malignant tumours of the squamous epithelium of the forestomach after two years' treatment at 1000 mg/kg. This lesion is not considered to be related to acid suppression. Once again it is difficult to know what if any relevance this overdosing by 1000 times the expected human dose may have.

Hyperplasia of endocrine cells has now been described in animals receiving loxtidine, a potent non-surmountable histamine H_2 antagonist, SK&F93479, and the hydrogen potassium adenosine triphosphatase inhibitor omeprazole, which is also a powerful suppressant of acid secretion. When loxtidine was given to rats in similar doses to SK&F93479 for over two years gastric tumours developed in over 10% of the treated animals irrespective of whether these were in the low, medium, or high dose groups.[19] The tumours were in the fundus and not, as with nitrosoguanidine, in the antrum. Electron microscopy showed that the proliferating cells contained typical neurosecretory granules, and further work has confirmed them to be carcinoids. Similar, if not identical, neuroendocrine cell hyperplasia and neoplasia were observed in the oxyntic mucosa after two years' treatment with SK&F93479 at 1000 mg/kg/day (G R Betton, personal communication). This may represent a response to intense acid suppression associated with the use of an insurmountable antagonist, ranitidine and cimetidine both being free of such effects in equivalent tests.

Omeprazole is a powerful non-competitive suppressant of acid secretion, inhibiting the hydrogen potassium adenosine triphosphatase of the stomach, and is not a histamine H_2 antagonist. The results of mutagenicity studies have been negative, but hyperplasia of enterochromaffin-like cells with formation of micronodules and occasional carcinoid proliferations into the submucosa were observed in low, medium, and high dose groups in rats.[20 21] These changes are similar to those described with loxtidine and SK&F93479, and, given the consistency of the finding, the possibility that similar changes would be induced in man needs to be considered.

Gastric carcinoids are rare in man but multiple polypoid or submucosal nodular tumours are well described in patients with pernicious anaemia[22 23] and non-antral gastric atrophy,[24] and antral hypergastrinaemia has been associated with the development of mixed endocrine tumours.[25] This suggests that a loss of gastric acidity releases a brake on enterochromaffin-like cells. Experimental support for this suggestion comes from studies in rats where sustained inhibition of acid secretion with very high doses of omeprazole (or ranitidine) was associated with increased densities of mucosal enterochromaffin cells, previous antrectomy preventing the increase.[21] Gastric neuroendocrine changes may then simply reflect the consequences of hypergastrinaemia during severe acid suppression, and would not be a direct drug effect.

How, then, should the development of potent secretory antagonists be viewed? The cautious might argue that since the long term safety of the current generation of relatively less powerful drugs such as cimetidine and ranitidine is unknown, development programmes for more potent drugs should be restricted or stopped. They might seek to justify this view by pointing out that these drugs are effective in treating gastric and duodenal ulcers. Nevertheless, adoption of such a policy ignores the fact that these drugs are not completely successful in treating patients with gastric and duodenal ulcers, or those with acid reflux with its tendency to oesophageal stricture, and that potent antisecretories may yet prove useful in managing patients with haematemesis and melaena, where cimetidine and ranitidine have yet to be proved of value.

A more balanced view would permit further development of new agents provided that obviously mutagenic drugs are discarded, together with those whose molecular structure would make direct nitrosation possible. The practice of gross overdosing of test animals might be abandoned or restricted to studies using a narrower dose range—say, up to 50 times the expected human dose—in animals with similar metabolic pathways. Whether hyperplasia of enterochromaffin cells turns out to be a simple byproduct of hypergastrinaemia remains to be seen. If it does the risks to man may still be minimal provided that potent antisecretory drugs are not envisaged as lifetime treatments for younger patients.

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Correction

Resuscitation needed for the curriculum?

In the seventh paragraph of the leading article "Resuscitation needed for the curriculum?" (25 May, p 1531) the address of the Resuscitation Council was wrongly quoted. This should have read: Resuscitation Council (UK), Department of Anaesthetics, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS. We apologise for this error.