

ORIGINAL ARTICLE

Gastric ciliated metaplasia. A study of 3406 gastrectomy specimens from dwellers of the Atlantic and the Pacific basins

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Background: Ciliated cells in gastrectomies from patients dwelling in the Pacific and Atlantic basins have been reported previously.

Aim: To compare all the results in an attempt to explain the findings.

Methods: Sections from 3406 gastrectomies were reviewed: 1966 and 1440 from the Atlantic and Pacific basins, respectively. Ciliated cells and intestinal metaplasia (IM) were recorded; IM was classified into focal or extensive IM. The total number of sections/gastrectomy was noted.

Results: In the Atlantic basin, 5% of specimens had ciliated metaplasia (CM); it was more frequent in intestinal carcinoma (IC; 9%) than diffuse carcinoma (DC; 3%) or miscellaneous gastric diseases (MGD; 3%). In the Pacific basin, the frequency of specimens with CM was 29%: it was more frequent in IC (43%) than in DC (16%) or MGD (10%). The difference between the frequency of CM in specimens with IC or with DC/MGD in the Atlantic and the Pacific basins was significant ($p \leq 0.05$). The presence of CM was influenced by age and the extent of IM in both basins, but not by sex or the number of sections investigated.

Conclusions: CM—apparently an independent microscopic marker—was significantly higher in the Pacific than in the Atlantic basin. Environmental carcinogens involved in the evolution of IM and IC seem to be implicated in gastric ciliogenesis. Carcinogens that differ in nature and/or in strength in both basins might activate the latent natural genes encoding ciliated processes in gastric cells in patients subsequently developing gastric carcinoma, more notably of intestinal type.

Although ciliated cells cover the oesophageal epithelium during ontogenesis, ciliated cells are not found in the normal gastric mucosa before or after birth.¹ Consequently, the presence of such cells in the gastric mucosa should be regarded as a pathological finding.

“A comparative study between all the results obtained in the two basins has never been undertaken”

Before 1983, only six patients with gastric ciliated cells had been reported, and all were Japanese. Kodaira *et al* (T Kodaira *et al*. Ciliated epithelium in gastric mucosa observed in chronic gastritis. An electron microscopic study. Proceedings of the Japanese Cancer Association, 33rd Annual Meeting, 1974, p184) found ciliated cells in two patients with chronic gastritis, Okuda and Ogata² in three patients (two with duodenal ulcers and one with a gastric adenoma), and Yamashiro and colleagues³ in one patient harbouring a carcinoma elsewhere in the stomach. The ciliated gastric cells were detected at the electron microscopical level.

In 1983, while looking at haematoxylin and eosin stained sections at high power ($\times 40$) using a conventional microscope, we found ciliated metaplasia in six Japanese patients with gastric adenoma.⁴ In 1984, Stemmermann and colleagues⁵ assumed that approximately 10% of the stomachs with intestinal metaplasia (IM; mainly from Japanese patients living in Hawaii) had ciliated cells. In 1986, we found that ciliated metaplasia occurred in 35% of 137 gastrectomy specimens taken from Japanese patients living in Japan.⁶ In

the same year, Torikata *et al* (C Torikata *et al*. Ciliated cells in human metaplastic gastric mucus. A proposal of a new term; ciliated metaplasia. Proceedings of the XI International Congress on Electron Microscopy, 1986, Kyoto, p3549–52.) reported “numerous ciliated cells in more than 30 cases of resected specimens in the pyloric gland and only two cases in the cardiac gland” in Japanese stomachs. Four years later, Torikata *et al* found ciliated metaplasia in 42 of 100 consecutive resected Japanese stomachs,⁷ and in 1992 in 51 of 100 consecutive gastrectomies (95 with carcinoma and five with peptic ulcer).⁸ In 1993, among Hong-Kong Chinese, Chan *et al* found ciliated metaplasia in 11 of 22 gastrectomies taken for carcinoma and in five of 13 gastrectomies taken for peptic ulcer.⁹ Those authors⁹ demonstrated cilia even in the tumour cells in one of the cases.

In subsequent studies in other countries at the rim of the Pacific basin,^{10–17} we found a high frequency of gastrectomies with ciliated metaplasia. In contrast, investigations of populations from the Atlantic basin^{18–23} found a lower frequency of specimens with ciliated metaplasia. Our reports were based on results obtained at individual institutions located in the Atlantic and in the Pacific basins. However, a comparative study between all the results obtained in the two basins has never been undertaken.

The purpose of our study was to compare the frequency of gastrectomies with ciliated gastric cells between patients

Abbreviations: DC, diffuse carcinoma; EIM, extensive intestinal metaplasia; IC, intestinal carcinoma; IM, intestinal metaplasia; MGD, miscellaneous gastric diseases

Table 1 The number of gastrectomies with ciliated metaplasia/total number of gastrectomies performed in 1966 patients dwelling at the rim of the Atlantic basin

Location	IC	DC	Adenoma	Miscellaneous	All cases with cilia
New York	14/344 (4%)	1/235 (0.4%)		2/48 (4%)	17/627 (3%)
London	3/65 (5%)	0/56 (0%)		4/56 (7%)	7/177 (4%)
Reykjavik	20/141 (15%)	6/160 (4%)		6/134 (4%)	32/435 (7%)
Florence	26/116 (22%)	9/70 (13%)		–	35/186 (19%)
Mexico City	1/16 (6%)	0/12 (0%)		0/177 (0%)	1/205 (0.5%)
Buenos Aires	2/76 (3%)	1/69 (1%)		2/53 (4%)	5/198 (3%)
Boston	0/11 (0%)	0/10 (0%)	1*/1	–	1/21 (5%)
Stockholm	4/47 (8%)	1/36 (3%)		2/34 (6%)	7/117 (6%)
Total	71/816 (9%)	18/648 (3%)	1*/1	16/502 (3%)	105/1966 (5%)

*Adenoma without invasion.
DC, diffuse carcinoma; IC, intestinal carcinoma.

dwelling at the rim of the Pacific^{10–17} and Atlantic^{18–23} basins. From that comparison, conclusions were drawn regarding the possible influence of environmental, ethnic, and genetic factors in the development of gastric ciliated metaplasia.

MATERIALS AND METHODS

Filed haematoxylin and eosin stained sections from 3406 gastrectomy specimens from dwellers of the Pacific (n = 1440) and the Atlantic (n = 1966) basins were reviewed. Some of the results of those studies have been reported elsewhere.^{10–23}

A review of that material, which originated from between 1981 and 1999, was carried out at the various hospitals by one of the authors (CAR). Randomly selected cases were discussed with host pathologists at the respective hospitals.

To detect glands with ciliated metaplasia, the basal aspect of gastric pyloric glands was carefully studied using ×20 or ×40 objective magnifications. In glands suspected to have ciliated metaplasia, sections were observed under oil immersion (×100 magnification).

The occurrence of IM was investigated at low power (×4 objective). Specimens with IM were classified into those with “spotty” IM (sections having one or more minor glandular groups with IM in one or more sections), and those with extensive IM (EIM; sections showing a continuous segment of IM occupying one or more entire low power fields/section in one or more sections²⁴).

Statistical analysis

The Wilcoxon non-parametric test and ANOVA analysis were performed using StatView Version 4.5 software (Abacus Concepts, Berkley, California, USA). Significance was defined as p < 0.05.

RESULTS

Filed sections from 3406 gastrectomy specimens were investigated.

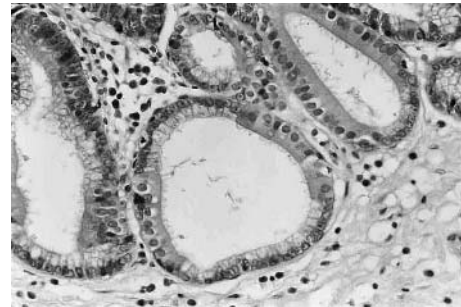


Figure 1 A group of pyloric gastric glands with ciliated metaplasia (haematoxylin and eosin stain; original magnification, ×25).

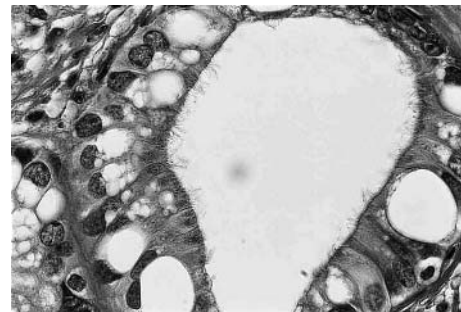


Figure 2 A closer view of a gastric gland to demonstrate both ciliated metaplasia and intestinal metaplasia (haematoxylin and eosin stain; original magnification, ×50).

Of the 1966 specimens reviewed in the Atlantic basin (table 1), 816 (41%) had carcinoma of intestinal type (IC), 648 (33%) had carcinoma of diffuse type (DC), one was an

Table 2 The number of gastrectomies with ciliated metaplasia/total number of gastrectomies performed in 1440 patients dwelling at the rim of the Pacific basin

Location	IC	DC	Adenoma	Miscellaneous	All gastrectomies with cilia
Tokyo	72/181 (40%)	29/166 (18%)	37/87 (43%)	5/35 (14%)	143/469 (30%)
Matsuyama	87/168 (52%)	13/73 (18%)		–	100/241 (41%)
New Zealand, Polynesians	2/9 (22%)	4/12 (33%)		7/46 (15%)	13/67 (19%)
New Zealand, whites	14/47 (30%)	5/15 (33%)		2/46 (4%)	21/108 (19%)
Honolulu, Asians	38/60 (63%)	4/29 (14%)		10/40 (25%)	52/129 (40%)
Honolulu, whites	11/40 (28%)	1/14 (7%)		2/11 (18%)	14/65 (22%)
Vancouver	16/45 (36%)	5/56 (9%)		7/140 (5%)	28/241 (12%)
Santiago	36/64 (67%)	4/45 (9%)		0/11 (0%)	40/120 (33%)
Total	276/614 (45%)	65/410 (16%)	37/87 (43%)	33/329 (10.0%)	411/1440 (29%)

DC, diffuse carcinoma; IC, intestinal carcinoma.

adenoma (0.05%) and the remaining 502 specimens (26%) had miscellaneous non-neoplastic gastric diseases (MGD).

Of the 1440 specimens reviewed in the Pacific basin (table 2), 614 (43%) had IC, 410 (28%) DC, 87 (6%) adenoma, and the remaining 329 (23%) had MGD. The difference between the proportions of IC, DC, and MGD between the two basins was non-significant ($p = 0.7$).

Localisation of the ciliated gastric cells

Ciliated metaplastic cells (figs 1–3) were found in the basal segments of the pyloric gastric glands, usually from the antrum, whose superficial parts had undergone IM. Ciliated metaplastic cells also occurred in the cardia and the corpus—in areas with pseudopyloric metaplasia in specimens with widely distributed EIM—and in dilated dysplastic glands in gastric adenomas.

Frequency of ciliated metaplasia

The Atlantic basin

The mean frequency of ciliated metaplasia in the Atlantic basin was 5% (table 1). Variations in the proportion of specimens with ciliated metaplasia were found depending upon the type of lesion present in the specimens: 9% for gastrectomies with IC and 3% for those with DC and MGD. In seven of the eight cities investigated in the Atlantic basin the frequency of specimens with ciliated metaplasia was 7% or lower (table 1). Table 1 also shows that the frequency of ciliated metaplasia in gastrectomies with IC varied between the different cities of the Atlantic basin, from 22% in Florence to 0% in Boston. In gastrectomies harbouring DC, the frequency of ciliated metaplasia also varied in the different cities, from 13% in Florence to 0% in New York, London, Mexico City, and Boston. In MGD the frequency varied from 7% in London to 0% in Mexico City.

The Pacific basin

Table 2 shows that the mean frequency of ciliated metaplasia in the Pacific basin was 29%. Variations in the number of positive specimens were found depending upon the type of lesion present in the specimen: 45% for gastrectomies with IC, 16% for those with DC, 43% for those with adenoma, and 10% for those with MGD. In seven of the eight cities investigated in the Pacific basin the frequency of gastrectomies with ciliated metaplasia was 19% or higher. Table 2 also shows that in the Pacific basin the frequency of ciliated metaplasia in specimens with IC varied from 67% in Santiago de Chile to 22% in New Zealand (Polynesians). In gastrectomies harbouring a DC, the frequency of ciliated metaplasia varied from 33% in New Zealand (both Polynesians and whites) to 7% in Honolulu (whites). In MGD, the frequency varied from 25% in Honolulu (Asians) to 0% in Santiago de Chile.

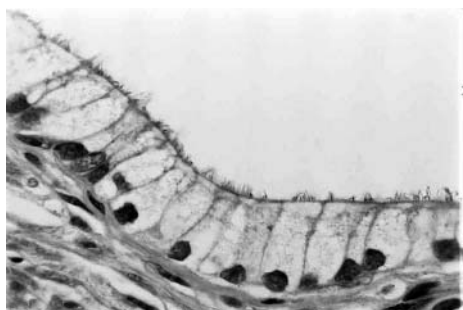


Figure 3 Detail of pyloric gland with ciliated metaplasia (Grimelius stain; original magnification, $\times 100$).

The difference in frequency of specimens with ciliated metaplasia having IC or DC/MGD was significant ($p < 0.05$). The difference was also significant between the two basins ($p < 0.05$).

Age and ciliated metaplasia

In the Atlantic basin, 74% of the 105 gastrectomies with ciliated metaplasia were performed in elderly patients (≥ 60 years; table 3). In the Pacific basin, 83% of the 411 gastrectomies with ciliated metaplasia were carried out in elderly patients (table 4). The difference between the occurrences of ciliated metaplasia among the elderly in individual basins was significant ($p < 0.05$).

Sex and ciliated metaplasia

In the Atlantic population, the highest percentage of men with ciliated metaplasia was found in New York (72%) and the lowest in Florence (57%). In the Pacific population, the highest percentage of men with ciliated metaplasia was found in Matsuyama (77%) and the lowest in New Zealand (whites), namely 54%. No difference in the percentage of men with ciliated metaplasia was found between the Atlantic and Pacific populations analysed ($p = 0.6$).

Men undergoing surgery for IC (where the proportion of cases with ciliated metaplasia was the highest) accounted for 76.7% of the gastrectomies performed in Matsuyama and for 75% of those performed in New York. However, the proportion of gastrectomies with ciliated metaplasia was 52% in Matsuyama and only 4% in New York. Thus, causes other than sex influenced the occurrence of ciliated metaplasia in the specimens.

EIM and ciliated metaplasia

In the Atlantic basin, 19% of gastrectomies with IC (where the proportion having EIM was the highest²⁴) had EIM and 9% of those also had ciliated metaplasia. In the Pacific basin, 63% of gastrectomies with IC had EIM and 45% of those had ciliated metaplasia. The difference between specimens showing EIM and ciliated metaplasia in the two basins was significant ($p < 0.05$).

Number of sections/gastrectomy and ciliated metaplasia

Table 5 shows the number of sections reviewed/gastrectomy. The mean number of sections reviewed/gastrectomy was somewhat higher in the Pacific (18.9) than in the Atlantic basin (16.5). In Stockholm, where entire gastrectomy specimens were sampled in blocks and sectioned for diagnostic and research purposes, a mean of 31.2 sections/gastrectomy was available.

The number of sections/specimen varied in the various cities. Although the mean number of sections reviewed/specimen in Florence was only 10.9, the percent of ciliated metaplasia was relatively high (19%). In contrast, the mean number of sections reviewed/gastrectomy in Stockholm was 31.2 sections, but only 6% of the specimens contained ciliated cells. The difference between the number of sections/gastrectomy and the occurrence of ciliated metaplasia in the two basins was not significant ($p = 0.7$).

DISCUSSION

Our comparative survey showed that gastric ciliated metaplasia was significantly more frequent in residents of the Pacific basin (mean, 29%; range, 19–41%) than in residents of the Atlantic basin (mean, 5%; range, 0.5–19%). Ciliated metaplasia was more common in specimens with IC than in those with DC, strongly suggesting that ciliated metaplasia is associated with the development of gastric neoplasia, more notably IC.

Table 3 Ages of 105 patients with ciliated metaplasia in gastrectomy specimens dwelling at the rim of the Atlantic basin

Location	Age					Ciliated metaplasia/patients ≥ 60 years of age
	≤ 39	40–49	50–59	60–69	≥ 70	
New York		1	3	7	6	13/17
London				3	4	7/7
Reykjavik	1	3	7	9	12	21/32
Florence			10	15	10	25/35
Mexico City			1			0/1
Buenos Aires				3	2	5/5
Boston					1	1/1
Stockholm			1	2	4	6/7
Total	1	4	22	39	39	78/105 (74%)

The mean frequency of MGD specimens with ciliated metaplasia was 3% in the Atlantic and 10% in the Pacific. Whether patients with MGD who also have ciliated metaplasia are at future risk of developing gastric carcinoma could not be answered by our study because it consisted of resected stomachs. The presence of ciliated cells in MGD indicates that the conditions that favour the transformation of native gastric cells into ciliated cells are not triggered only by the presence of a fully developed gastric tumour.

Torikata *et al* found ciliated cells in four of 50 cardia resections performed for oesophageal cancer.⁸ We found proximal ciliated metaplasia in 34% of 573 gastrectomies performed for cardia cancer in Tokyo-Matsuyama,²³ but only in 1.2% of 317 similar gastrectomies performed in New York.²² Thus, the difference in frequency of ciliated metaplasia between the two basins also applies to patients with cardia carcinoma. Ciliated metaplasia seems to develop irrespective of the localisation of the tumour within the stomach.

The results showed that ciliated metaplasia was influenced by increasing age and by EIM,²⁴ suggesting that ciliated cells may arise in the environment of extensive IM in the aging gastric mucosa. However, 10% and 18% of gastrectomies with IC and EIM in the Atlantic and Pacific basins, respectively, had no ciliated cells, suggesting that ciliated metaplasia might be generated through a molecular pathway different to that in EIM.

Migration within the same geographical basin did not alter the frequency of ciliated metaplasia: elderly Japanese migrants to Hawaii subsequently developing gastric carcinoma in Hawaii had a high frequency of ciliated metaplasia, similar to that seen in elderly Japanese dwelling in Japan. In contrast, populations with IC residing at similar latitudes but in different basins (Vancouver Canadians and New Yorkers in the Northern Hemisphere and those from Santiago de Chile and in Buenos Aires in the Southern Hemisphere) had different frequencies of ciliated metaplasia (36% and 4%, and 67% and 3%, respectively).

This work was initiated in 1981—before the discovery of *Helicobacter pylori* by Warren and Marshall.²⁵ In our

subsequent studies, these bacteria were not investigated because special stains were not available at the different hospitals. *Helicobacter pylori* is usually absent in cases with IM because the pH is not optimal for the growth of these bacteria in these cases. Furthermore, the flushing of the specimens with saline after surgery (to permit the inspection of the lesion) and, in the past, the autolytic necrosis of the superficial mucosal cell layers by the intense light required for photographic documentation were detrimental to the bacteria. In retrospect, and based on the aforementioned pitfalls in the handling and processing of the resected specimens, it is assumed that the search for *H pylori* in this survey would have led to questionable results and to unreliable conclusions. It is likely, however, that ciliated metaplasia is not triggered by *H pylori*; Mexicans, who have a high prevalence of *H pylori*,²⁶ had the lowest frequency of ciliated metaplasia (0.5%).

“Our results show that another cellular mutation—ciliated metaplasia—is associated with gastric carcinoma, particularly intestinal carcinoma”

It may be argued that our study has many drawbacks, namely: the size of the resected specimen varied with the topographical location of the tumour, with the size of the tumour removed, and with the technique of resection used by individual surgeons within the same hospital, between different hospitals, and between different countries. In addition, the number of blocks taken from the resected specimens by pathologists at various hospitals also varied. Despite these disadvantages, the method allowed the comparison of the state of the gastric mucosa in a considerable number of gastrectomies with carcinoma and other gastric diseases from patients dwelling in disparate geographical regions. This belief is substantiated by the fact that the detection of ciliated metaplasia was not limited by the number of sections/specimen: in the Atlantic basin, ciliated metaplasia was low (3%) in Buenos Aires, where the mean number of sections/specimen was also low, and also in

Table 4 Ages of 411 patients with ciliated metaplasia in gastrectomy specimens dwelling at the rim of the Pacific basin

Location	Age					Ciliated metaplasia/patients ≥ 60 years of age
	≤ 39	40–49	50–59	60–69	≥ 70	
Tokyo-Matsuyama		7	43	83	110	193/243
New Zealand		1	9	10	14	24/34
Honolulu		2	6	19	39	58/66
Vancouver*			2	5	21	26/28
Santiago			1	12	27	39/40
Total		10	61	129	211	340/411 (83%)

*The age in 21 of patients with peptic ulcer was not available.

Table 5 The mean number of sections reviewed in 3385 gastrectomy specimens seen in the Pacific (n = 1945) and Atlantic basins (n = 1440).

City in Atlantic basin	No. sections/no. cases	City in Pacific basin	No. sections/no. cases
New York	4452/627 (7.1 sections)	Tokyo	10787/469 (23.0 sections)
London	4283/177 (24.2 sections)	Matsuyama	5543/241 (23.0 sections)
Reykjavik	4480/435 (10.3 sections)	Honolulu	3065/194 (15.8 sections)
Florence	2027/186 (10.9 sections)	Auckland/Otahuhu	1557/175 (8.9 sections)
Mexico City	820/205 (4.0 sections)	Santiago	3288/120 (27.4 sections)
Buenos Aires	475/198 (2.4 sections)	Vancouver	2940/241 (12.2 sections)
Stockholm	3650/117 (31.2 sections)		
All cities in Atlantic basin	20187/1945* (16.5 sections)	All cities in Pacific basin	27180/1440 (18.9 sections)

*The number of sections in 21 gastrectomies in Boston was not recorded.

Stockholm (6%), where the mean number of sections/gastrectomy was the highest in our present survey. In contrast, ciliated metaplasia in Santiago was high (33%), despite the mean number of sections being lower than in Stockholm. Thus, the number of sections did not influence the detection of ciliated metaplasia in the gastrectomy specimens in our survey.

It is generally accepted that environmental carcinogens encourage the development of IM.²⁷ With that hypothesis in mind, over an 18 year period we investigated a substantial number of resected stomachs in distant parts of the World. Because the frequency of ciliated metaplasia was lower in the Atlantic than in the Pacific basin we speculated that environmental factors acting in the Atlantic basin were either much weaker than those in the Pacific basin, or that the gastric mucosa in the Atlantic basin—for reasons unknown—was more resistant to those factors. It should be borne in mind that the Pacific basin is a higher risk zone for gastric cancer development than the Atlantic basin.

According to Correa *et al*,²⁸ mutagenic–carcinogenic agent(s) present in the gastric microenvironment would trigger the sequence of cellular mutations leading to IM and to gastric carcinoma, particularly IC. We have also found that IM is associated with IC.²⁴ Our results show that another cellular mutation—ciliated metaplasia—is associated with gastric carcinoma, particularly IC.

Snell *et al* postulated that nearly all mammalian cells can form cilia and that cilia are connected with cell proliferation and homeostasis.²⁹ More recently Judd *et al* succeeded in eliciting gastric ciliated metaplasia in genetically manipulated

mice.³⁰ The studies of Judd *et al* may provide the opportunity to monitor, under experimental laboratory conditions, the influence of environment carcinogens on the genetic changes that unlock gastric ciliated metaplasia.³⁰

In conclusion, our findings support the hypothesis that gastric ciliated metaplasia is an independent microscopic marker that is triggered by environmental agents. Those agents that differ in nature and/or in strength in the two basins might activate the latent natural genes that encode ciliated processes in gastric cells in patients subsequently developing gastric carcinoma, more notably of intestinal type.

Further research is necessary to disclose the environmental agents responsible for the difference in frequency of ciliated gastric cells between patients with gastric carcinoma dwelling at the rim of the two disparate oceanic basins.

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Take home messages

- We have previously reported the prevalence of ciliated cells in gastrectomies from patients dwelling in the Pacific and Atlantic basins and here we compared these results
- Ciliated metaplasia appeared to be an independent microscopic marker for the development of gastric carcinoma, and was significantly higher in the Pacific than in the Atlantic basin
- The presence of ciliated metaplasia was influenced by age and the extent of IM in both basins, but not by sex or the number of sections investigated
- Environmental carcinogens involved in the evolution of intestinal metaplasia and intestinal carcinoma seem to be implicated in gastric ciliogenesis
- Carcinogens that differ in nature and/or in strength in both basins might activate the latent natural genes encoding ciliated processes in gastric cells in patients subsequently developing gastric carcinoma, more notably of intestinal type

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