increased γ-glutamyltransferase activities (three quarters of whom were hazardous drinkers), and this test is under evaluation as a tool for further investigation, treatment, and control of high alcohol consumption.[26]

In conclusion, commonly available laboratory markers, either individually or in combination, are not effective screening tests for detecting hazardous drinking but do identify those subjects whose alcohol consumption is producing possibly harmful metabolic changes. Further studies are needed to evaluate the place of other promising biological markers such as red blood cell aldehyde dehydrogenase activity,[27] serum desialotransferrin,[28] and serum mitochondrial aspartate aminotransferase activity.[29]

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Regular Review

Antisecretory drugs and gastric cancer

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Many clinicians are worried that prolonged treatment with powerful antisecretory drugs may increase patients' chances of developing gastric cancer, either through hypochlorhydria favouring bacterial growth or through the direct carcinogenic effect of drug molecules. Whether these fears are justified is not clear. We do, however, know that patients with pernicious anaemia have an increased risk of developing gastric cancer, and that patients who have had gastric resections for peptic ulcer may also be at risk. The reasons for this are not understood, but may include mucosal instability associated with atrophic gastritis leading to dysplasia and then gastric cancer, or reduced gastric acidity favouring bacterial growth in the stomach and then the formation of carcinogenic nitrosamines in the presence of ingested nitrates and nitrites.

Four sorts of test are in use to screen drugs for possible carcinogenic effects, but of these no single one may be relied on to reject what is potentially dangerous and to select all, and only, those drugs that are safe.

Drugs are examined for mutagenic activity by searching for changes in the ability of bacterial cultures to survive in media deficient of nutrients when concurrently exposed to the drug. There is no certainty, however, that such screening identifies all potentially mutagenic compounds.

To take this a stage further, prolonged studies in animals are carried out with a dose often 100 times or more than the expected dose in man for the duration of the animal's life. Although efforts are made to ensure that the metabolic pathways of the animals studied do not differ too much from those of man, the meaning of positive or negative results is not clear. Gross overdosing during a two year period in an animal which may be more or less susceptible to cancer is of questionable relevance to intermittent low dose treatment in man over an indefinite period.

Screening procedures in man may be carried out, firstly, by conducting experiments during ordinary dosing to determine if trace amounts of carcinogens are detectable, and, secondly, by surveillance studies on patients having treatment. Again there are problems. Although we believe that gastric cancer occurs, at least in some people, because carcinogens in general, and perhaps nitrosamines in particular, are formed in the stomach, we do not know for sure. Furthermore, any form of surveillance has to take account of the fact that gastric cancer is common in the ordinary community, with an annual incidence of about one in every 4000 men at the age of 50 and one in every 600 aged 70.[1] Finally, the assumption that patients exposed to a drug are, in all other respects, the same as any ordinary population group with absolutely parallel and equivalent disease experience and expectations (apart from the illness for which treatment is being prescribed) is unlikely to be correct.

Cimetidine has been available for seven years, and ranitidine for half that time. Commercially their success has been enormous, and inevitably they are being followed by a group of similar or more powerful agents. But despite a lot of data suggesting that antisecretory drugs either are, or are not, likely to be safe can we confidently say that we are selecting drugs wisely and using them well?

Extensive tests of mutagenicity and safety in animals have given no cause for alarm, and by ordinary clinical criteria both cimetidine and ranitidine have proved safe during short term and maintenance treatment. Opinions diverge, however, about the pathological importance of cases of gastric cancer detected during or after treatment and about a possible rise in intragastric nitrosamine concentration. Thus Reed[2] and Stockbrugger[3] and their colleagues have detected increased concentrations of *N*-nitroso compounds after sampling the gastric contents of patients treated with cimetidine and of patients who had had gastric surgery,[4] and the same analyst detected a transiently raised *N*-nitrosamine concentration in normal people given the new secretory antagonist omeprazole in doses sufficient to reduce intragastric acidity by three quarters.[5]

By contrast, others have failed to detect changes in intragastric conditions that might increase the formation of *N*-nitroso compounds; nor have they found any increase in their concentration in normal people or patients with duodenal ulcers treated with cimetidine,[6-8] nor any increase in total *N*-nitroso compound concentrations in gastric juice after gastric surgery that significantly lowered gastric acidity.[9] In another study a transient increase in mutagenicity was detected in the gastric juice obtained from patients treated with conventional doses of cimetidine or ranitidine, but the results were not unexpected because of the rise in pH and did not seem to be associated with drug use.[10]

Interpretation of the data is complicated by the fact that all those who measure *N*-nitroso compounds may not measure the same things—or even *N*-nitroso compounds at all.[11] Keighley *et al* claimed deliberately to have included unstable and thus more locally active cocarcinogens such as nitrosamides and point out that concentrations of *N*-nitroso compounds may differ fivefold between studies.[9] Sharma *et al*[5] suggest that the methods used in earlier studies cannot be relied on to distinguish between potentially harmful *N*-nitroso compounds and simple nitrite or nitrate,[7,8] although one advantage of these studies was the choice of methods selected for use at pH 4 which reflects the level of acid suppression that is achieved with drug treatment.

Those confused with the conflicting evidence are unlikely to be helped by the results of clinical follow up studies. Cases of gastric cancer were soon detected during treatment with cimetidine, sometimes in patients previously believed to have duodenal ulcers and thus probably already at reduced risk of developing cancer.[12,13] The interval between starting treatment and detecting cancer was so short that cause and effect must be unlikely.

Evidence from individual case reports is inevitably less strong than the results of planned clinical studies, but do follow up studies of the many patients included in controlled clinical trials or properly planned surveillance studies produce more definitive answers? Unfortunately, the answer is probably no, because interpretation of data from controlled trials is made virtually impossible by the probability that control patients may later receive the drug under study. Surveillance studies offer the opportunity to study outcome in large numbers of patients, but again a control group of dyspeptic patients would be impossible to obtain given the high market penetration of histamine H_2 antagonists. Furthermore, in a large surveillance study of 10 000 takers and controls it was evident when the first follow up year's data were reviewed that takers and non-takers were likely to differ radically.[14] Overall death rates were roughly twice as high in takers as in non-takers, as were admissions to hospital and outpatient attendance rates, for a wide variety of conditions, gastric and non-gastric; many, such as lung cancer, cirrhosis, chronic lung disease, accidents, poisonings, and violence were likely to be associated with differing smoking and drinking habits. Scrutiny of the 74 cases of gastric cancer detected in the first survey year suggested that about one third had been present before treatment with cimetidine had been started, and over one third more were advanced tumours detected within six months and therefore likely to have been present well before treatment was started.[15] Of the remaining third, five were diagnosed over a year after initial treatment, and four were thought to be relatively early tumours. Eight cancers were also detected in the non-takers, and the early tumours detected in takers probably represent disease found as a result of the investigative effort rather than a direct effect of the drug.

The belief remains that treatment with the histamine H_2 antagonists cimetidine and ranitidine is generally safe, although we might wish for harder evidence. But how do we assess the risks that may be associated with the more potent antisecretory drugs? Several such compounds have now come to an advanced stage of development but programmes have been halted, temporarily or permanently, after untoward findings in the stomachs of animals treated with large doses over long periods. Lesions described include dysplasia or carcinoma of the squamous forestomach in rats, carcinoma of the glandular pyloric area, and carcinoid changes.

Tiotidine is a potent histamine H_2 antagonist and a guanidinothiazole derivative.[16] Dysplastic or carcinomatous lesions were detected in the pyloric region in 17 of 828 rats treated with 75 to 750 mg/g/day for six to 24 months, with none in 432 controls, tumours being at a site where they have been described after exposure to the carcinogen *N*-methyl-*N*-nitro-*N*-nitrosoguanidine, suggesting that tiotidine may itself be a carcinogen.[17]

SK&F93479 is a selective long acting potent compound with an effective dose of 1 mg/g in man. In rats given doses of 40, 200, and 1000 mg/kg/day for a year focal hyperplasia and hyperkeratosis of the forestomach were noted in about half the animals receiving 1000 mg/kg/day, with two small focal lesions of doubtful importance in 54 given the lowest dose. Lesions were reversible on stopping treatment.[18] These changes were, however, associated with several benign and

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.