronic peptic ulcer with early diffusely—infiltrating scirrhous carcinoma developing on one side of ulcer. Infiltration of border of ulcer with small round carcinoma cells, some showing "signet-ring" mucoid degeneration. Carcinoma arising in primary peptic ulcer.

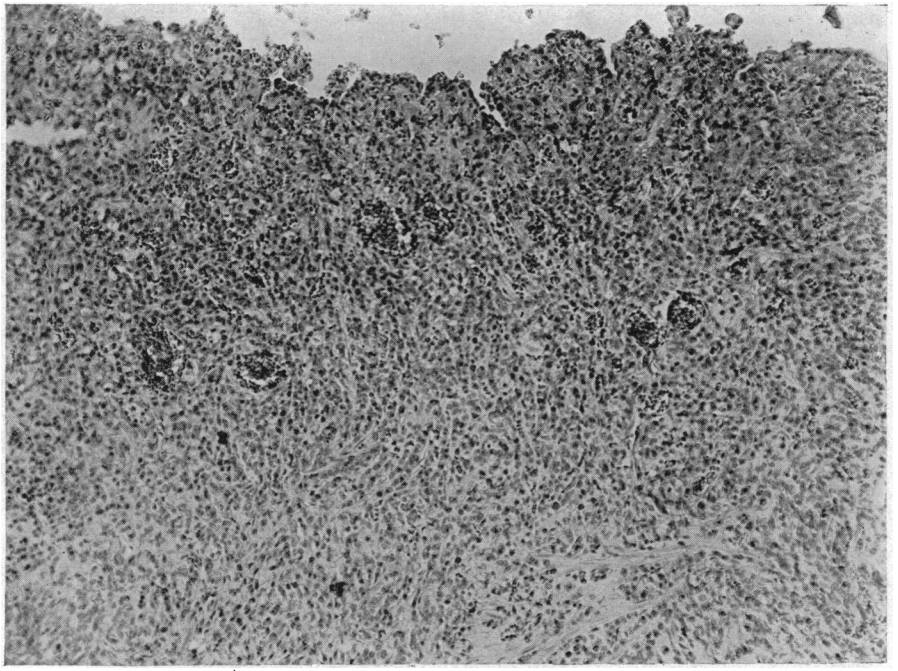

FIG. 9.—Case II, 1607-AA, C. C. Base of ulcer near carcinomatous border, showing cords of small round carcinoma, cells infiltrating scar tissue. Carcinoma arising in primary ulcer.

FIG. 10.—Case II, 1607-AA, C. C. Base of centre of ulcer above, exudate on floor of ulcer; below scar-tissue infiltrated with plasma-cells, lymphocytes and leucocytes. No carcinoma cells.

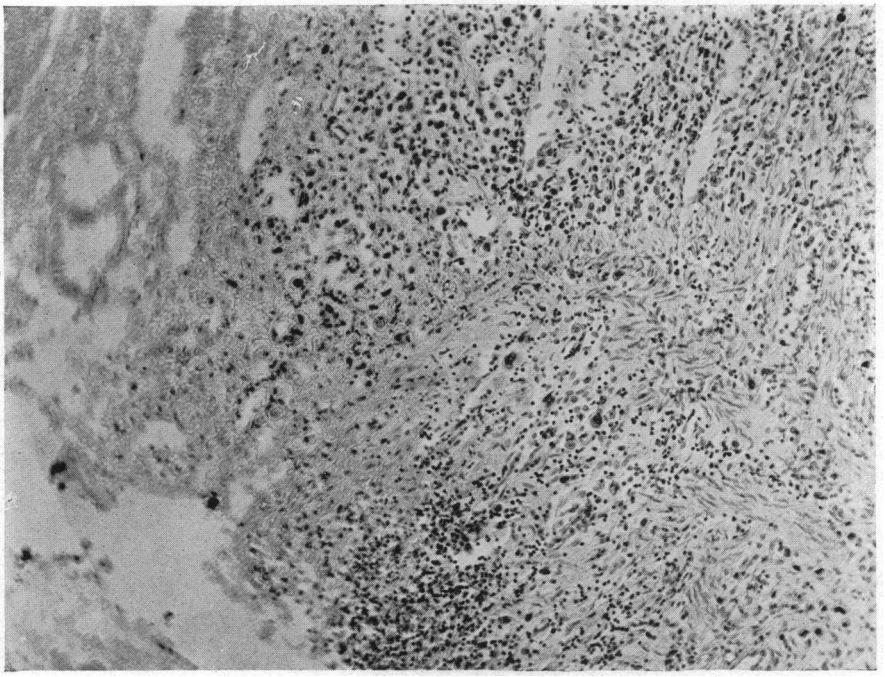

FIG. 11.—Case III, A-116-AB, V. B. Scirrhous carcinoma at border of older gastric ulcer.

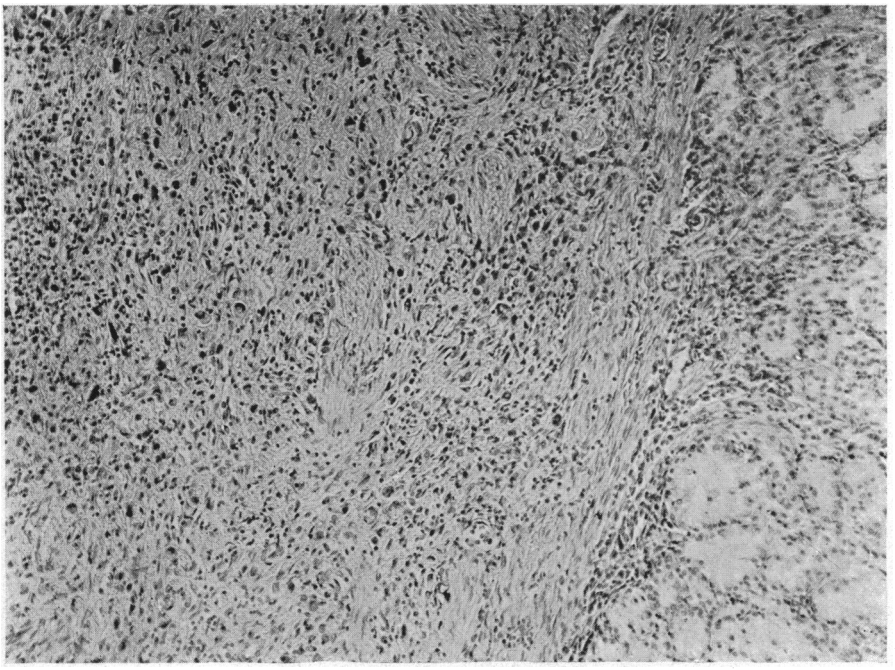

FIG. 12.—Case III, A-116-AB, V. B. Scirrhous carcinoma infiltrating gastric submucosa of border of older ulcer.

Of the cases in our series there are fifty-six in which the whole region was at the disposal of the pathologist. We have not included cases in which only a portion of the specimen was available, since it might easily be suggested that some other portion not at the disposal of the pathologist might have shown evidence of cancer. In this group there are five cases in which there is clear evidence of both peptic ulcer and cancer and using the criteria laid down above, Professor Warthin has come to the conclusion that they are true instances of cancer developing secondary to chronic ulcer. This would appear to require the admission that cancer is a definite result of ulcer in a certain proportion of cases.

The following is a brief abstract of these cases:

CASE I.—J. G., male, fifty-seven. No history of previous ulcer. Duration of symptoms, two months. Loss of weight, twenty pounds. Palpable mass in epigastrium. Operation: Partial gastrectomy. Pathological report: Scirrhous carcinoma of the stomach. Chronic peptic ulcer. Base of ulcer shows no carcinomatous infiltration, but the stomach wall and the borders do.

CASE II.—C. C., male, forty. No history of previous ulcer. Doubtful loss of weight. Partial gastrectomy. Pathological report: Very severe chronic hyperplastic catarrh. Two small subacute ulcers with a little island of preserved mucosa between them. These are relatively recent. The induration is still quite cellular and extending only to the muscles. The mucous membrane on one side is very atypical. The gland cells are small and infiltrate the stroma, and in one place extending through the mucosa. Early scirrhous carcinoma. In the other side of the ulcer there is also a group of carcinoma cells showing mucoid degeneration with signet-ring cells. The ulcer here has involved the carcinoma. There is no deep infiltration of the wall and this is about as early a stomach cancer as we have ever seen.

CASE III.—V. B., male, fifty-five. Entered on account of abdominal pain. Eighteen months' duration. No previous history suggesting ulcer. Loss of weight, twenty-five pounds. Operation: Partial gastrectomy. Pathological report: On the lesser curvature just above the pyloric opening on the posterior wall of the stomach there is an ulcer 8 cm. long by 4 cm. wide with definite borders. The floor is irregular and at its lowest part there is a feeling of induration imparted to the examining finger. Edges appeared firmer in consistency than the floor. The depth of the ulcer is 5 mm. No induration or infiltration outside of it. Numerous small enlarged glands found along the greater curvature. Decided feeling of infiltration around the pyloric orifice. Microscopic examination: Old chronic peptic ulcer of large size. Marked fibroid. Induration of base. At border of ulcer is large area of scirrhous carcinoma infiltrating the mucosa and submucosa and into the muscular coats. No carcinoma at base or at other border. A carcinoma developing at the border of a chronic peptic ulcer. Mucosa shows chronic catarrhal gastritis. Lymphatic glands show atrophy and chronic passive congestion. Œdema. Early metastasis of carcinoma.

CASE IV.—W. C. G. The three photomicrographs shown below demonstrate the mistake that might be made in diagnosing carcinoma arising from chronic gastric ulcer.

CASE V.—J. J. V., male, thirty-nine. Enters on account of abdominal pain. No previous history of ulcer. Duration of symptoms twelve months. Loss of weight, twenty-five pounds. Operation: Partial gastrectomy. Pathological report: Chronic catarrhal gastritis. Large chronic peptic ulcer with dense inflammatory base. At the margin of the ulcer there is an adenocarcinoma which in its older portions shows the structure of an adenocarcinoma mucosum. This is apparently another example of the development of a carcinoma near the margin of a chronic ulcer. Two small lymph-nodes show no metastasis. The carcinoma is so well advanced, however, that we believe metastasis has probably taken place.

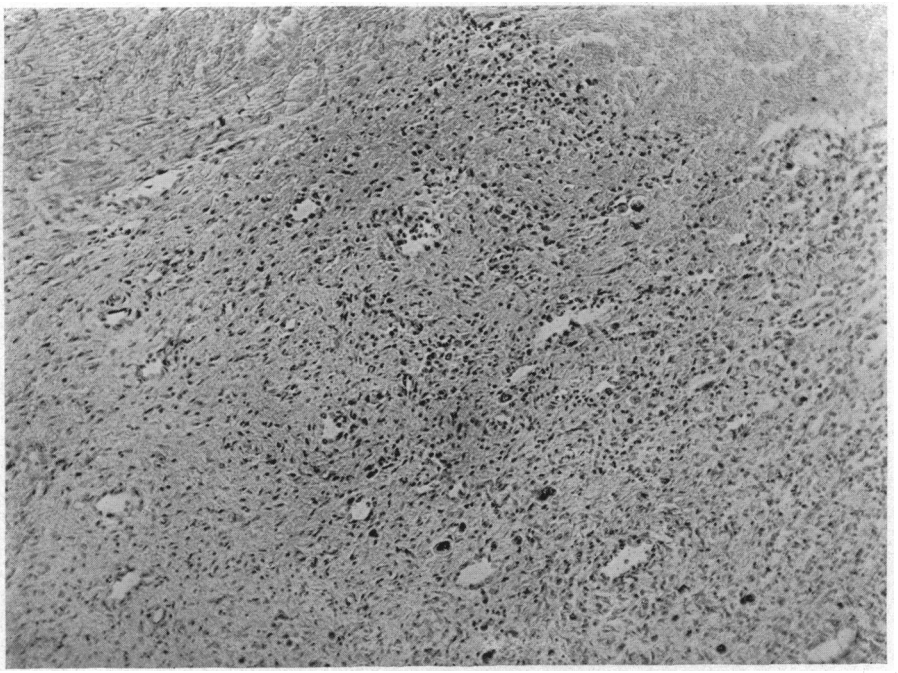

FIG. 13.—Case III, A-116-AB, V. B. Scirrhous carcinoma infiltrating cicatricial tissue of floor of ulcer at one border of the older ulcer. Carcinoma secondary to ulcer.

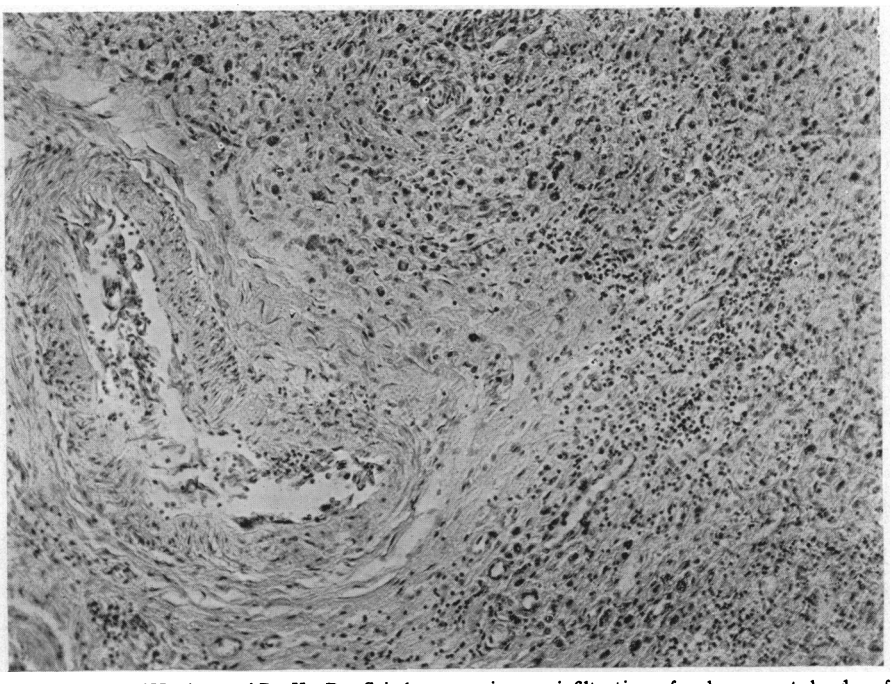

FIG. 14.—Case III, A-116-AB, V. B. Scirrhous carcinoma infiltration of subserosa at border of chronic peptic ulcer. Carcinoma arising in older ulcer and infiltrating floor and border of ulcer.

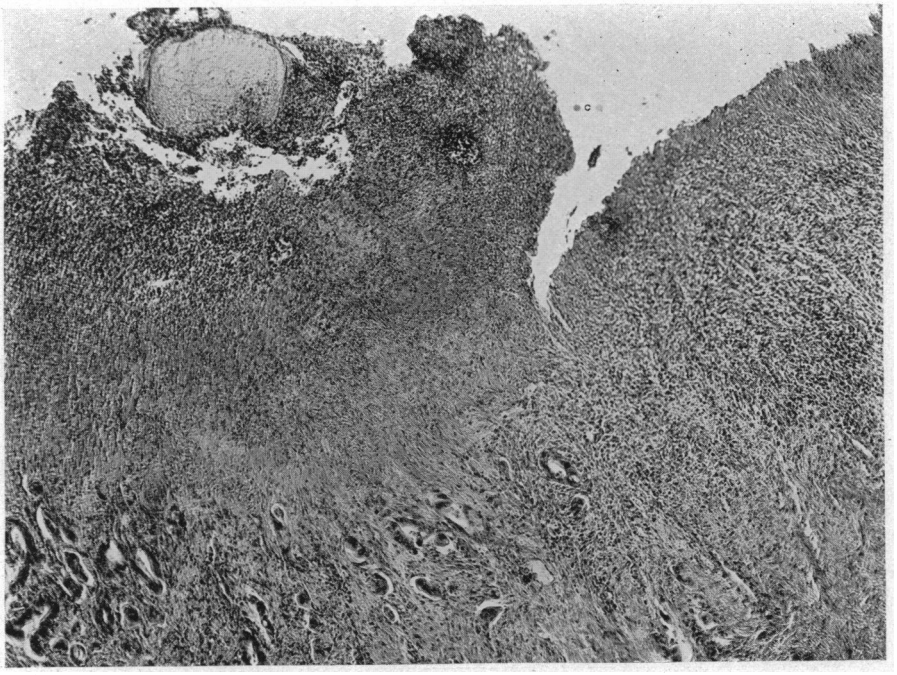

FIG. 15.—Case IV, 2530-AB, W. C. G. Low-power view of ulcerating adenocarcinoma. Ulcer is primarily carcinomatous.

FIG. 16.—Case IV, 2530-AB, W. C. G. Floor of ulcer near opposite border from that seen in preceding adenocarcinomatous infiltration. Primary ulcerating adenocarcinoma.

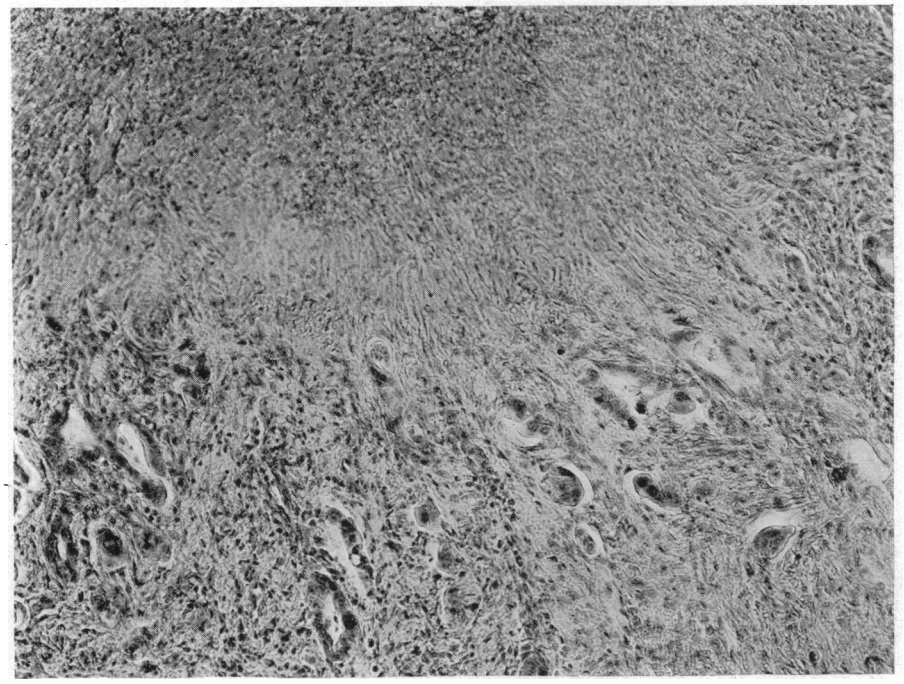

FIG. 17.—Case IV, 2530-AB, W. C. G. High-power view of preceding adenocarcinomatous ulcer.

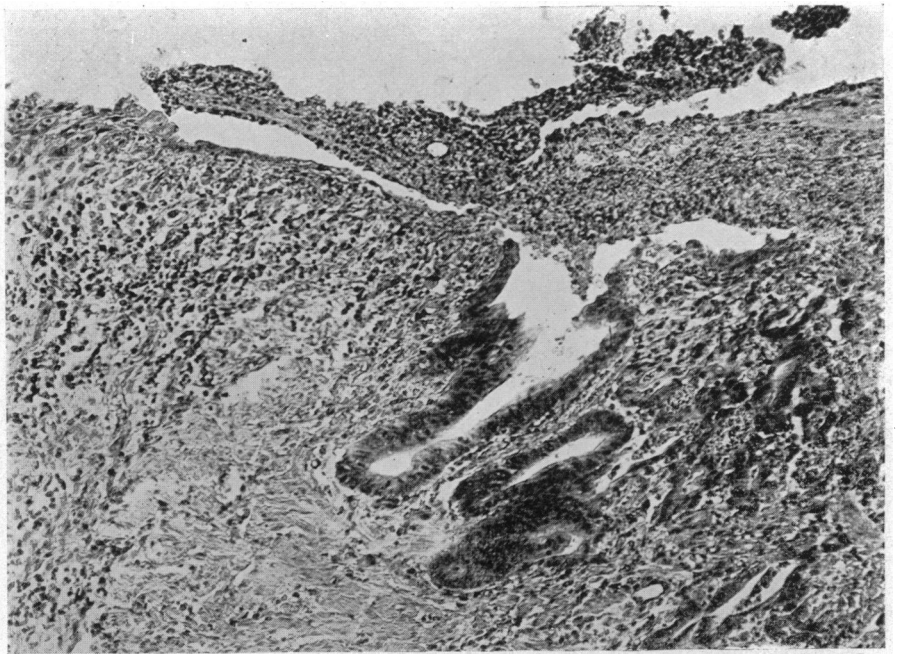

FIG. 18.—Case V, 4266-AB, J. J. V. Edge of chronic gastric ulcer. Adenocarcinomatous border. Atypical, hyperchromatic gland tissue infiltrating border of ulcer. Floor of ulcer showed no carcinoma. Primary adenocarcinoma developing in border of chronic ulcer.

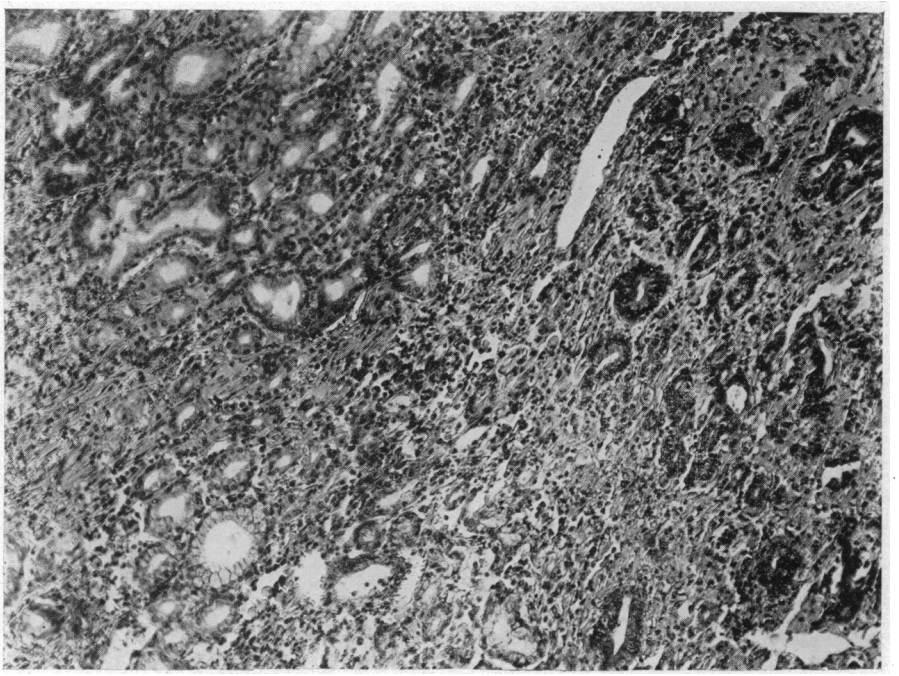

FIG. 19.—Case V, 4266-AB, J. J. V. Border of same ulcer as in preceding, a little farther from the ulcer, showing adenocarcinomatous infiltration of mucosa.

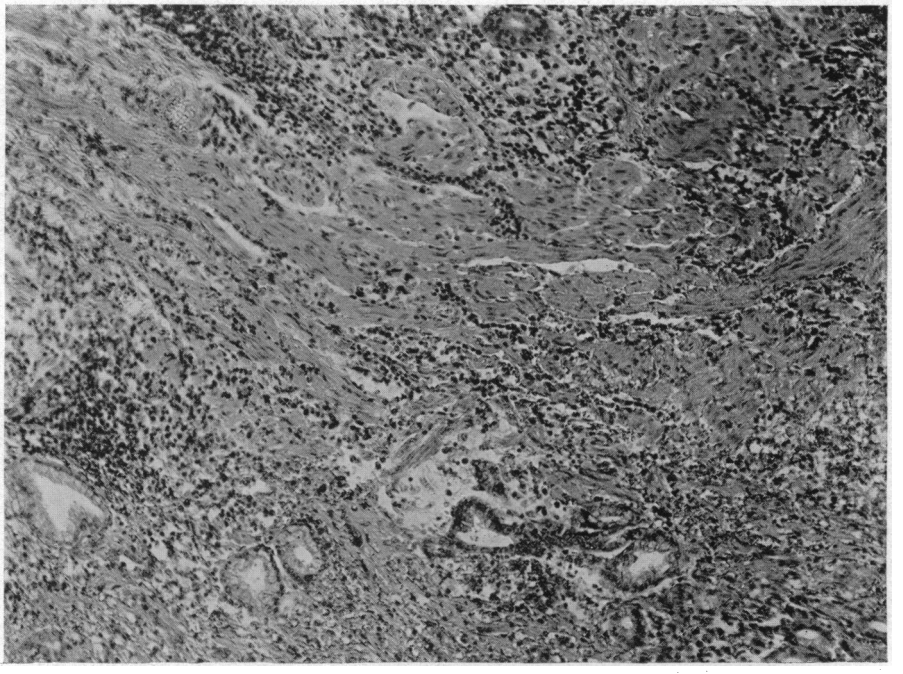

FIG. 20.—Case V, 4266-AB, J. J. V. Adenocarcinomatous infiltration of muscularis at border of chronic ulcer. Carcinoma arising at border of ulcer.

CASE VI.—W. H. S., male, seventy. Several years of indigestion. Possible ulcer history. Acute pain two months. Loss of weight, ten pounds. Operation: Partial gastrectomy. Pathological report: A scirrhous carcinoma arising from scar of old peptic ulcer. The carcinoma is rather superficial in the mucosa, but shows some infiltration into the submucosa and muscularis. The greater part of the induration due to the old chronic ulcer.

In some of the literature on the subject there appears to be confusion as to precisely what is being discussed. The most important question at issue appears to us to be not the proportion of cases of cancer in which ulcer has previously existed, and to which the cancer may be adjudged to be secondary, but what proportion of cases of chronic peptic ulcer of the stomach are likely to show malignant changes after a term of years. Now obviously the proportion of cases of cancer showing evidence of previous ulcer bears no relation to the whole number of cases of ulcer upon which cancer ultimately develops. This is a very difficult subject upon which to get convincing evidence. The best evidence obviously would be a collection of a large number of cases of demonstrated ulcer which after a term of years were known with equal certainty to have developed cancer. The literature on this point is not large and the relatively small number of cases which have been reported throws little light upon the proportion.

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