Gastrin and Colorectal Neoplasia: Cause and Effect

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Gastrin is a peptide hormone, synthesized and released from gastric antral G cells. Hypergastrinemia is a pathological state where gastrin concentration, usually gastrin 17, is increased in the circulation. There are four main reasons for this phenomenon: *Helicobacter pylori* infection; treatment with proton pump inhibitors (PPIs); autonomic secretion of gastrin from tumor, gastrinoma, in Zollinger Ellison Syndrome (ZES) or in multiple endocrine neoplasm type I (MEN I), and atrophic gastropathy, where the physiological negative feedback on gastrin secretion by G cells is not functioning. Eradication of *H. pylori*, stopping PPIs, resection of the tumor in ZES and the gastric antrum in atrophic gastropathy may return gastrin levels to within the normal range. In *H. pylori* infection and in ZES, hypergastrinemia may cause severe peptic disease because of the high rate of gastric secretion by the parietal cells. In PPI therapy and atrophic gastropathy, when parietal cells are inhibited or lost, acid secretion is not a clinical problem but the high gastrin concentration in the peripheral blood may be dangerous for other reasons. Gastric endocrine cells (ECL) may proliferate because of gastric trophic effect, and ECLomas and carcinoid tumors may develop [1].

Gastrin has a trophic effect on epithelial cell growth and proliferation not only in the stomach, and may have a role in the development of colonic adenomas and the polyp-carcinoma sequence [1, 2]. There are several lines of evidence to support this role. Gastrin effects are mediated by CCKB (CCK-2) receptors, which have been detected in colon cancer tissues [2]. Furthermore, gastrin stimulates cell line and xenograft growth [3], and hypergastrinemia has been associated with an increased risk of colorectal cancer [4]. Altered colonic proliferation of the normal mucosa, with a movement of the proliferative zone to the upper crypt, has been demonstrated in patients with hypergastrinemia due to pernicious anemia or in patients with a hereditary predisposition to colorectal cancer [6, 7]. Colucci et al. [5] demonstrated increased transcriptional activity of COX-2 gene followed by prostaglandin E2 production in HT-29 (a human colonic cancer cell line) after CCKB receptor activation by gastrin-17. Prostaglandin E2 stimulates growth and proliferation of epithelial cells, and may be the final common pathway by which gastrin exerts its activity. Other possible mechanisms are by enhancing angiogenesis or inhibition of apoptosis, as recently described [8–10]. Amidated gastrin-17, glycine-extended gastrin-17 and other precursors, as well as CCKB receptor isoforms, CCKC and glycine-extended gastrin receptor may all play an important role in colonic epithelial cell proliferation and adenoma formation in endocrine, paracrine or autocrine pathways [3].

In this issue of *Digestion*, Georgopoulos et al. [11] demonstrate a positive correlation between hypergastrinemia and colonic adenomas. Comparing a group of 78 consecutive patients with colonic adenomas with matched colonoscopy negative controls, hypergastrin-
emia was the only independent risk factor for adenomas, especially of the distal colon, by multivariate analysis, but not *H. pylori* infection or cagA positivity. This study joins many others that established the role of gastrin in adenoma formation and colorectal cancer development. Since hypergastrinemia due to *H. pylori* infection, PPI therapy or atrophic gastropathy is common, the danger of developing colonic adenomas should be taken into account by the medical community and a preventive strategy is needed. *H. pylori* eradication, PPI dose reduction and screening colonoscopy should be more aggressively applied to these patients. A new approach for prevention of colorectal cancer by developing monoclonal antibodies to glycine-extended gastrin-17 and carboxy-amidated gastrin-17 has been recently described and may have an important role in this regard [12].

References