creased and whether a maximal NDGA effect is additive in inhibiting the amebic lysate-induced increase in short-circuit current with that of verapamil vs. that of indomethacin. That is, we support the view that further studies are worth doing to deal with involvement of the lipoxygenase pathway in the amebic lysate-induced Cl secretion.

We continue believing that it is remarkable that these single-cell organisms have figured out a way to interact so complexly with the signal-transduction systems of intestinal epithelial cells.

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Reflux Esophagitis in Zollinger-Ellison Syndrome

Dear Sir:

In a recent issue of GASTROENTEROLOGY, Miller et al. report that reflux esophagitis occurs in the majority of patients with Zollinger-Ellison syndrome (ZES) (1). In this study, among 122 patients with ZES, 61% had esophageal symptoms, endoscopic findings of reflux esophagitis, or both at the initial examination. Nearly all patients were taking H_2-receptor antagonists alone or in combination with anticholinergic drugs, propantheline bromide, or isopropamide at the time of entry to the study. It is well known that anticholinergic drugs have a distinct relaxant effect on the lower esophageal sphincter and can result in increased gastroesophageal reflux (2,3).

The authors do not comment on the impact of use of these anticholinergic drugs that might have contributed to their findings of reflux esophagitis in patients with ZES.

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2. Goyal RK. Identification, localisation and classification of muscarinic receptor subtypes in the gut. Life Sciences 1988;43:2209-2220.
3. Hogan WJ, Dodds WJ. Gastroesophageal reflux disease. In: Sleisenger MH, Fordtran JS, eds. Gastrointestinal disease. Volume 1. 4th ed. Philadelphia: Saunders, 1989:609.

Reply. Dr. Tankurt makes a valid point about the use of anticholinergic agents and reflux that we should have addressed in the paper. We welcome the opportunity to present the data on the use of anticholinergic agents in our patients with Zollinger-Ellison syndrome and esophageal disease.

Because of the lack of safety data with high doses of histamine H_2-receptor antagonists, our initial studies controlled gastric secretion by using low doses of H_2 antagonists together with anticholinergic agents because of the known potentiation of the action of the two classes of drug. Later, when it became clear that high doses of H_2 antagonists were safe, and because of the very points raised by Dr. Tankurt, H_2 antagonists, or more recently omeprazole, were used alone.

Of the 74 patients in the study with reflux disease, 69% never received anticholinergic agents at any time. In these patients, the reduction of acid output to <10 mEq/h (or to <5 or <1 mEq/h in the minority of cases) was sufficient to cause resolution of the esophageal disease. These data therefore suggest that acid hypersecretion alone is sufficient cause for reflux disease in patients with Zollinger-Ellison syndrome and that the reduction of acid is sufficient to resolve the disease.

Sixteen patients (22%) received anticholinergic agents before coming to the National Institutes of Health. In these patients, reduction of acid to <10 mEq/h by increasing the dose of H_2 antagonist produced resolution of the reflux disease irrespective of whether anticholinergic agent therapy was continued (10 patients) or not (6 patients). Nevertheless, the effect of anticholinergic agents was never studied in a formal way in these patients by first stopping the anticholinergic and assessing the esophagus and then increasing the dose of H_2 antagonist to reduce acid output and reassessing. Therefore, we cannot be certain that in these patients anticholinergic agents did not have some role in their disease. However, our data from seven patients discussed below suggest that it is unlikely.

Seven patients arrived at the National Institutes of Health with esophageal disease who were not taking anticholinergics but who were given anticholinergic agents for the first time as part of the regime to reduce acid outputs to <10 mEq/h. The esophageal disease resolved completely in 3, indicating that at least in these patients acid outputs were more important determinants of response than anticholinergic agents. In the other 4 patients symptoms improved but did not resolve even when acid was reduced to <5 mEq/h (with regimes that included anticholinergic agents in 2 cases); reflux disease disease did resolve in all 4 when acid outputs were reduced to <1 mEq/h with omeprazole, again suggesting that acid outputs were the major factor.

For these reasons, we believe that the use of anticholinergic agents per se did not play a major role in the genesis of esophageal disease or its response to therapy in our patients, but that acid secretion and its control was the most important factor. Fortunately, with the availability of omeprazole to control acid secretion, there is no longer a need to use anticholinergic agents in patients with Zollinger-Ellison syndrome.

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Ulcer Healing: Does Omeprazole Efficacy Depend on Daytime or 24-Hour Acid Inhibition?

Dear Sir:

In their recent clinical trial (1), McFarland et al. first compared omeprazole once daily, 20 mg in the morning, with the traditional single bedtime dose of ranitidine, 300 mg, and they found significantly quicker duodenal ulcer healing with the former drug. These authors argued that this finding may depend on the greater efficacy of omeprazole in the control of intragastric acidity, in keeping with the conclusions of Hunt et al.'s meta-analysis (2). However, the success of omeprazole may be mainly related to its excellent suppression of daytime acidity. In fact, three low premeal doses (400 mg) of cimetidine have recently been shown to promote a signifi-