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Helicobacter pylori and Its Interaction with Chief and Parietal Cells

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Helicobacter pylori has been shown, along with other *Helicobacter* species to produce effector molecules that induce substantial physiological changes on acid and pepsin secretion. The effects are clinically evident, and long-term achlorhydria may be a risk factor for gastric cancer. Further identification and characterization of the factors may lead to additional understanding of gastric physiology.

INTRODUCTION

Helicobacter pylori is regarded as a slow bacterium [1] that parasitizes the gastric mucosa for long periods. It has evolved the unique capacity to colonize a niche under the gastric mucus layer in close association with the gastric epithelium. The close proximity of a single bacterial species to physiologically active epithelial cells provides an opportunity to observe the consequences of this interaction. It has become clear since the seminal paper of Marshall and Warren [2] that the concept of Koch's postulates as applied to *H. pylori* infection are tenable only to a limited degree. Koch postulated that 1) the organism must be present in every case; 2) the organism must be isolated and grown in pure culture; 3) the organism must cause the specific disease when inoculated into a susceptible animal; and 4) the organism must the be recovered from the animal and identified. These postulates apply to *H. pylori*-induced gastritis, but they do not yet apply to peptic ulcer and gastric cancer. Hill [3] proposed less specific postulates that are more appropriate to *H. pylori*, which has been associated with a variety of different disorders. These postulates involve issues of temporality, strength, dose-response, reversibility, consistency and biological plausibility.

The majority of those infected with *H. pylori* never develop more than a mild histological change in the gastric mucosa. The clear clinical associations are epidemic [4] and sporadic hypochlorhydria [5], peptic ulcer disease [6], gastric carcinoma [7, 8], primary gastric lymphoma [9] and mucosa associated lymphoid tissue (MALT)[b] lymphoma [10]. The conditions that predispose to each of the above disorders are likely to vary and represent the end result of different interactions between host and bacterium. An example of the interaction of the parietal cell and *H. pylori* is that peptic ulcers require the presence of acid secretion, not an achlorhydric stomach as occurs in epidemic hypochlorhydria. Similarly, there is an old clinical observation that duodenal ulcer patients are protected from the later development of gastric cancer. This anecdotal observation has been given further credence by Parsonnet et al. [9] who noted a negative correlation between duodenal ulcer and gastric cancer.

It is becoming clear that there are variations in the properties of the individual isolates of *H. pylori* and that these can change as a function of the duration of infection or the local

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[b]*Abbreviations:* MALT, mucosa associated lymphoid tissue; AIF, acid inhibitory factor.

environment. The clearest data on this phenomenon is the alteration in the genotype of *H. pylori* by the insertion of a 20 to 30 kilobase piece of DNA [11], termed a "pathogenicity island" by Stanley Falkow. This DNA insert carries homologues of as many as 20 virulence genes from different sources, which include an exporter molecule for Bordetella pertussis, a malarial protein and an invasion factor for Salmonella among others. The presence of this insert creates the genotype, referred to as *cag* 1 or Type 1, and it is present in about 70 percent of strains isolated. Furthermore, if it is present there is a greater likelihood of the development of peptic ulcer disease or gastric cancer. It should, however, be emphasized that the majority of those infected with *H. pylori* never develop clinically apparent disease.

The effect that *H. pylori* has on the chief cell has received little interest. The patterns of change of the serum pepsinogens as a genetic marker for those susceptible to ulcer disease and gastric cancer have become a historical footnote [12], since the abnormal patterns resolve after the eradication of *H. pylori* [13]. Pepsin, however, is thought to play a role in peptic ulceration, and the possible role that *H. pylori* has in increasing pepsin secretion is discussed below.

CLINICAL OBSERVATIONS ON THE EARLY PHASE OF *H. PYLORI* INFECTION AND PARIETAL CELL FUNCTION

The earliest description of what was likely to be *H. pylori* infection was by Sir William Osler, who eloquently described the acute signs and symptoms of infection [14]. He did not describe the incidence of his observations, but his description closely resembles that of subsequent volunteer studies [15, 16] and those with closely observed inadvertent infection [5]. The consensus of description of the early clinical changes are that within seven days of infection there may be headache, nausea and vomiting, epigastric pain and halitosis. Changes in bowel habit are variable: sometimes mild diarrhea develops and others have constipation. Symptoms subside within three days. Signs include a mild fever, particularly in children, a coated tongue, epigastric tenderness and achlorhydria, starting about day eight after infection.

Two investigators took the extreme measure of deliberately infecting themselves with *H. pylori*. Marshall reported epigastric distress, vomiting and halitosis after ingesting an isolate of *H. pylori* (1×10^9 cfu) obtained from a patient with non-ulcer dyspepsia [17]. Morris ingested a different isolate and reported similar changes. In addition, he was found to have developed achlorhydria eight days after infection. He had a gastric pH of 7.6 [15]. This achlorhydria persisted until he took doxycycline on day 26 after the initiation of infection. Acid secretion became normal within three days. His gastric pH went from 7 to 1.6, but *H. pylori* persisted as did the acute superficial gastritis. At no time was there any evidence for the loss of parietal cells. A similar case was reported by Graham et al. [5] in a volunteer who had been infected by the passage of an endoscope during a study on the effects of aspirin on the gastric mucosa. In this volunteer, there was a transient increase in acid and pepsin release, followed in the second week by the disappearance of basal acid secretion. Eight weeks after infection, acid secretion became detectable and had spontaneously returned to normal by six months. These studies provide strong evidence for the role of *H. pylori* in the etiology of achlorhydria. Earlier studies [18, 19] of similar phenomena, although less clearly linked to *H. pylori* infection, appear comparable and provide additional insights into the capacity of *H. pylori* to alter acid secretion.

In a study of gastric acid secretion in 34 volunteers, 17 became achlorhydric for 53 to 235 days [4]. Of these, eight were entirely asymptomatic; the remaining nine had epigastric pain; nausea developed in four and vomiting in two. Those of the 37 who became hypochlorhydric were significantly younger (25 ± 1.0 years vs. 41 ± 3.0 years). All the patients with achlorhydria had gastritis with intact parietal cells and demonstrated a raised

serum gastrin to about twice the normal range. Interestingly, the elevated serum gastrin is numerically comparable to the elevations seen in *H. pylori* infection when acid secretion is within the normal range. Among the 37 volunteers were three who did not recover their acid secretion as long as they were studied. In addition, one patient with pre-existent Zollinger Ellison syndrome of four years duration became achlorhydric in Nov. 1976. In March 1977 and in March 1978, he still had a severe gastritis but no acid secretion. During follow-up, the serum gastrin remained very high, implying that the gastrinoma was still functional. Studies of mucosal permeability were performed on some of the achlorhydric patients to determine whether the loss of acid secretion was due to back diffusion. No evidence for this was found. There have been other reports of epidemics and sporadic cases of apparent parietal cell failure, including one with Zollinger-Ellison syndrome [20]. All of the cases with achlorhydria had histological gastritis and normal but presumably non-functional parietal cells.

In a study designed to determine the prevalence of *H. pylori* infection in healthy asymptomatic healthy young adult volunteers [21], 25 percent of those with *H. pylori* infection had diminished acid secretion. El Omar et al. [22] recently reported finding 11 patients with *H. pylori* infection who unexpectedly had achlorhydria, even when stimulated to secrete acid. In the absence of a non-invasive means of detecting achlorhydria and no symptoms to suggest its presence, we can only speculate as to its true prevalence in the community and to its incidence on initial infection.

EXPERIMENTAL EVIDENCE FOR THE ASSOCIATION OF *H. PYLORI* AND ACHLORHYDRIA

The previous section provides clinical evidence for the association of *H. pylori* and achlorhydria, but the mechanisms involved are not clear. The achlorhydria could be a response to a factor(s) produced by the organism or mediated by the host itself. It is known that both *E. coli* [23] and *Pseudomonas* [24] lipopolysaccharide, given intravenously to rats and dogs, respectively, can inhibit acid secretion. On the host side of the equation, interleukin-1 has been shown to reduce acid secretion when given intravenously to rats [25]. Similar finding have been reported with T cell growth factor. (There remains the intransigent problem as to whether these factors are functioning as a physiological or pharmaceutical agent in the doses used in these studies.

The likelihood of the achlorhydria being mediated by a cytokine released as part of the inflammatory process of the gastritis process is low. This was particularly well demonstrated in the Morris study [15] when the gastritis continued unabated after the volunteers' acid secretion recovered, presumably with continued production of inflammatory cytokines. Back diffusion of acid is unlikely to be the explanation, as evidenced by the testing performed by Ramsey et al. [4] in the epidemic of achlorhydria, leaving the possibility of *H. pylori* itself causing the achlorhydria. It should be noted that in some of the patients studied by Ramsey et al. [4] there was abolition of both basal and stimulated acid secretion. Such a profound effect raises the possibility that the mechanism involves the final common pathway of acid secretion.

Studies designed to establish animal models of *Helicobacter* infection have been reported in several animal species, using various *Helicobacter* species. Intact animal studies in ferrets have shown that when four non-infected ferrets were infected with 1.5 x108.5 cfu of *H. mustelae*, four weeks later they developed transient achlorhydria for two weeks, as measured by elevated gastric pH. (pH 4-5.2) [26]. Interestingly, during this phase it was possible to recover viable *H. mustelae* from the stool [27]. This suggests the concept that the achlorhydric phase may be induced by the bacteria as a spreading mechanism, by which it can find new hosts via the fecal/oral route. The subsequent return to normal levels of gastric secretion and the inability to subsequently culture *H. mustelae* from the stool

supports this view. The achlorhydria occurs too late after infection has been established for it to be regarded as a colonization factor. Canine gastritis has been reported in beagle dogs infected with *H. felis* [28]. The dogs were infected at seven days of age with 1 x 10^9 *H. felis*. At 30 days, immediately after euthanasia, the gastric pH was measured in five dogs and was 7.7, 6.0, 2.6, 3.7 and 2.9; in two control dogs, the gastric pH was 2.0 and 3.6. Thus, there is evidence that *H. felis* can cause achlorhydria in an alternative host. There are no reports of changes in acid secretion in other animal model systems.

The mediators of the hypochlorhydria seen in response to infection with *H. pylori*, *H. mustelae* and *H. felis* have received some attention. In 1989, there were two preliminary reports of the effect of either whole *H. pylori* or its sonicate on the uptake of ^{14}C-aminopyrine, a weak base, into isolated gastric glands from rabbits or guinea pigs [29, 30]. In both systems, there was a substantial reduction of uptake of the aminopyrine, which on entry into low pH compartments of the cell becomes ionized and trapped. This method is widely accepted as a means of measuring acid secretion *in vitro*. Cave and Vargas expanded the initial observations and were able to show that the effect on the parietal cells was not due to alterations in protein synthesis [31]. The inhibitory factor was not significantly impaired by heating to 60°C for 30 minutes, but boiling for the same period destroyed its activity. The material was not dialysable (12kD cut-off) and was present in low concentrations, especially in the bacterial supernatant. The factor was not inhibited by trypsin, but was destroyed by pronase, a non-selective protease. Subsequently, the same group evaluated the effect of different *Helicobacter* species on isolated rabbit and ferret gastric glands [32]. They showed that *H. pylori*, *H. felis* and *H. mustelae* all caused acid inhibition, but with some variations in degree, depending on the individual isolate. Control organisms, including *Escherichia coli*, *Proteus vulgaris* and *Klebsiella oxytoca*, had some inhibitory effect on the ^{14}C-aminopyrine uptake [33]. No effect was seen with *Campylobacter jejuni*. The authors concluded that there may be a general property of *Helicobacter* species that inhibit acid secretion *in vitro*. Jablonski et al. have shown a similar effect with *H. pylori* on isolated human gastric glands obtained at surgical resection [34]. Progress in this field has been slowed by difficulties in growing large amounts of *H. pylori* and the inability to obtain sufficient material for biochemical analysis. The problem was solved by Kane et al. [35] who have been able to grow 10 liter batches of the bacterium in 24-48 hr to high optical densities. They used a bacterial fermenter and used one percent cyclodextrin as a growth factor. Most importantly, they found that the anti-foaming agent, used to minimize the froth formed when proteinaceous solutions are agitated, was inhibitory to *H. pylori*. Elimination of this from the culture profoundly enhanced the growth of the organism.

There are now four candidate factors for the inhibition of acid secretion: First, ammonia is produced by all isolates of *H. pylori* by the hydrolysis of urea by bacterial urease. This base is present all the time that the organism is present, as a function of constitutively-expressed urease and could not, therefore, account for the episodic nature of the achlorhydria. Indeed, the etiologic role of ammonia in gastritis has been seriously question by acute animal experiments in which sonicates of urease-positive and negative mutants showed no differences in the resulting tissue injury, which was attributable to *cagA* and *vacA* [36]. It is also arguable that there is insufficient ammonia to cause complete neutralization of acid secretion. Second, Beil et al. [37] have shown that the fatty acids, cis-9,10-methyleneoctadecanoic acid and tetradecanoic acid, are able to inhibit the H^+/K^+-ATPase of isolated guinea pig parietal cells. These fatty acids, which are constituents of the bacterial cell wall of *H. pylori*, gave comparable results to those with lysates of *H. pylori*. However, the experiments were performed differently to those reported by Cave et al. [38], who used an organic solvent to extract what they have called acid inhibitory factor 2 (AIF-2). The fatty acids were used as emulsions because of solubility

problems. Beil et al. suggested that the effect of these fatty acids explained the acid inhibitory effect reported by Cave et al. as being due to AIF-2. The likely constitutive presence of the fatty acids do not explain the changes seen in acid secretion with respect to time as discussed above. Huang et al. [39] have recently reported the purification of a water soluble 92 kD protein from *H. pylori* that has two subunits of 46 kD. This protein has an isoelectric point of 7.3 and does not appear to be glycosylated. Preliminary evaluation of the N-terminal amino acid sequence suggests that this is a unique protein as compared with other reported proteins. The last factor so far described is AIF-2 [38]. The presence of this factor became apparent, when it was noted that there was residual acid inhibitory activity after AIF-1 had been inactivated by heating. This factor is much smaller than AIF-1, being about 1-2 kD, and is extractable into a variety of organic solvents. The solubility profile suggests that the molecule is comparable to nigericin, a cyclic ether, that functions as an ionophore for H^+ and K^+ ions. Preliminary studies using porcine vesicles derived from gastric epithelium containing the K^+/H^+-ATPase, support this view. Progress with further definition of this factor has been slow because of its insolubility in water. The solvents used to date all interfere with the ^{14}C-aminopyrine assay. Thus, there are a number of candidate molecules that might be involved with reduction of acid secretion. For one of them to be the causative factor in epidemic achlorhydria, it has to be a factor that can be regulated, either by the bacterium itself of by environmental factors. Clearly, a factor(s) that can cause such a profound change in a physiological process will be of great interest.

EVIDENCE FOR THE INTERACTION OF *H. PYLORI* AND CHIEF CELLS

Interest in pepsin as a mediator of peptic ulcer disease has always played a subsidiary role to that of acid secretion. This, at least in part, is due to the fact that measurement of pepsin is much more difficult than hydrochloric acid and that there has been the tacit assumption that the two are secreted together. That there is an increase in serum pepsinogens in ulcer disease has been known for many years. More recently, there has been the demonstration that pepsin 1 becomes the predominant species in one-half to two-thirds of patients with ulcer disease [40]. Pepsin 1 is biologically active over a much wider pH range than the predominant pepsin 3 found in normal individuals. This observation was extended to show that the degradation of mucus by pepsin 1 was significantly more effective than by pepsin 3 [41]. The alteration of the serum pepsinogens, originally thought to be genetically mediated, is now, clearly, a function of *H. pylori* infection. Several authors have described normalization of the changes after eradication of infection [13, 42].

The change in pattern of the serum pepsinogens and the increase in pepsin secretion in response to *H. pylori* infection, which is a non-invasive organism, raises some important questions as to how the changes are mediated. Are these changes a nonspecific response to the inflammatory process? Do they reflect anatomical changes of bacterial population? Or is this a specific signaled event? Two groups have started to examine the possibility of there being a specific mechanism whereby *H. pylori* mediates changes in pepsin release. Cave and Cave [43] tested three *H. pylori* isolates for their ability to stimulate pepsin release from isolated gastric glands. Two of the three isolates significantly increased pepsin release. This effect was additive to that of known stimulants such as cholecystokinin or carbachol and isobutylmethlyxanthine, a phosphodiesterase inhibitor. The effect was not blocked by atropine or cimetidine but was destroyed by boiling, pronase treatment or dialysis (12 kD cutoff). They further confirmed that in these short term experiments of 1 hr, there was no increase in the release of lactate dehydrogenase. These data were interpreted to show that there was no immediate non-specific cell injury and that pepsinogen release was mediated by a small peptide or protein. The second group used a different approach by testing for the release of pepsin in an Ussing chamber [44].

With this system, they were able to show that there was a 50-fold increase in release of pepsin with one isolate of *H. pylori* and only 12-fold with *E. coli.* The method had the advantage that whole tissues were used, and these could be monitored for function and integrity by measurement of resistance and current across the tissues. The preparation of the sonicates and subsequent extraction showed the activity was present in the water soluble component of the bacterial lipopolysaccharide. The lipopolysaccharide of *H. pylori* is, by most criteria, remarkably non-toxic as compared with that of *E. coli*, implying that the effect may be specific. The authors could not exclude the possibility of an associated peptide being the active ingredient. Thus, both studies suggest comparable molecules are increasing pepsinogen secretion. Whether these factors are capable of not only releasing pepsin into the lumen but also increasing serum pepsinogens remains to be defined. Further purification and characterization of the factor(s) is awaited.

CONCLUSION

H. pylori has been shown, along with other *Helicobacter* species to produce effector molecules that induce substantial physiological changes on acid and pepsin secretion. The effects are clinically evident, and long-term achlorhydria may be a risk factor for gastric cancer. Further identification and characterization of the factors may lead to additional understanding of gastric physiology.

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REFERENCES

1. Blaser, M.J. and Parsonnet, J. Parasitism by the slow bacterium *Helicobacter pylori* leads to altered gastric homeostasis and neoplasia. J. Clin. Invest. 94:4-8, 1994.
2. Marshall, B.J. and Warren, J.R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1:1311-1315, 1984.
3. Hill, A.B. The environment and disease. Association and causation. Proc. R. Soc. Med. 58:295-300, 1965.
4. Ramsey, E.J., Carey, K.V., Peterson, W.L., Jackson, J.J., Murphy, F.K., Read, N.W., Taylor, K.B., Trier, J.S., and Fordtran, J.S. Epidemic gastritis with hypochlorhydria. Gastroenterology 76:1449-1457, 1979.
5. Graham, D.Y., Alpert, L.C., Lacey Smith, J., and Yoshimura, H.H. Iatrogenic *Campylobacter pylori* infection is a cause of epidemic achlorhydria. Am. J. Gastroenterol. 83:974-980, 1995.
6. Graham, D.Y. and Go, M.F. *Helicobacter pylori*: current status. Gastroenterology 105:279-282, 1993.
7. Parsonnet, J., Friedman, G.D., Vandersteen, D.P., Chang, Y., Vogelman, J.H., Orentreich, N., and Sibley, R.K. *Helicobacter pylori* infection and the risk of gastric carcinoma. N. Engl. J. Med. 325:1127-1131, 1991.
8. Nomura, A., Stemmerman, G.N., Chyou, P.H., Kato, I., Perez-Perez, G., and Blaser, M.J. *Helicobacter pylori* infection among Japanese-Americans living in Hawaii. N. Engl. J. Med. 1325:1132-1136, 1991.
9. Parsonnet, J., Hansen, S., Rodriguez, L., Gelb, A.B., Warnko, R.A., Jellum, E., Orentreich, N., Vogelman, J.H., and Friedman, G.D. *Helicobacter pylori* infection and gastric lymphoma. N. Engl. J. Med. 330:1267-1271, 1994.
10. Wotherspoon, A.C., Doglioni, C., Diss, T.C., Pan, L., Moschini, A., DeBoni, M., and Isaacson, P.G. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori.* Lancet 342:575-577, 1993.
11. Akopyants, N.S., Kersulyte, D., and Berg, D.E. CAG11, a new multigene locus associated with virulence in *Helicobacter pylori.* Gut 1995; 37(suppl 1 A1) (Abstract).
12. Moran, A.P., Helander, I.M., and Kosunen, T.U. Compositional analysis of *Helicobacter pylori* rough-form lipopolysaccharides. J. Bacteriol. 174:1370-1377, 1992.
13. Hunter, F.M., Correa, P., Fontham, E., Ruiz, B., Sobhan, M., and Samloff, I.M. Serum pepsinogens as markers of response to therapy for *Helicobacter pylori* gastritis. Dig. Dis. Sci. 38:2081-2086, 1993.

14. Osler, W. Diseases of the stomach. In: Osler, W., ed. The Principles and Practice of Medicine. New York: Appleton; 1920.
15. Morris, A. and Nicholson, G. Ingestion of *Campylobacter pylori* causes gastritis and raised fasting pH. Am. J. Gastroenterol. 82:192-199, 1987.
16. Morris, A.J., Ali, R., Nicholson, G.I., Perez-Perez, G.I., Blaser, M.J. Long-term follow-up of voluntary ingestion of *Helicobacter pylori*. Ann. Int. Med. 114:662-663, 1991.
17. Marshall, B.J., Armstrong, J.A., McGechie, D.B., and Glancy, R.J. Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. Med. J. Australia 142:436-439, 1985.
18. Spiro, H.M. and Schwartz, R.D. Superficial gastritis: a cause of temporary achlorhydria and hyperpepsinemia. N. Engl. J. Med. 259:682-684, 1958.
19. Sonnenberg, A., Bartmess, J., Kern, L., Siebenmann, R.E., Joris, F., Blum, A.L. Hypochlorhydrie bei akuter Gastritis. Dtsche. Med. Wochensch. 104:1-3,1979.
20. Wiersinga, W.M. and Tytgat, G.N. Clinical recovery owing to target parietal cell failure in a patient with Zollinger-Ellison syndrome. Gastroenterology 73:1413-1417, 1977.
21. Barthel, J.S., Westblom, T.U., Havey, A.D., Gonzalez, F., Everett, E.D. Gastritis and *Campylobacter pylori* in healthy, asymptomatic volunteers. Arch. Intern. Med. 148:1149-1151, 1988.
22. el-Omar, E., Wirz, A., and McColl, K.E.L. Divergent effect of *H. pylori* on acid secretion. Gut 37:A82(Abstract), 1995.
23. Baume, P.E., Nicholls, A., and Baxter, C.H. Inhibition of gastric acid secretion by a purified bacterial lipopolysaccharide. Nature 215:59-60, 1967.
24. Wyllie, J.H., Limbosch, J.M., and Nyhus, L.M. Inhibition of gastric acid secretion by bacterial lipopolysaccharide (Lett). Nature 215:879, 1967.
25. Wallace, J.L., Cucala, M., Mugridge, K., and Parente, L. Secretagogue specific effects of interleukin-1 on gastric secretion. Am. J. Physiol. 261:G559-G564, 1991.
26. Fox, J.G., Blanco, M.C., Yan, L., Shames, B., Polidoro, D., Dewhirst, F.E., and Paster, B.J. Role of gastric pH in isolation of *Helicobacter mustelae* from the feces of ferrets. Gastroenterology 104:,86-92, 1993.
27. Fox, J.G., Paster, B..J, and Dewhirst, F.E., Taylor, N.S., Yan, L.L., Macuch, P.J., and Chmura, L.M. *Helicobacter mustelae* isolation from feces of ferrets: evidence to support fecal-oral transmission of a gastric *Helicobacter*. Infect. Immun. 60:606-611, 1992.
28. Lee, A., Krakowka, S., Fox, J.G., Otto, G., Eaton, K.A., and Murphy, J.C. Role of Helicobacter felis in chronic canine gastritis. Vet. Pathol. 29:487-494, 1992.
29. Cave, D.R. and Vargas, M. *Campylobacter pylori* (CP) inhibits uptake of ^{14}C-aminopyrine by rabbit gastric epithelial cells. Gastroenterology 96:A79(Abstract), 1989.
30. Defize, J., Goldie, J., and Hunt, R.H. Inhibition of acid production by *Campylobacter pylori* in isolated guinea pig parietal cells. Gastroenterology 96:114(Abstract), 1989.
31. Cave, D.R. and Vargas, M. Effect of a *Campylobacter pylori* protein on acid secretion by parietal cells. Lancet 2:187-189, 1989.
32. Hoffman, J.S., King, W.W., Fox, J.G., Janik, D., and Cave, D.R. Rabbit and ferret parietal cell inhibition by *Helicobacter* species. Dig. Dis. Sci. 40:147-152, 1995.
33. Vargas, M., Lee, A., Fox, J.G., and Cave, D.R. Inhibition of acid secretion from parietal cells by non-human-infecting *Helicobacter* species: a factor in colonization of gastric mucosa? Infect. Immun. 59:3694-3699, 1991.
34. Jablonski, H., Hengels, K.J., Savade, C., and Strohmeyer, G. *Helicobacter pylori* (H.p) from patients with gastritis inhibit acid production more frequently than H.p. from duodenal ulcer patients. Gastroenterology 104:A110(Abstract), 1993.
35. Kane, A.V. and Plaut, A.G. Emulsifiers in antifoam/antigas preparations are bactericidal *in vitro* for *Helicobacter pylori*. Gastroenterology 108: A128(Abstract), 1995.
36. Ghiara, P., Marchetti, M., Blaser, M.J., Tummuru, M.K., Cover, T.L., Segal, E.D., Tompkins, L.S., and Rappuoli, R. Role of the *Helicobacter pylori* virulence factors vacuolating cytotoxin, CagA, and urease in a mouse model of disease. Infect. Immun. 63:4154-4160, 1995.
37. Beil, W., Birkholz, C., Wagner, S., and Sewing, K.F. Interaction of *Helicobacter pylori* and its fatty acids with parietal cells and gastric H^+/K^+-ATPase. Gut 35:1176-1180, 1995.
38. Cave, D.R., King, W.W., Hoffman, J.S. Production of two chemically distinct acid-inhibitory factors by *Helicobacter pylori*. Eur. J. Gastro. Hepatol. 5:S23-S27, 1995.
39. Huang, L.L., Cave, D.R., Kane, A.V. Purification and characterization of an acid inhibitory protein from *Helicobacter pylori*. Gastroenterology 108:(Abstract), 1995.
40. Rotter, J.I., Petersen, G., Samloff, I.M., McConnell, R.B., Ellis, A., Spence, M.A., and Rimoin, D.L. Genetic heterogeneity of hyperpepsinogenemic I and normopepsinogenemic I duodenal ulcer disease. Ann. Intern. Med. 91: 372-377, 1979.

41. Pearson, J.P., Ward, R., Allen, A., Roberts, N.B., and Taylor, W.H. Mucus degradation by pepsin:comparison of mucolytic activity of human pepsin 1 and 3: implications in peptic ulcer. Gut 27:243-246, 1986.
42. Wagner, S., Haruma, K., Gladziwa, U., Soudah, B., Gebel, M., Bleck, J., Schmidt, H., and Manns, M. *Helicobacter pylori* infection and serum pepsinogen A, pepsinogen C, and gastrin in gastritis and peptic ulcer: significance of inflammation and effect of bacterial eradication. Am J Gastroenterol 89:1211-1218, 1994.
43. Cave, T.R. and Cave, D.R. *Helicobacter pylori* stimulates pepsin secretion from isolated rabbit gastric glands. Scand. J. of Gastro. 181(Suppl.):9-14, 1991.
44. Young, G.O., Stemmet, N., Lastovica, A., van der Merwe, E.L., Louw, J.A., Modlin, I.M., and Marks, I.N. *Helicobacter pylori* lipopolysaccharide stimulates gastric mucosal pepsinogen secretion. Aliment. Pharmacol. Ther. 6:169-177, 1992.