Correspondence

Achlorhydria: hypergastrinaemia: carcinoids — a flawed hypothesis

Sir.—In their paper (Gut 1987; 28: 488–505) Drs Penston and Wormsley point out a number of what they regard as inconsistencies and as yet unproved assumptions in the hypothesis that links achlorhydria with hypergastrinaemia and hypergastrinaemia with ECL cell hyperplasia and gastric carcinoids. Unfortunately, however, the arguments they present in support of alternative explanations have been carefully selected to favour their own views on the matter. They address three questions: (1) Does inhibition of acid increase plasma gastrin? (2) Does hypergastrinaemia stimulate proliferation of ECL cells in fundic-type mucosa? (3) Does long lasting hypergastrinaemia promote the development of ECL cell carcinoids?

(1) Does inhibition of acid increase plasma gastrin?

We believe that there is fairly convincing evidence that suppression of acid leads to hypergastrinaemia. Surgery of the rat stomach resulting in raised antral pH invariably leads to increased plasma gastrin. In man, plasma gastrin concentrations are raised in disorders associated with reduced gastric acid, such as non-antral atrophic gastritis and postvagotomy states. Also drug induced acid inhibition results in raised plasma gastrin. This is independent of the type of inhibitor used, because both histamine H2-receptor antagonists and H+K+-ATPase inhibitors produce hypergastrinaemia. In rats the hypergastrinaemia evoked by antisecretory drugs can be counteracted by infusion of acid into the stomach (Ryberg to be published).

Available data suggest, therefore, that raised antral pH raises plasma gastrin, although additional factors may contribute.

(2) Does hypergastrinaemia stimulate proliferation of ECL cells in fundic-type mucosa?

Experimental evidence from studies of rats suggests a causal link between increases in plasma gastrin and increases in the rate of ECL cell proliferation. Gastric surgery, for example antral exclusion, which raises basal plasma gastrin concentrations, causes an increased ECL cell density. In contrast, antrectomy lowers plasma gastrin and reduces the ECL cell density. In the rat high doses of ranitidine and omeprazole markedly raised plasma gastrin, which was associated with a slowly developing (and fully reversible) hyperplasia of the ECL cells. Antrectomy prevented the drug induced hypergastrinaemia and the proliferation of ECL cells. Perhaps the most direct evidence for gastrin being the

agent responsible for ECL proliferation comes from experiments where pentagastrin administered to rats induced first ECL cell activation and then hyperplasia.

In man ECL cell hyperplasia occurs in connection with non-antral atrophic gastritis and Zollinger Ellison (Z-E) syndrome, conditions associated with marked hypergastrinaemia but differing with respect to the amount of acid secreted. In patients with non-antral atrophic gastritis there is a good correlation between the degree of hypergastrinaemia and the density of ECL cells in the gastric mucosa.

Drs Penston and Wormsley claim that hypergastrinaemia does not stimulate proliferation of gastric ECL cells. They cite examples of ECL cell proliferation where gastrin may not be involved and conclude that a causal relationship with gastrin is unproved. We suggest that although gastrin may not be the only factor of importance there is much evidence that gastrin is important for both ECL cell activation and proliferation.

(3) Does long lasting hypergastrinaemia promote the development of ECL cell carcinoids?

In rats, life long treatment with high dosages of antisecretory drugs induces not only hyperplasia of ECL cells but also ECL cell carcinoids in some individuals. This has been described for several long acting acid inhibitors, two H2-receptor antagonists (lloxidine and SK&F 93479) and one H+K+-ATPase inhibitor (omeprazole). When given in sufficient doses short-acting H2-receptor antagonists also induce ECL cell hyperplasia in rats.

In man ECL cell carcinoids are rare but have been described in patients with marked hypergastrinaemia (non-antral atrophic gastritis, Z-E syndrome). Hypergastrinaemia is the common factor in these conditions and not achlorhydria. This type of carcinoid has been found to develop against a background of diffuse ECL cell hyperplasia and there are strong indications of a continuum from a diffuse ECL cell hyperplasia to focal hyperplasia and ultimately, in some individuals, to carcinoids. While ECL cell hyperplasia is a prominent finding in most Z-E patients reported cases of ECL cell carcinoids in these patients are very few. The development of ECL cell hyperplasia is a slow process. Also ECL cell carcinoids grow slowly and exhibit a low degree of malignancy.

Effective acid inhibition might raise the concentration of potentially noxious N-nitroso compounds in the stomach, and Drs Penston and Wormsley raise the question whether acid secretion inhibitors can provide a non-specific stimulus to carcinogenesis. This argument obscures the distinction between adenocarcinomas and carcinoids. Admittedly, in rats...
certain H₂ receptor antagonists (tiotidine, SK&F 93479) have been found to cause gastric neoplasia distinct from carcinoids.⁷ This may reflect genotoxic effects of these two chemicals, however, rather than implying that all antisecretory drugs are potentially carcinogenic.

In man gastric adenocarcinomas may occur with a higher frequency in atrophic gastritis (for a different opinion see refs 14 and 15); there is no proof that gastrin is responsible. In fact, the incidence of adenocarcinomas seems increased after antrectomy when gastrin concentrations are low. Millions of patients have been treated with acid secretion inhibitors during the last decade but no indication of increased gastric malignancy has been found,⁶ and there are no reports of increased incidence of gastric adenocarcinoma in Z-E patients having very high gastrin concentrations.

Available evidence indicates that gastrin is an important factor behind ECL cell proliferation and carcinoid development in the oxyntic mucosa both in rat and man. Reduced acid secretion is not a prerequisite for this process. There is no evidence that gastrin promotes the development of gastric adenocarcinoma.

In man currently used antisecretory drugs (cimetidine, ranitidine, famotidine and omeprazole) in therapeutic doses produce moderately increased serum gastrin concentrations. These are far from the high concentrations observed in patients with Z-E syndrome or atrophic gastritis who sometimes develop ECL cell hyperplasia and carcinoids. The development of ECL cell hyperplasia and carcinoids in man proceeds slowly during many years. Thus short term treatment with acid secretion inhibitors cannot be judged as a risk.

At present it cannot be excluded that long term therapy with effective antisecretory drugs might give rise to hyperplasia of ECL cells. The possibility that ultimately such hyperplasia may generate carcinoids seems rather remote in man given the rarity with which the ECL hyperplasia of severely hypergastrinaemic patients develop into carcinoids.⁵ None the less, endoscopic surveillance with biopsies and staining for ECL cells seems desirable before the safety of long term use of any effective antisecretory drug can be assessed adequately. The fact that in rats and mice treated with antisecretory drugs ECL cell hyperplasia invariably precedes the development of carcinoids, and the finding that ECL hyperplasia is fully reversible when gastrin concentrations are normalised make this approach justifiable.

In their paper Drs Penston and Wormsley blur the distinction between well differentiated endocrine tumours and other forms of gastric neoplasia. By indiscriminate reference to chemicals known to induce various forms of neoplastic change, they allow compound specific toxicological effects to obscure the evidence favouring a common mechanism of gastric carcinoid formation involving gastrin. It is regrettable that in their desire to be provocative Drs Penston and Wormsley have chosen to reject a logical hypothesis which can be, and is being tested, in favour of mere speculation. By mixing facts with fiction they confuse rather than clarify the issues under discussion.

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Reply

Sir,—It seems strange that essential points in the presentation of our case have eluded five very distinguished gastroenterologists who repeat in their letter precisely those fashionable arguments which we have considered so badly flawed as to have gravely distorted the current attitude to a very important set of topics. (1) It has long been known that acid in the antrum decreases or abolishes the release of gastrin. The converse — that little or no acid in the antrum (that is, hypo- or achlorhydria) results in hypergastrinaemia — is one of the leaps of ‘logic’, however, which are made with abandon and which, when actually tested are found to be wrong.

We have tried to show that there is no evidence that hypo- or achlorhydria is a cause of hypergastrinaemia. We discussed in detail the facts (not beliefs) that increase in the pH of the antral contents was not the cause of the hypergastrinaemia accompanying various mutilations of the stomachs of rats; and that hypergastrinaemia accompanying therapeutic gastric inhibitory drugs, gastric mucosal disease, etc, could or should not be interpreted as indicating some causal relationship between the gastrin concentrations and the associated condition.

Indeed, we quoted the doyen of gastroenterology, MI Grossman, in support of our case. (2) We discussed, at length, the total lack of direct evidence that gastrin influences the proliferation of gastric fundic ECL cells. Gastrin may, of course, do so. We merely point out that there is no satisfactory evidence, because the effect of administering gastrin has never, actually, been studied. The investigations of Dr Blom were quoted, but he did not tell us about the number of ECL cells in the stomach of rats treated with pentagastrin. He merely mentions that there is a... a considerable increase in the relative number of endocrine cells in the lower part of the corpus glands. Furthermore, he used pentagastrin which, as Dr Hakanson has pointed out, has effects on the alimentary tract different from those of gastrin.

We did, of course, discuss all the experimental modifications of the antrum. It is worth remembering that removal of the antrum so distorts the proliferation kinetics of the gastric mucosa that “atrophic gastritis” results with, not surprisingly, decrease in the number of ECL cells (together with all other cells except mucous cells). We pointed out that, despite antrectomy, the number of ECL cells in omeprazole treated rats increased at least two fold, an increase presumably attributable to the omeprazole.

We also discussed, at length and in detail, the absence of a satisfactory causal connection between gastric mucosal disease, hypergastrinaemia and hyperplasia of the ECL cells. The three quoted references, which have appeared since our review was written, do not add anything new. They just repeat the same assumption that association equals causal relationship — precisely the assumption about which we tried so hard (and, clearly, unsuccessfully) to provoke some new thoughts. (3) We then come to the nub of the problem — that some drugs produce gastric cancer in rats, while others do not. It does not matter a jot what form the cancer takes — the phenotypic expression of the malignant process is quite unpredictable, at present, and merely depends on which genes are aberrantly expressed. Indeed, different morphological features coexist, merge or change one into another, as we have tried to illustrate with interesting examples from throughout the alimentary tract.

No one yet knows why some drugs are carcinogenic and why other drugs do not produce gastric cancer. We have certainly never implied that all antisecretory drugs are potentially carcinogenic. Indeed, we have categorically stated the opposite. We agree that, very fortunately, the gastric secretory inhibitors in current use (cimetidine and ranitidine) do not produce gastric cancer in animals or man — a point which we have made repeatedly. It seems probable that the...
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