

## Consequences of Long-Term Proton Pump Blockade: Insights from Studies of Patients with Gastrinomas

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**Abstract:** Proton pump inhibitors are being increasingly used and for longer periods of time, especially in patients with gastroesophageal reflux disease. Each of these trends has led to numerous studies and reviews of the potential risk-benefit ratio of the long-term use of proton pump inhibitors. Both long-term effects of hypergastrinaemia due to the profound acid suppression caused by proton pump inhibitors as well as the effects of hypo-/achlorhydria *per se* have been raised and studied. Potential areas of concern that have been raised in the long-term use of proton pump inhibitors, which could alter this risk-benefit ratio include: gastric carcinoid formation; the development of rebound acid hypersecretion when proton pump inhibitor treatment is stopped; the development of tolerance; increased oxyntic gastritis in *H. pylori* patients and the possibility of increasing the risk of gastric cancer; the possible stimulation of growth of non-gastric tumours due to hypergastrinaemia; and the possible effect of the hypo-/achlorhydria on nutrient absorption, particularly iron and vitamin B12. Because few patients with idiopathic gastro-oesophageal reflux disease/peptic ulcer disease have been treated long-term (i.e., >10 years), there is little known to address the above areas of potential concern. Most patients with gastrinomas with Zollinger-Ellison syndrome have life-long hypergastrinaemia, require continuous proton pump inhibitors treatment and a number of studies report results of >5–10 years of treatment and follow-up. Therefore, an analysis of Zollinger-Ellison syndrome patients can provide important insights into some of the safety concerns raised above. In this paper, results from studies of Zollinger-Ellison syndrome patients and other recent studies dealing with the safety concerns above, are briefly reviewed.

Proton pump inhibitors are being used with increased frequency for both approved and non-approved indications in many countries (Naunton *et al.* 2000; Gillen & McColl 2001a). Furthermore, proton pump inhibitors are being increasingly used for prolonged periods of time, especially in patients with gastroesophageal reflux disease (Klinkenberg-Knol *et al.* 1994 & 2000; Naunton *et al.* 2000; Kuipers *et al.* 2004; McColl 2004). Whereas many studies have demonstrated the proton pump inhibitors are a well-tolerated class of drugs (Reilly 1999), there continues to be concern about the possible consequences of the marked acid suppression these agents cause (Creutzfeldt 1999; Reilly 1999; Laine *et al.* 2000; Naunton *et al.* 2000; Waldum & Brenna 2000; Yeomans & Dent 2000; Gillen & McColl 2001a). These acid suppressive concerns include the possible long-term effects of hypergastrinaemia that develop in 70–100% of patients with chronic proton pump inhibitor treatment (Jansen *et al.* 1990; Lamberts *et al.* 1993) as well as the effect of the acid suppression leading to a possible increased occurrence of bacterial/viral infections (Laine *et al.* 2000; Waldum *et al.*

2002), malabsorption of nutrients, which could be important in subgroups of patients, especially the elderly or its effect on *H. pylori* gastritis (Kuipers *et al.* 1996 & 2004; Lundell *et al.* 1999; Laine *et al.* 2000; Gillen & McColl 2001a; McColl 2004; Fossmark *et al.* 2005a). The effects of proton pump inhibitors on *H. pylori* gastritis have received particular attention because of epidemiological evidence showing an association between it and gastric cancer (Gillen & McColl 2001a; Uemura *et al.* 2001) as well as its possible effects on gastroesophageal reflux disease symptoms and/or therapeutic response to antisecretory agents (Gillen & McColl 2001a; Kuipers *et al.* 2004). The possible important effects of the hypergastrinaemia *per se* that have received the most attention are the possibility of chronic proton pump inhibitors use increasing the development of gastric carcinoids, causing acid rebound when the proton pump inhibitors is stopped or, less likely, promoting the growth of some other tumour (Creutzfeldt 1999; Laine *et al.* 2000; Kuipers *et al.* 2004; Qvigstad & Waldum 2004). The importance of many of these possible long-term consequences of proton pump inhibitors treatment remain controversial in large part because relatively few patients have been treated long-term (>10 years) that have been systematically studied, and there are no studies of life-long treatment.

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Patients with gastrinomas, which are neuroendocrine tumours that ectopically secrete gastrin resulting in marked gastric acid hypersecretion (Jensen & Gardner 1993; Roy *et al.* 2001), provide a natural model for studying the long-term effects of hypergastrinaemia in man (Jensen 1993, 2002 & 2004). Many of these patients require life-long treatment of the gastric acid hypersecretion with gastric antisecretory drugs such as proton pump inhibitors because <30% are cured by surgical resection of the gastrinoma (Jensen 1993, 1999 & 2004; Norton *et al.* 1999). At the National Institute of Health more than 200 of these patients been continuously treated with proton pump inhibitors for >5 years and >100 patients for >10 years up to a maximum of 22 years. Further, our group as well as others have provided detailed reports of the results of long-term proton pump inhibitors treatment as well as follow-up evaluations in these patients (Maton *et al.* 1989b; Pisegna *et al.* 1992; Metz *et al.* 1993a, b & c; Yu *et al.* 1999; Roy *et al.* 2000; Hirschowitz *et al.* 2001 & 2005) that provide some insights into a number of the areas raised by the questions above on long-term proton pump inhibitor safety. In this report, recent findings in Zollinger-Ellison syndrome patients as well as those from other studies as pertained to the above questions raised about the possible consequences of long-term proton pump inhibitor treatment, will be briefly reviewed.

#### Gastric carcinoids

Early studies in female rats but not mice treated long-term with the proton pump inhibitor, omeprazole, demonstrated long-term high dose treatment resulted in the development of hyperplasia of the gastric enterochromaffin-like cells (ECL cells) and gastric carcinoids, which were shown to be due to the hypergastrinaemia due to acid-suppressive effects of omeprazole (Havu 1986; Hakanson & Sundler 1986). Gastric carcinoid tumours were also reported in human hypergastrinaemic states without proton pump inhibitor treatment such as Zollinger-Ellison syndrome and pernicious anaemia/atrophic gastritis (Borch *et al.* 1985; Solcia *et al.* 1990; Frucht *et al.* 1991). Subsequently, studies (D'Adda *et al.* 1990; Bordi *et al.* 1995) demonstrated that of the seven types of neuroendocrine cells of the gastric mucosa, only the enterochromaffin-like (ECL) cells were stimulated by gastrin (D'Adda *et al.* 1990; Bordi *et al.* 1995). In both animal and human studies a small proportion (<30%) of the ECLomas can demonstrate malignant behaviour (Wangberg *et al.* 1995; Rindi *et al.* 1999). It has been proposed that the gastric carcinoids develop through a progression of gastrin-stimulated events from increasing hyperplasia of ECL cells to dysplasia and carcinoid formation (Creutzfeldt 1988; Bordi *et al.* 1995; Solcia *et al.* 1988 & 2000).

In patients with idiopathic peptic ulcer disease/gastroesophageal reflux disease treated long-term with proton pump inhibitors, the development of linear and micronodular ECL hyperplasia has been reported in some studies (Solcia *et al.* 1992; Lamberts *et al.* 1993; Klinkenberg-Knol

*et al.* 1994), but not other studies (Creutzfeldt *et al.* 1989; Solcia *et al.* 1989; Singh *et al.* 2000). A major difference between these studies showing different results was that the follow-up was generally shorter in the studies not showing advanced ECL cell changes. Studies of patients with sporadic Zollinger-Ellison syndrome [i.e., not associated with Multiple Endocrine Neoplasia-type 1] demonstrate that gastric carcinoid tumours only rarely occur in these patients (<1%), despite long-term and marked hypergastrinaemia, whereas in patients with Zollinger-Ellison syndrome with Multiple Endocrine Neoplasia-type 1 they occur in 13–43% (Cadiot *et al.* 1993; Jensen 1993 & 2004; Lehy *et al.* 1989; Peghini *et al.* 2002). These results, combined with the fact that in three early studies (Maton *et al.* 1990; Helander *et al.* 1992; Lehy *et al.* 1992) of patients with sporadic Zollinger-Ellison syndrome, 0% of patients were found to have advanced ECL changes (micronodular hyperplasia or dysplasia), led to the proposal that chronic hypergastrinaemia alone is only ECL cell growth-promoting and does not lead to advanced ECL cell changes or carcinoid development without the participation of other factors such as gastritis, gastric atrophy, or the presence of a disorder such as Multiple Endocrine Neoplasia-type 1 (Bordi *et al.* 1995; Peghini *et al.* 2002). Furthermore, in most animal and human studies of patients with hypergastrinaemic states (Zollinger-Ellison syndrome, atrophic gastritis) (Borch *et al.* 1986; Hakanson & Sundler 1986; Lamberts *et al.* 1988; Sjoblom *et al.* 1989; Delle Fave *et al.* 1998; Peghini *et al.* 2002), there was a strong correlation between the severity of the ECL cell change and the magnitude of the hypergastrinaemia. Because in humans, ECL cell changes were not observed when fasting gastrin was <5 times elevated, it was proposed that a threshold value for serum gastrin, approximately 5 times the normal, existed in man to produce an effect on ECL cells (Coupe *et al.* 1990; Bordi *et al.* 1995; Modlin & Tang 1996). This concept had important implications for extrapolation to possible long-term effects of proton pump inhibitor treatment in patients with idiopathic gastroesophageal reflux disease/peptic disease because the majority of such patients have <5 times increase in fasting gastrin with long-term proton pump inhibitor treatment (Jansen *et al.* 1990; Lamberts *et al.* 1993; Klinkenberg-Knol *et al.* 2000; Ligumsky *et al.* 2001). The findings reviewed above, combined with no clear increased occurrence of gastric carcinoids in patients with idiopathic gastroesophageal reflux disease/peptic disease treated up to 5–7 years with proton pump inhibitors, have led to the general conclusion that proton pump inhibitor treatment for these time periods has a low probability of causing the development of carcinoid tumours (Reilly 1999; Robinson 1999; Laine *et al.* 2000; Peghini *et al.* 2002). Recent studies in patients with sporadic Zollinger-Ellison syndrome (Peghini *et al.* 2002) raise a few cautionary notes about necessarily assuming very long-term or life-long treatment will be equally risk-free. In a recent detailed study of 106 patients with sporadic Zollinger-Ellison syndrome (Peghini *et al.* 2002), 99% were found to have ECL cell hyperplasia with 17% showing lin-

ear hyperplasia, 11% micronodular hyperplasia, and 7% dysplasia. This result demonstrates that chronic hypergastrinaemia alone can cause advanced ECL cell changes because only a minority of the patients in this study possessed gastritis and/or atrophy (Peghini *et al.* 2002). Furthermore, no threshold effect was seen for fasting gastrin levels as there was a significant correlation for increasing severity of ECL cells with gastrin levels  $\leq 5$  times elevated. This result supported the conclusion that prolonged low level hypergastrinaemia can cause increasingly severe ECL cell changes. The result in this study on sporadic Zollinger-Ellison syndrome (Peghini *et al.* 2002) agrees with the conclusion of two other recent human studies of ECL cell changes in patients with gastric hypersecretory states (Sanduleanu *et al.* 1999; Hirschowitz & Haber 2001) which also suggested that a threshold effect for gastrin's effect on ECL cells does not exist in humans. Although most patients with idiopathic gastroesophageal reflux disease/peptic disease treated with proton pump inhibitors develop modest increases ( $< 2.5$  times) in fasting gastrin levels, a proportion of patients (10–30%) develop gastrin increases  $> 5$  times elevated (Jansen *et al.* 1990; Lamberts *et al.* 1993; Klinkenberg-Knol *et al.* 2000; Ligumsky *et al.* 2001), increasing the probability of developing more advanced ECL cell changes because numerous studies have shown a close correlation between the degree of hypergastrinaemia and severity of ECL cell changes (Borch *et al.* 1986; Håkanson & Sundler 1986; Lamberts *et al.* 1988; Sjöblom *et al.* 1989; Delle Fave *et al.* 1998; Peghini *et al.* 2002). It was originally proposed that high serum gastrin levels only occurred in patients with idiopathic peptic disease/gastroesophageal reflux disease treated with proton pump inhibitors who had abnormal gastric emptying (Freston 1994). However, a detailed study (Schenk *et al.* 1998) of 12 patients with idiopathic gastroesophageal reflux disease who developed fasting gastrin levels  $> 4$  times normal while being treated with omeprazole demonstrated the development of severe hypergastrinaemia correlated with the duration of omeprazole treatment and the presence of *H. pylori* infection, but not with the presence of gastric emptying abnormalities or abnormalities of vagal nerve integrity. Numerous studies in various species (rats, mouse, mastomys) using different methods of inducing hypergastrinaemia with or without hypochlorhydria (i.e. antisecretory drugs, peroxisome proliferators, surgical procedures) demonstrate that hypergastrinemia *per se* can stimulate advanced ECL cell proliferative changes and cause the development of gastric carcinoids (Poynter *et al.* 1985 & 1986; Havu 1986; Håkanson & Sundler 1986; Sundler *et al.* 1986; Creutzfeldt 1988; Eason *et al.* 1988; Spencer *et al.* 1989; Mattsson *et al.* 1991; Wangberg *et al.* 1995; Waldum *et al.* 1998b). As discussed earlier the ability of chronic hypergastrinaemia alone to lead to similar changes in man has been questioned. However, our result in sporadic Zollinger-Ellison syndrome combined with a few case reports of gastric carcinoids in patients with sporadic Zollinger-Ellison syndrome (Solcia *et al.* 1988; Jensen 1993; Feurle 1994; Bordi *et al.* 1995; Cadiot *et al.* 1995) show that sus-

tained hypergastrinaemia *per se* in man can result in the development of advanced ECL cell changes, and suggest that with increasing time of prolonged hypergastrinaemia in man, there is likely an increasing possibility of developing a gastric carcinoid. These conclusions suggest that continual, systematic long-term surveillance of patients taking chronic proton pump inhibitors should be carried out to clearly define any increased risk.

One important finding in this recent study (Peghini *et al.* 2002) of sporadic Zollinger-Ellison syndrome patients was that there was no difference in the severity of ECL cell changes between males and females who had similar gastrin levels. At present it is unclear why this result shows such a marked difference from studies in rats, in which females had much more profound ECL cell changes, as well as an increased rate of developing carcinoids with hypergastrinemia caused by omeprazole (Havu 1986; Håkanson & Sundler 1986). Gastrin levels were not measured in the rat studies and one possibility is that female rats had more profound hypergastrinaemia with proton pump inhibitor treatment than males, resulting in increased ECL cell changes. In some (Borch *et al.* 1986 & 1988; Green *et al.* 1989; Diebold *et al.* 1998), but not other (Lamberts *et al.* 1993) studies in man, female sex is associated with more advanced ECL cell changes; however, whether this difference is due to a difference in fasting gastrin levels has not been defined. This question has possible clinical significance because it raises the possibility that females will be more likely to develop advanced ECL cell changes with prolonged hypergastrinaemia such as occurs with long-term proton pump inhibitor treatment, as occurs in the case of rats. The recent Zollinger-Ellison syndrome study (Peghini *et al.* 2002) demonstrates that if males and females have equal degrees of hypergastrinemia, there is equal risk in both sexes of developing advanced ECL cell changes.

Studies of patients with Zollinger-Ellison syndrome provide two other additional insights that have pertinence to monitoring for possible carcinoid development in patients with idiopathic gastroesophageal reflux disease /peptic disease treated long-term with proton pump inhibitors. First, in these latter patients there have been no systematic studies of the best method to detect carcinoids and/or assess the extent of ECL cell changes. It is unknown specifically whether the true incidence of gastric carcinoids is being underestimated because mucosal abnormalities may not always be present to direct the biopsy. Furthermore, it is unknown whether ECL cell changes are uniform and similar in different gastric locations and thus a single biopsy adequately assesses the extent of ECL cell change. Numerous studies (Rindi *et al.* 1996 & 1999; Norton *et al.* 2004b) have shown in chronic gastric hypergastrinaemic states that the gastric carcinoids that are clinically significant (i.e., causing symptoms, metastases), are generally large and usually easily seen at endoscopy. However, in terms of accurately assessing the possible long-term side effects of proton pump inhibitors, it is important to know the actual extent of ECL cell change with time, and the frequency of any gastric car-

cinoid. A recent study in patients with Zollinger-Ellison syndrome (Bordi *et al.* 2000) provides information on these points. In this prospective study of 149 patients with Zollinger-Ellison syndrome, gastric biopsies were taken systematically from four different areas of the greater and lesser curvature as well as from any mucosal abnormalities and analyzed for extent of ECL cell change and presence of gastric carcinoids. The results demonstrated that for assessment of ECL cell changes there was a close correlation between each of the four biopsies from the lesser curvature, or between each of the four from the greater curvature. However, the greater curvature generally showed more advanced ECL cell changes than the lesser curvature (Bordi *et al.* 2000). For detection of gastric carcinoids and dysplastic lesions, the frequency of their detection was directly related to the number of biopsies taken with one biopsy detecting only 8% of the total of each detected, whereas six biopsies detected 50–60% of the total. This occurred in large part because small carcinoids found histologically were not frequently associated with mucosal abnormalities identified at endoscopy. These results (Bordi *et al.* 2000) demonstrate extensive sampling of the lesser and greater curvature is needed for early diagnosis of dysplastic and/or gastric carcinoids. In contrast, limited sampling of the greater curvature is adequate to assess the extent of ECL cell change (Bordi *et al.* 2000). These results support the conclusion that in the usual endoscopic surveillance carried out in patients with idiopathic gastroesophageal reflux disease/peptic ulcer disease treated with proton pump inhibitors, which involve biopsies of only endoscopic abnormalities, the incidence of carcinoids or advanced ECL cell changes such as dysplasia, are likely to be underestimated. Second, studies of patients with both Zollinger-Ellison syndrome and atrophic gastritis demonstrate that the probability of a gastric carcinoid developing metastases and in many cases of causing clinical symptoms is influenced by the size of the gastric carcinoid tumor (Rindi *et al.* 1996 & 1999; Norton *et al.* 2004b). In general, gastric carcinoid tumours in human hypergastrinaemic states are small [97% of type-1 (atrophic gastritis; <1.5 cm), 73% of type-2 (MEN1/ZES; <1.5 cm)] (Rindi *et al.* 1996), and are rarely associated with metastases. These results suggest that in the future, even if microscopic carcinoids are found in patients taking proton pump inhibitors, they are unlikely to be associated with advanced disease. Furthermore, they are rarely reported to become clinically important by causing a carcinoid syndrome (Gough *et al.* 1994; Rindi *et al.* 1996; Modlin *et al.* 2003; Norton *et al.* 2004b). Before these results are interpreted to suggest that if gastric carcinoids do develop with proton pump inhibitor treatment, they are likely to be clinically unimportant, some additional points should be considered. First, the true natural history of gastric carcinoids in patients with hypergastrinaemic states is poorly defined. This has occurred because until recently it has been difficult to assess the extent of the tumour in patients with gastric carcinoids, especially since surgery is increasingly not performed. With the availability of octreoscanning and other imaging modalities, it is likely

this can be more accurately assessed in the future. Second, a recent study (Norton *et al.* 2004b) on patients with MEN1/ZES reports the gastric carcinoids can be symptomatic, aggressive, and metastasize to the liver in a subset of these patients. These results demonstrate that under special circumstances gastric carcinoids in hypergastrinaemic states can be aggressive.

### Rebound hypersecretion

Increased gastric acid secretory rates after stopping antisecretory drug treatment is well described after the long-term use of histamine H<sub>2</sub>-receptor antagonists (El-Omar *et al.* 1996; Sandvik *et al.* 1997; Qvigstad & Waldum 2004). The occurrence of rebound hypersecretion may be clinically important because it has been reported in a study of healthy volunteers, 59% develop dyspeptic symptoms co-incident with the rebound acid hypersecretion after discontinuing ranitidine after two months of treatment (Smith *et al.* 1999). Initially a short-term study in man (Prewett *et al.* 1991) did not demonstrate rebound hypersecretion after proton pump inhibitor withdrawal; however, more recent studies report it does occur after proton pump inhibitor treatment and may not be infrequent, occurring in 62–90% of patients (Waldum *et al.* 1996; Gillen *et al.* 1999a; Fossmark *et al.* 2005a). The degree of rebound hypersecretion manifested as the extent of increase in maximal acid output in *H. pylori* negative patients after proton pump inhibitor treatment is related to the extent of increase in serum gastrin and degree of suppression in gastric acidity while on proton pump inhibitor treatment. From these observations and others in humans as well as extensive studies in animals with proton pump inhibitors (for review see Sandvik *et al.* (1997); Gillen & McColl (2001a & b); Qvigstad & Waldum (2004)) it has been proposed the mechanism of proton pump inhibitor-induced rebound hypersecretion is due to the effect of the hypergastrinaemia induced by the profound gastric acid suppression on the gastric mucosa (Gillen & McColl 2001a; Qvigstad & Waldum 2004). It is proposed that the gastric mucosa changes that mediate the rebound hypersecretion include hypergastrinaemia-induced increases in parietal cell mass, ECL cell mass and ECL cell activity (Qvigstad & Waldum 2004; Fossmark *et al.* 2005a). Numerous studies have provided evidence that in man chronic proton pump inhibitor treatment not only increases ECL cell density but also increases parietal cell mass (Gillen & McColl 2001a & b; Qvigstad & Waldum 2004; Fossmark *et al.* 2005a). The proposal (Fossmark *et al.* 2005a) that increased ECL cell activity is also involved in mediating proton pump inhibitor-induced rebound acid hypersecretion is supported by the finding that in patients given omeprazole for three months, an increased mucosal histamine concentration occurred (Qvigstad *et al.* 1998). Furthermore, there was a reduced inhibitory effect of the histamine H<sub>2</sub>-receptor antagonist, ranitidine, after proton pump inhibitor treatment, which was proposed to be due to the increased histamine release by the ECL cells (Qvigstad

*et al.* 1998). It was proposed (Qvigstad *et al.* 1998) that a similar mechanism is involved in causing tolerance to histamine H<sub>2</sub>-receptor antagonists in patients with Zollinger-Ellison syndrome.

The duration of rebound hypersecretion after chronic proton pump inhibitor treatment in relation to the duration of treatment with proton pump inhibitors has not been examined systematically. In rats, after stopping a three-month course of proton pump inhibitor treatment, rebound hypersecretion was present for 10 weeks (Larsson *et al.* 1988). In one study in man, rebound acid secretion after stopping proton pump inhibitors after at least one year of proton pump inhibitor treatment, lasted longer than eight weeks but less than 26 weeks (Fossmark *et al.* 2005a). In a second study (Gillen *et al.* 2000) after stopping proton pump inhibitors after at least a two-month course of proton pump inhibitor treatment, rebound hypersecretion lasted at least two months, whereas in a third report (Gillen *et al.* 2001) acid rebound hypersecretion lasted 11 months. The duration of rebound acid hypersecretion after chronic proton pump inhibitor treatment is much longer than that reported after chronic treatment with histamine H<sub>2</sub>-receptor antagonists (Gillen & McColl 2001a), suggesting that the magnitude of acid suppression and likely the extent of the resultant hypergastrinaemia are important in the pathogenesis of this disorder. The importance of acid rebound after proton pump inhibitor treatment in the clinical management of patients with idiopathic gastroesophageal reflux disease/peptic disease is not clear (Gillen & McColl 2001a & b; Qvigstad & Waldum 2004). However, in studies of healthy volunteers treated with a histamine H<sub>2</sub>-receptor antagonist for two months, rebound hypersecretion resulted in dyspeptic symptoms in 59% (Smith *et al.* 1999). Furthermore, it is unknown if chronic proton pump inhibitor treatment is extended to years if either the magnitude or duration of rebound hypersecretion are increased further which could result in an increased likelihood of the rebound hypersecretion becoming clinically important. This question is particularly important in the case of patients with mild-to-moderate symptoms of gastroesophageal reflux disease who increasingly use proton pump inhibitors for relief. It is unknown if the increased chronic use of proton pump inhibitors with these patients will increase the occurrence or severity of dyspeptic symptoms when an attempt to stop the proton pump inhibitor is made, and therefore prolong their use.

Studies in patients with Zollinger-Ellison syndrome provide a number of insights that are likely relevant to rebound hypersecretion. A proportion of patients (up to 40%) with Zollinger-Ellison syndrome may be cured by resection of the gastrinoma (Pisegna *et al.* 1992; Metz *et al.* 1993a; Norton *et al.* 1999 & 2004a; Norton & Jensen 2004); therefore, these patients represent a naturally-occurring model for studying the result of suddenly correcting the chronic hypergastrinaemia, as occurs in patients with idiopathic gastroesophageal reflux disease/peptic disease when proton pump inhibitors are stopped and rebound hypersecretion

develops. Patients with Zollinger-Ellison syndrome have clinical evidence of the disease for a mean of eight years (range up to 22 years) (Norton *et al.* 1999) prior to surgery and the median gastrin elevation is approximately six times elevated (Jensen 1993; Norton *et al.* 1999). Therefore, a significant proportion of Zollinger-Ellison syndrome patients (approximately 40%) have chronic gastrin levels of <5 times normal and overlap with the gastrin levels commonly seen in patients without the syndrome taking proton pump inhibitors (Jansen *et al.* 1990; Jensen 1993; Lamberts *et al.* 1993; Ligumsky *et al.* 2001). Detailed studies of Zollinger-Ellison syndrome patients after curative resection of the gastrinoma (Pisegna *et al.* 1992; Metz *et al.* 1993a) at yearly intervals for up to four years have shown some unexpected results. Despite these patients remaining cured of their gastrinoma (normal fasting gastrin level, negative secretin test, negative imaging studies), 55% at three to six months post-curative resection and 67% of those followed for up to four years continued to remain mild gastric acid hypersecretors (Pisegna *et al.* 1992; Metz *et al.* 1993a). At three years after curative resection the mean basal acid output for men was 15 mEq/hr (normal <10.5) and for females was 10.5 mEq/hr (normal <5.6) which represented a 69% and 85% decrease from the preoperative levels, but still elevated above normal (Pisegna *et al.* 1992). Similarly, the mean maximal acid output decrease by 29–48% at three years after curative resection; however, the maximal acid output remained mildly elevated in 45% of the patients for up to two years (Pisegna *et al.* 1992). These results show that after prolonged chronic hypergastrinaemia in these Zollinger-Ellison syndrome patients (mean – eight years), the effects of the chronic hypergastrinaemia are not completely reversible and continual acid hypersecretion persists for up to four years. At present the mechanisms involved in the process remain unclear. This persistent hypersecretion is not due to recurrence of the tumour because all of these patients have remained cured, some for almost 20 years after resection. These data raise the possibility that prolonged hypergastrinaemia, whether drug induced or by other mechanisms, may lead to rebound acid secretory changes that are only slowly reversible or not reversible at all (Pisegna *et al.* 1992) and which could be clinically significant. This latter point is supported by the finding that more than one-half of these Zollinger-Ellison syndrome patients (Pisegna *et al.* 1992) continued to require low doses of antisecretory drugs due to this persistent mild acid hypersecretion, even though cured of the gastrinoma.

### Tolerance

Tolerance to histamine H<sub>2</sub>-receptor antagonists, defined as a decreased response to drug treatment after previous drug treatment, has been well described in healthy volunteers and patients with idiopathic gastroesophageal reflux disease/peptic disease after both oral and intravenous formulations (Smith *et al.* 1990; WilderSmith & Merki 1992; Gillen & McColl 2001a; Qvigstad & Waldum 2004; Ley *et al.* 2005).

It has been proposed that the mechanism of development of tolerance is similar to that for rebound hypersecretion and related to histamine and the ECL cell (Qvigstad & Waldum 2004); however, at present this is unproven. Tolerance to proton pump inhibitors has not been reported, perhaps due to their mechanism of action resulting in irreversibly inactivating the  $H^+-K^+$  ATPase, which causes a blockade of the final step in the secretory process and thus inhibits secretion from all physiological stimuli (Yeomans & Dent 2000; Qvigstad & Waldum 2004).

Studies in patients with Zollinger-Ellison syndrome treated long-term with histamine  $H_2$ -receptor antagonists or proton pump inhibitors confirm the above findings that tolerance can frequently develop with  $H_2$ -receptor antagonists, but is not seen with proton pump inhibitors, even after >five years of constant treatment. Prior to the availability of proton pump inhibitors the acid hypersecretion in these patients was controlled by continuous use of histamine  $H_2$ -receptor antagonists (Collen *et al.* 1984; Jensen *et al.* 1984; Howard *et al.* 1985; Metz & Jensen 1995; Jensen 1999). High doses of histamine  $H_2$ -receptor antagonists (up to 10 times the dose usually used in patients with idiopathic gastroesophageal reflux disease/peptic disease) and frequent dosing (4–6 hr) was commonly required to control the marked hypersecretion in these patients (Collen *et al.* 1984; Jensen *et al.* 1984; Howard *et al.* 1985; Metz & Jensen 1995; Jensen 1999). All patients required continuous daily treatment and many were treated for up to 10 years (Collen *et al.* 1984; Jensen *et al.* 1984; Howard *et al.* 1985; Metz & Jensen 1995; Jensen 1999). Patients with Zollinger-Ellison syndrome with MEN1, moderate to severe gastroesophageal reflux disease or prior Billroth 2 gastric resections require even higher and more frequent doses of histamine  $H_2$ -receptor antagonists as well as proton pump inhibitors (Maton *et al.* 1989a; Miller *et al.* 1990; Metz *et al.* 1992 & 1993c; Metz & Jensen 1995; Jensen 1999). Studies in patients with Zollinger-Ellison syndrome support the conclusion that a slow development of tolerance to histamine  $H_2$ -receptor antagonists did occur with an average dose escalation of 1–2 times per year occurring (Collen *et al.* 1984; Jensen *et al.* 1984; Howard *et al.* 1985; Metz & Jensen 1995; Jensen 1999). This tolerance occurred independent of tumour progression, significant changes in basal acid secretory rate, or often without any change in serum gastrin, suggesting that none of these factors was likely involved in the pathogenesis of the tolerance to these drugs seen in the patients (Collen *et al.* 1984; Jensen *et al.* 1984; Howard *et al.* 1985; Metz & Jensen 1995; Jensen 1999). The exact underlying mechanism for the tolerance to histamine  $H_2$ -receptor antagonists remains unclear. In contrast, in patients with Zollinger-Ellison syndrome treated long-term with proton pump inhibitors, tolerance for the proton pump inhibitors has not developed. In fact, many patients with Zollinger-Ellison syndrome had their initial proton pump inhibitor doses decreased over time and in many patients, conventional doses of proton pump inhibitors using in treating idiopathic peptic ulcer disease/gastroesophageal

reflux disease have remained effective at controlling the acid hypersecretion (Maton *et al.* 1989b; Metz *et al.* 1992, 1993b & c; Jensen *et al.* 1993; Jensen 1999; Hirschowitz *et al.* 2005).

### Oxyntic gastritis and gastric cancers

In patients with *H. pylori* infections treatment with proton pump inhibitors has been shown to cause a shift in the intensity of the gastritis from the antrum to the oxyntic region (Kuipers *et al.* 1995; Eissele *et al.* 1997). It has been proposed that the enhanced acid-secretory potency of proton pump inhibitors in *H. pylori* patients may be due to this gastritis (Gillen *et al.* 1999b; Gillen & McColl 2001a). Furthermore, studies by some (Kuipers *et al.* 1996) but not others (Lundell *et al.* 1999) report that atrophic gastritis developed more frequently with chronic treatment with PPIs than in *H. pylori*-positive patients treated with fundoplication. In *H. pylori*-negative patients no difference was seen, with each group having a low rate of developing atrophic gastritis (Kuipers *et al.* 1996; Lundell *et al.* 1999). Both of these studies have been criticized for various methodological shortcomings (Gillen *et al.* 1999a; Gillen & McColl 2001a; McColl 2004). However, the findings of these studies have a number of important clinical implications. The development of atrophic gastritis and the development of corpus predominant gastritis are major prognostic factors for increasing the risk of *H. pylori* infection to be associated with gastric cancer (Uemura *et al.* 2001). Furthermore, most studies (Elsborg & Mosbech 1979; Brinton *et al.* 1989; Hsing *et al.* 1993; Kokkola *et al.* 1998; Ye & Nyren 2003), but not all (Eriksson *et al.* 1981; Schafer *et al.* 1985; Svendsen *et al.* 1986), have shown that pernicious anaemia which is associated with gastric atrophy and/or gastritis (Borch *et al.* 1986; Solcia *et al.* 1995; Delle Fave *et al.* 1998), is associated with an increased risk of gastric cancer. These findings have led some experts to recommend that *H. pylori* infection should be eradicated prior to long-term proton pump inhibitor treatment (Kuipers *et al.* 1996 & 2004; Malfertheiner *et al.* 2002b); for review see Gillen & McColl (2001a). A recent study by Kuipers *et al.* (2004) demonstrated that eradication of *H. pylori* in patients on long-term proton pump inhibitor treatment for gastroesophageal reflux disease resulted in an improvement in corpus gastritis and atrophic gastritis over a two-year period, compared to patients with *H. pylori* treated with proton pump inhibitors only without eradication. In this study (Kuipers *et al.* 2004) long-term, chronic proton pump inhibitor treatment had no adverse effect on the severity of the gastroesophageal reflux disease or on its control by the proton pump inhibitor, leading the authors to support the recommendation that all patients with gastroesophageal reflux disease who require chronic proton pump inhibitor treatment should be tested for *H. pylori* and, if it is present, eradicated. The question of whether *H. pylori* should be eradicated in patients with gastroesophageal reflux disease prior to long-term proton pump inhibitor treatment is an

important issue that remains unresolved with the result that the US Food and Drug Administration in 1996 concluded their was insufficient data to recommend prior eradication of *H. pylori*, whereas both the original and updated Maastricht guidelines recommended *H. pylori* eradication prior to proton pump inhibitor treatment for gastroesophageal reflux disease (Kuipers *et al.* 1996 & 2004; Anonymous 1997; Kuipers & Meuwissen 2000; Moayyedi *et al.* 2000; Meuwissen *et al.* 2001; Malfertheiner *et al.* 2002a; McColl 2004). Three studies (Klinkenberg-Knol *et al.* 2000; Kuipers *et al.* 1996; Moayyedi *et al.* 2000) have reported an increase in the development of gastric atrophy with chronic proton pump inhibitor treatment for gastroesophageal reflux disease in patients with *H. pylori*, other studies (Stolte *et al.* 1998; Singh *et al.* 2000; Geboes *et al.* 2001; Kuipers *et al.* 2004) report no increase in the development of gastric corpus atrophy with proton pump inhibitor treatment in *H. pylori*-positive patients. The different results in these studies has been attributed to differences in the length of patient follow-up, patient numbers, type of patients, treatment differences and differences in the study design (Kuipers *et al.* 1996 & 2004; Armstrong 2000; Kuipers & Meuwissen 2000).

Many studies demonstrate that chronic proton pump inhibitor treatment in patients with *H. pylori* results in increased chronic inflammatory cells and polymorphonuclear leukocyte infiltration in the gastric corpus mucosa (Solcia *et al.* 1992; Lamberts *et al.* 1993; Klinkenberg-Knol *et al.* 1994 & 2000; Kuipers *et al.* 1995 & 1996; Berstad *et al.* 1997; Eissele *et al.* 1997; Moayyedi *et al.* 2000). Because epidemiological studies demonstrate the presence of pangastritis or corpus predominant gastritis (Uemura *et al.* 2001) is strongly associated with the development of gastric cancer, these results, even without the development of atrophy, which is also an important risk factor (Uemura *et al.* 2001), are a cause for concern. An additional factor leading to the controversy over whether *H. pylori* should be eradicated prior to chronic proton pump inhibitor treatment is whether the *H. pylori* eradication might increase either the severity of the gastroesophageal reflux disease symptoms, or alter the effectiveness of treatment with proton pump inhibitors (Kuipers *et al.* 1996; Klinkenberg-Knol *et al.* 2000; Kuipers & Meuwissen 2000; McColl 2004). Epidemiological studies demonstrate *H. pylori*-positive individuals have a lower gastroesophageal reflux disease prevalence (Sonnenberg & El-Serag 1999). Numerous studies demonstrate that proton pump inhibitor treatment has a greater acid suppressive effect in the *H. pylori*-positive than *H. pylori*-negative patients (Verdu *et al.* 1995a & b). Furthermore, studies have reported better control of symptoms and/or enhanced healing of mucosal lesions in patients infected with *H. pylori* with gastroesophageal reflux disease treated with proton pump inhibitors than in *H. pylori*-negative patients (Hatlebakk *et al.* 1999; Holtmann *et al.* 1999; Wu *et al.* 2004). Studies of the effect of *H. pylori* eradication on gastroesophageal reflux disease symptoms/treatment provide conflicting results. Some studies (Labenz *et al.* 1997; Moayyedi *et al.* 2000; Kuipers *et al.* 2004) show no effects

or even an improvement after *H. pylori* eradication in gastroesophageal reflux disease symptoms/control, whereas others (Labenz *et al.* 1997; Schwizer *et al.* 2001) show a worsening of symptoms/control.

At present, whether *H. pylori* should be eradicated prior to chronic proton pump inhibitor treatment remains unresolved because of the differing results in the studies reviewed above and because of a lack of agreement of what the most important factors are in the pathogenesis of the development of *H. pylori*-associated gastric cancer. Epidemiological studies have shown gastric atrophy, the presence of pangastritis or corpus predominant gastritis, and the development of intestinal metaplasia with *H. pylori* infection are all associated with an increase of gastric cancer (Uemura *et al.* 2001). However, results from other studies have been interpreted to suggest that the hypergastrinaemia itself may be an important risk factor for the development of gastric cancer (Kuipers *et al.* 1996; Waldum *et al.* 1998a & 2002; Wang *et al.* 2000; Fossmark *et al.* 2005b; Takaishi *et al.* 2005). In pernicious anaemia there is an increased incidence of ECLomas (gastric carcinoids) (Carney *et al.* 1983; Borch *et al.* 1985; Bordi *et al.* 1995; Kokkola *et al.* 1998) as well as gastric cancer in some (Brinton *et al.* 1989; Hsing *et al.* 1993; Kokkola *et al.* 1998; Karlson *et al.* 2001), but not other studies (Eriksson *et al.* 1981; Schafer *et al.* 1985; Svendsen *et al.* 1986). At present the exact contribution of the atrophy or the hypergastrinaemia to the possible development of each type of malignancy is unclear. Mice with an INS-GAS transgene develop hypergastrinaemia initially as well as increased acid secretion with increased parietal cell density, however with time gastric atrophy develops and invasive gastric cancers (Wang *et al.* 2000; Takaishi *et al.* 2005). A concomitant *Helicobacter felis* infection in these mice accelerates the development of the gastric cancer (Wang *et al.* 2000). Furthermore, some recent studies have provided evidence for a possible involvement of ECL cells in the development of gastric cancers. ECL cell differentiation has been shown in a proportion of gastric carcinomas (Qvigstad *et al.* 2002; Waldum *et al.* 1998a & 2002) and one study (Qvigstad *et al.* 2000) reported that most gastric carcinomas in patients with pernicious anaemia are actually malignant ECLomas. A patient with pernicious anaemia has been described (Qvigstad *et al.* 1999) who originally developed a well-differentiated ECLoma which over a 5 year period became progressively more aggressive and dedifferentiated into a carcinoma. Female cotton rats develop spontaneous hypergastrinaemia, ECL hyperplasia with dysplasia and eventually develop carcinomas which have an adenocarcinoma phenotype (Fossmark *et al.* 2005b). The development of carcinomas in these rats was associated with a progressive loss of ECL cell secretory vesicles and granules and it was proposed that the ECL cell dedifferentiated with and the gastric carcinomas developed from these dedifferentiated ECL cells (Fossmark *et al.* 2005b). The increased occurrence of a number of these risk factors (atrophy, gastritis, hypergastrinemia) with chronic proton pump inhibitor treatment suggests that careful pros-

pective studies will be needed to clearly define any increased risk of gastric cancer from chronic proton pump inhibitor use and to elucidate the pathogenesis.

Studies in patients with Zollinger-Ellison syndrome provide no insight in this area for a number of reasons. Despite the fact life-long hypergastrinaemia is present in most patients with Zollinger-Ellison syndrome (i.e., 60–70%), these patients uncommonly (20–50%) have *H. pylori* infections (23–30%) (Fich *et al.* 1991; Saeed *et al.* 1991; Weber *et al.* 1997), have a relatively low incidence (28%) of gastritis, and uncommonly (9–10%) develop gastric atrophy (Hirschowitz & Haber 2001; Peghini *et al.* 2002). Therefore, in terms of gastritis, atrophy, and *H. pylori* infection frequency, most patients with Zollinger-Ellison syndrome differ from the typical patient with gastroesophageal reflux disease with *H. pylori* receiving chronic proton pump inhibitor treatment. Furthermore, the development of gastric adenocarcinomas is a very rare event in Zollinger-Ellison syndrome with only one case reported (de Leval *et al.* 2002) suggesting that if chronic hypergastrinaemia is an important factor in the development of gastric cancer than hypergastrinaemia alone, even when present in an extreme degree, may not be sufficient to produce this effect.

#### Possible effects on other tumours (non-gastric)

In addition to its growth effects on the gastric mucosa, gastrin and its processing intermediates are reported to have growth effects on normal tissues and to stimulate the growth of a number of different tumours (Baldwin 1995; Baldwin & Shulkes 1998b; Guo & Townsend, Jr. 2000; Jensen 2002; Koh 2002; Aly *et al.* 2004). Håkanson *et al.* (1986 & 1988) demonstrated that omeprazole stimulated only the growth of the gastric mucosa in rat, guinea pig, chicken, and hamster. Numerous studies in animals as well as studies of tumour cells have shown growth effects of gastrin on numerous cancers (Baldwin 1995; Clere *et al.* 1997; Guo & Townsend, Jr. 2000; Jensen 2002) including those of the pancreas (Guo & Townsend, Jr. 2000; Harris *et al.* 2004b; Morisset *et al.* 2004; Smith *et al.* 2004), liver (Caplin *et al.* 2001), oesophagus (Abdalla *et al.* 2004; Moore *et al.* 2004), and colon (Baldwin & Shulkes 1998a & b; Smith & Watson 2000; Takhar *et al.* 2004). At present no studies in man have clearly established that hypergastrinemia caused by any means (proton pump inhibitors, gastrinomas, achlorhydria) is associated with an increased risk of cancer at any of these sites (Jensen 2002). Nevertheless, the possible involvement of gastrin and/or gastrin-related peptides in the growth and/or development of especially colon cancer has received considerable attention over the last 10 years (Baldwin & Shulkes 1998a & b; Smith & Watson 2000; Jensen 2002). Over the last five years considerable attention has been paid to the possible role of gastrin in either the development or growth of oesophageal cancer as well as its effect on Barrett's oesophagus, which is associated with an increased occurrence of oesophageal cancer (Van Nieuwenhove *et al.* 1998; Haigh *et al.* 2003; Abdalla *et al.* 2004; Harris

*et al.* 2004a; Moore *et al.* 2004). Numerous animal and *in vitro* studies demonstrate that gastrin can stimulate growth of colonic cancers (Chu *et al.* 1995; Baldwin & Shulkes 1998b; Smith & Watson 2000; Jensen 2002; Thomas *et al.* 2003; Takhar *et al.* 2004). Studies demonstrate gastrin-related peptides can be synthesized by colonic cancer although it remains controversial about the type of gastrin-related peptide present (Rehfeld & van Solinge 1994; Baldwin 1995; Dickinson 1995; Rehfeld 1995; Shulkes & Baldwin 1997; Smith & Watson 2000; Jensen 2002). The importance of gastrin precursor forms is receiving particular attention because of recent studies showing their growth-promoting effects on colonic mucosa and colonic cancers (Baldwin & Shulkes 1998a; Jensen 2002; Koh 2002; Baba *et al.* 2005). Controversy also exists about whether colorectal cancer cells possess CCKB receptors (gastrin receptors), some other non-CCKA/CCKB receptor or no CCKA or CCKB receptor, and about the importance of a splice variant of the CCKB receptor with constitutive activity (Baldwin 1995; Baldwin & Shulkes 1998b; Jensen 2002). However, clinical or epidemiological studies in man with hypergastrinaemic states including Zollinger-Ellison syndrome (Sobhani *et al.* 1993; Orbuch *et al.* 1996) and atrophic gastritis (Brinton *et al.* 1989; Creutzfeldt & Lamberts 1991; Maton 1995) have generally provided no evidence for an increased incidence of colon cancer/polyps in these patients (Jensen 2002). Even though these clinical studies and epidemiological studies demonstrate no increase in the rate of colonic tumours in patients with hypergastrinaemic states (Zollinger-Ellison syndrome, atrophic gastritis), some findings in these patients are a potential cause for concern. In patients with Zollinger-Ellison syndrome an increased proliferative rate in the mucosal cells of the right and left colon without hyperplasia was found in one study (Sobhani *et al.* 1993), and in another study (Renga *et al.* 1997) increased rectal cell proliferative rates were reported in patients with hypergastrinaemic states (Zollinger-Ellison syndrome and atrophic gastritis). At present the long-term significance of these findings remain unclear. Although most studies do not support a role for autocrine involvement of amidated gastrin in colorectal cancers (Baldwin & Shulkes 1998b), the possibility of an autocrine loop involving non-amidated gastrins is still an open question (Baldwin & Shulkes 1998a & b; Jensen 2002). Detailed studies of patients with Zollinger-Ellison syndrome may help address the importance of gastrin precursors or non-amidated forms of gastrin in stimulating colorectal tumours because gastrinomas secrete large amounts of these forms in addition to fully processed amidated gastrins (Jensen & Gardner 1993; Rehfeld & van Solinge 1994).

Gastrin can stimulate growth of pancreatic, liver, and oesophageal tumours (Baldwin 1995; Jensen 2002; Thomas *et al.* 2003; Aly *et al.* 2004). At present there is no evidence that chronic treatment with proton pump inhibitors increases the occurrence of any of these tumours. Whereas no studies in patients with Zollinger-Ellison syndrome show an increased incidence of any of these tumours, four epidemio-

logical studies (Borch *et al.* 1988; Hsing *et al.* 1993; Karlson *et al.* 2001; Thomas *et al.* 2003) in patients with pernicious anaemia showed an increased occurrence of pancreatic cancer, three studies (Hsing *et al.* 1993; Karlson *et al.* 2001; Ye & Nyren 2003) showed an increased incidence of oesophageal cancer and other studies showed an increased incidence of buccal cavity and/or pharyngeal cancers (Brinton *et al.* 1989), melanoma (Brinton *et al.* 1989), multiple myeloma (Brinton *et al.* 1989; Hsing *et al.* 1993), and leukemia (Brinton *et al.* 1989; Hsing *et al.* 1993). In contrast, three other epidemiological studies in pernicious anaemia patients did not find an increased incidence of pancreatic cancer (Brinton *et al.* 1989; Ye & Nyren 2003) and other studies did not show an increased occurrence of oesophageal (Brinton *et al.* 1989), buccal (Hsing *et al.* 1993; Karlson *et al.* 2001), or the other cancers reported above (Karlson *et al.* 2001). The possible importance of gastrin as a stimulant for the development and/or growth of oesophageal cancer is currently being very actively investigated. Some investigators (Haigh *et al.* 2003; Younes 2003) have raised the possibility that proton pump inhibitor treatment resulting in hypergastrinemia could be important for the increased occurrence in oesophageal cancer over the last two decades. Barrett's oesophagus is a premalignant condition of the oesophagus associated with an increased risk of developing adenocarcinoma that is defined as the metaplastic conversion of normal oesophageal squamous epithelium to a columnar intestinal epithelium with the presence of goblet cells (Flejou 2005). Studies have demonstrated increased gastrin in Barrett's mucosa (Buchan *et al.* 1985; Konturek *et al.* 2004) as well as the presence of gastrin receptor (CCK<sub>2</sub> receptor) mRNA in up to 100% of Barrett's mucosa (Haigh *et al.* 2003; Abdalla *et al.* 2004; Konturek *et al.* 2004). Also, gastrin stimulated thymidine uptake in Barrett's mucosal biopsies (Haigh *et al.* 2003). Furthermore, gastrin stimulates cyclooxygenase-2 activation in Barrett's, which has been shown in other cells to inhibit apoptosis, stimulate cell proliferation, promote angiogenesis, and stimulate invasion by cancer cells (Morris *et al.* 2001; Haigh *et al.* 2003; Abdalla *et al.* 2004; Harris *et al.* 2004a). Gastrin has also been shown to stimulate oesophageal epithelium proliferation in rats (Van Nieuwenhove *et al.* 1998). Oesophageal cancers possess CCK<sub>2</sub> receptors and gastrin can stimulate their growth by activation of this receptor (Baldwin & Shulkes 1998b; Moore *et al.* 2004). At present the clinical significance of these findings is unclear. One study in patients with Zollinger-Ellison syndrome (Strader *et al.* 1995) demonstrated a frequency of Barrett's mucosa of 3%, which was similar to that found in the general population. An increased occurrence of oesophageal adenocarcinoma has not been reported in Zollinger-Ellison syndrome patients (Roy *et al.* 2000; Strader *et al.* 1995) and there is only one case report of this association in the literature (Symonds & Ramsey 1980). Whereas the above findings of gastrin's effect on Barrett's and the possible growth effect on oesophageal cancer coupled with the epidemiological evidence showing an increased occurrence of oesophageal cancer in

some studies of patients with pernicious anaemia (Hsing *et al.* 1993; Karlson *et al.* 2001; Ye & Nyren 2003) suggest hypergastrinaemia, whether proton pump inhibitor-induced or due to other causes, could increase the risk of oesophageal cancer, other recent studies suggest this may not be the case.

Two recent studies (Hillman *et al.* 2004; El-Serag *et al.* 2005) demonstrate that chronic proton pump inhibitor treatment reduced the risk of developing dysplasia in patients with Barrett's oesophagus with idiopathic gastro-oesophageal reflux disease/peptic disease. In one study (El-Serag *et al.* 2005) involving 236 patients with Barrett's oesophagus followed over a 19-year period by a single endoscopist, the cumulative incidence of dysplasia was significantly reduced by chronic proton pump inhibitor use compared to no treatment or histamine H<sub>2</sub>-receptor antagonists ( $P < 0.001$ ). Furthermore, a longer use of proton pump inhibitors was associated with a greater reduction of the rate of developing dysplasia. In the second study (Hillman *et al.* 2004) involving 350 patients with Barretts, those who delayed using proton pump inhibitors for  $\geq$ two years had a 5- to 6 times increased risk of developing low-grade dysplasia.

#### Absorption of nutrients

Hypochlorhydria can affect the absorption of a number of important nutrients, particularly iron, calcium, and vitamin B12 (Skikne *et al.* 1981; Festen 1991; Koop 1992; Koop & Bachem 1992; Stewart *et al.* 1998; Termanini *et al.* 1998; Reilly 1999; Laine *et al.* 2000; Sharma *et al.* 2004). At present the clinical significance of this in regard to long-term, continuous PPI treatment is largely unknown, especially in at-risk groups such as the elderly and has been systematically examined in only a few studies.

Vitamin B12 (cobalamin) is an essential nutrient that requires gastric acid and pepsin to release it from its protein-bound form in most foods, and allow it to be bound first by salivary R factor and later by intrinsic factor (Festen 1991). Proton pump inhibitors do not alter the secretion of intrinsic factor by the parietal cell but, by causing hypo- or achlorhydria, malabsorption of vitamin B12 can occur (Kittang *et al.* 1985 1987; Koop 1992; Koop & Bachem 1992; Dutta 1994; Marcuard *et al.* 1994; Saltzman *et al.* 1994; Termanini *et al.* 1998). Four short-term studies (Festen & Tertoolen 1988; Marcuard *et al.* 1994; Saltzman *et al.* 1994; Schenk *et al.* 1996) demonstrated that omeprazole could decrease vitamin B12 absorption. The effects of long-term proton pump inhibitor treatment on vitamin B12 has only been examined in a few studies (Maton *et al.* 1989b; Koop 1992; Koop & Bachem 1992; Termanini *et al.* 1998) and there is no data for >10 years of proton pump inhibitor treatment. In some studies (1–4 years) (Maton *et al.* 1989b; Koop & Bachem 1992) no significant change in vitamin B12 levels occurred with chronic proton pump inhibitor treatment, whereas in other studies (Koop 1992; Termanini *et al.* 1998; Valuck & Ruscin 2004) there was a significant de-

crease in vitamin B12 levels. Long-term studies are important to accurately assess the effect of chronic acid suppression on vitamin B12 absorption if serum vitamin B12 levels are assessed because body stores in a healthy individual can last up to five years (Festen 1991; Seetharam 1994). In one study (Termanini *et al.* 1998) of patients with Zollinger-Ellison syndrome who were treated for a mean prospective of 4.5 years with proton pump inhibitors or with histamine H<sub>2</sub>-receptor antagonists for up to 10 years, the serum vitamin B12 was significantly lower in patients treated with omeprazole, especially in those patients with sustained drug-induced hyposecretion and/or achlorhydria ( $P < 0.0001$ ) (Termanini *et al.* 1998). In this study (Termanini *et al.* 1998) in 68 patients with two serum vitamin B12 levels at least five years apart while taking proton pump inhibitors, serum vitamin B12 levels decreased 30% ( $P = 0.001$ ) in patients who were achlorhydric. Furthermore, in eight patients the serum vitamin B12 levels fell below the normal level. Although only a minority of patients (11%) developed serum vitamin B12 below normal, this study (Termanini *et al.* 1998) demonstrated serum vitamin B12 levels can decrease with prolonged use of proton pump inhibitors. This study (Termanini *et al.* 1998) raised the possibility that a proton pump inhibitor-induced decrease in serum vitamin could become particularly important in elderly patients (Termanini *et al.* 1998) who frequently have nutritional deficiencies including low levels of vitamin B12 as well as decreased body stores of vitamin B12 (Lindenbaum *et al.* 1994; Wolters *et al.* 2004). In a recent case-control study in geriatric patients (Valuck & Ruscin 2004), chronic use of proton pump inhibitors or histamine H<sub>2</sub>-receptors ( $\geq 1$  year; mean 4 years) was associated with a 4 times increase in vitamin B12 deficiency. In a second study (Mitchell & Rockwood 2001) in the elderly the use of proton pump inhibitors or histamine H<sub>2</sub>-receptor antagonists was associated with a 2.6 times increase in the need for cobalamin therapy. Two other recent studies (Sagar *et al.* 1999; Schenk *et al.* 1999) identify additional subsets of patients who might be at increased risk of chronic proton pump inhibitor treatment reducing serum vitamin B12 levels. In one study (Schenk *et al.* 1999) of 49 patients who were *H. pylori*-positive with gastroesophageal reflux disease treated for a mean of five years with proton pump inhibitors, there was no change in the median serum vitamin B12 levels in the patients who did not develop gastric atrophy ( $n = 34$ ). However, in the 15 patients with gastric atrophy while taking proton pump inhibitors, a significant decrease ( $P < 0.01$ ) in serum vitamin B12 levels occurred. In this study (Schenk *et al.* 1999), because *H. pylori*-positive patients who developed gastric atrophy (33% in this study) on chronic proton pump inhibitor treatment have an increased risk of developing lower serum vitamin B12 levels, it was recommended that this group of patients should have periodic measurements of serum vitamin B12 levels after prolonged use of proton pump inhibitors. A second study (Sagar *et al.* 1999) demonstrated the patients' genotype of S-mephenytoin hydroxylase (CYP2C19), a polymorphic cyto-

chrome P450 (CYP) enzyme (which catalyses the metabolism of omeprazole) can influence serum vitamin B12 levels after long-term omeprazole treatment. After one year of omeprazole (20 mg/day), serum vitamin B12 levels were lower in individuals who were heterozygous (28%) for a mutant form of CYP2C19 than in those homozygous for the wild type. It was proposed (Bezwooda *et al.* 1978) genotyping of CYP2C19 might be helpful in the future for patients on long-term treatment with omeprazole or other proton pump inhibitors to identify those at increased risk of developing lower serum vitamin B12 levels (Sagar *et al.* 1999).

The results from the above studies support the conclusion that prolonged treatment with proton pump inhibitors can decrease serum vitamin B12 levels in various subsets of patients. During the times of follow-up in these studies ( $< 5$  years), few patients develop serum vitamin B12 below the normal level or an altered haematological finding, although there are a few case reports of such patients (Bellou *et al.* 1996; Ruscin *et al.* 2002). Nevertheless, the above results show that vitamin B12 malabsorption can occur with chronic proton pump inhibitor use and therefore, in patients at an increased risk of developing significant vitamin B12 deficiency (elderly, poor nutrition, patients with *H. pylori* infection), serum vitamin B12 levels should be periodically assessed.

Numerous studies demonstrate that gastric acid secretion is important for optimal absorption of non-haem iron (Bezwooda *et al.* 1978; Conrad 1987; Rucker *et al.* 1994; Stewart *et al.* 1998). The mechanism of this enhancing effect has been attributed to the ability of acid to dissociate the iron salts in food, to help solubilize the iron salts which allows them to be reduced to the ferrous form and form complexes with amines, sugars and ascorbate (Bezwooda *et al.* 1978; Conrad 1987; Rucker *et al.* 1994; Stewart *et al.* 1998). In an animal study (Golubov *et al.* 1991) omeprazole decreased iron absorption in rats on an iron-deficient diet, but not on a normal diet. This result (Golubov *et al.* 1991) led the authors to conclude that omeprazole treatment is unlikely to be associated with significant iron malabsorption in normal patients but might reduce iron absorption in pathologic states associated with increased iron absorption such as iron deficiency. A recent report (Sharma *et al.* 2004) of two patients with iron deficiency treated with iron before and after stopping omeprazole treatment supports the conclusion that in man, profound hypochlorhydria, induced by omeprazole can impair optimal absorption of orally administered iron in iron-deficient individuals. In one study (Koop & Bachem 1992) of 34 patients with idiopathic peptic disease treated with omeprazole for up to four years there was no evidence of iron malabsorption, assessed by following serum ferritin levels, which are a measure of body iron stores. In a second study (Stewart *et al.* 1998) of 109 patients with Zollinger-Ellison syndrome, of which 89 patients were being treated with omeprazole (mean duration – 6 years; range 1–12 years), no evidence of iron malabsorption was found. In this study (Stewart *et al.* 1998) serum ferritin, transferrin, ferritin/transferrin ratio, as well as

haematological studies, were performed to assess body iron stores. Furthermore, in the subgroup of patients with prolonged, severe hypochlorhydria, there was also no evidence of iron malabsorption due to prolonged treatment with omeprazole.

These results suggest that chronic proton pump inhibitor treatment does not cause iron malabsorption in patients on a normal diet. Whether it might cause significant malabsorption in patients that are iron-deficient and who became hypochlorhydric, remains an open question.

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