

relatives of drug takers, in common with the drug takers themselves, must undergo a similar period of self examination before they too "kick the habit." Families Anonymous now has many branches throughout the United Kingdom and can help a great deal with the kind of family problems described in Dr O'Donnell's article.

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1 Drummond DC, Taylor JA, Mullin PJ. Replacement of a prescribing service by an opiate free day programme in a Glasgow drug clinic. *Br J Addict* (in press).

Antisecretory drugs and gastric cancer

SIR,—Professor M J S Langman ended his Regular Review (22 June, p 1850) by asking the same questions about the possible place of omeprazole like drugs in medicine that we faced several years ago with loxidine. Loxidine,¹ an unsurmountable histamine H₂ antagonist, differs from ranitidine in being much longer acting and capable of inducing total achlorhydria in the rat and other animals. Omeprazole also causes achlorhydria but by irreversible inhibition of the parietal cell hydrogen/potassium ion adenosine triphosphatase.²

In considering results of carcinogenicity tests in the rat and the possibility of gastric cancer in man, we think it is essential to distinguish between drugs such as loxidine and omeprazole, which induce achlorhydria in the rat, and competitive H₂ antagonists such as cimetidine and ranitidine, which do not. Only drugs such as loxidine and omeprazole have been found to cause carcinoid tumours in the rat stomach. For example, we found that about 10% of treated animals developed such tumours in the fundus of the stomach after prolonged ingestion of loxidine in the diet at concentrations that abolished acid secretion³; the incidence of tumours was not related to dose, and neither hyperplasia of the enterochromaffin like cells nor tumours were seen until the drug had been given for 22 months or more. The gastric changes, therefore, occurred in aged animals after lifelong achlorhydria. Chronic administration of omeprazole to the rat causes similar tumours,⁴ and so the critical factor for the mucosal response is prolonged achlorhydria and not the mechanism of inhibition of acid secretion. By contrast, no such changes were seen in the gastric mucosa during a similar lifespan study in rats given ranitidine in their diet at daily intakes as high as 2000 mg/kg and, so far as we know, carcinoid tumours of this type have not occurred with any other competitive H₂ antagonist.

Although the general conditions for gastric carcinoid formation in the rat by antisecretory agents have now been experimentally defined, the fundamental mechanism for tumour induction is not known. All laboratory evidence known to us indicates, however, that neither loxidine nor omeprazole is a directly acting carcinogen or a cocarcinogen. Larsson *et al* suggested that the primary cause of the proliferation of enterochromaffin like cells is hypergastrinaemia caused by achlorhydria.⁵ We agree that the trophic effect of gastrin on enterochromaffin like cells may contribute to the mucosal response but do not think that it is the primary determinant of it. One reason is that whereas these workers found that high doses of omeprazole and ranitidine, 400 mg/kg daily in divided oral doses, caused similar increases in plasma gastrin concentrations in the rat after 10 weeks' treatment only omeprazole induces carcinoids. We also find it difficult to

accommodate the delayed nature of the response within the simple hypergastrinaemia hypothesis.

Until we know better our preferred interpretation of the gastric carcinoid phenomenon depends on its occurrence only in aged animals, of whom an increasing proportion would be expected to have a defective immune surveillance system. The tumours may, therefore, result from failure to detect and eliminate aberrant, potentially malignant enterochromaffin like cells induced by mutagenic agents formed in the achlorhydric stomach. If this explanation is correct any drug capable of causing achlorhydria in clinical use should not be used in patients likely to be immunocompromised for any reason.

We adopted a conservative approach with loxidine when we became aware that its unsurmountable prolonged action made achlorhydria possible at ordinary therapeutic doses in at least some people and decided, therefore, that it should not be given to patients until the results of animal carcinogenicity tests were known. Its development was abandoned when gastric carcinoid tumours were found in the rat as we believed that a drug that induced tumours should not be used unless the likely advantage to the patient clearly outweighed any potential risk. Using these criteria, we believe that loxidine or omeprazole may properly be used to treat patients with Zollinger-Ellison syndrome as control of their acid secretion would undoubtedly be easier than with competitive H₂ antagonists and most of them already have malignant tumours. For all other patients we think that drugs that cause less intense inhibition of acid secretion are preferable, their dosage being increased, if need be, in difficult patients.

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- 1 Brittain RT, Jack D, Reeves JJ, Stables R. Pharmacological basis for the induction of gastric carcinoid tumours in the rat by loxidine, an unsurmountable histamine H₂ receptor blocking drug. *Br J Pharmacol* 1985;85:843-7.
- 2 Rackur G, Bickel M, Fehlhaber HW, *et al*. 2-[(2-pyridylmethyl)sulfonyl] benzimidazoles; acid sensitive suicide inhibitors of the proton transport system in the parietal cell. *Biochem Biophys Res Commun* 1985;128:477-84.
- 3 Poynter D, Pick CR, Harcourt RA, *et al*. Association of long lasting unsurmountable histamine H₂-blockade and gastric carcinoid tumours in the rat. *Gut* (in press).
- 4 Ekman L, Hansson E, Havn N, Carlsson E, Lundberg C. Toxicological studies on omeprazole. *Scand J Gastroenterol* 1985;20 (suppl 108):53-69.
- 5 Larsson H, Carlsson E, Hakansson R, Mattsson H, Sundler F. Relation of plasma gastrin levels and oxyntic mucosal ECL density during inhibition of gastric acid secretion in the rat. *Gut* 1985;26:558.

Medical patients aged 65 and over admitted to an accident and emergency department

SIR,—In the now fashionable game of doctor bashing the medical profession has scored yet another own goal. Dr Gillian H Jenner (13 July, p 113) is highly critical of local general practitioners and suggests that patients and relatives can estimate the need for emergency care as well as a GP. The only evidence she gives in support of this is the observation, from a small number of patients, that self referred and GP referred patients are comparable in terms of their mobility, biochemistry, and prognosis. She appears to overlook the fact that she has not compared like with like. In most districts when a GP decides on admission to hospital the patient bypasses casualty (if Romford is an exception, we are not told this). Such direct admissions would need to be included in the study. Perhaps GPs refer patients to casualty only where

there is genuine doubt about the need for admission. Conversely, maybe casualty officers find it difficult not to admit self referred patients because of uncertainty about the patients' history, background, and support and the relatively limited range of therapeutic alternatives at their disposal.

Dr Jenner states that no previous study has made the type of comparison described. This is not so, though this may indeed be the first study which has confined itself to the elderly. No reference is made to Reilly's study of 784 casualty attenders,¹ which found that the GP referred group contained a relatively large proportion of elderly and overall had a four times greater likelihood of being admitted.

Even if the paper had succeeded in showing that in Romford the elderly use the casualty department only in desperation, an alternative explanation for this is the possibility that most find their GPs more available than the group described. It certainly does not follow that patients should be encouraged to use casualty as a routine source of primary care. Indeed, by doing so they would ensure that they were seen by a doctor unfamiliar with their problems and unable to provide personal follow up.

Dr Jenner's motivation is suggested in some of the sad anecdotal tales of patients finding the GP unavailable or reluctant to visit. This article appears to be a cry for help from an exasperated casualty department. But surely it would be better to find out the reasons behind apparently inexplicable behaviour by fellow professionals and bring about change by persuasion and possibly peer group pressure? Have the author and her collaborators tried to approach their local GPs directly? Did they send a preliminary draft of their paper to the local medical committee—or has their medical training and experience led them to the view that bitter language and public denigration are the most appropriate ways for them to communicate with their local colleagues?

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1 Reilly PM. Primary care and accident and emergency departments in an urban area. *J R Coll Gen Pract* 1981;31:223-30.

SIR,—As general practitioners working in the locale of Oldchurch Hospital we feel we cannot allow the paper by Dr Gillian H Jenner to pass without comment.

She makes fundamental statistical errors in her analysis. She concentrates only on the population who went to the accident and emergency department and uses parametric statistics which on this population may well not be appropriate. What in fact we need to know is the numbers of patients who stayed at home or were admitted directly to admitting physicians, including those at the neighbouring hospital where there is no accident and emergency department. From these limited results the suggestion is made that all patients who are over 65 and ill "should be encouraged to refer themselves to a casualty department and bypass their GP altogether." If this advice were followed no district general hospital could cope with the deluge of patients that would result.

Two of us have carried out an audit of our new visits—that is, excluding follow up visits—to the over 65s for the first six months of 1985. We assumed that patients who request visits are more ill than those who come to the surgery and that therefore the referral rate might be higher. We hope the results shed some light on this issue.

SJN carried out 200 new visits. Only 20 of