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Reply

SIR,—We appreciate the comments of Dr Antonin and Professor Bieck. As pointed out in the introduction to our manuscript, we agree that our observations differ from those of other investigators. Our experiments were, however, carried out under randomised, double blinded controlled conditions, not always the case in other studies.¹ We evaluated for the first time the effect of TDS on total 24 hour acid secretion and measured acid secretion under basal conditions, in response to food, between meals and during the night. We evaluated the effect of TDS on gastric acid secretion when the drug was used alone and when it was used in combination with cimetidine. We could not show an effect of the medication on acid secretion in either case.

While we did not measure urine levels of scopolamine, as suggested, we assume that the drug used by our patients was similar to that used in other studies as it was sent to us as coded medication directly from the manufacturer, Ciba-Geigy Corp, Summit, NJ, USA. It is possible that the bioavailability of TDS varies from batch to batch and that we received a preparation with relatively low bioavailability.

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Reference

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Vagal control of gastric alkaline secretion

SIR,—The paper of Professor Konturek and co-workers on the vagal control of gastric alkaline secretion (*Gut* 1987; **28**: 739-44) was very informative. Most of the findings are well in agreement with those of Feldman *et al*¹ and Forsell *et al*.² A comparison between the non-selective anti-muscarinic atropine and the M1-selective anti-muscarinic pirenzepine with respect to gastric alkaline secretion has, however, not been reported before.

Unfortunately, this comparison has not been carried out in an appropriate way, and the results do therefore not support the authors' conclusions, that M2-receptors rather than M1-receptors are involved in the regulation of gastric alkaline secretion. It is well known that the dose/effect relation between atropine and pirenzepine is 1:5 to 1:10 in weight units concerning the inhibition of exocrine glands using parenteral application.³

It would have been logical, therefore, to compare considerably higher doses of pirenzepine than the maximum 20 µg/kg chosen for atropine. It should be remembered that 10 mg is the smallest dose of pirenzepine available for parenteral application in clinical use, and that the highest dose given in the study of Konturek and coworkers to a volunteer of 70 kg body weight was 1.4 mg.

In conclusion, I feel that the question of whether gastric alkaline secretion is an M1- or M2-receptor dependent process is not yet clarified.

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Reply

SIR,—We greatly appreciate Dr Stockbrügger's comments concerning our recent paper.¹ He raised an interesting theoretical point that our suggestion concerning the involvement of M2 rather than M1 subtypes of muscarinic receptors in the stimulation of gastric alkaline secretion may not be properly documented, because doses of pirenzepine used were too low.

The existence of at least two types of muscarinic receptors (M1 and M2) is based entirely on the comparison of the pharmacological effects of classical antimuscarinic drugs such as atropine, which is believed to be a non selective antagonist and to block M1 and M2 receptors. It is also based on actions of newer agents such as pirenzepine,² or telenzepine,³ which are considered to be more selective by blocking M1 receptors. Hirschowitz and

Molina⁴ reported that vagally stimulated acid secretion in gastric fistula dogs was equally sensitive to inhibition by atropine or pirenzepine, the difference in ED₅₀ being within one order of magnitude. They postulated therefore, that vagal stimulation of gastric acid secretion involves a muscarinic pathway with high affinity for pirenzepine or M1 receptors. In contrast, Soll⁵ found that the potency of pirenzepine in inhibiting acid production in the isolated parietal cells was about 100 times less than that of atropine and postulated that muscarinic receptors of these cells are mainly of M2 type. This difference between atropine and pirenzepine *in vivo* and *in vitro* studies has been explained by the additional action of pirenzepine on M1 receptors on the postganglionic cholinergic neurons of the stomach.

In our study on gastric alkaline secretion the potency ratio between atropine and pirenzepine was at least 5:1, because the dose of atropine as low as 5 µg/kg caused significant suppression of gastric alkaline secretion, while pirenzepine even at a dose of 20 µg/kg was without any influence on basal or vagally stimulated alkaline secretion. This suggests the involvement of M2 rather than M1 receptors, but I agree that using higher doses of pirenzepine could provide stronger support for our conclusion. In our recent studies on gastric fistula dogs, pirenzepine and telenzepine in a dose as large as 80 µg/kg were without any influence on gastric alkaline secretion, but atropine suppressed this secretion at a dose of 5 µg/kg. Moreover, Safsten and Flemstrom⁶ recently reported that in rats pirenzepine may stimulate duodenal alkaline secretion possibly by acting through the M1 receptors in the brain. We did not observe such a stimulatory effect on gastric alkaline secretion in man or dogs, probably because the drug does not penetrate the blood brain barrier in these species.⁷

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Cimetidine and ranitidine on basal and ACTH-stimulated steroidogenesis

SIR,—Recently you published an article on the above by Kenyon *et al* (*Gut* 1986; **27**: 1143–6). Using isolated bovine adrenocortical cell suspensions, the authors evaluated the effect of a wide range of doses of cimetidine and ranitidine (10–1000 mcg/ml) on basal and ACTH-stimulated synthesis of cortisol, corticosterone, and deoxycorticosterone, *in vitro*. Under these conditions, the authors reported that cimetidine and ranitidine inhibited ACTH-stimulated corticosterone and cortisol synthesis. Cimetidine also decreased basal cortisol synthesis and increased ACTH-stimulated deoxycorticosterone synthesis. From their data, the authors postulated: (1) that cimetidine and ranitidine were capable of inhibiting cortisol and corticosterone synthesis in man *in vivo*; (2) that the inhibitory concentrations of drug observed in their study might be achieved in man after bolus intravenous dosing or by selective adrenal accumulation of drug; and (3) that cimetidine exerted its effect on steroid synthesis through cytochrome P-450 dependent enzyme inhibition. The article deserves comment if only to clarify certain points and correct several inaccuracies.

It is not true^{1–14} that ranitidine 'does not interfere with the metabolism of other drugs.' Whether this effect of ranitidine on drug metabolism is related to its inhibition of cortisol and cortisone synthesis, as shown by Kenyon *et al*, is conjectural. The authors assumed that reversible binding by ranitidine to cytochrome P-450 does not occur. It has been shown, however, that ranitidine is capable of binding to cytochrome P-450, but has a 10-fold lower binding affinity than cimetidine.^{15–16} In this case, the inhibition of cortisol and cortisone synthesis probably does not involve inhibition of cytochrome P-450-mediated hydroxylation.

The effects observed by Kenyon *et al* occurred with drug concentrations that were, as they indicated, far in excess of those achieved in normal clinical use. An intravenous bolus dose of cimetidine (300 mg) has