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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 considerable increase in the relative number of endocrine cells in the lower part of the corpus glands... Moreover, 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

gastric cancers (adenocarcinomas, squamous cell carcinomas, carcinoids) which are produced by some gastric antisecretory drugs are produced not as a result of the gastric secretory inhibition, but depend on specific and unrelated effects of the drugs. That is precisely our message and it is a point which we wish to reemphasise now. (4) The reason we wrote the review was the apparent assumption that the mechanism of development of gastric carcinoids during treatment with some gastric secretory inhibitors depended, in some unique way, on some unique mechanism and (by another 'logical' leap) that carcinoids were therefore really a problem for rats, and not for man. Moreover (another 'logical saltation') human carcinoids grow slowly and are not really cancers. We tried to show that this whole rigmarole might be wrong and therefore potentially disastrous if used as a basis for the use of drugs. Many attempts have been made to determine the risk of cancer in man from the results of animal studies, precisely in order to permit prediction of such risk. Despite much study and argument, it is not possible to make valid and reliable extrapolations. At present, we can only assume and hope that if drugs do not produce cancer in animals, they will not produce cancer in man. The converse (if drugs produce cancer in animals they may produce cancer in man) is the reason why, very sensibly, Drug Regulatory Authorities insist on animal studies before the therapeutic use of a drug is permitted in man; why the argument that 'rats are not human beings' is rejected as a criterion for the use of a drug; and why all of the half dozen or so new and powerful H₂-receptor antagonists which have produced carcinoids in rats have, very responsibly, been withdrawn from use by their manufacturers. The gastric secretory inhibitors which we use at present for the longterm treatment of ulcers (and we never use drugs short term in the therapy of ulcer disease, because most ulcers relapse repeatedly for many decades) have been tested in animals and shown not to produce gastric cancer in very thorough studies. As clinicians, we consider the latter results sufficiently reassuring to permit us to use cimetidine and ranitidine in the treatment of ulcers and oesophagitis.

We regret that the message of our review is so unclear. We have said, first, that it is always necessary to question and test assumptions, rather than uncritically accept; and, second, that in our view it may be unwise to treat patients suffering from ulcer disease with drugs which cause gastric cancer in rats.

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News

Italian Society of Gastroenterology

The 26th Congress of this Society will be held from 5–7 November, 1987, at the Palace Sorrento, Naples, Italy. Details from: Scientific Secretariat, Cattedra Gastroenterologica Nuovo Policlinico, Via Pansini, 5, University of Naples, 80131, Naples, Italy.

Bayliss and Starling Society

The next annual scientific meeting will be held at Queen's University, Belfast, N Ireland on 28 and 29 September, 1987, and will cover aspects of regulatory peptides in the brain and in the GI tract. Details from: Prof KD Buchanan, Dept of Medicine, Institute of Clinical Science, Grosvenor Rd, Belfast BT12 6BJ.

American Pancreatic Association

Annual joint scientific meeting of the APA and the Pancreas Section of the NCI Organ Systems Program will be held on 5 and 6 November, 1987 at the Ambassador West Hotel in Chicago, Illinois, USA. Further information may be obtained from Midge Kellerhaus, American Pancreatic Association, Dept of Surgery, M580, University of Missouri Medical Center, Columbia, MO 65212, USA.

Third International Symposium on Obesity Surgery

To be held in Genova, Italy, from 20–23 September, 1987. Details from Dr Enrico Traverso, Istituto di Patologia Chirurgica, Università di Genova, Ospedale S Martino, 16132, Genova, Italy.