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# Site-dependent Development of Complete and Incomplete Intestinal Metaplasia Types in the Human Stomach

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**The topographical distribution of complete and incomplete types of intestinal metaplasia in human stomach samples was investigated in order to elucidate their mutual histogenetic relationship and significance in carcinogenesis. Subgross stereomicroscopic examination of alcian blue and hematoxylin-stained gastric mucosae allowed clear distinction of complete and incomplete intestinal metaplasia types as white (with or without purple hue) and purple foci, respectively, against the background magenta areas of non-intestinalized mucosa. Intestinal metaplasias which developed in the fundic area were predominantly of the complete type whereas those of the antrum were a mixture of both with a distinct predilection for expression of the incomplete type. Although there was some variation among foci regarding the hue of white or purple, the color feature was principally homogeneous within each individual intestinal metaplasia focus. Thus phenotypic analysis indicated intestinal metaplasia expression to be clearly influenced by intragastric topography. The study did not provide any evidence that a shift from incomplete to complete type intestinal metaplasia may occur with time or that the incomplete type may be more intimately associated with development of well-differentiated carcinomas.**

Key words: Intestinal metaplasia — Human stomach — Carcinogenesis

The strong link between intestinal metaplasia (IM) and carcinoma in the human stomach has been well documented: populations demonstrating high incidences of gastric carcinoma also have high incidences of IM[1–5] and histological analyses have revealed microcarcinomas of intestinal type to be surrounded by IM at very high frequency.[6–10] Accordingly IM has been assumed to be a precancerous lesion for gastric carcinoma.[11]

IM has been subclassified into complete and incomplete types on the basis of presence or absence of brush border and Paneth's cells histologically, and trehalase and alkaline phosphatase activities biochemically, goblet cells as well as sucrase and aminopeptidase activities serving as common markers.[8, 12–14] Since incomplete IM has been much more frequently found in mucosa surrounding minute carcinomas, it was suggested that this type may be the more important as a precancerous lesion[8, 14–16] and later, more specifically, the close association of sulfomucin-positive types of incomplete IM with the development of intestinal type carcinoma was emphasized.[17] It was also speculated that incomplete IM might be an immature form, with a shift to complete IM occurring with time.[8, 17]

Although these suggestions are intriguing, certain differences in the intragastric distribution of IM of various phenotypes have been pointed out.[18, 19] Since gastric carcinomas develop far more frequently in the antral area,[20] precise topographical analysis of individual lesions is necessary to allow appraisal of the significance of any association.

In the present investigation, we therefore carefully analyzed the intragastric distributions of complete and incomplete types of IM. For this purpose subgross stereomicroscopic observation combined with alcian blue-hematoxylin double staining was applied. It was earlier shown that this particular technique, initially introduced by Yoshii,[21] enables clear distinction between complete and incomplete types of IM.[22]

## MATERIALS AND METHODS

A total of 19 human stomach samples removed by subtotal gastrectomy for carcinoma or ulcer treatment were used. In the investigation, the stomachs were opened along the greater curvature immediately after removal, washed with tap water, expanded and pinned on a wooden plate, and fixed in 15% formalin. Keeping the material in a refrigerator for several hours unfixed or touching the mucosal surface with fingers after fixation greatly interfered with the staining properties and were therefore avoided. The fixed stomach preparations were dipped in 1–3% alcian blue solution (pH 2.5) for 5–10 min, and then in Carazzi's hematoxylin for 3–5 min, being well washed in tap water after each staining procedure.

Abbreviation used in this paper: IM, intestinal metaplasia.

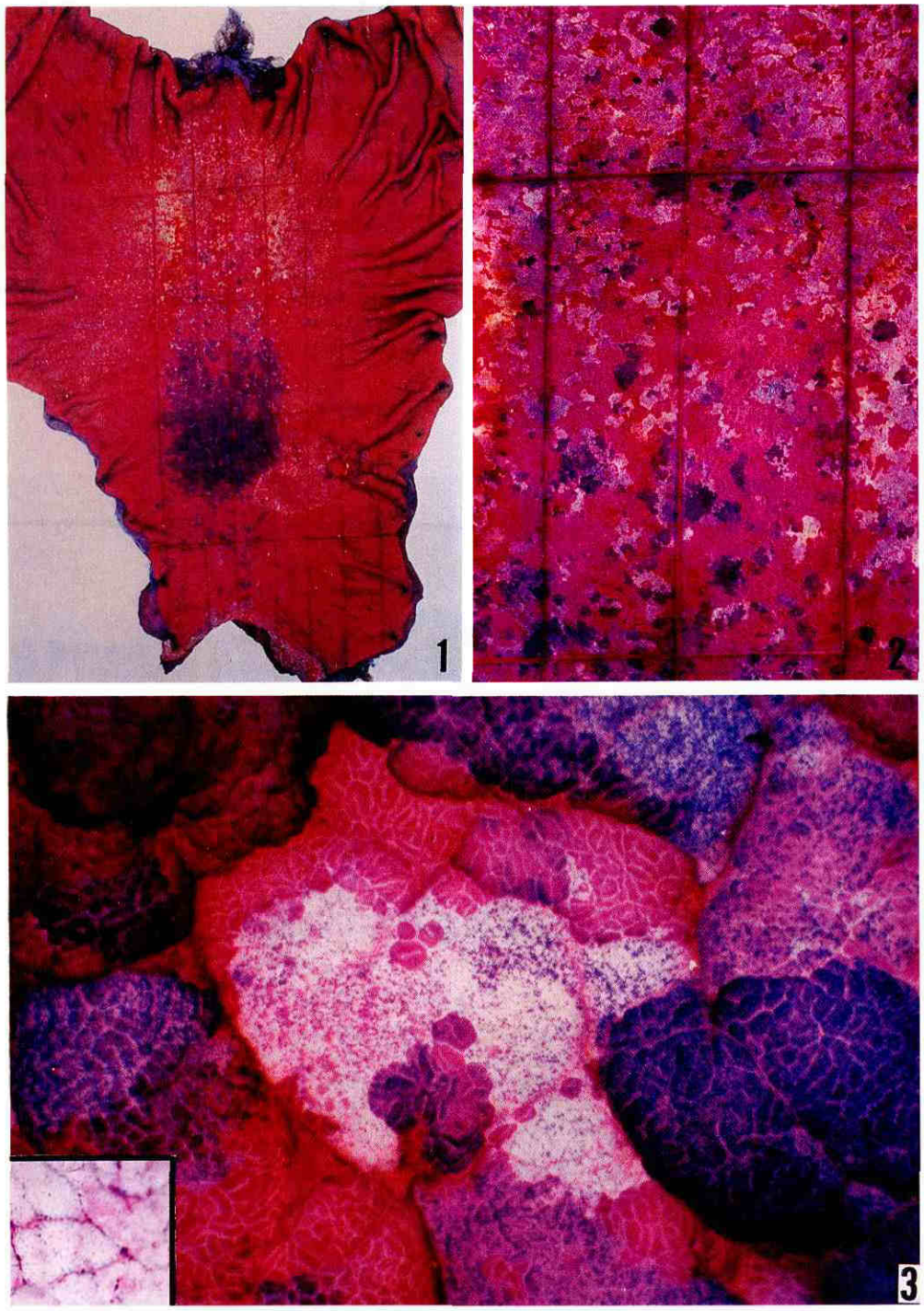
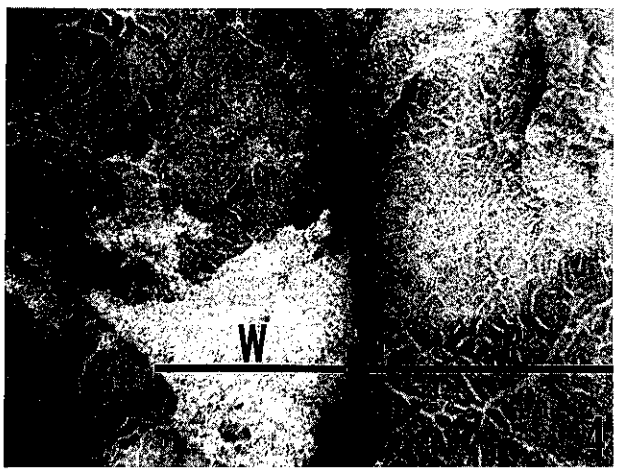


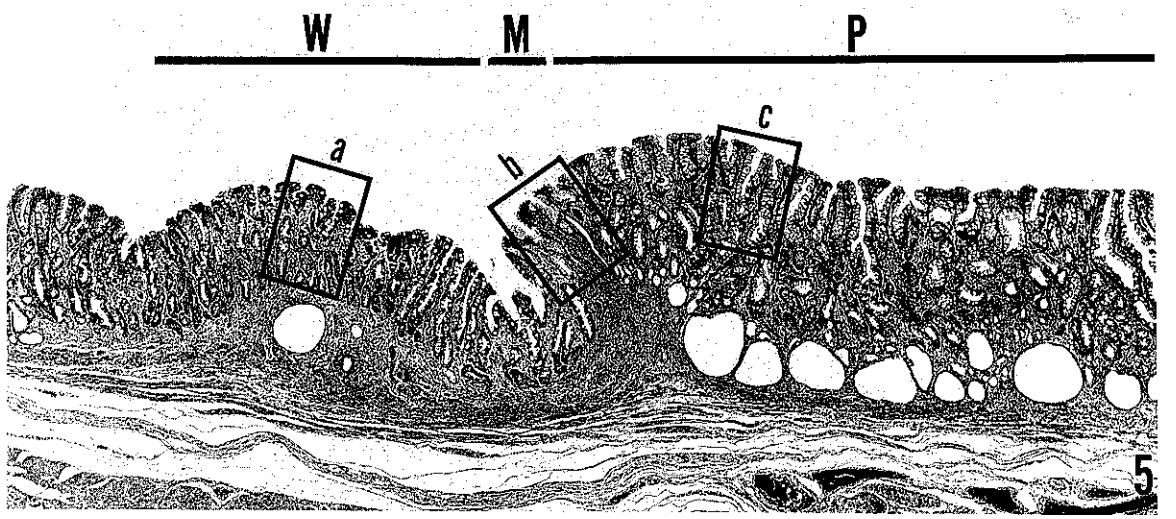

Fig. 1. Gross appearance of a stomach mucosa (Case No. 16) stained by alcian blue and hematoxylin, showing a site-specific distribution of IM foci of complete (white) and incomplete (purple) types, the former being predominant in the fundic area (upper portion) and the latter in the antral area (lower portion). An early carcinoma is visible on the anterior aspect of the pyloric area (right lower portion). ×1/2.

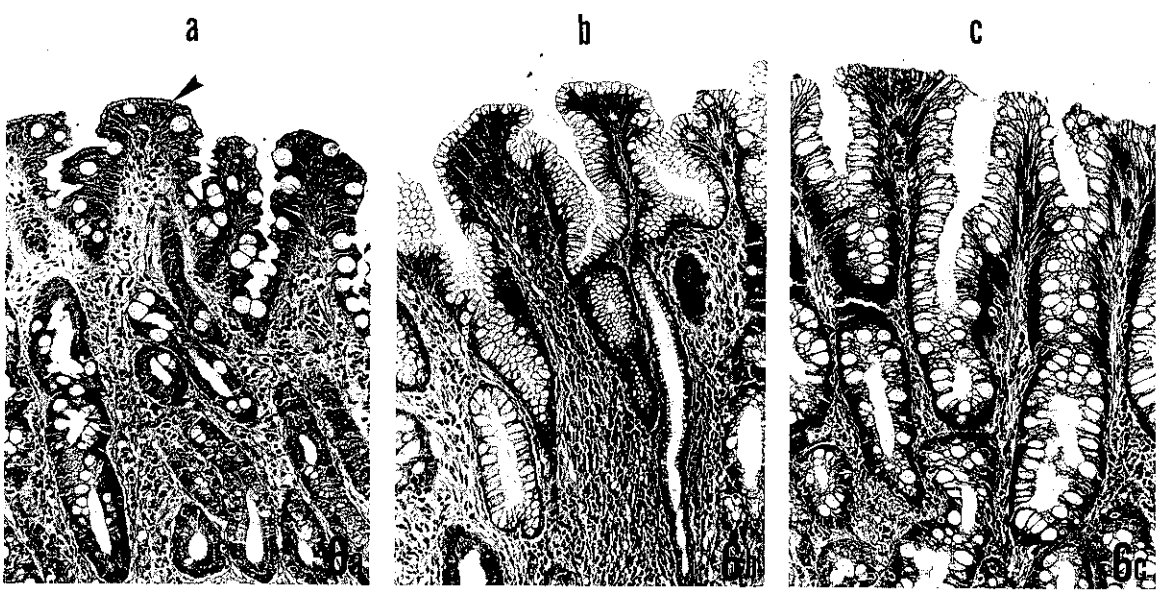
Fig. 2. Stereomicroscopic observation of part of the stomach mucosa shown in Fig. 1. Mutually independent white and purple IMs are visible against the background magenta area of non-intestinalized mucosa. ×2.

Fig. 3. Stereomicroscopic observation of a stomach mucosa (Case No. 3) at higher magnification, showing clonal-appearing development of white (complete) and purple (incomplete) foci of IM. Insert: duodenal mucosa. ×20.




Figs. 4–6. Comparative stereomicroscopic and histological observations. The white (W), purple (P) and magenta (M) foci shown in Fig. 4 (Case 3, ×14) correspond to the complete and incomplete type IMs, and non-intestinalized mucosa, respectively shown histologically in Fig. 5 (H&E. ×28). Parts of these portions indicated as a–c in Fig. 5 are demonstrated at a higher magnification in Fig. 6 (H&E. ×140). Complete IM (a) featured goblet cells, Paneth cells and the brush border (arrow), whereas the incomplete IM (c) showed goblet cells only.



Several shallow cross-cut lines were made on the mucosa to facilitate orientation, the stomachs being placed in water with the mucosal aspect accessible to subgross stereomicroscopical observation. After color photographs were taken and schemes of the staining pattern were drawn, the whole stomach specimens were step-sectioned at intervals of about 7 mm and at a length of about 5 cm and processed for routine histological examination. Each section was numbered and the numbers were recorded on the drawing so that a precise correspondence between the color photographs and histological findings was possible.

## RESULTS

Representative gastric mucosa specimens for the double staining method observed grossly or stereomicroscopically are shown in Figs. 1–3. The insert in Fig. 3 illustrates the appearance of duodenal mucosa treated similarly. Mucosa with intestinal metaplasia presented a geographical staining pattern of mixed white (with or without purple hue), purple and magenta foci.

The histological appearance of the mucosa from the stomach section shown in Fig. 4 is illustrated in Figs. 5 and 6a–c. The result of comparative studies on the relationship between the mucosal hue and histological findings on foci randomly selected from 5 cases is presented in Table I. It is apparent that the white, purple and magenta foci corresponded to complete and incomplete types of IM and ordinary (non-intestinalized) mucosa, respectively. The white foci occasionally demonstrated purple hues of various intensities, but all those tending towards whiteness could be histologically confirmed as being of the complete type of IM. This white hue was essentially similar to the color of duodenal mucosa stained by the same method (insert in Fig. 3).

Although there was some variation among foci regarding the hue of white or purple, individual foci principally demonstrated homogenous staining patterns and gradual transition from one type to another was not apparent.

The relative frequencies of complete and incomplete types of IM in the antrum and fundus regions of the 19 cases studied are summarized in Table II. In the fundic area the complete type was clearly predominant [in 10 (71%) out of 14 cases, all or the larger portion of the IM were of complete type and in only 3 (21%) were both types observed at similar rates], whereas in the antrum incomplete type IM was more frequent [in 9 (47%) of 19 cases only incomplete type was observed and in 8 (42%) both types existed at similar rates].

## DISCUSSION

The results of the present investigation confirmed that complete and incomplete types of IM can be clearly visualized as white or purple foci, respectively, in alcian blue-hematoxylin-stained gastric mucosa. With the use of this technique, it was demonstrated that IMs occurring in the fundic area are predominantly of complete type whereas those arising in the antral area are a mixture of both types with a distinct predilection for the incomplete type to predominate. Thus, the type of IM appeared to be primarily determined by the intragastric site of development.

It is well known that the majority of gastric carcinomas, roughly two-thirds, develop in the antral area.[20] The relatively frequent association, in the order of 60–80%,[8, 10, 14] of incomplete type IM with cancer is therefore, as revealed by the present data, interpretable as a natural consequence and does not by itself indicate any specific importance of the incomplete type as a precancerous lesion. Our previous histological investigation of the mucosae surrounding 71 microcarcinomas of intestinal type also revealed the rate of association of both types of IM with carcinoma to be only proportional to their site-dependent incidences; over 80% of antral carcinomas were surrounded by incomplete type IM, and over 70% of fundic ones by complete type.[23]

An interesting finding obtained by the present study is the clonal-appearing developmental pattern of individual foci. As shown in the figures, all IMs could be unequivocally classified into either white (with or without purple hue) or purple categories, and although a certain amount of variation in hue was evident among foci of

Table I. Relationship between the Hue of Alcian Blue-Hematoxylin-stained Gastric Mucosa and Histological Findings

| | No. of foci | Brush border | | | Goblet cell | | Ordinary mucosa | Type of IM |
|---|---|---|---|---|---|---|---|---|
| | | + | ++ | (č Paneth) | + | ++ | | |
| White | 21 | 0 | 21 | (21) | 2 | 19 | 0 | Complete |
| White+Purple | 35 | 6 | 29 | (30) | 17 | 18 | 0[a] | Complete |
| Purple | 17 | 4 | 0 | (2) | 1 | 16 | 0[a] | Imcompl.≫Compl. |
| Magenta | 24 | 0 | 0 | (0) | 3 | 0 | 24 | — |

*a*) Occasional mixtures of tiny foci of ordinary mucosa were neglected.

Table II. Distribution of Complete and Incomplete Type Intestinal Metaplasia in the Stomach

| Case No. | Age | Sex | Intestinal metaplasia | | | Main disease |
|---|---|---|---|---|---|---|
| | | | Degree | Antrum | Fundus | |
| 1 | 49 | M | +++ | i=c | | Ulcer |
| 2 | 50 | M | ++ | i | | |
| 3 | 60 | M | +++ | i | c | |
| 4 | 61 | M | + | i=c | c | |
| 5 | 62 | F | +++ | i=c | i=c | |
| 6 | 72 | F | +++ | c | c | Well-differentiated carcinoma |
| 7 | 71 | F | ++ | i | i | |
| 8 | 62 | M | +++ | i=c | c | |
| 9 | 68 | M | + | i=c | | |
| 10 | 41 | M | ++ | i | i=c | |
| 11 | 62 | M | +++ | i=c | c>i | |
| 12 | 64 | M | +++ | i | c>i | |
| 13 | 77 | M | +++ | c>i | c>i | |
| 14 | 40 | M | ++ | c=i | | |
| 15 | 51 | M | +++ | i | i=c | Poorly differentiated carcinoma |
| 16 | 44 | M | ++ | i | c | |
| 17 | 74 | F | + | i | | |
| 18 | 79 | M | +++ | i | c | |
| 19 | 32 | F | + | i=c | c | |

i: incomplete type intestinal metaplasia. c: complete type intestinal metaplasia. >, =: indicate relative frequency of both types.

one type, staining within each individual focus was essentially homogeneous. It is tempting to speculate that IM foci might be derived through monoclonal propagation of single altered cells, as proven in macroscopic regenerative epithelial foci developing in the duodenum after irradiation by making use of X-chromosome inactivation mosaicism in the mouse.[24] However, histologically the earliest foci of IM are observed as single glands of simple or branched tubular structure scattered within one area gastricae. Stereomicroscopically observable foci of IM are one order of magnitude larger than the microscopic glands and measure up to 5 mm in diameter, often covering several areae gastricae. On the basis of spatial requirements, therefore, it is more natural to conclude that the foci of IM are derived through coalescence of multiple tiny intestinalized glands. If such is the case, locally operative factors should provide the mechanism(s) underlying determination of the character of individual IMs. The elucidation of this mechanism remains open for future research.

The idea that the incomplete type of IM may be an immature stage which shifts to complete type expression with time[8, 17] is not supported by the present finding showing principally homogenous staining patterns of individual foci, giving a minimal impression of gradual transition from one type to another within each individual focus. In addition, it is well-known that IM in the fundic area (complete-prone) develops later than that of antral area (incomplete-prone) in individual stomachs.[6]

With regard to the staining technique itself, the purple hue seen with the double staining is apparently due to the presence of goblet cells which are usually more prominent in the incomplete type of IM. The reason why the complete type IM, together with duodenal mucosa, demonstrates a white hue is not entirely clear but it may be related to the existence of abundant absorptive cells with a brush border, which may reflect incident light.

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