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Commentary

Hypergastrinemia is the Pathogenetic Factor in Helicobacter Pylori Carcinogenesis. Clinical Consequences, Particularly for Treatment with Inhibitors of Gastric Acid Secretion

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Since the nineteen fifties gastritis has been associated to gastric cancer [1, 2]. Shortly after Marshall and Warren showed Helicobacter pylori (Hp) as the main cause of gastritis [3], Hp was established as the major cause of gastritis as well [4]. The mechanism for the carcinogenic effect by Hp gastritis has despite extensive research not been found. However, it has been shown without ambiguity that Hp predisposes to gastric cancer only after having induced atrophy of the oxyntic mucosa [5, 6], resulting in gastric hypoacidity and hypergastrinemia. Since hypergastrinemia in every condition and in every examined species increases the risk of gastric malignancy [7], we proposed that the mechanism for gastric cancer secondary to Hp gastritis also was hypergastrinemia [8]. It may be argued that Hp gastritis often only induce a moderate hypergastrinemia [9]. However, the present upper normal level for gastrin is much too high since at the time of establishing gastrin immunoassays, asymptomatic, but nevertheless Hp infected, individuals were included in the normal reference group [10]. Moreover, there is no threshold for the biological effects of gastrin (stimulation of the ECL cell histamine release ([11] and proliferation [12] and near maximal effects are reached at lower concentration than mostly believed [12, 13]. Thus, the long-term Hp induced hypergastrinemia may explain the carcinogenic effect of Hp gastritis [8].

Hp gastritis not only predisposes to gastric cancer, but also to gastric lymphoma [14]. Hp eradication most often cures the Hp induced gastric lymphoma [15], whereas the risk of gastric cancer often persists [15, 16]. However, if it is correct that hypergastrinemia mediates the carcinogenic effect of Hp gastritis, it would be expected that Hp eradication before development of oxyntic atrophy also would eliminate the gastric cancer risk. Thus, Hp should be eradicated whenever possible. Afterwards, the health of the oxyntic mucosa should be assessed either by endoscopy and biopsies and/or indirectly by pepsinogen I [17], chromogranin A [18] and gastrin [19]. Individuals without signs of oxyntic atrophy after Hp eradication may accordingly be reassured without further follow-up. Those with signs of oxyntic atrophy should preferably be followed-up at intervals depending of the extent of the oxyntic changes. In the future it may be that those with high gastrin values will be treated with the gastrin antagonist netazepide which at an early phase can reverse gastrin induced changes [20].

Finally, inhibitors of gastric acid secretion and especially the most efficient one, the proton pump inhibitors (PPIs), also increase the risk of gastric neoplasia by inducing hypergastrinemia [7, 10]. In patients with Hp gastritis PPI treatment was associated with an increased risk of oxyntic atrophy as well as linear/micronodular ECL hyperplasia [21]. It is therefore wise to examine every patient for Hp infection when starting long-term PPI treatment and to eradicate Hp when it is present. I have for a long-time warned about long-term PPI treatment in young and middle-aged patients, but based upon the latency of 20 to 30 years for development of neoplasia with a congenital defect proton pump [22], I have thought that PPI treatment would be safe in older people. However, the studies from East-Asia describing increased frequency of gastric cancer in PPI users compared with non-users during a period of few years after Hp eradication [23, 24], show that there is an additive effect of Hp gastritis and PPI treatment in agreement of a common pathogenesis. Therefore, PPI treatment is not safe regarding development of neoplasia even in older people having or having had Hp infection.

To conclude, Hp should be eradicated in all individuals with a reasonable life expectancy. Eradication should be controlled by endoscopy and biopsies, and at the same time the oxyntic mucosa should be assessed by biopsies regarding oxyntic atrophy as well as indirectly by relevant blood tests as outlined. Those having oxyntic atrophy of any degree should not be given PPIs which they probably do not need either. Patients with acid related symptoms and a degree of oxyntic atrophy should in stead be treated with a less efficient inhibitor of acid secretion like histamine-2 blockers.

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