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POSSIBLE ROLE OF *CAMPYLOBACTER PYLORI* IN IDIOPATHIC HYPERAMMONEMIA

To the Editor:

Mitchell and colleagues (Am J Med 1988; 85: 662–667) reported the occurrence of severe unexplained hyperammonemia in a group of patients undergoing intensive chemotherapy. The condition was fatal in several of the patients. No cause could be determined despite extensive investigation, which included histologic examination of the liver in several of the patients at autopsy. In all patients, hyperammonemia was associated with profound leukopenia, suggesting an infectious cause. However, no diagnostic pattern from stool or blood cultures was found. We wonder if data regarding the presence or absence of histologic gastritis and *Campylobacter pylori* are available.

C. pylori produces large quantities of urease [1]. The enzyme may protect the organism from gastric acid, provide a source of utilizable nitrogen, and may also act as a local toxin [2]. *C. pylori* infects about one in 10 otherwise healthy adults in the age range reported by Mitchell *et al* (mean age, 21 years) [3]. The infection is often occult but is almost always associated with type B gastritis [4]. The organism has recently been shown to commonly infect the stomachs of patients with alcoholic liver disease, and concern has been raised regarding its role in urea hydrolysis in this setting [5,6].

Gastric juice urea is significantly decreased and ammonia is increased in patients with *C. pylori* gastritis [5]. A crude estimate (which does not account for juxtamucosal urea hydrolysis) of the amount of ammonia potentially generated by the stomach of infected patients can be made from knowledge of the available amount of urea. Assuming production of 4 L of saliva and gastric juice per day with a urea concentration of 3 mmol/L, hydrolysis of one half of this amount could raise the total body water ammonia concentration to 300 μmol/L. In the stomach, *C. pylori* elicits both a neutrophilic and a monocytic response [4]. That this response is to some extent protective is suggested by a recent report of invasive *C. pylori* in a patient with the acquired immunodeficiency syndrome [7]. The effect of severe drug-induced leukopenia on the organism is unknown.

C. pylori infection quickly relapses after therapy with most commonly used antibiotics unless they are given in combination with bismuth salts. Silver or Giemsa staining of histologic gastric specimens in immunocompromised patients with unexplained hyperammonemia may reveal the presence of *C. pylori*, although inflammatory changes may be minimal if leukopenia is present. Whether or not the production of ammonia by the organism in this group of patients is sufficient to overcome the normal metabolic pathways for ammonia disposal is unknown. This potential complication deserves further investigation.

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The Reply:

In response to the proposal made by Drs. Caldwell and Marshall on the possible role of *Campylobacter pylori* in the pathogenesis of idiopathic hyperammonemia (Am J Med 1988; 85: 662–667), we re-evaluated the culture and histologic data obtained on five patients in whom autopsy was performed. It is interesting that one patient (Patient 5) did indeed have *C. pylori*-associated gastritis. As for the remaining four patients, however, there was neither macroscopic nor microscopic evidence of acute or chronic gastritis. Esophagitis and focal hemorrhages throughout the colon were the only abnormalities found in the gastrointestinal tract.

Although *C. pylori* is only rarely seen in the setting of a histologically normal gastric mucosa [1], we obtained gastric tissue from the latter four patients and re-evaluated these specimens with Giemsa stain. None of the specimens from the four patients, however, showed any evidence of bacterial invasion of the gastric mucosa. Of note, only tissue from the gastric fundus was available for this retrospective analysis and may not have been optimal for making the diagnosis.

On review of the data available thus far, the evidence suggests (but does not rule out) that *C. pylori* is not likely to be the agent responsible for idiopathic hyperammonemia. All nine of the affected patients were receiving at least two parenteral antibiotics (a beta-lactam and aminoglycoside) prior to and during the period of hyperammonemia. Additionally, four of the more recently diagnosed patients were also receiving a fluoroquinolone orally for the purpose of gastrointestinal decontamination. Although resistant organisms have been reported, *C. pylori* should have been controlled by at least one of the antibiotics. Furthermore, each of the nine patients had a low to normal carbon dioxide content (range, 17 to 26 mEq/L) and normal to high blood urea nitrogen level (range, 14 to 109 mg/dL) at the time of diagnosis. Theoretically, *C. pylori*-associated urea hydrolysis should have resulted in elevated levels of carbon dioxide and depressed levels of urea; this was not the case in any patient. Finally, the age of the patients (median, 21 years; range, 18 to 47 years) also suggests that *C. pylori* infection is not likely. As noted by Caldwell and Marshall, the prevalence of *C. pylori* infection is only 10% within this age group. It could be argued, however, that primary infection and the lack of neutralizing antibody in these patients might permit more invasive disease. Whether antibody has any effect on the course of this disease has yet to be demonstrated.