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Histology and Histopathology

Gastric cancer preceeded by severe dysplasia

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Summary. For elucidation of histogenesis of gastric cancer derived from relatively flat mucosa, 77 cases of surgically resected stomachs with lesions of severe dysplasia in cancerous mucosae or with cancerous changes in severely dysplastic mucosae were detected out of 380 recently examined cases of early gastric cancer.

Several examples of early gastric cancer of the superficial type, showing histological changes indicating that they had developed on the preexisted dysplastic mucosal lesions, have been presented, together with the background data.

The frequency for detecting such changes was higher in the slightly elevated lesions than in the depressed or eroded ones.

Key words: Gastric cancer - Histogenesis - Dysplasia

Introduction

Gastric cancer develops through various macroscopical and histological changes. Some cancer develops from a circumscribed, non-malignant lesion such as polyp or ulcer but it is known from recent histological studies on early gastric cancer that most develops in the relatively flat mucosa with no apparent focal macroscopical change. From these results, chronic gastritis especially with diffuse intestinal metaplasia is assumed to be the most frequent and important precursor of gastric cancer. However, owing to the obscure histological nature of this disease and to not a few cases of minute gastric cancer without any metaplastic and dysplastic changes in the surrounding mucosa, histogenesis of gastric cancer from flat mucosa has not yet been entirely clarified.

For elucidation of the developmental courses of gastric cancer, the cases of early gastric cancer with slight mucosal elevation or depression were examined histologically from the viewpoint of presence or absence of dysplasia within the cancerous lesions.

In this paper, the author would like to point out that some types of early gastric cancer derived from non-polypoid, non-ulcerated flat mucosa had a histological background indicating that they had developed from preexisting dysplastic mucosal lesions. Several cases are considered with the microphotographs.

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Materials and methods

From 1976 to 1984, 2521 cases of stomach were resected surgically in the Yokoyama Hospital, 1131 cases being histologically diagnosed as cancer and. 1390 cases as peptic ulcer. Dysplastic lesions of moderate to severe grades were detected in 136 cases (5.4%), the frequency being far higher in the cases with cancer (10.7%) than in the cases with an ulcer (1.1 To) (Table 1).

When 136 dysplastic lesions were classified by their sites, 81 lesions (60.0%) were found in the mucosa in, or adjacent to, the main lesions -mostly cancer- and 55 lesions (40.0%) were found apart from the main lesions, in which cancer was four times more prevalent than were ulcers. Apart from these 136 cases, 24 cases of solitary dysplastic lesions were obtained of which 17 lesions showed slight mucosal elevation and the other 7 slight mucosal depression (Table 2).

77 cases of dysplastic changes seen in, or adjacent to, the cancerous lesions in Table 2 were the main object of this study.

After stepwise sectioning of the entire lesions, cancerous mucosa were selected out into several types according to:

a) Severely dysplastic changes remaining in the obvious cancerous lesion.

b) Cancerous change seen in the mucosal lesion of severe dysplasia.

For elimination of the possibility that dysplastic changes had developed concomitantly or secondarily after development of the carcinoma, dysplastic changes seen only in the peripheral part of the cancerous lesion were excluded from the study.

In all cases, histological discrimination of severe dysplasia from adenocarcinoma was made according to the nature of the cellular and structural abnormalities of the affected mucosa, as described in previous papers. (Nagayo, 1981, 1983).

For scrutinized examination, specific staining such as PAS-Alcianblue (pH 2.5) or the silver impregnation method for demonstration of basement membrane between glandular epithelia and lamina propria were used to supplement the usual hematoxylin-eosin staining in several specimens.

For comparative and analytical examinations.

c) Adenocarcinomas almost reaching the state of carcinoma in situ. were also taken as on object of this study.

Results

Owing to the severe criteria of the lesions, the number of cases fulfilling conditions a) and b) was low - 77 cases (20.3%) out of the 380 cases of early gastric cancer obtained in the nine year period. The frequency for detecting a) and b) was higher in the slightly protruding or elevated mucosal lesions (27.3% and 46.9%, respectively) than in slightly depreseed or eroded ones (12.7% and 17.0%) (Table 3).

Several examples in each category, will be explained with micro-photographs, of the histological changes.

a) Severely dysplastic changes remained in the obvious cancerous lesion

1. H.O (14560 58yrs. male). A histological specimen cut through the center of the large eroded lesion (3.5 x 2.5cm) developed near the angulus. The eroded lesion is mostly occupied by adenocarcinoma and slight fibrosis is visible in the submucosal layer owing to shallow ulceration in the center of the lesion. In the right half of the figure, cancerous infiltration into the fibrotic submucosa, together with heterotopic downgrowth of non-malignant glandular cysts, is also visible. (Fig. 1).

High power view of the central part of the eroded mucosa in Fig. 1. The right half of the figure is occupied by moderately differentiated adenocarcinoma with cystically dilated glands in the deeper layer but the left half of the figure is made up of metaplastic foveolae gastricae composed of tall columnar epithelia with a dense arrangement of the elongated and hyperchromatic nuclei. The border of both tissues is clear but this indicates that the area of the atypical tubules is replaced by lateral growth of the cancerous tissue. (Fig. 2).

From these findings, we conclude that in this case the cancer developed in the fairly large, atrophic, metaplastic and dysplastic mucosa and occupied most of the atrophic mucosa by its superficial spreading accompanied by erosion and shallow ulceration.

Table **1**
FREQUENCIES OF DYSPLASTIC LESIONS FOUND IN SURGICALLY RESECTED STOMACHS

Histol. diag.	No. of cases resected	No. of cases with dyspl.	Freq. (%) cases with dyspl.
Cancer	1131	121	10.7
Ulcer	1390	15	1.1
Total	2521	136	5.4

1976-'84

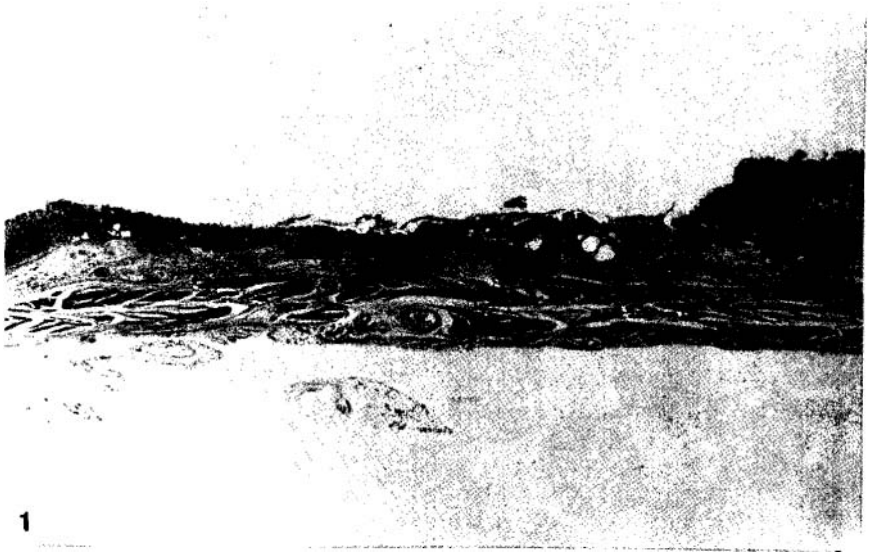
Table **2**
HISTOLOGICAL SITES OF DYSPLASTIC LESIONS

In or adjacent to main lesion	81	
Cancer		77
Ulcer		4
Apart from main lesion	55	
Cancer		44
Ulcer		11
Solitary	24	
Elevated		17
Depressed		7

Table 3
FREQUENCIES OF DYSPLASTIC CHANGES SEEN IN LESIONS OF EARLY GASTRIC CANCER

Macroscopical appearances	No. of cases	No. of cases with dyspl.	Freq. (%) cases with dyspl.
Polypoid protruded	22	6	27.3
Flatly elevated	49	23	46.9
Focally depressed	102	13	12.7
Superficially eroded	207	35	17.0
Total	380	77	20.3

1976-'84



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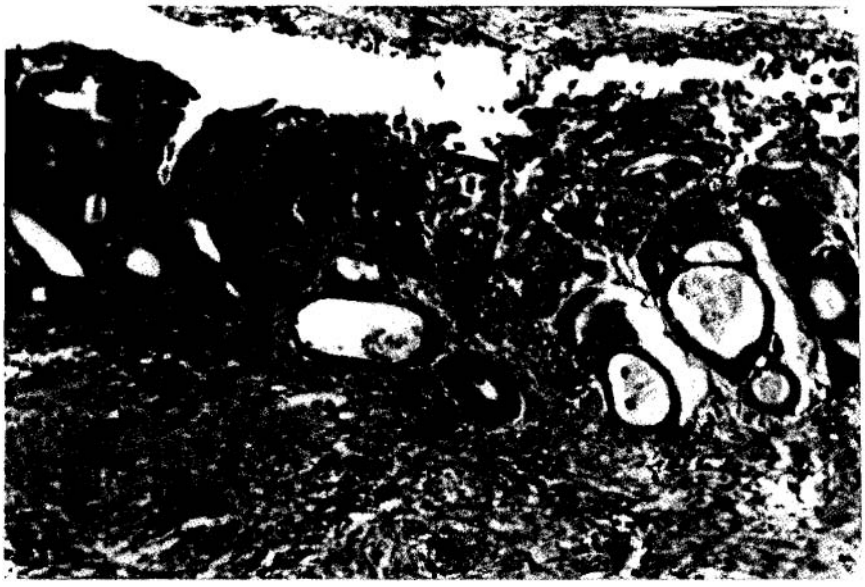

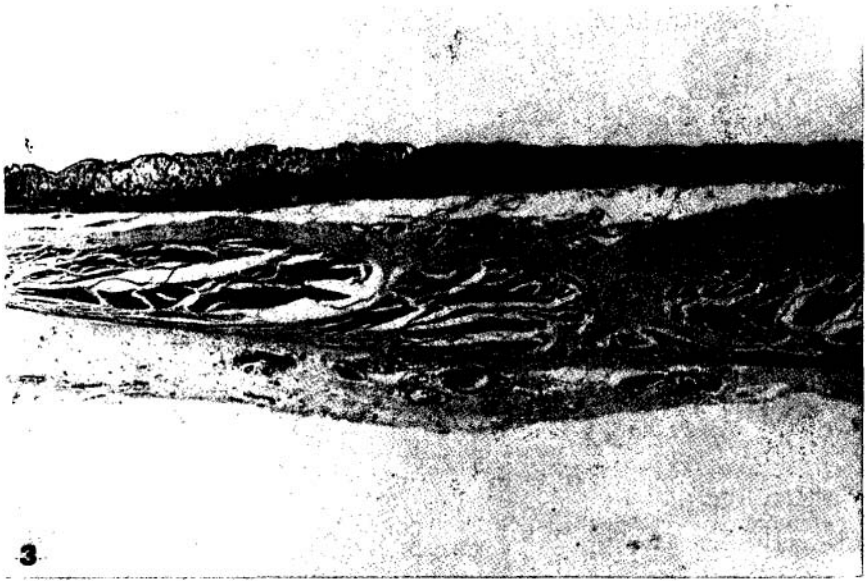

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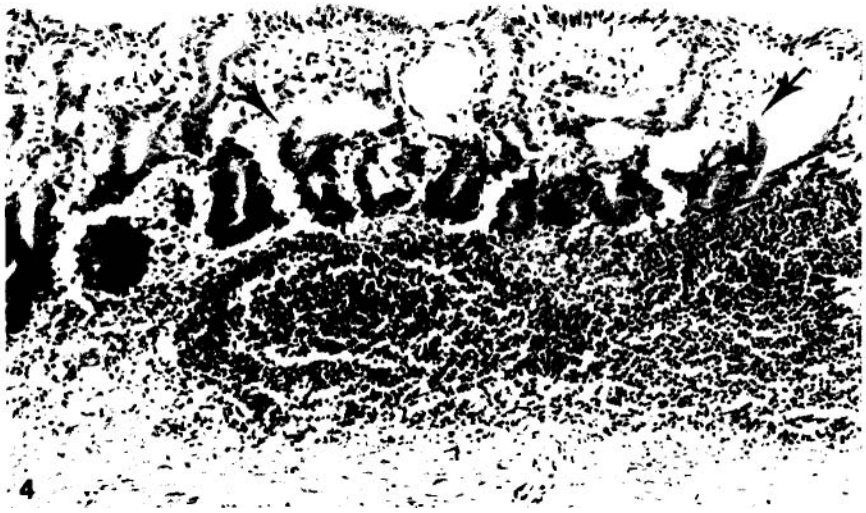

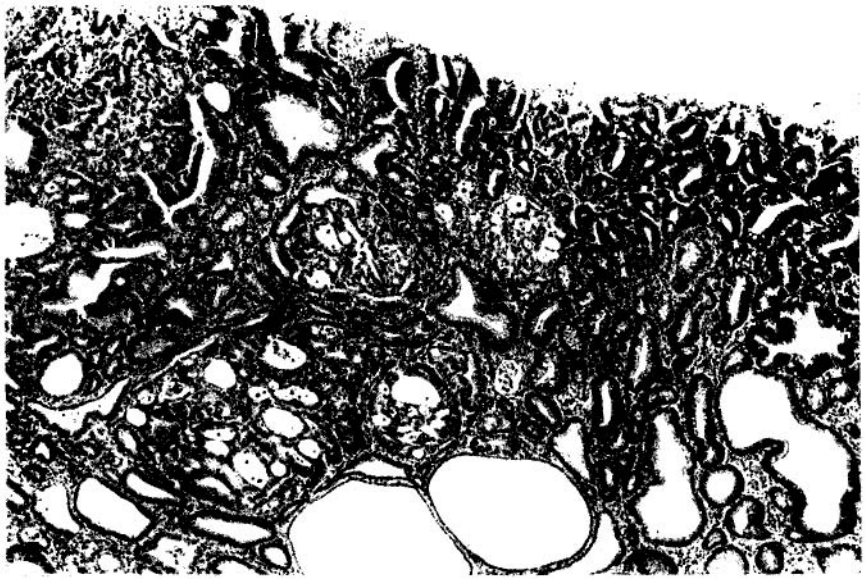

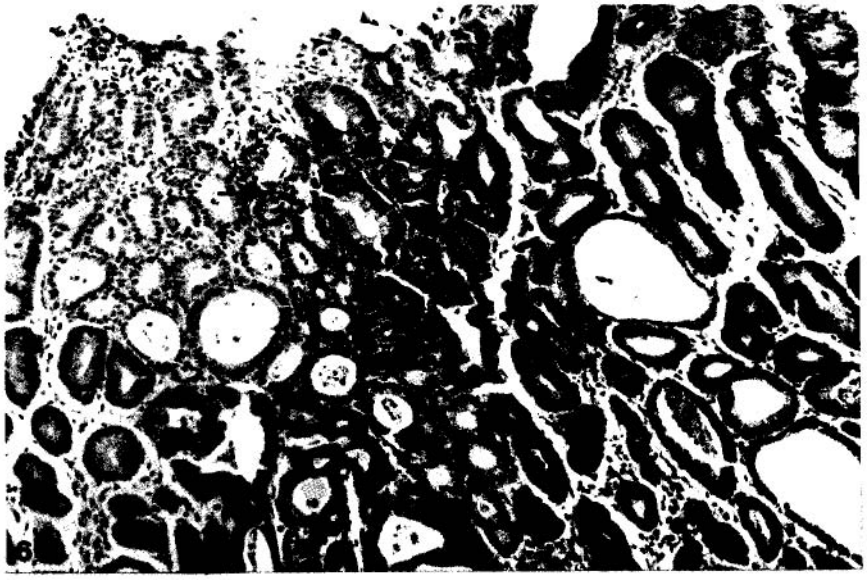

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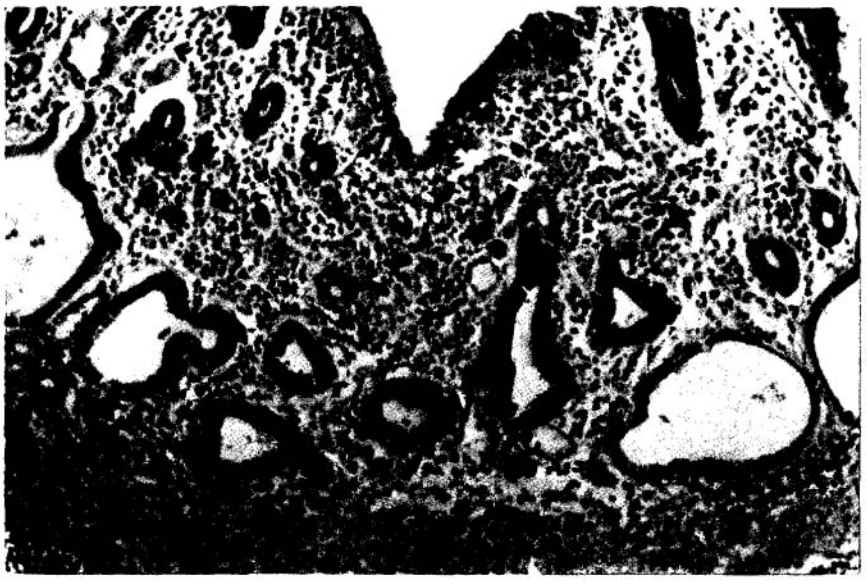


Gastric cancer preceeded by severe dysplasia

2. T.K (100903 9yrs. male). A histological specimen cut through the center of the large erosion (5.0 x 4.5 cm) near the angulus. Mucinous adenocarcinoma of intramucosal growth is seen in the left half of the atrophic mucosa. The right half of the severely atrophic mucosa is made up diffusely of darkly-stained and irregularly arranged foveolae without invasive growth. The same foveolar structures can be seen sporadically in the mucosa suffered from mucinous adenocarcinoma. (Fig. 3).

Higher magnification of the right half of the mucosa in Fig. 3. The upper half of the atrophic mucosa is made up of lightly-stained, irregularly-running and deformed tubules, indicative of adenocarcinoma from the irregular arrangement of the small nuclei. The lower half of the mucosa is composed of darkly-stained foveolar tubules, and have severe cellular atypia. Abrupt transitions of both tissues (arrows) are seen in several places. (Fig. 4).

It is known from these findings that the severely dysplastic change of the atrophic rnucosa seen in Fig. 4 represents the stage before development of the mucinous adenocarcinoma, seen in the left half of Fig. 3.

3. Y.S (802468 65yrs. male). Adenocarcinoma with a cyst-papillary nature is visible mainly in left half of the slightly-elevated mucosa. The cancer invaded encroachingly into the darkly-stained, metaplastic and dysplastic mucosa seen in the right half of the figure. Replacement growth of the cancer into the surrounding atypical and proliferative tubules (arrow) is seen. Irregularly-branched and darkly-stained atypical tubules sporadically remain within the cancerous tissue. (Fig. 5).

These findings together with entire view of the lesion indicate that the adenocarcinoma developed on the dysplastic, eleveted mucosa with many glandular cysts is growing laterally into the dysplastic mucosa.

4. J.K (16983 64yrs. male). A similar change to that shown in Fig. 5. Lightly-stained tubular adenocarcinoma seen in the left half of the figure and darkly-stained, atypically metaplastic and proliferative tubules seen in the right half of the figure collide in the center of the figure. Abrupt transition from the cancerous to the dysplastic epithelia is also visible (arrow). On the left, near this lesion, the adenocarcinoma has already invaded into the submucosa, which is not seen in this figure (Fig. 6).

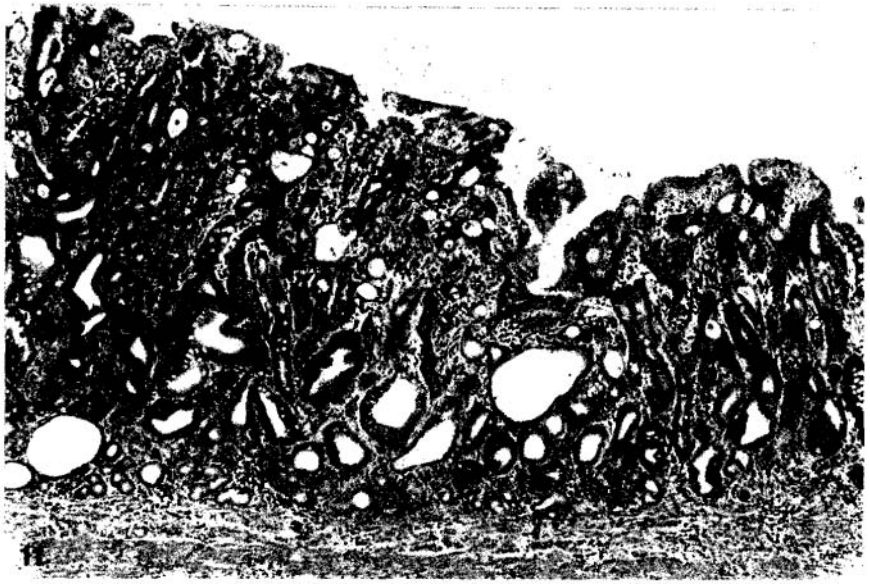
This picture also indicates that the lesion of severe dysplasia is transformed into obvious adenocarcinoma and that the cancer enlarges its space by replacement growth in the affected mucosa.

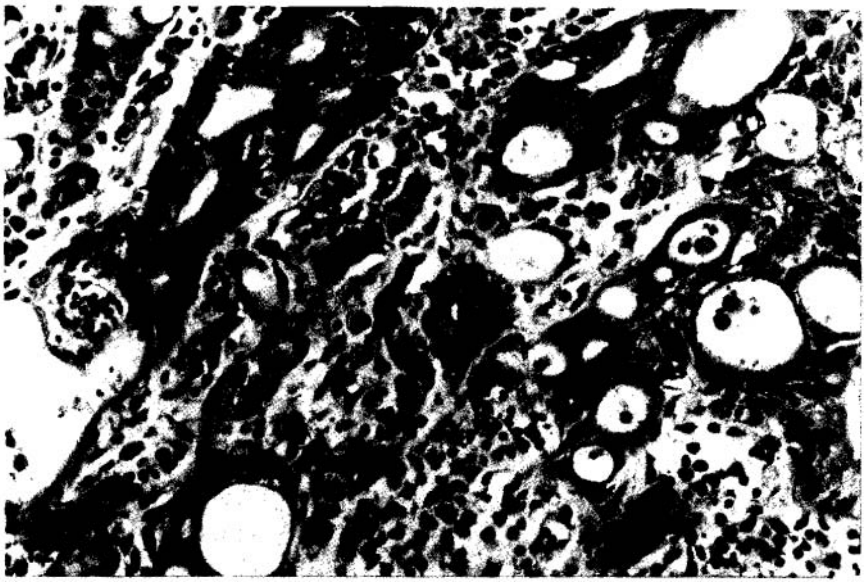
b) Cancerous change seen in the lesion of severe dysplasia

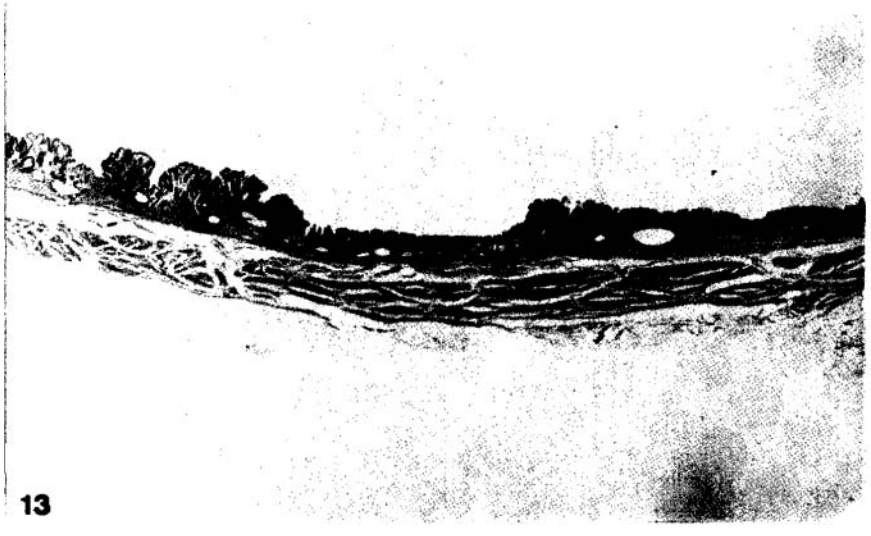
5. H.A (15821 75yrs. male). In an area adjacent to the large and polypoid protruded cancer, the mucosa is slightly-elevated and shows a change similar to villous adenoma with many glandular cysts in its basal layer. In this elevated lesion, a tiny, isolated and expanding focus composed of tubulo-papillary adenocarcinoma, mimic in structure to the surrounding mucosa, is visible in the center of the figure (Fig. 7).

This change seems essentially to be the same as that of "carcinoma in adenoma", seen not infrequently in the adenomatous polyp of colorectum.

6. S.Y (17244 66yrs. male). Apart from crater-forming advanced cancer, tiny mucosal elevation with central indentation was noticed in an area of the angulus. Histologically, this lesion shows severe dysplasia of a







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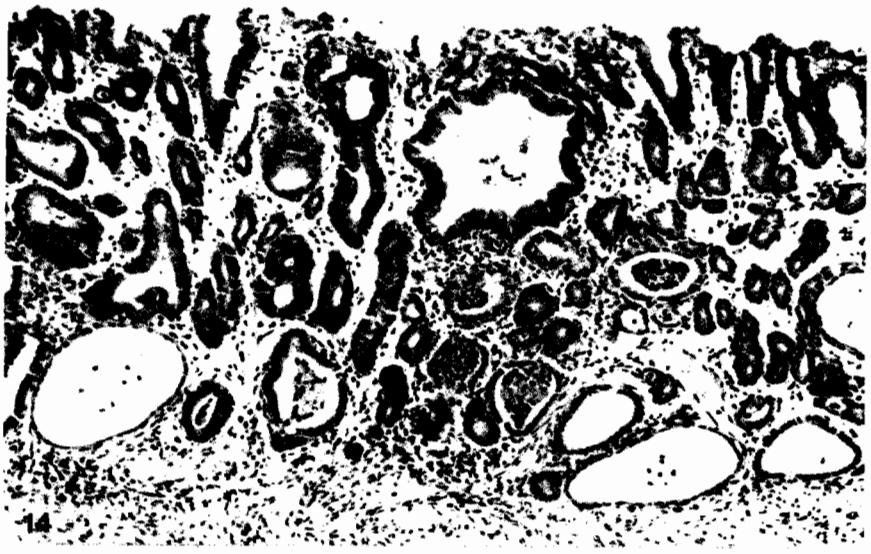
but also in the surroundings (Fig. 13).

By higher magnification of the central part of Fig. 13, it is known that small adenocarcinomatous glands, composed of cuboidal epithelia and heavily -stained and often cystically- dilated glands, made up nf tall columnar

[illegible] dysplastic changes in the biopsied specimens has greatly increased in recent years. It is known from the results of this study that the possibility of detecting severely dyplastic changes in, or adjacent to, the obvious cancerous lesions and of detecting severely dysplastic lesion alone is by no means infrequent



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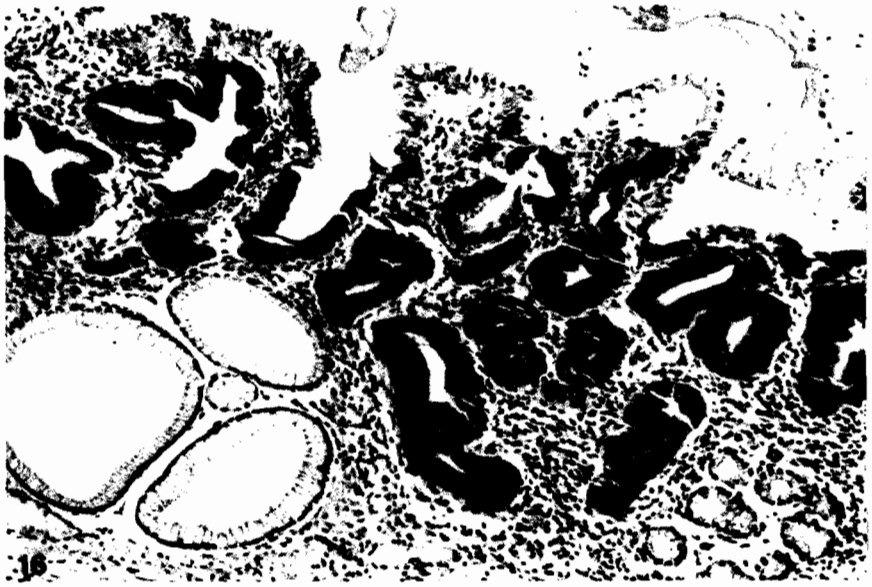

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metaplastic nature. In the central grooved area of the mucosa, a tiny spouting-out, downward growth of small adenocarcinomatous glands composed of cuboidal cells with irregularly distributed oval nuclei is seen (Fig. 8).

In this case, the border of the cancer and severe dysplasia is not clear enough but it is apparent fosrm the findings with step sectionings that cancerisation commenced in the grooved area of the metaplastic and severely dysplastic mucosa.

7. M.K (8390 62yrs, male). In the peripheral part of the large hyperplastic and somewhat dysplastic lesion, the mucosa is atrophic, metaplastic and accompanied by irregular dilatation of the atypical glands in the basal layer. In the grooved area of these atrophic mucosa, a small group of palely-stained and PAS-positive cells, suggesting signet-ring type cancer cells, infiltrated within the stroma. In the adjacent specimes, no infiltrative change by serial sectionings (Fig. 9).

The figure suggests that tiny microscopical lesion of signet-ring cell cancer developed on the basis of atrophic, metaplastic and dysplastic mucosa.

8. K.K (17214 29yrs. female). A large eroded lesion (5.0 × 4.0 cm) showing signet-ring cell cancer in the angulus. Even in a specimen cut through the central part of the lesion, the change as shown in this figure was visible. Namely, the atrophic mucosa is composed of diffusely distorted and irregularly-running tubules and glands. Within these atrophic and dysplastic mucosa, infiltrative growth, composed of small and solid cancerous nests, is sporadically seen (Fig. 10).

This change seems to be an example of the earliest stage of signet-ring cell cancer developed in the atrophic, dysplastic and non-metaplastic mucosa.

9. Y.G (802976 66yrs. female). Slightly-elevated mucosa shows the change of severe dysplasia, as indicated by cellular atypia, abnormal differentiation and disorganized mucosal architecture. Intestinal mataplasia is sporadically seen in this lesion (Fig. 11).

By higher magnification of the central part of Fig. 11, tiny cancer cell nests of cord or cribriform-like structures, indicative of the initial change in infiltrative growth of signet-ring cancer can be seen in the stroma (Fig. 12).

It is apparent from these two figures that the poorly-differentiated adenocarcinoma has developed in the severely dysplastic, but slightly metaplastic, mucosa.

c) Adenocarcinoma near the state of carcinoma in situ

10. T.S (15146 69yrs. female). Focal mucosal depression developed in the antrum is stained heavier by H.E than the adjacent mucosa and is surrounded by atrophic mucosa with diffuse intestinal metaplasia. Glandular cysts are seen not only in the depressed lesion but also in the surroundings (Fig. 13).

By higher magnification of the central part of Fig. 13, it is known that small adenocarcinomatous glands, composed of cuboidal epithelia and heavily -stained and often cystically- dilated glands, made up of tall columnar epithelia with elongated nuclei, are intermingled and form an integral part of the depressed lesion. No apparent invasive growth is seen in this lesion (Fig. 14).

11. K.Y (11500 49yrs. male). The mucosa is widely-eroded near the gastric fold and the eroded lesion covered by fibrin is stained heavier by H.E. than the surrounding mucosa. Irregular extensive growth of this lesion is known by the change seen on the extreme right of this figure (Fig. 15).

Even in the central part of Fig. 15, the eroded mucosa covered by non-malignant regenerative epithelia is diffusely occupied by the tubules composed of tall columnar epithelia having severe cellular atypia. From the lateral invasive growth of the tubules, seen on the extreme left of the figure, and the piled-up and dense arrangement of their elongated, hyperchromatic nuclei, the tubules are known to have already become malignant (Fig. 16).

Discussion

In most cases of surgically resected advanced gastric cancers, the precancerous change cannot be known owing to the overwhelming growth of the cancer. An analytical approach to establish the presence or absence of precancer is easier in the lesions of early gastric cancer but, even in the early stage, histological recognition of precancerous change in the cancerous lesions is often difficult due to great modification, or sometimes loss of the basic structure of the affected mucosa by cancerous growth. To avoid such difficulties, the author selected the foci fulfilling the following histological criteria, namely i) the mucosal lesion is not entirely occupied by the cancerous tissues and ii) dysplastic changes are visible even in the central part of the cancerous mucosa.

As shown in the tables, cases satisfying the above histological conditions were not common although there is also a possibility that the lesions suitable for the study escaped out of the notice, owing to the lesion in the routine histological examinations being overlooked. Thus, frequency detecting precancerous changes in the cancerous lesions depends upon scrutiny of the histological examination and the frequencies shown in Table 3, do not necessarily represent real frequency.

It has to be noted here that this kind of approach is not only necessary for studying the histogenesis of early gastric cancer but also provides quite important information for detecting the earliest stage in the development of gastric cancer in routine laboratory examinations. Owing to the great advance and popularization of histological examination of the biopsies specimens taken from the suspicious lesions using a fibergastroscope, the chances of encountering dysplastic changes in the biopsied specimens has greatly increased in recent years. It is known from the results of this study that the possibility of detecting severely dyplastic changes in, or adjacent to, the obvious cancerous lesions and of detecting severely dysplastic lesion alone is by no means infrequent.

Thus, when dysplastic changes were detected in the biopsied specimens, careful short-interval follow-up observation or re-examination of the lesion with endoscopy and biopsy are required.

Even though definition, criteria and classification of dysplasia are not entirely the same, several investigators have reported on dysplastic change of the stomach. (Oehlert 1975, 1979; Grundmann and Schlake, 1979; Cuello et al., 1979; Serck-Hansen, 1979; Ming, 1979, 1984; Morson et al., 1980; Nagayo, 1981, 1985; Farini et al., 1981; Jass, 1983) All the reports coincide in that the highest grade of dysplasia is often difficult to discriminate from carcinoma in an early state, which was also true in this study. The author put the standard of discrimination on the histological appearance of the nuclei, composing atypically proliferated tubules or glands in the suspicious lesions. The presence or absence of pleomorphy and polarity, grades of derrangement of the nuclei, a steep or dull edge at the top of the elongated nuclei all have decisive importance for the discrimination, together with irregularity in the shape and structures of the growing tubules. Based upon these findings, the author tried to obtain histological evidence that some types of gastric cancer developed on the pre-existing dysplastic lesions. As observed in several figures in this paper, irregularly-dilated and distorted tubules and glands were good indicators for histological recognition of severely dysplastic lesions.

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