

sociated with the use of anthracene laxatives. The pigmentation of the colon is due to residual bodies containing lipofuscin.^{6,17} However, the nature of the pigment in the duodenum remains controversial. The pigment has been claimed to be melanin,^{1,9,10} lipomelanin or pseudomelanin,^{2,11} hemosiderin,¹² and ferrous sulfide.^{6,13-17} In our patients, special staining with Warthin-Starry stain and Prussian blue showed positive results. Fontana-Masson stain was positive in 1 patient and negative in 2 patients. PAS staining was negative in all. This indicated that the pigment was heterogeneous and that it contained iron and/or melanin, but it was not lipofuscin. However, because the pigment was quite dark, it was difficult to interpret the results the Warthin-Starry staining, and this may have resulted in a false positive reaction for melanin.

This pigment was first characterized as ferrous sulfide by Pounder et al,¹³ and this was later confirmed by others.^{6,14-17} Prussian blue reacts with ferric iron (Fe^{+++}), but ferrous sulfide (Fe^{++}) produces a negative Prussian blue reaction. It was speculated that there may be auto-oxidation of ferrous sulfide (Fe^{++}) to ferric oxide (Fe^{+++}) resulting in varying amounts of ferrous sulfide and ferric oxide in pigment granules which would explain a variable staining reaction for iron in previous reports of pseudomelanosis duodeni.^{13,17} Kang correlated electron-probe x-ray analysis with histochemical staining and confirmed that the characteristics of staining depend on the amount of sulfur incorporated into the granules.⁶ When a large amount of sulfur is incorporated with iron, those pigment granules were positive for Fontana-Masson and negative for iron staining. Those granules with a minimal amount of sulfur were positive for iron stain and negative for Fontana-Mason stain, and those granules with indeterminate amounts of sulfur were positive for both stains.⁶

In normal conditions, iron is absorbed in particulate form without coupling with sulfur during the digestive process. In patients with pseudomelanosis duodeni, iron is incorporated with sulfur in macrophages.¹³⁻¹⁵ It is postulated that impairment of iron transport and utilization in patients with pseudomelanosis duodeni may result in accumulation of iron within macrophages in the lamina propria of

villi.^{5,18} Some inherent defects in macrophages that cause transformation of iron into ferrous sulfide may be responsible for the accumulation of pigment granules in patients with pseudomelanosis duodeni.¹⁴

Among those 46 reported cases, only 3 cases demonstrated completely reversible change of the duodenal pigmentation,^{2,6,18} and 1 case showed partial regression of this pigmentation.⁵ In our patients, the duodenal pigmentation showed regression on follow-up endoscopy, and the follow-up period was 21 and 36 months, respectively, in 2 patients who demonstrated complete disappearance of the duodenal pigmentation. However, the actual time needed for complete regression of this pigmentation is not clear, and it may be related to the accumulative amount of pigment granules in the duodenal mucosa.

Most authors suggested that iron in duodenal pigments might originate from ingested foods or iron supplements,^{12,14,18,19} gastrointestinal bleeding,^{13,15} or intramucosal hemorrhage.⁶ It was presumed that the source of sulfur was probably derived from ingested foods or drugs.^{13,17} Diuretics such as thiazides and furosemide, which contain sulfur atoms, are commonly used in patients with chronic renal disease and hypertension. Ninety-four percent of the reported patients (including our 3 patients) had been suffering from chronic renal failure and/or hypertension. Among these reported 46 cases, the medication history was not described in 5 cases,^{1,8,10,13,14} and 90% of the remainder had consumed at least 1 drug which contained sulfur such as furosemide, thiazides, or ferrous sulfate.

In our first 2 patients, the duodenal pigmentation disappeared after withdrawal of hydralazine, propranolol and thiazide. Among these drugs, only thiazide contains sulfur atoms; therefore, this was the only drug we discontinued in the third patient. The duodenal pigmentation did show partial regression after withdrawal of thiazide from the patient for 6 months. Accordingly, we suggest that drugs containing sulfur atom such as thiazide, furosemide, and ferrous sulfate, are mainly responsible for the formation of these pigmented granules, and other anti-hypertensive agents might play only a minor role in this condition.