Progress report

Achlorhydria: hypergastrinaemia: carcinoids – a flawed hypothesis?

The continuous, prolonged administration of several drugs with powerful inhibitory effects on gastric secretion has resulted in the development of malignant gastric carcinoid tumours in rats. It has been proposed that this type of carcinogenesis depends on a causal sequence of drug induced achlorhydria which elicits hypergastrinaemia, the latter in turn exerting a trophic effect on fundic mucosal ECL cells of the rat stomach, resulting not only in general hyperplasia of the ECL cells, but also evoking focal proliferation and finally malignant ECL cell (carcinoid) tumours.

The toxicological impact of this type of drug induced gastric carcinogenesis has been lessened both because the hypothetical causal sequence is considered to be unique to rats, and also by the recent rediscovery that carcinoid tumours occur with increased frequency in some gastric mucosal diseases characterised by hypo- or achlorhydria and hypergastrinaemia, but that these tumours are usually clinically insignificant.

We consider that the toxicological implications of the drug induced gastric carcinogenesis have, perhaps, been undervalued with potentially serious consequences for the currently satisfactory therapy of ulcer disease and for the development of further anti-ulcer drugs. We have, therefore, sought to review and assess some of the ‘facts’ underlying the hypothesis that ‘achlorhydria results in hypergastrinaemia, which in turn causes gastric carcinoid tumours’.

Does achlorhydria increase circulating concentrations of gastrin?

Acute antral alkalinisation

It has long been known that acid in contact with the antral mucosa lessens the release of gastrin into the circulation in response to food materials in the antral lumen. The converse, that alkaline antral contents promote gastrin release, has therefore seemed a reasonable extrapolation.

In cats, antral perfusion with alkaline solutions was reported to increase serum gastrin concentrations, findings which were refuted by other studies which found no increase in circulating gastrin under similar experimental circumstances. In dogs, antral alkalinisation has also been reported to increase circulating gastrin concentrations although this finding, too, has been refuted.

In man, early studies indicated that antral alkalinisation increased serum gastrin concentrations but subsequent studies have found no such hypergastrinaemia, even when sodium bicarbonate has been perfused for as long as 10 hours. Indeed, it has been reported that antral alkalinisation actually decreases the gastrin secretory response to food and decreases the density of antral G cells in man.

We conclude that there is, at present, no satisfactory evidence that neutral or alkaline contents in contact with the antral mucosa elicit release of gastrin.
into the circulation. We concur with the view that 'alkali has little or no effect on unstimulated resting gastrin levels'.

**Chronic antral alkalisation**

**EXPERIMENTAL HYPERGASTRINAEMIA**

A number of different types of experimental manipulation have been used in rats and other animals in an attempt to elicit hypergastrinaemia by 'removing the antrum from the path of acid containing gastric juice', either operatively or by decreasing the amounts of acid secreted by the gastric mucosa.

Rats have been reported to develop fasting hypergastrinaemia after operations such as fundectomy (removal of the acid secreting mucosa); antral exclusion; antrocolic transposition (reseting the antrum in the colon); and various types of vagotomy with drainage. Fundectomy and antral exclusion are also associated with hypergastrinaemia after feeding. Antral transposition to the jejunum, however, does not increase circulating concentrations of gastrin, although transposition to the colon does. Similarly, transposition of the antrum into the urinary bladder does not result in hypergastrinaemia.

Small intestinal resection has been reported to produce hypergastrinaemia in rats although small intestinal bypass does not result in hypergastrinaemia. Colectomy (in dogs) has also been noted to produce hypergastrinaemia.

Treatment of rats with gastric inhibitory drugs may result in hypergastrinaemia. For example, treatment with cimetidine, ranitidine, and omeprazole has been found to result in hypergastrinaemia. It has been suggested, however, that the drug induced hypergastrinaemia is perhaps dependent directly on the gastric inhibitory drug, as famotidine is reported not to produce hypergastrinaemia, compared with cimetidine in rats with antrum similarly maintained at a pH of 5.5.

**HYPERGASTRINAEMIA IN MAN**

Experimental circumstances which elicit hypergastrinaemia in rats have also on occasion been found to be associated with hypergastrinaemia in man. For example, patients who have undergone vagotomy usually show basal hypergastrinaemia and increased gastrin secretory responses to food. Similarly, patients who have a 'retained antrum syndrome', with residual antral tissue in the duodenal stump after Polya or Billroth II gastrectomy suffer from hypergastrinaemia. Small intestinal resection has been shown to produce hypergastrinaemia in man as has treatment with antisecretory drugs.

More important from the point of view of the current hypothesis, hypergastrinaemia is generally associated with disease of the gastric fundic mucosa. Thus, increased circulating gastrin concentrations have frequently been described in patients with atrophic gastritis and with gastric atrophy (pernicious anaemia), in whom gastric secretion is grossly impaired as a consequence of the disappearance of parietal cells from the gastric mucosa. Patients with these gastric fundic mucosal diseases who do not show hypergastrinaemia usually also suffer from atrophic gastritis of the antral mucosa.
In summary, it is clear that mild to moderate hypergastrinaemia can be produced experimentally in animals and man, while severe and persistent hypergastrinaemia is found in patients with disease of the gastric mucosa. In none of these circumstances, however, is removal of acid from the antrum the only, or even a very important, condition of the experiment or disease. Indeed, from the animal studies, it has been concluded that in the rat non-acid antral luminal contents do not, by themselves, cause hypergastrinaemia.36

The interpretation of the hypergastrinaemia associated with pernicious anaemia is equally difficult and best summed up by Walsh and Grossman20 who conclude that ‘the mechanism of gastrin increase in long-term hypoacidity is not known. The G cells behave as if under constant submaximal stimulation’.

**Mechanisms of hypergastrinaemia**

Several mechanisms have been invoked to explain hypergastrinaemia, including absence of (acid-evoked) inhibition of gastrin release; increased numbers of (inappropriately secreting) gastrin producing G cells; increased or inappropriate stimulation of gastrin production and secretion; and defective metabolism or removal of gastrin from the circulation.

**Defective inhibition of gastrin secretion**

In the previous sections, we have discussed some of the reasons for considering that antral alkalinisation is not responsible for hypergastrinaemia. Moreover, in view of the fact that normal gastric contents include little or no acid for much of each day, particularly at times when ‘basal’ gastrin values are normally low, it also seems unlikely that absence of intraluminal acid evoked inhibition of gastrin secretion is responsible for sustained hypergastrinaemia. The hypergastrinaemia secondary to fundusectomy, however, and to vagotomy in rats could be explained by removal of some factor or agencies originating in the fundic mucosa which normally inhibit gastrin release (and G cell proliferation).22

**Change in the number of G cells**

In most of the conditions associated with hypergastrinaemia, increases in the antral content of G cells have been proposed. The matter has often not been tested directly, and at best the antral content of G cells has been inferred from ‘G cell density’ in selected biopsy samples of antral mucosa.

Antral G cell density is increased in patients with pernicious anaemia39 43-44 and G cells are also reported to be present in large numbers in the fundic mucosa of these patients,36 45 as well as in areas of pyloric metaplasia in the fundic mucosa of patients with atrophic gastritis.45 46 G cells in the antral mucosa are also increased in rats22 33 47 48 and man48 after vagotomy.

Antral G cell density is increased in rats after fundusectomy22 25 and after antrectomy or transposition.49 50 While it has been reported that antral exclusion in man produces hypergastrinaemia and increases the number of G cells,51 it has also been noted that antral exclusion in the rat causes hypergastrinaemia with decrease in the number of G cells.22 52

No change in the number of G cells was found in rats made hyper-
Achlorhydria: hypergastrinaemia: carcinoids – a flawed hypothesis?

491

gastrinaemic by treatment with metiamide \(^3\) nor in patients treated with cimetidine for 12 months. \(^4\)

The mechanism of the increase in G cells in these different diseases and under the different experimental conditions is not known. Gastrin does not cause proliferative activity in the antrum \(^5\) and it seems unlikely that increased serum gastrin concentrations induce G cell hyperplasia. \(^3\)

Moreover, it has been concluded that high antral pH, by itself, is insufficient to produce G cell hyperplasia. \(^2^,^4\) Instead, it has been suggested that the acid secreting region of the stomach is the source of an agent which suppresses G cell proliferation. \(^2^,^5\) Because G cell hyperplasia may also result (in dogs) from small intestinal resection, \(^6^,^7\) it seems possible that the small intestine is an additional source of an inhibitor of G cell proliferation.

Stimulants of G cell proliferation are less frequently mentioned as explanations for G cell hyperplasia. In this connection, it has been proposed that saliva may contain an agent which stimulates G cells \(^7\) (a suggestion not as improbable as it appears, in view of fact that saliva contains peptides (such as epidermal growth factor) which not only stimulate cellular proliferation but also inhibit gastric secretion).

**Potential Mediators of Excessive Gastrin Release**

Gastrin is released not only by food materials in the antral lumen, but also when divalent cations such as calcium, magnesium, and aluminium; \(^7^,^8\) dietary ammonia; \(^9^,^10\) and sulphonuric drugs \(^11\) come into contact with the antral mucosa.

Perhaps the most important mechanisms involved in the release of gastrin include peptides such as bombesin and gastrin releasing peptide. Bombesin increases release of gastrin from the antral mucosa in rats \(^12^,^13\) and man \(^14^,^15\) and stimulates the proliferation of antral G cells in the rat. \(^16\) Similarly, gastrin releasing peptide stimulates gastrin release in animals \(^17^,^18\) and man. \(^19\) Interestingly, it seems that vagal stimulation releases gastrin through the mediation of gastrin releasing peptide \(^20\) while bombesin is involved in modulating the antral release of gastrin (in dogs) during intestinal perfusion of liver extract. \(^21\)

It has also been shown that beta-adrenergic mediation is involved in gastrin release. \(^22^,^23\) The beta-adrenergic stimulation of gastrin release is mediated, at least in part, by gastrin releasing peptide. \(^24^,^25\) Gastrin release is also stimulated by serotonin in the rat. \(^26\) In addition, anti-somatostatin gamma globulin increases gastrin release. \(^27,^28\) a finding of interest as the D cells, which release somatostatin in antral mucosa, are decreased in numbers in pernicious anaemia and after vagotomy. \(^29\)

**Defective Metabolism of Gastrin**

The gastric mucosa may play an important role in the metabolism of gastrin not only by inhibiting the release of gastrin from the G cells, but also by direct involvement in the elimination of gastrin from the circulation. Thus, it has been reported that there is a marked increase in the concentration of circulating gastrin if the gastrin is infused into the stomach of individuals whose gastric contents are maintained alkaline, compared with controls. \(^30\)

Circulating gastrin appears to be extracted by secreting, but not by non-secreting, fundic mucosa. \(^31\)

A quite different mechanism of hypergastrinaemia has been noted in
subjects with acute gastric mucosal damage. These individuals seem to have greatly increased proportions of the NH$_2$-terminal fragment of gastrin in their circulation. Similar changes have been reported in the Zollinger-Ellison syndrome.61

ASSOCIATED GASTRIC FUNCTIONAL DISORDERS
It is apparent that both hypergastrinaemia and G cell hyperplasia may accompany conditions resulting in high gastric luminal pH. For example, in patients with gastric mucosal disease, there appears to be an increased incidence and degree of duodenogastric reflux. In this connection, it has been shown (in dogs) that postprandial serum gastrin concentrations are increased by duodenogastric reflux62,83 and similarly, antral instillation of bile salts in alkaline solution increases gastrin concentrations in man.84

Does hypergastrinaemia stimulate proliferation of gastric ECL cells?
The second part of the hypothesis proposes that hypergastrinaemia, resulting from achlorhydria, stimulates the proliferation of the ECL cells of the gastric fundic mucosa. The matter has not been tested directly. There is only one brief note to the effect that treatment with pentagastrin for three months increased the number of ECL cells in rat gastric mucosa.85 The evidence for the effect of hypergastrinaemia on gastric ECL cells is therefore almost entirely indirect and rests on the finding that hypergastrinaemia may be associated, under some circumstances, with hyperplasia, focal proliferation and malignant change of the gastric ECL cells.

EVIDENCE FOR ASSOCIATION BETWEEN HYPERGASTRINAEMIA AND ECL CELL PROLIFERATION
In general, ECL cell hyperplasia or neoplasia occurs in patients with hypergastrinaemia, irrespective of whether they are suffering from achlorhydria37,30,36,39 or from hyperchlorhydria (in patients with gastrinoma).50,90,91 For example, many reports now confirm the proliferation of the argyrophil ECL cells in patients with chronic atrophic gastritis or gastric atrophy of the fundic mucosa.37,90,91,94 In these patients, the fundic mucosa may also show scattered argyrophil nodules or microadenomatous carcinoids, as well as fully developed carcinoid tumours.88,87,91,94-101 On the other hand, in the Zollinger-Ellison syndrome, while ECL cell hyperplasia is common, carcinoid tumours are very rare.24

Experimentally, antrocolic transposition in rats has resulted not only in hypergastrinaemia but also in increased numbers of argyrophil cells of the gastric fundic mucosa.90 Similar changes have been observed in rats which have undergone antral exclusion or fundectomy.52

ECL cell proliferation also occurs after portocaval shunt24,102 despite absence of hypergastrinaemia.22,24 This sort of ECL cell proliferation is prevented by antrectomy.102

General and focal argyrophil cell hyperplasia and the development of multiple carcinoid tumours has been observed in rats treated with omeprazole.3,4 These rats were hypergastrinaemic. The fact that antrectomy prevented the ECL cell hyperplasia was interpreted as showing that antral gastrin release was involved in the stimulation of ECL cell proliferation.4

While there is clearly an association between hypergastrinaemia and
Achlorhydria: hypergastrinaemia: carcinoids – a flawed hypothesis?

hyperplasia or neoplasia of the gastric fundic ECL cells, there is no evidence that the relationship is a causal one. In assessing the evidence from the surgical manipulation of the rat stomach, it was concluded that 'hypergastrinaemia is not the only, perhaps not even the most important, factor behind the pathogenesis of EC Lomas'.

The fact that antrectomy prevented the ECL cell hyperplasia resulting from treatment with omeprazole was also interpreted as showing that antral gastrin release was involved in the stimulation of ECL cell proliferation. The number of ECL cells did increase (from less than control to control values), however, during treatment of the antrectomised rats with omeprazole. In any case, these studies are difficult to interpret in terms of mechanisms, because antrectomy produces atrophy of the gastric mucosa of rats with decrease in the number of ECL cells and this type of resection therefore clearly interferes with the proliferative activity and capacity of the fundic mucosa.

It is worth mentioning that omeprazole, like loxtidine, has been considered to evoke the development of gastric carcinoids by producing achlorhydria as a result of 'unsurmountable' inhibition of (histamine-stimulated) gastric secretion. While this hypothesis may be correct, two other drugs which produce gastric neoplastic change in rats (tiotidine and SK&F 93479) behave as competitive inhibitors of histamine stimulated gastric secretion.

We conclude that a causal link between hypergastrinaemia and proliferation of gastric fundic ECL cells has not been proven either in disease or under experimental circumstances.

Alternative explanations for the association between hypergastrinaemia and proliferation of the gastric ECL cells

It seems possible that the association between hypergastrinaemia and proliferation of the ECL cells depends, on the one hand, on stimulation of hypergastrinaemia by some product of the proliferating ECL cells, the cause of the latter being some not yet specified trophic agent. Alternatively, both the hypergastrinaemia and the proliferation of the ECL cells may depend on some common underlying cause.

Could ECL cell hyperplasia 'cause' hypergastrinaemia?

The nature of the product of the gastric ECL cells and carcinoids is not known. Occasionally, the gastric carcinoids produce gastrin and one patient has been described with a polyp like gastrinoma in association with atrophic gastritis. It has also been reported that the argyrophil cells involved in the hyperplasia stain for 5-hydroxytryptamine (which, as mentioned above, stimulates gastrin release from antral G cells).

Perhaps more interestingly, both intestinal and bronchial carcinoids contain gastrin releasing peptide and bombesin. Indeed, in small cell carcinoma of the lung, gastrin releasing peptide appears to be an autocrine (growth-regulating) factor. The content of gastrin releasing peptide or bombesin in gastric carcinoids does not appear to have been studied. It is worth noting, however, that the endocrine cells of the foregut (arising from gastric and bronchial mucosa) are ontogenetically and morphologically related. It might be objected that in mammals,
gastrin releasing peptide is normally found mainly in the intramuscular neurones, although the peptide is present in the endocrine cells of the gut of birds and frogs. The capacity to produce peptides like gastrin releasing peptide, however, can develop if neuroendocrine cells (in the lung) have become hyperplastic or have been exposed to carcinogens.

What might be the functional connection between ECL and G cells? One of the obvious target organs for the product of the G cells is the mass of parietal cells of the stomach. In this connection, it may be relevant that in the gastric fundic mucosa, the ECL cells are frequently embedded in epithelial cells such as the parietal and chief cells. The proportion of such embedded ECL cells is greater than 33% in atrophic gastric mucosa. It seems possible that this type of juxtaposition serves a functional role, with the ECL cells monitoring the pH of the local milieu, just as the bronchial ECL cells monitor oxygen or carbon dioxide tension. If the ECL cells released gastrin releasing peptide or some such peptide, defective or absent function of the target cells might result not only in stimulus to gastrin release and G cell proliferation, but also an autocrine effect on the ECL cells themselves. In this connection, interruption of feedback loops does result in hyperplasia and neoplasia of the cells of origin of the ‘trophic’ hormone. For example, in mice after thyroidectomy or after the administration of antithyroid hormones, as well as in patients with primary thyroid failure or TSH-producing pituitary adenomata may arise. Under these circumstances, there is ultimately loss of negative feedback control. Similarly, hypocalcaemia of many years’ duration may result in hyperplasia and adenomata of the parathyroid glands.

NEOPLASTIC POTENTIAL OF THE GASTRIC MUCOSA

It has long been recognised that pernicious anaemia and atrophic gastritis predispose to carcinoma as well as carcinoids of the gastric mucosa. The risk varies with geographic area and time, but has been estimated to range from three to 10-fold. It is perhaps significant that the gastric carcinomas associated with pernicious anaemia are sited in the fundus (like the carcinoids) and unlike the antral situation of the ‘usual’ type of carcinoma of control populations. It has been presumed that some of the predisposition to gastric cancer in patients with mucosal disease is attributable to the cellular kinetic abnormalities of the mucosae. Similarly, the gastric mucosal proliferation in patients with antral resection predisposes to cancer, although under these circumstances the serum concentration of gastrin is low.

The conclusion, that the abnormal mucosa of pernicious anaemia and atrophic gastritis predisposes to neoplastic transformation, is supported by the finding that experimental atrophic gastritis and gastric resection also both predispose to, or promote the gastric carcinogenesis produced by N-methyl-N’-nitro-N-nitrosoguanidine (MNNG).

Two additional factors may contribute to the development of neoplasms in patients with gastric mucosal disease. Firstly, the intraluminal milieu of the stomach of patients with pernicious anaemia, atrophic gastritis and gastric resection permits the development of abnormally great concentrations of potentially noxious N-nitroso compounds. In addition, associated functional disturbances may act to promote gastric carcinogenesis. For example, duodeno-gastric reflux promotes the action of MNNG in the
Achlorhydria: hypergastrinaemia: carcinoids – a flawed hypothesis?

development of cancer of the gastric remnant after antral resection in rats,\textsuperscript{141,147} by increasing cellular proliferation;\textsuperscript{146} because bile acids enhance gastric carcinogenesis;\textsuperscript{149} and possibly by increasing the concentration of N-nitroso compounds.\textsuperscript{146}

The role of hypergastrinaemia in carcinogenesis is not clear. It has been reported that gastrin potentiates the development of experimental gastric cancer\textsuperscript{150} and that gastrin (and also serotonin) promotes particularly the development of scirrhous carcinoma of the rat stomach.\textsuperscript{151} It has also been suggested, however, that hypergastrinaemia may protect against gastric carcinogenesis.\textsuperscript{152-153}

Genotoxic carcinogens produce both carcinomas and carcinoids of the gastric mucosa. Thus, MNNG has often been shown to produce antral carcinoma in rats\textsuperscript{154} but has also been reported to produce proliferation of the argyrophil cells and G cells in athymic mice\textsuperscript{155} as well as the formation of carcinoids of the fundic mucosa of rats\textsuperscript{156} (which may develop further into scirrhous carcinomas). N-methyl-N'-nitro-N-nitrosoguanidine also produces tumours in rats which contain both gastrointestinal and neuroendocrine cells.\textsuperscript{157,158} In part, alteration of the duration of exposure or dosage of a carcinogen may change the pattern of the neoplastic response (to MNNG) in the rat stomach.\textsuperscript{159}

A further informative example of a chemical evoking different types of neoplastic reaction in the rat stomach is provided by the effects of a gastric secretory inhibitor SK&F 93479. This drug has produced squamous cell carcinomas of the forestomach and neuroendocrine cell hyperplasia and neoplasia of the oxyntic mucosa (W L Burland, personal communication). In this respect, the neoplastic reaction of the gastric mucosa to SK&F 93479 resembles, in some respects, the response of the neuroendocrine cells of the bronchial mucosa to carcinogens such as nitrosamines, as initial hyperplasia of the neuroendocrine cells may ultimately result in carcinomas which show predominantly squamous or glandular differentiation.\textsuperscript{160}

These types of morphological variability observed during experimental carcinogenesis are also seen in human gastric neoplasms. Thus, many reports mention that a high proportion of gastric adenocarcinomas contain argyrophil cells\textsuperscript{161} or that there is coincident occurrence of adenocarcinoma and carcinoid tumour in the same stomach.\textsuperscript{162-165} The adenocarcinoma in these patients is often of the mucus producing signet cell type.\textsuperscript{164} It has also been repeatedly pointed out that the highest incidence of argyrophil cells occurs in scirrhous gastric tumours with signet ring cells.\textsuperscript{166} In addition, some ‘dedifferentiated’ gastric carcinoids are biologically similar to anaplastic gastric carcinomas.\textsuperscript{168}

The presence of both argyrophilic endocrine and exocrine cells in gastric cancers has been interpreted as indicating that neoplastic change has occurred in both endocrine and epithelial cell precursors. While the histological variability has shed some light on the morphogenesis of the gastric neoplasms, it has proved necessary, however, to invent a special descriptive terminology – ‘amphicrine carcinoma’ – to explain why cells which are apparently epithelial display both exocrine and endocrine features. For example, in well differentiated gastric carcinoma cells there may be both argyrophil features and neurosecretory granules.\textsuperscript{169} It has therefore been proposed that amphicrine cells have biosynthetic properties both for mucus and for hormonal peptides, so that the two cell types have a
'monoclonal' origin\textsuperscript{166,166} and reflect divergent differentiation within neoplastic stem cells. Experimental studies have supported the latter view. For example, regeneration of the gastric mucosa after wounding results in the formation of endocrine and other mucosal cells, which appear to be derived from common precursor cells.\textsuperscript{167} More interestingly, allografts of single cells from a rat gastric adenocarcinoma developed into tumours composed of mucinous, columnar, endocrine and undifferentiated cells.\textsuperscript{158,166} Further, experimental transplantation studies showed the transformation of human (colonic) carcinoid tumour into a mucin-secreting carcinoma when transplanted into hamsters.\textsuperscript{169}

From the above studies, it seems that if an abnormally proliferating gastric mucosa, like that of pernicious anaemia, is exposed for some reason to a further stimulus to growth, the proliferation may become expressed as hyperplasia of the endocrine cells. For reasons which have not yet been defined, but probably include exposure to genotoxic carcinogens, some of the proliferating cells may undergo further progression to become focal 'microcarcinoids' and subsequently develop into malignant carcinoids.

We conclude that the development of both carcinoid tumours and carcinomas in human gastric mucosal disease and in rats treated with drugs reflects the predisposition of the proliferatively abnormal mucosa to undergo malignant change. That the morphological manifestation of the neoplastic process happens to comprise an endocrine rather than an exocrine phenotype merely reflects the products of the oncogenic transformation and activation evoked by as yet undefined carcinogens.

This type of unpredictable morphological variability is not restricted to the gastric mucosa but appears to reflect a much more general carcinogenic reaction. Thus, carcinoma and carcinoid tumours both occur during the course of chronic dysplastic reactions of alimentary mucosae other than stomach. For example, carcinoids have been described in the small intestine during the course of coeliac disease,\textsuperscript{170} arising perhaps for the same reason that these patients develop carcinomas and lymphomas\textsuperscript{174-175} of the proliferatively abnormal small intestinal mucosa. Similarly, argyrophil cell hyperplasia and atypical carcinoid tumours have been described in the colonic mucosa of patients with ulcerative colitis\textsuperscript{171-176} — mucosa which is also very likely to undergo carcinomatous change.\textsuperscript{177}

**Conclusion**

Rats treated with powerful inhibitors of gastric secretion develop hyperplasia and neoplasia of the gastric endocrine cells. Similar 'carcinoid' tumours develop in some patients with severe disease of the gastric fundic mucosa (such as pernicious anaemia or atrophic gastritis). In all reports and discussions, it has been assumed that the progression from generalised hyperplasia of the ECL cells to clonal (focal) proliferation and thence to (often multiple) carcinoid tumours depends on a single, and simple, causal link. The assumption has not been tested or proved.

Both the drug treated rats and the patients with gastric mucosal disease suffer from marked or complete inability to secrete gastric juice (because there is inhibition of secretion in the rats and because the parietal cells have disappeared in the patients). Inability to secrete gastric juice may predispose
to, but is not necessary for proliferation of gastric ECL cells because similar proliferation occurs, for example, in rats after portocaval shunt and in patients with gastrinoma.

The physiological consequences of the failure to secrete acid are numerous, because other functions (secretory and motor) of the stomach are also altered, as is the milieu of the remainder of the alimentary tract and, therefore, the whole organism. Only one aspect of this dysfunction, however, hypergastrinaemia, has received attention in the search for a ‘causal’ link between achlorhydria and ECL cells. Hypergastrinaemia, like achlorhydria, is considered to be causally involved in the development of ECL cell proliferation. The association between achlorhydria and hypergastrinaemia has not been shown to be causally based, however, while the mechanism for the development of hypergastrinaemia has not been defined in either the drug treated rats nor in patients with gastric mucosal disease. The current assumption that removal of the ‘acid brake’ results in a positive and continuous stimulation of the G cells remains unproved.

While conditions characterised by hypergastrinaemia may also be characterised by the frequent, or even ubiquitous presence of ECL cell proliferation, no causal link between hypergastrinaemia and change in the endocrine cells has been proven. Indeed, it is not even clear that the hypergastrinaemia is a ‘causal’ precedent of the ECL cell proliferation, as the function (and result of hyperfunction) of the ECL cells of the gastric mucosa is not known. Clearly, the ECL cells of the oxyntic mucosa are not necessary for the development of hypergastrinaemia, since hypergastrinaemia occurs after fundusectomy in the rat, but the latter observation merely indicates that whatever ‘drives’ gastrin secretion is not restricted to the oxyntic mucosa of the stomach. We have outlined some of the mediators of gastrin secretion and consider that the bombesin-GRP group of peptides may be involved.

It seems to us that the situation in patients with gastric mucosal disease is merely a special example of the general rule that a tissue undergoing proliferation is often more ‘sensitive’ to, and promotes the development of, neoplastic change in that tissue, provided that the tissue is exposed to an ‘organ-specific’ genotoxic carcinogen.17 18 In patients with gastric mucosal disease, the concentration and perhaps also the content of potential carcinogens is increased, not only because gastric juice is unavailable to dilute and wash away the carcinogens, but also because the milieu is satisfactory for the growth of bacteria, some of which may be involved in (for example) nitrosation. The cellular kinetic indices of the drug treated gastric mucosa have not (as far as we know) been defined, nor have measurements of the carcinogen content of the gut of drug treated rats been published. No information is therefore available by which we can compare the carcinogenic antecedents of drug treated rats and patients with gastric mucosal disease. We conclude that similarity of some criteria (such as achlorhydria; hypergastrinaemia; proliferation of ECL cells) does not necessarily confirm the identity of the processes underlying the carcinogenesis under these different circumstances.

Moreover, the proliferation of ECL cells and the development of carcinoids has not been shown to be more specific and unique than, for example, hyperplasia of mucus secreting cells and the development of adenocarcinomas, as a manifestation of the carcinogenic process. In this
connection, prolonged treatment with other powerful gastric inhibitory drugs has resulted in the development not only of carcinoids but also, or alternatively, in the development of adenocarcinomas. Furthermore, MNNG, a defined genotoxic gastric carcinogen, has produced both carcinoids and adenocarcinomas in experimental rats. Similarly, in man, gastric mucosal diseases predisposes to the development of adenocarcinomas and carcinoids. The factors responsible for the different phenotypic manifestations of the neoplastic process are not known but there is no reason to suppose that any one expression is the result of some unique carcinogenic process – either in the stomach or elsewhere in the alimentary tract, because similar variability in neoplastic morphology is also observed in the small intestine and colon.

From the above analysis, we suggest that for the purpose of evaluating the gastric toxicological reaction to antisecretory drugs, all morphological variants of gastric neoplasms should be combined. As has been suggested previously, we consider that for the purposes of these toxicological studies ‘neoplasms of different morphological classification may be combined when the histomorphogenesis is comparable’. Moreover, in our present state of knowledge, we propose that ill defined and potentially inaccurate pathogenetic mechanisms must not be used to specify ‘separate risk categories for the purposes of regulation’ (of drugs which produce neoplasms).

Finally, we consider that in its present state, the hypothesis that ‘achlorhydria causes hypergastrinaemia, which in turn causes proliferation and neoplastic change in the gastric ECL cells’ bids fair to become yet another chapter in the book of gastroenterological fairy tales.

We wish to thank Dr W L Burland and Dr G Beeton for kindly providing information about SK&F 93479.

**J PENSTON AND K G WORMSLEY**

Dept of Therapeutics,
Ninewells Hospital,
University of Dundee,
Dundee DD1 9SY,
Scotland

Received for publication 9 September 1986.

**References**

Achlorhydria: hypergastrinaemia: carcinoids—a flawed hypothesis?


14 Fordtran JS, Walsh JH. Gastric acid secretion rate and buffer content of the stomach after eating. *J Clin Invest* 1973; 52; 645–57.


33 Korman MG, Scott DF, Hansky J, Wilson H. Hypergastrinaemia due to an excluded

Achlorhydria: hypergastrinaemia: carcinoids – a flawed hypothesis?


60 Lichtenberger LM, Graziani LA. Possible importance of dietary ammonia (NH₃) in the postprandial release of gastrin (G). Gastroenterology 1981; 80: 1212.


86 Hodges JR, Isaacson P, Wright R. Diffuse enterochromaffin-like ECL cell hyperplasia and
100 Lehtola J, Karttunen T, Kreckelä I, Niemelä S, Räsänen O. Gastric carcinoids with minimal or no macroscopic lesion in patients with pernicious anemia. Hepato-Gastroenterol 1985; 32: 72–6.
Achlorhydria: hypergastrinaemia: carcinoids — a flawed hypothesis?


139 Geboes K, Rutgeerts P, Broeckaert L, Vantrappen G, Desmet V. Histologic appearances


158 Kobori O, Oota K. Neuroendocrine cells in serially passed rat stomach cancers induced by MNNG. Int J Cancer 1979; 23: 536–41.


Achlorhydria: hypergastrinaemia: carcinoids – a flawed hypothesis?


Achlorhydria: hypergastrinaemia: carcinoids--a flawed hypothesis?

J Penston and K G Wormsley

*Gut* 1987 28: 488-505
doi: 10.1136/gut.28.4.488

Updated information and services can be found at:
http://gut.bmj.com/content/28/4/488.citation

**Email alerting service**

*These include:*

Receive free email alerts when new articles cite this article.
Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Stomach and duodenum (1689)
- Gastrointestinal hormones (848)
- Pancreatic cancer (660)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/