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Emergence of Diverse *Helicobacter* Species in the Pathogenesis of Gastric and Enterohepatic Diseases

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INTRODUCTION

It was long believed that the normal human stomach was sterile or colonized only with small numbers of bacteria. The mechanism of what was referred to as the "gastric bactericidal barrier" was debated in the early part of this century (22), but most authors then, as well as more recently (171), concluded that the predominant effect was due to gastric acid. However, the cultivation of a novel bacterium from gastric mucosa in 1982 marked a turning point in our understanding of gastrointestinal microbial ecology and disease. Marshall and Warren (265) described spiral or curved bacilli in histologic sections from 58 of 100 consecutive biopsy specimens of human gastric antral mucosa, 11 of which were culture positive for a gram-negative, microaerophilic bacterium. The organism was thought originally to be a member of the genus *Campylobacter* and was named *Campylobacter pyloridis*, later corrected to *Campylobacter pylori*. Because subsequent 16S rRNA sequence analysis showed that the distance between the true campylobacters and *C. pylori* was sufficient to exclude it from the *Campylobacter* genus (336), it was renamed *Helicobacter pylori* (180), the first member of the new genus *Helicobacter*.

The early proposal of Marshall and Warren (265) that the newly described bacterium caused gastritis and peptic ulcer proved correct. Furthermore, there is now overwhelming evidence that *H. pylori* is linked to gastric adenocarcinoma (208, 301, 317), the second most common cause of cancer morbidity and mortality worldwide, and to the development of gastric non-Hodgkin's lymphoma (318, 435). The clinical significance of this bacterium has recently been emphasized by a National Institutes of Health consensus panel that recommended antibiotic therapy for the large majority of peptic ulcer patients who are infected with *H. pylori* (12) and by classification of *H. pylori* as a class I (definite) carcinogen by the World Health Organization (13). The vast literature on *H. pylori* has been reviewed recently in this journal (93), and the complete genome sequence of two strains is now available (6, 82, 260, 395).

Nevertheless, Marshall and Warren were not the first to detect gastric spiral bacteria. Spiral organisms were first seen in human gastric mucosa beginning early in the 20th century (235) and were subsequently described by several investigators (reviewed in reference 264). The bacteria were often seen in malignant or ulcerated gastric tissue (165), and the possibility of an infectious cause of peptic ulcer disease was considered (19). Some even specifically proposed that a search be made for an organism "thriving in hydrochloric acid medium . . . as a possible factor of chronicity, if not an etiological factor, in peptic ulcer" (see the discussion following reference 165). The suggestion that ulcers might be caused by infection was not new at that time, although an authoritative review published in 1950 concluded that the evidence did not support infection as a cause of peptic ulcer in humans (216). Even before the early observations of gastric spiral bacteria in humans, similar organisms were seen in animals. In his 1881 thesis submitted to the Faculty of Medicine, Rappin described spiral bacteria in gastric scrapings from dogs (330). This observation was later confirmed by Bizzozero (30) and Salomon (344), who performed experimental inoculations with gastric scrapings to transmit infection to mice. Gastric spiral bacteria were subsequently seen in cats (255), rhesus macaques (81), and, more recently, in a variety of other animals.

The cultivation of *H. pylori* and the recognition of its clinical significance served to renew interest in bacteria associated with the gastrointestinal and hepatobiliary tracts of humans and other animals, many of which have now been identified as novel species of *Helicobacter*. These organisms are of interest both because of their pathogenic role in humans and animals

TABLE 1. Gastric *Helicobacter* taxa

Taxon	Natural host	Strain or clone	GenBank 16S rRNA accession no.	Reference
H. acinonychis	Cheetah	ATCC 51101^T	M88148	97
H. bizzozeroni	Dog	ATCC 700030^T	Y09404	195
Candidatus Helicobacter bovis	Cattle	Clone R2XA	AF127027	71
H. felis	Cat, dog	ATCC 49179^T	M37642	319
"*H. heilmannii*"[a]	Human, nonhuman primate[a]	Clone G1A1	L10079	371
Candidatus Helicobacter suis	Pig	Clone V2BXA	AF127028	70
H. mustelae	Ferret	ATCC 43772^T	M35048	180
H. nemestrinae[b]	Pigtailed macaque	ATCC 49396^T	X67854	42
H. pylori	Human, rhesus macaque	ATCC 43504^T	M88157	180
H. salomonis	Dog	CCUG37845^T	U89351	219
"*H. suncus*"	House musk shrew	Kaz-1	AB006147	182

[a] Probably identical to *Candidatus* Helicobacter suis. Bacteria with the 16S rRNA sequence present in "*H. heilmannii*" type 1 have to date been identified in humans, pigs, and nonhuman primates, although the host range is probably more extensive. Other hosts have organisms with the "*H. heilmannii*" morphology that may represent *H. bizzozeronii* or other *Helicobacter* species not yet identified.

[b] Unpublished data suggest that *H. nemestrinae* may be identical to *H. pylori* (see the text).

and because of their value as models of human disease. Other bacteria have also been newly identified, or in some cases reclassified, as novel *Helicobacter* species that infect humans. The purpose of this review is to describe these other *Helicobacter* species, characterize their role in the pathogenesis of gastrointestinal and enterohepatic diseases, and discuss their implications for our understanding of *H. pylori* infection in humans. We conclude with a discussion of an ecological perspective on *Helicobacter* pathogenesis and recommendations for future work.

GASTRIC *HELICOBACTER* SPECIES

To date, eight cultivated *Helicobacter* species have been found in the stomach of humans and other animals, as well as two uncultivated organisms (Table 1). Occasionally a species such as *Helicobacter muridarum*, which typically colonizes the rodent bowel, is found in the stomach. These organisms are considered later along with other enterohepatic *Helicobacter* species.

Early Morphological Observations

Most of the early observations on gastric spiral bacteria were made in dogs and cats. When the first electron micrograph of these bacteria was published, it was immediately apparent that more than one morphological form could be found (418). Lockard and Boler (257) provided the first high-quality electron micrographs of what are now called Lockard type 1, 2, and 3 bacteria (150, 151); all are now known to represent *Helicobacter* species. Lockard type 1, which is representative of *Helicobacter* sp. flexispira, *Helicobacter bilis*, and others (see "Enterohepatic *Helicobacter* species" below), has a fusiform to slightly spiral morphology with tapered ends. Multiple periplasmic fibers appear to cover the entire surface of the bacterium (Fig. 1). Lockard type 2 is spiral rather than cylindrical and has periplasmic fibers that are more sparsely distributed and can appear singly or in groups of two, three, and occasionally four (Fig. 2). This organism is the typical morphology of *Helicobacter felis*. Lockard type 3, which resembles type 2 but is somewhat more tightly coiled and does not have periplasmic fibers, is typical of *Helicobacter bizzozeronii* and the uncultivated "*Helicobacter heilmannii*" (Fig. 3). A fourth type, similar to Lockard type 3 but thicker and with fewer coils, was described in the original electron micrographs published by Weber and Schmittdiel (418) but not by Lockard and Boler. This organism may represent *Helicobacter salomonis*, recently cultivated from dogs (219). The morphology of gastric *Helicobacter* species isolated from hosts other than dogs and cats is sometimes distinctive (e.g., *Helicobacter mustelae* [Fig. 4]) and in other cases resembles *H. pylori* (eg., *H. acinonychis*).

Helicobacter mustelae

The ferret (*Mustela putorius*) stomach has anatomical and physiological similarities to that of humans (135) and is known to experience naturally occurring gastritis and gastric ulcers (191). Shortly after the publication in 1984 of the seminal observations of Marshall and Warren, a *Campylobacter*-like organism was isolated by Fox et al. from gastric tissue of one ferret with a gastric ulcer and from two others with normal gastric mucosa (148). This observation was quickly confirmed by others (331, 396). The ferret organism was morphologically and biochemically very similar to what was then called *C. pylori*, and it was originally designated *C. pylori* subsp. *mustelae* (139). However, DNA relatedness and 16S rRNA sequence analyses showed that the organism isolated from ferrets was a novel species, which was named *C. mustelae* (141) and later renamed *H. mustelae* (180).

Microbiology and phylogeny. Compared with *H. pylori* (Fig. 5), *H. mustelae* is a small rod (0.5 by 2 μm), sometimes slightly curved, with multiple sheathed flagella located at both poles as well as laterally (Fig. 4). Like all gastric *Helicobacter* species, *H. mustelae* hydrolyzes urea, although it has other distinctive characteristics such as susceptibility to nalidixic acid (Table 2). The fatty acid composition (379) and protein profiles (287) of *H. mustelae* are also distinct from those of *H. pylori*. A phylogenetic tree (Fig. 6) based on a 16S rRNA similarity matrix (Table 3) places *H. mustelae* closer to *Helicobacter* species that infect the colon or the hepatobiliary system, particularly *H. pametensis* and *H. cholecystus*, than to other gastric *Helicobacter* species. *H. mustelae* has a preponderance of hexadecanoic fatty acids, which is characteristic of enteric *Helicobacter* species and unusual among species that infect the stomach (198). The genome size of *H. mustelae* is approximately 1.7 Mb

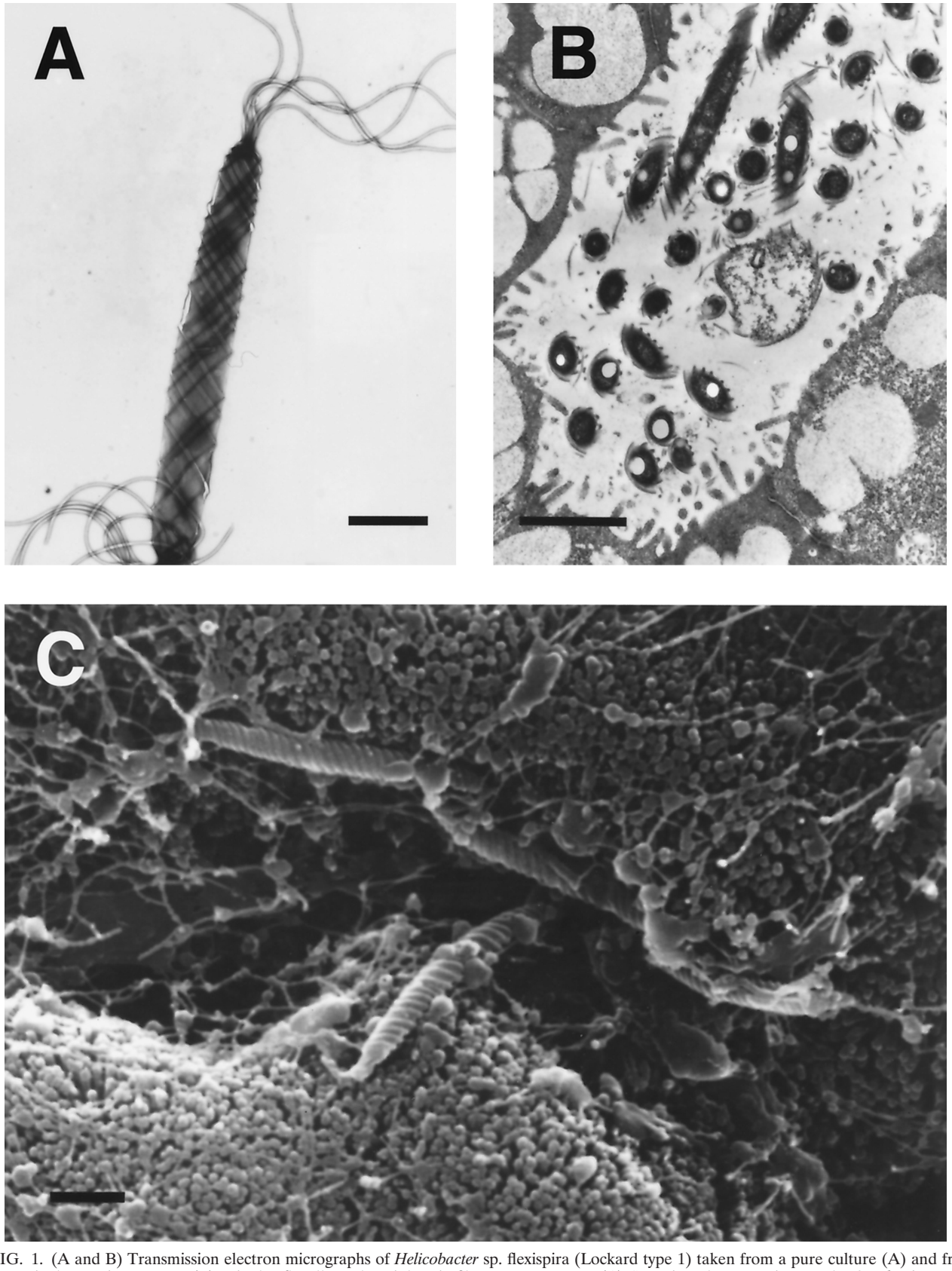

FIG. 1. (A and B) Transmission electron micrographs of *Helicobacter* sp. flexispira (Lockard type 1) taken from a pure culture (A) and from an intestinal crypt in a mouse (B). Bipolar flagella and periplasmic fibers are apparent. (C) Scanning electron micrograph of *Helicobacter* sp. flexispira shows the organisms among intestinal microvilli in a mouse. Bars, 1 μm. Reprinted from reference 346 with permission from the publisher.

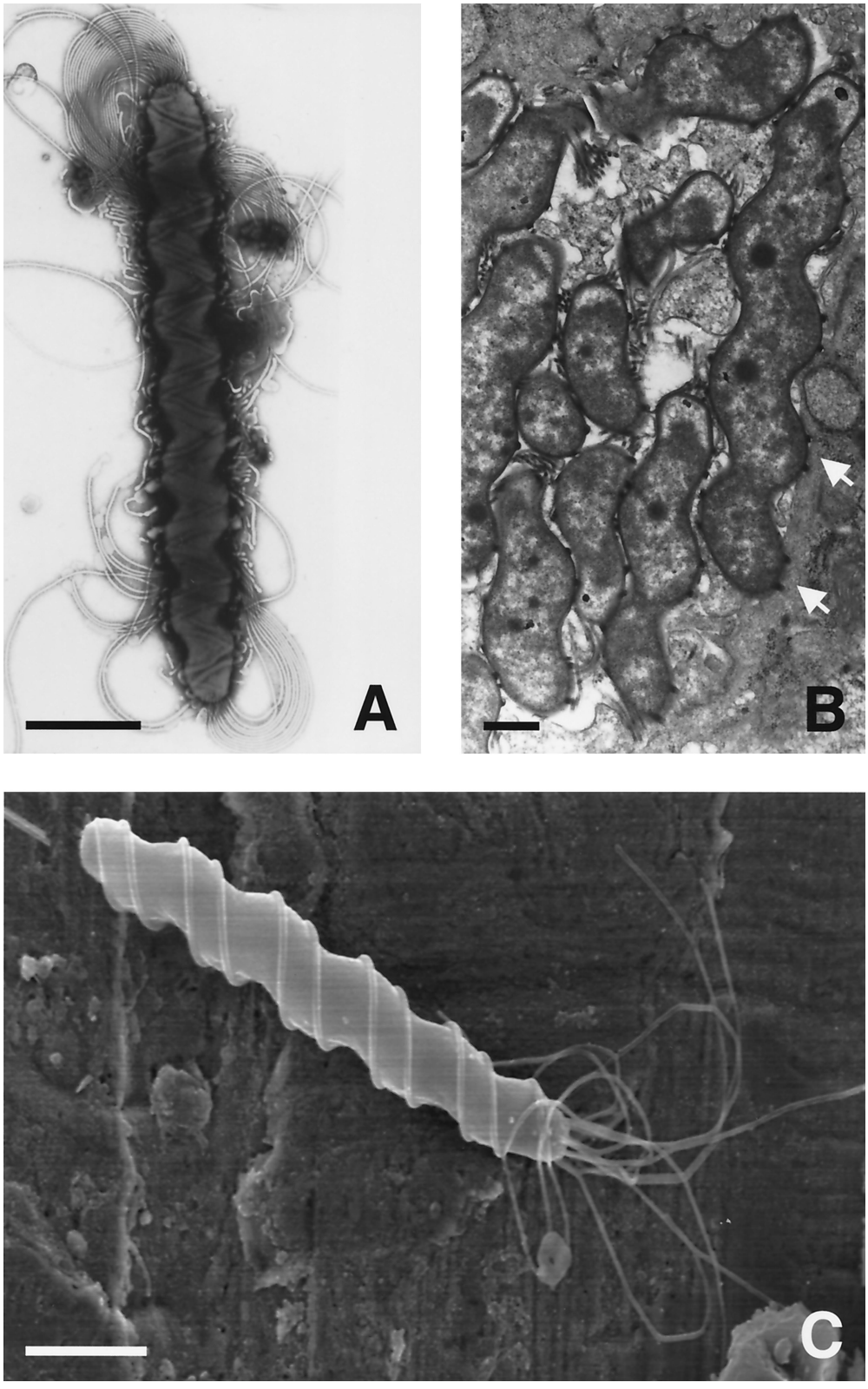

FIG. 2. (A) Negatively stained preparation of *H. felis* (Lockard type 2) isolated from the gastric mucosa of an adult cat shows the multiple bipolar flagella. Bar, 1 μm. (C) Although faintly seen in Panel A, the characteristic periplasmic fibers are better visualized on a scanning electron micrograph. Bar, 1 μm. (B) Transmission electron micrograph of *H. felis* in the gastric mucosa of a germ-free mouse shows the characteristic spiral morphology. Pairs of periplasmic fibers can be seen en face (arrows). Bar, 0.5 μm. Photos courtesy of Adrian Lee, Jani O'Rourke, and Lucinda Thompson.

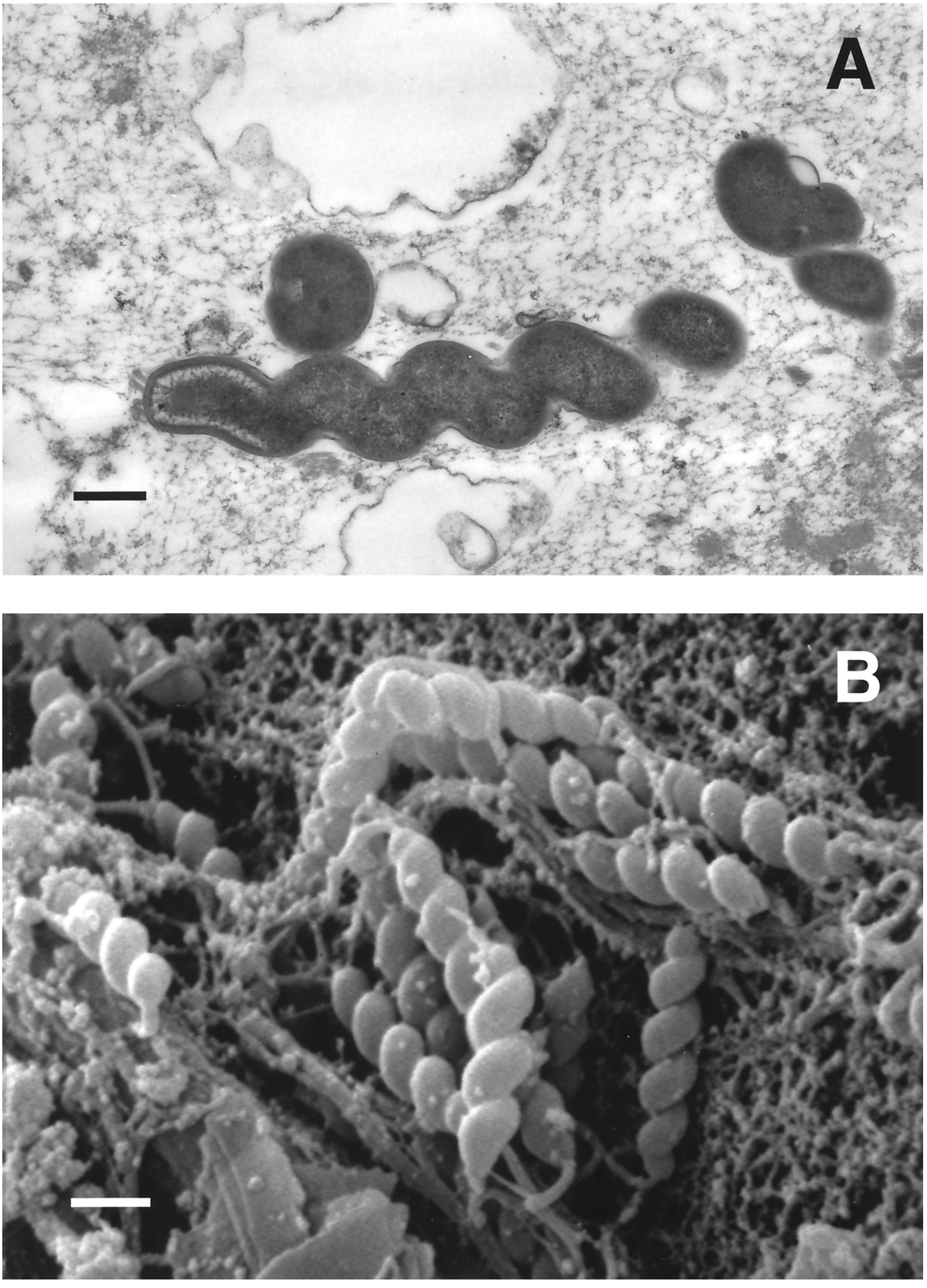

FIG. 3. Transmission (A) and scanning (B) electron micrographs of bacteria in the gastric mucosa of a healthy pet cat. The helical morphology without periplasmic fibers (Lockard type 3) is characteristic of "*H. heilmannii*" and *H. bizzozeronii*. Bars, 0.5 μm. (A) Reprinted from reference 303 with permission from the American Society for Microbiology. (B) Photo courtesy of Robert Munn.

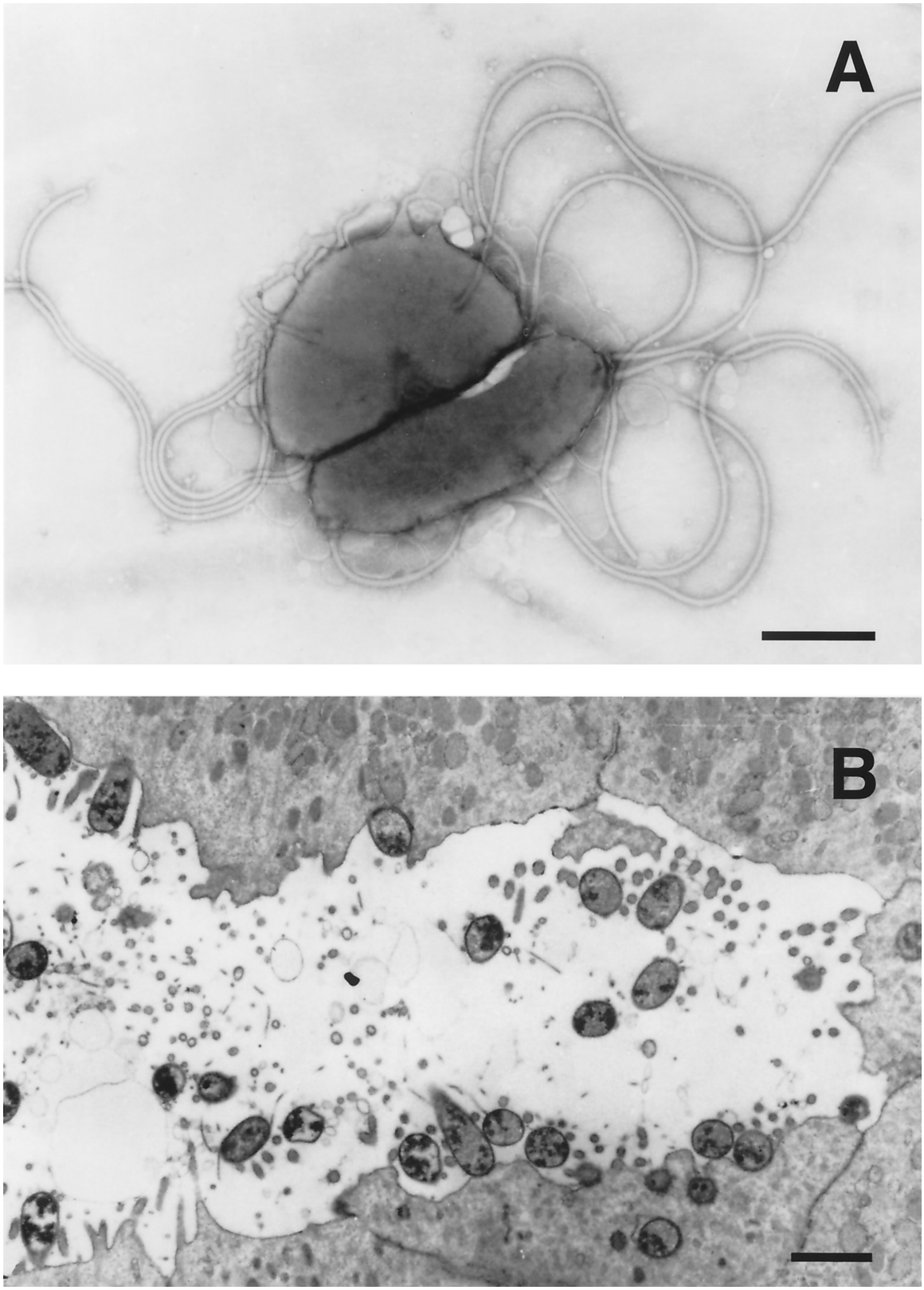

FIG. 4. (A) Negatively stained preparation of *H. mustelae* shows the bipolar and lateral flagella (bar, 0.5 μm). (B) Thin section of a ferret antral gastric pit shows the intimate association of the bacterium with the epithelial surface, including the apparent formation of adhesion pedestals, Bar, 1 μm. Reprinted from reference 309 with permission from the publisher.

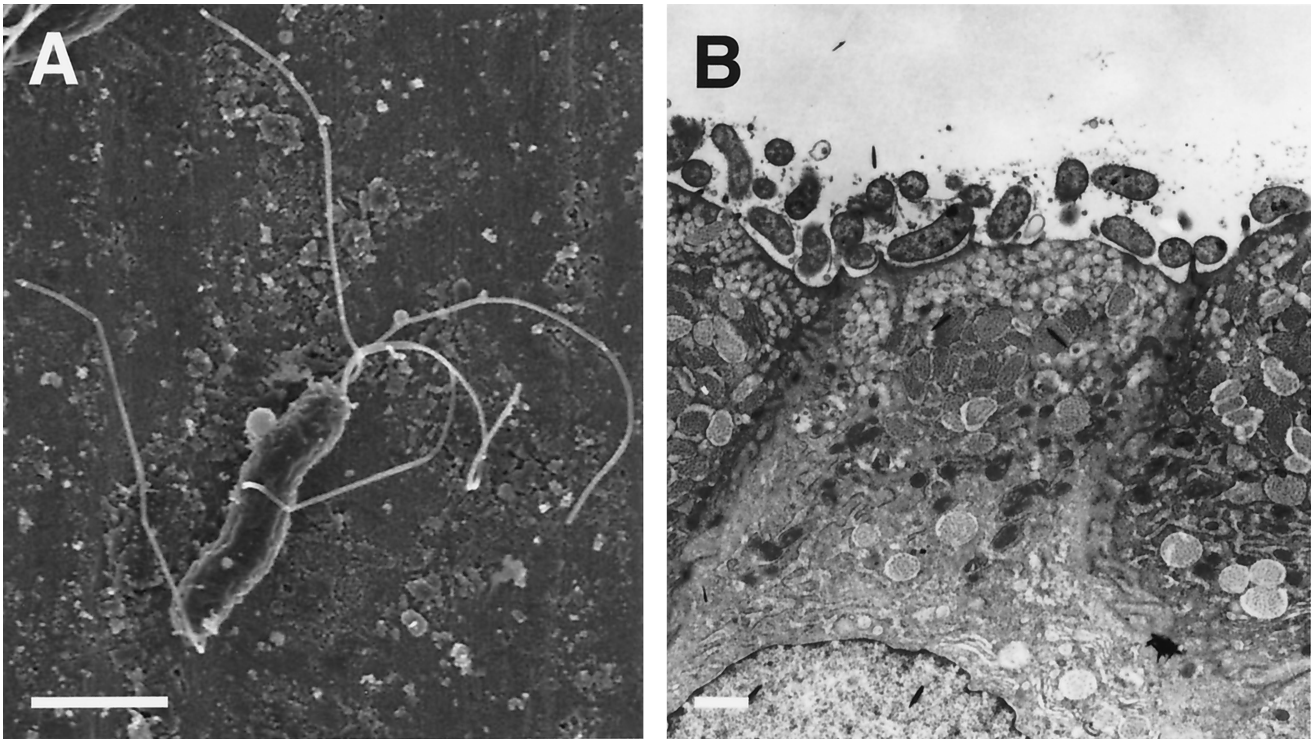

FIG. 5. (A) Scanning electron micrograph of *H. pylori* shows the gently curved morphology, multiple bipolar flagella, and absence of periplasmic fibers. Bar, 1 μm. Photo courtesy of Adrian Lee, Jani O'Rourke, and Lucinda Thompson. (B) Transmission electron micrograph of human gastric epithelium with large numbers of *H. pylori* intimately attached to the surface. Bar, 1 μm. Reprinted from reference 248a with permission from the publisher.

(387), which is nearly the same as that determined by sequencing the *H. pylori* genome (395). Interestingly, there appears to be significant genomic conservation among isolates of *H. mustelae* (286, 387). This is in marked contrast to the heterogeneity seen among isolates of *H. pylori*, which are nearly always genetically unique unless derived from the same or related persons (3, 174).

Epizootiology. In the original report, 3 (18%) of 17 ferrets aged 9 to 10 months were found to be infected with *H. mustelae* when examined at necropsy (148). Subsequent studies showed that the prevalence of *H. mustelae* infection increases with age, from 0% in kits less than 1 month of age to 100% in adults over 1 year (139, 156). This relationship of prevalence to age mimics the seroepidemiology of *H. pylori* in humans, particularly in developing countries (21), as well as the seroepizootiology of *H. pylori* in nonhuman primates (89, 369). Like *H. pylori*, infection with *H. mustelae* is apparently persistent. *H. mustelae* is widespread among colonies of laboratory ferrets (180, 331, 396) and has also been seen in ferrets kept as pets (156). Although examination of adult ferrets from one New Zealand pelt farm failed to find any evidence of infection (290), more recently *H. mustelae* has been isolated from captive and wild ferrets in New Zealand (131). It seems likely that *H. mustelae* is a member of the resident flora of the ferret stomach that infects virtually all animals by adulthood, much as is true for human *H. pylori* infection in most of the world.

Transmission. Direct person-to-person transmission of *H. pylori* is supported by the clustering of cases in families (86), the similarity of *H. pylori* genotypes that is sometimes found among isolates from related persons (409), and the failure to find evidence of an environmental reservoir, although transmission in developing countries by contaminated food or water remains possible (209, 232). Nevertheless, the mechanism by which *H. pylori* moves from the stomach of one host to that of another remains an enigma. Fox and colleagues have offered a series of observations which suggest that transmission of *H. mustelae* may occur by the fecal-oral route and that it is promoted by hypochlorhydria. Fecal cultures from 9-week-old ferrets were positive for *H. mustelae* in 8 (31%) of 26 animals, but cultures from the same ferrets at 20 weeks of age were negative (158). The authors hypothesized that the animals were naturally infected at 5 to 6 weeks of age and were hyphochlorhydric when sampled at 9 weeks of age, a time course which roughly corresponds to the period of transient hypochlorhydria seen in experimentally inoculated animals (157). The increased gastric pH may have permitted greater numbers of bacteria to exit the stomach and enter the lower gastrointestinal tract, where they could be cultivated from feces and possibly serve as a mechanism for transmission. However, the gastric pH was not measured, nor was the timing of acute infection documented, although subsequent rising titers suggested that it was recent. Furthermore, fecal cultures from three (75%) of four ferrets that were 8 months old, and probably not in the window of transient hypochlorhydria, were also positive for *H. mustelae*. When adult ferrets chronically infected with *H. mustelae* were treated with a proton pump inhibitor (omeprazole) to raise their gastric pH, recovery of *H. mustelae* in fecal cultures was increased compared to that before treatment, although in one

TABLE 2. Characteristics of cultivated *Helicobacter* species[a,b]

Taxon	Catalase production	Nitrate reduction	Alkaline phosphatase hydrolysis	Urease production	Indoxyl acetate hydrolysis	γ-Glutamyl transferase production	Growth at 42°C	Growth with 1% glycine	Susceptibility to:		Periplasmic fibers	No. of flagella	Distribution of flagella	G+C content (mol%)
									Nalidixic acid (30-μg disk)	Cephalothin (30-μg disk)				
Gastric														
H. mustelae	+	+	+	+	+	+	+	−	S	R	−	4–8	Peritrichous	36
H. pylori	+	−	+	+	−	+	−	−	R	S	−	4–8	Bipolar	39
H. bizzozeronii	+	+	+	+	+	+	+	−	R	S	−	10–20	Bipolar	ND
H. felis	+	+	+	+	−	+	+	−	R	S	+	14–20	Bipolar	42
H. acinonychis	+	−	+	+	−	+	−	−	R	S	−	2–5	Bipolar	30
H. nemestrinae[c]	+	−	+	+	−	ND	+	−	R	S	−	4–8	Bipolar	24
H. salomonis	+	+	+	+	+	ND	−	ND	R	S	−	10–23	Bipolar	ND
H. suncus	+	+	+	+	−	−	ND	ND	R	R	−	2	Bipolar	ND
Enterohepatic														
H. rodentium	+	+	−	−	−	−	+	+	R	R	−	2	Bipolar	ND
H. pullorum	+	+	−	−	−	ND	+	ND	R	S	−	1	Monopolar	34–35
"*H. canadensis*"	+	V	−	−	+	−	+	+	R	R	−	1–2	Bipolar	ND
H. fennelliae	+	−	+	−	+	−	−	+	S	S	−	2	Bipolar	35
H. trogontum	+	+	−	+	ND	+	+	ND	R	R	+	5–7	Bipolar	ND
H. muridarum	+	−	+	+	+	+	−	−	R	R	+	10–14	Bipolar	34
H. hepaticus	+	+	ND	+	+	ND	−	+	R	R	−	2	Bipolar	ND
H. canis	−	−	+	−	+	ND	+	ND	S	I	−	2	Bipolar	48
H. bilis	+	+	ND	+	−	ND	+	+	R	R	+	3–14	Bipolar	ND
H. cinaedi	+	+	−	−	−	−	−	+	S	I	−	1–2	Bipolar	37–38
"*Helicobacter* sp. flexispira"	+	−	−	+	ND	+	+	−	R	R	+	10–20	Bipolar	34
H. cholecystus	+	+	+	−	−	−	+	+	I	R	−	1–3	Monopolar	ND
"*H. typhlonicus*"	+	+	−	−	−	−	−	+	ND	ND	−	2	Bipolar	ND
"*H. mesocricetorum*"	+	+	+	−	ND	−	+	−	S	R	−	1	Bipolar	ND
H. pametensis	+	+	+	−	−	−	+	+	S	S	−	2	Bipolar	38
"*Helicobacter westmeadii*"	+	+	+	+	ND	ND	−	ND	S	R	−	1	Monopolar	ND
Helicobacter sp. cotton top	+	+	+	+	−	+	+	+	S	R	−	2	Bipolar	31
"*Helicobacter mainz*"	+	−	−	−	−	ND	−	ND	R	S	ND	ND	ND	ND

[a] Adapted from reference 151 with permission from the publisher.
[b] +, positive reaction; −, negative reaction; S, susceptible; R, resistant; I, intermediate; ND, not determined; V, variable.
[c] Unpublished data suggest that *H. nemestrinae* may be identical to *H. pylori* (see the text).

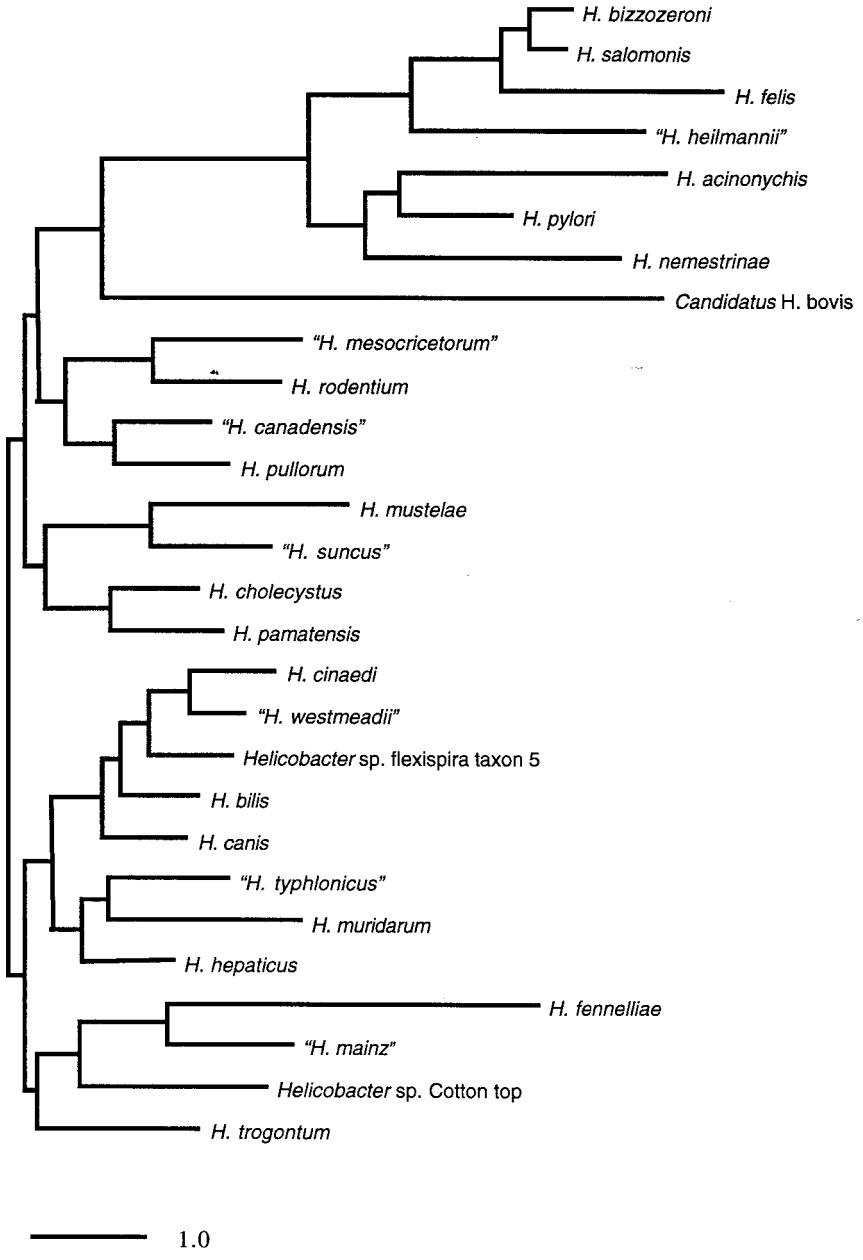

FIG. 6. Phylogenetic tree for 19 validated *Helicobacter* species and 9 additional provisional species, based on 16S rRNA sequence. The scale bar represents a 1% difference in nucleotide sequence as determined by measuring the lengths of horizontal lines connecting any two species. The tree was constructed from the differences matrix (Table 3) using TREEVIEW (314a).

animal the fecal cultures were positive even though the gastric pH failed to rise (138). On balance, these experiments suggest a role for raised gastric pH in transmission of *H. mustelae* by the fecal-oral route, although they do not directly demonstrate fecal-oral transmission. Replication of these results by an alternate method of raising the gastric pH, such as blockade of histamine 2 receptors, might exclude the possibility that the effect of omeprazole was through a mechanism other than alteration of gastric pH. Future studies on transmission may find it useful to exploit the nonhuman primate model of *H. pylori* (87, 88, 369) to extend the provocative work by Fox et al.

Development of the ferret model. Early attempts to develop a small-animal model of *H. pylori* were unsuccessful. Although small laboratory animals have subsequently been infected with *H. pylori* (261, 361, 424), none of these animals is naturally infected. *H. mustelae* infection of ferrets remains the best-studied animal model of a gastric *Helicobacter* in its natural host and provides the opportunity to study the relationship between infection and disease.

(i) Gastritis. Ferrets naturally infected with *H. mustelae* have a predominantly mononuclear gastritis composed of lymphocytes and plasma cells, with only occasional eosinophilic and polymorphonuclear leukocytes (142, 183). The near absence of an active (polymorphonuclear) component to the inflammation distinguishes the gastritis from that often seen in adults infected with *H. pylori*, although children and most other ani-

TABLE 3. Distance matrix based on 16S rRNA comparisons

Taxon	% Difference[a]																											
	H. acinonychis	*H. pylori*	*H. nemestrinae*	*H. bizzozeronii*	*H. salomonis*	*H. felis*	*"H. heilmannii"*	*H. mustelae*	*"H. suncus"*	*"H. mesocricetorum"*	*H. rodentium*	*H. cholecystus*	*H. pamatensis*	*"H. canadensis"*	*H. pullorum*	*H. cinaedi*	*"H. westmeadii"*	*"Helicobacter* sp. flexispira"	*H. bilis*	*H. canis*	*H. hepaticus*	*"H. typhlonicus"*	*H. trogontum*	*H. muridarum*	*H. fennelliae*	*"H. mainz"*	*"Helicobacter* sp. cottontop"	*Candidatus* H. bovis
H. acinonychis		4.2	6.7	5.8	5.7	6.2	7.6	9.9	9.6	9.2	9.5	8.8	8.4	8.8	8.4	10.5	10.4	10.5	10.2	9.2	9.2	10.3	10.1	9.6	12.3	10.0	9.1	12.6
H. pylori			3.8	5.6	5.6	6.7	6.3	8.3	8.0	6.9	7.3	7.3	6.8	7.2	6.6	9.2	9.0	8.7	8.2	7.4	7.8	8.8	8.4	8.5	10.4	8.0	7.2	11.1
H. nemestrinae[b]				6.3	6.3	8.1	7.3	9.7	8.3	8.8	8.8	8.1	8.5	8.6	8.2	10.1	9.5	9.6	9.1	8.6	8.8	9.5	9.5	10.4	12.1	9.4	8.5	11.6
H. bizzozeronii					0.9	3.3	3.9	9.4	8.7	9.2	8.6	7.3	8.0	8.1	7.2	9.5	9.3	9.3	9.0	8.4	8.1	8.9	8.6	9.5	10.7	9.1	7.0	10.8
H. salomonis						3.0	3.9	9.2	8.5	9.1	8.7	7.1	7.8	8.1	7.0	9.5	9.1	9.3	9.1	8.1	8.1	8.9	8.5	9.8	10.6	9.0	7.0	11.0
H. felis							6.3	10.2	10.5	11.1	10.6	9.3	9.2	9.8	9.0	11.1	11.1	10.8	11.0	10.1	9.9	11.0	10.4	10.4	11.8	10.8	9.0	13.1
"H. heilmannii"								10.7	9.6	9.3	9.0	9.1	9.5	8.5	8.0	10.0	9.8	9.5	9.5	8.9	8.9	9.7	9.6	10.4	10.9	9.6	8.0	11.6
H. mustelae									3.4	6.7	7.0	5.1	4.5	6.2	6.7	7.1	6.8	5.9	6.0	5.5	5.5	6.8	5.3	6.2	9.4	6.5	6.5	9.7
"H. suncus"										6.0	5.6	4.4	4.5	4.6	5.0	5.9	5.6	5.6	4.9	4.5	4.3	5.4	4.0	6.0	10.0	6.2	5.7	9.1
"H. mesocricetorum"											3.0	5.2	4.3	4.3	4.1	5.8	5.0	5.7	5.3	5.4	5.6	6.1	4.6	6.9	7.9	5.0	5.8	9.8
H. rodentium												4.6	4.9	3.7	4.3	5.4	5.0	5.1	4.6	4.9	5.0	5.8	4.9	6.5	8.4	6.0	5.9	9.1
H. cholecystus													2.2	3.6	3.7	5.1	4.5	4.1	3.6	3.6	3.9	4.5	4.6	5.0	7.9	5.6	5.2	8.7
H. pamatensis														3.7	3.6	5.8	5.2	4.5	4.2	4.5	4.4	5.5	4.6	5.0	7.8	5.5	5.8	9.3
"H. canadensis"															2.2	5.2	4.9	4.0	4.0	3.9	2.8	4.1	4.6	4.6	8.3	5.6	5.5	8.6
H. pullorum																5.2	4.9	4.6	4.3	3.9	4.4	4.7	4.2	6.0	7.5	4.9	4.7	9.2
H. cinaedi																	1.5	2.0	2.6	3.0	3.8	3.1	4.5	5.6	7.6	4.8	4.9	10.3
"H. westmeadii"																		2.2	2.4	2.6	3.6	3.0	3.9	5.5	7.2	4.3	4.5	10.0
"Helicobacter sp. flexispira"[c]																			2.0	2.6	3.0	3.2	4.9	5.1	7.6	5.2	5.1	9.5
H. bilis																				1.7	2.9	2.8	4.1	4.9	7.6	4.8	4.4	9.2
H. canis																					3.0	2.7	4.0	4.6	7.9	4.5	3.6	9.2
H. hepaticus																						2.5	3.1	3.3	7.6	4.7	4.4	8.1
"H. typhlonicus"																							3.7	3.4	7.6	4.7	4.3	9.8
H. trogontum																								4.8	7.1	4.3	4.4	9.5
H. muridarum																									8.5	5.8	5.4	10.1
H. fennelliae																										5.4	6.6	13.6
"H. mainz"																											4.7	11.2
"Helicobacter sp. cottontop"																												10.1
Candidatus H. bovis																												

[a] Sequences from strains shown in Tables 1 and 2 were aligned with PILEUP and compared with DISTANCES (Wisconsin Sequence Analysis Package; Genetics Computer Group). Only sequence positions for which data were available for at least 90% of strains were included in the analysis (*E. coli* positions 28 to 1473). Intervening sequences were removed from *H. bilis*, *H. typhlonicus*, and *Helicobacter* sp. cottontop. Percentages of difference were corrected for multiple base changes by the method of Jukes and Cantor.

[b] Unpublished data sugggest that *H. nemestrinae* may be identical to *H. pylori*.

[c] Taxon 5.

mals infected with a gastric *Helicobacter* strain tend also to have a mononuclear infiltrate. In the corpus of the ferret stomach, the gastritis is minimal or only superficial. However, in the antrum, where the bacteria predominate, the inflammatory infiltrate may occupy the full thickness of the mucosa, similar to the diffuse antral gastritis seen in humans infected with *H. pylori*. Gastric glands may also be affected, with evidence of both atrophy and regeneration. Experimental inoculation of ferrets with *H. mustelae* produces elevated immunoglobulin G (IgG) titers to *H. mustelae* and a histologic gastritis (157) which resembles that seen in naturally infected animals (157). These changes are also accompanied by an elevation in meal-stimulated gastrin levels similar to what is seen in humans infected with *H. pylori* (320). Surprisingly, very minimal gastritis was seen in *H. mustelae*-infected ferrets in England (396). This observation has not been repeated, and it is unknown whether it was due to differences in the host, the pathogen, or both.

(ii) Ulcers. Unlike gastritis, which is seen in all cases, most patients infected with *H. pylori* do not develop peptic ulcer disease. While the association between *H. pylori* and peptic ulcer disease is undisputed—the current standard of care is to use antibiotics to treat patients with peptic ulcers and *H. pylori* infection—the evidence for this association is nonetheless indirect. It is based primarily on the demonstration that ulcer recurrence in patients treated with antibiotics, with or without acid suppression, is markedly lower than in patients treated with acid suppression alone (184). Limited case-control data also show that preexisting *H. pylori* infection increases the risk for subsequent development of duodenal and gastric ulcers (302). In principle, *H. mustelae* infection in the ferret offers the opportunity to study experimentally the association between *Helicobacter* infection and peptic ulcer. Ferrets sometimes develop gastric ulcers and hemorrhagic gastric erosions (191), with a prevalence of 35% in a series of 31 ferrets in England (9) but only 1.4% in a large postmortem study of 350 animals performed by the same author (8). Gastric ulcers have also been found in related fur-bearing animals (26) and other laboratory species (269). However, there are no studies which provide convincing evidence that *H. mustelae* infection in the ferret causes peptic ulcer disease, although *H. mustelae* has occasionally been seen in ferrets with gastric ulcer. Such a demonstration would require long-term observation of experimentally infected and pathogen-free ferrets, which has not been done. Nevertheless, since *H. mustelae*-infected ferrets may develop duodenal ulcer or gastric ulcer, the latter of which may be associated with atrophic gastritis, dysplasia, and gastric adenocarcinoma, the model mimics in many respects the relationship between human hosts and infection with *H. pylori*.

(iii) Gastric malignancy. *H. mustelae* also provides an opportunity to study *Helicobacter* infection and gastric tumorigenesis, but, as with ulcer disease, the role of *H. mustelae* in gastric tumors of the ferret has not yet been clearly demonstrated. Gastric adenocarcinoma (333) and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (110) have been found occasionally in the ferret, sometimes in association with *H. mustelae* infection (143). However, since ferrets are routinely infected with *H. mustelae*, infection alone must be insufficient to produce malignancy with any frequency, at least during the first few years of the animal's life, when most studies are performed. Treatment of *H. mustelae*-infected ferrets with *N*-methyl-*N*-nitro-*N*′-nitrosoguanidine (MNNG), a gastric carcinogen in several animal species, produced adenocarcinoma in 9 of 10 animals (159). Unfortunately, uninfected animals were not studied, and MMNG alone produces gastric adenocarcinoma in many species (166, 381, 382). *H. mustelae*-infected ferrets do have an increase in gastric epithelial-cell proliferation, especially in the antrum, where colonization is heaviest. This cell proliferation might promote the development of carcinoma in the setting of an appropriate initiation event (434). Although definitive evidence for the role of *H. mustelae* in gastric malignancy and peptic ulcer disease is lacking, the model remains a valuable tool for the study of gastritis and epithelial proliferation. Future studies will probably clarify the role of *H. mustelae* in the development of peptic ulcer disease and gastric cancer.

(iv) Therapy. Limited studies of antibiotic therapy for *H. mustelae* indicate that it is sensitive in vitro to many of the agents effective against *H. pylori*. The MIC of amoxicillin is 1 to 2 log units higher than for *H. pylori* (4, 221, 313), and therefore combination treatment containing amoxicillin may be less effective in ferrets than in humans (4, 313). The combination of ranitidine bismuth citrate and clarithromycin is effective therapy for *H. mustelae* infection in ferrets (263). Both these drugs are often used to treat *H. pylori* infection in humans, although this combination is not a generally recommended treatment regimen.

Virulence determinants. (i) Urease. *H. mustelae* produces a urease, composed of two subunits, that is similar in stoichiometry (hexameric 1:1), molecular mass (564 kDa), K_m (0.45 mM), and percentage of total cellular protein (2%) to that from *H. pylori* and other gastric *Helicobacter* species (94, 401, 402). Partial DNA sequencing of the *H. mustelae* urease genes showed that the predicted proteins were 67 to 68% identical to other *Helicobacter* ureases for UreA and 79% identical for UreB (370). The ureases of *H. pylori*, *H. felis*, and "*H. heilmannii*" are more closely related to one another than they are to the urease of *H. mustelae*. This finding is similar to the results of a phylogenetic study based on 16S rRNA sequence as well as G+C content (370), demonstrating that the urease structural genes can be used as a basis for phylogenetic analysis. An isogenic urease-negative mutant of *H. mustelae* does not colonize the ferret (11), much the same as has been found for *H. pylori* in the pig and mouse models (98, 101, 400). The mechanism for this failure is unknown, but it probably involves more than buffering of gastric acid, since an isogenic urease-negative *H. pylori* strain will not colonize the pig even if the gastric pH is raised pharmacologically (100). *H. mustelae* appears to have reduced survival at pH 6.0 if physiological concentrations of urea are present, which has been attributed to the accumulation of ammonia and its metabolism by the cell (423). However, a similar observation made with *H. pylori* appears to result from a rise in the pH of the medium rather than from ammonia accumulation (54). The apparent requirement of urease for colonization has led to an investigation of the therapeutic potential of fluorofamide, a potent urease inhibitor. Although fluorofamide markedly inhibited *H. mustelae* urease in vitro and in vivo (270, 324) and reduced bacterial numbers, it failed to eradicate *H. mustelae*, even when administered with amoxicillin. This may be due to inadequate drug delivery or to residual intracellular urease. It may also suggest that in vivo

some bacteria are not completely dependent on urease for survival (324). *H. mustelae* has a gene identical to the *H. pylori hpn* locus, which codes for a protein with 47% histidine residues that binds nickel but is not required for urease activity (172).

(ii) Flagella. Flagellar organization in *H. mustelae* (and *H. pylori*) resembles that seen in *Campylobacter*, where the mature flagella are assembled from two flagellin proteins, FlaA and FlaB. The *flaB* gene has a sigma 54-type promoter that is functionally active, which suggests that it may be environmentally regulated. FlaA and FlaB of *H. mustelae* have 80% amino acid identity to the corresponding proteins in *H. pylori*. Unlike in *Campylobacter*, the *Helicobacter flaA* and *flaB* genes are not linked on the chromosome, nor are they closely related to one another (225, 380). Many other genes have been identified in the *H. pylori* genome that are probably involved in secretion, regulation, and assembly of flagella (395). One of these, the flagellar hook gene (*flgE*), has also been identified in *H. mustelae* (312), and it is likely that others will be found. A *flaA* isogenic mutant of *H. mustelae* has markedly diminished motility, while the motility of a *flaB* mutant is diminished 30 to 40% (225). Single-gene mutations in *flaA* or *flaB* reduce the density of colonization, whereas the nonmotile *flaA flaB* double mutant is unable to colonize the ferret (10). These results clearly indicate that motility is an important virulence factor for colonization in the *H. mustelae* ferret model.

(iii) Attachment. *H. mustelae* is found almost exclusively in intimate association with ferret gastric epithelial cells (Fig. 4), with few if any bacteria in the overlying mucus gel (309). Occasionally, bacteria are actually endocytosed into the gastric epithelial cells. Studies of attachment in *Helicobacter* have sometimes been plagued by a discrepancy between the striking host and tissue specificity seen in vivo and the sometimes nonspecific attachment seen in vitro. When examined by flow cytometry, *H. pylori* but not *H. mustelae* attached well to AGS cells, a human gastric carcinoma cell line. This observation suggests some specificity for the appropriate host cell (258), but *H. mustelae* adhered to explants of stomach from pigs, rats, and rabbits, as well as to pig duodenum and urinary bladder (279). *H. pylori* attachment to gastric epithelial cell lines causes pedestal formation similar to that seen with enteropathogenic *Escherichia coli*, accompanied by cytoskeletal rearrangements and tyrosine phosphorylation of host cell proteins (350). Similar adhesion pedestals have been seen with *H. mustelae* (309), but recruitment of filamentous actin was not apparent when examined in tissue culture by electron microscopy (176). The *alpAB* locus, which codes for outer membrane proteins that are required for in vitro attachment of *H. pylori* to gastric epithelium, is not present in *H. mustelae* or in *H. felis* (306).

The mechanism by which *H. mustelae* attaches to gastric epithelium is unknown. Most strains of *H. mustelae* agglutinate red blood cells derived from various hosts (389). Although hemagglutination is inhibited by pronase, heat, and trypsin, thereby implying the presence of a protein ligand, it is also sometimes partially inhibited by blocking with fetuin or neuraminidase. *H. mustelae* and *H. pylori* appear to bind common lipid receptors, particularly phosphatidylethanolamine (PE), and adhesion to intact eukaryotic cells correlates with the amount of PE present (176, 178). Attachment of *H. mustelae* to PE can be partially inhibited by bovine and human colostrum (29). This may result from inhibition by colostral PE or PE derivatives, but the importance of other constituents of colostrum cannot yet be excluded. Nonspecific cell surface properties such as hydrophobicity may also contribute to *H. mustelae* binding to gastric epithelium (177). Estimates of the relative hydrophobicity of *H. mustelae* depend on the assay used, and there may also be local differences at different places on the bacterial cell membrane. However, *H. mustelae* is thought to be predominantly hydrophilic. Inflammation induced by *H. mustelae* is associated with a reduction in mucosal hydrophobicity, which may promote nonspecific attachment. Similar findings have been reported with *H. pylori* (175). Attachment based on surface characteristics may explain the apparent nonspecific binding that is sometimes observed (279) in vitro but that contrasts strikingly with the host and tissue specificity of *H. mustelae*. It is likely that attachment of *H. mustelae* to gastric epithelium is dependent on more than a single ligand-receptor interaction.

The outer membrane of *H. mustelae* is studded with an array of 8.5-nm-diameter rings that are composed of a 150-kDa protein designated Hsr (for "*Helicobacter* surface ring") (310). The C-terminal portion of Hsr has limited homology to a cleaved portion of SepA, the major extracellular protein of *Shigella flexneri* (25). Cross-reactive proteins are present in three strains of *H. mustelae*, but the protein and the *hsr* gene are absent in *H. pylori*. Determination whether Hsr contributes to colonization, either as an adhesin or perhaps by inhibition of complement-mediated killing as is the case for the S-layer of *Campylobacter fetus* (37), will require examination of isogenic *hsr* mutants in the ferret model.

(iv) Lipopolysaccharide. *H. pylori* lipopolysaccharide (LPS) has relatively low biological activity compared to that from the family *Enterobacteriaceae* (294), but it is of particular interest because of evidence that it expresses human Lewis (Le) antigens that are also present on the gastric epithelium (358). The relatively inactive LPS, combined with host antigens on its surface, may be a mechanism for *H. pylori* to down regulate and evade the host inflammatory response and thereby favor long-term colonization (36). Autoantibodies against the bacterial Le antigens may also be important in the pathogenesis of gastroduodenal pathology (15). *H. mustelae* LPS does not express Le antigens, nor are they expressed on ferret gastric epithelial cells. However, both ferret gastric epithelium and *H. mustelae* LPS express blood group antigen A, which may be a mechanism of molecular mimicry similar to expression of Le antigens by *H. pylori* (285, 305).

Helicobacter felis

Spiral bacteria have long been seen on histologic sections of gastric mucosa from cats and dogs. In 1988 Lee et al. reported for the first time the culture of one of these organisms from the cat stomach (246). A similar organism was found in dogs, and both were designated *H. felis* (319).

Microbiology and phylogeny. *H. felis* is biochemically similar to other gastric *Helicobacter* species (Table 2). It has a helical morphology (Fig. 2), rather than the curved or loosely spiral appearance of *H. pylori*. *H. felis* is also characterized by periplasmic fibers, usually in pairs, that wind around the organism and have been used to distinguish it microscopically from the

morphologically very similar but uncultivated "*H. heilmannii.*" However, these fibers may not be present on all strains of *H. felis* and may disappear on subculture (96). Their function and genetic basis of expression are unknown. The sequence of the 16S rRNA gene from several cat and dog isolates of *H. felis* shows that they differ by less than 1% (96) and are most similar to other gastric *Helicobacter* species (Fig. 6; Table 3). The cat isolates are more closely related to one another, as are the dog isolates, but these differences are subtle. The fatty acid composition of *H. felis* is typical of other gastric *Helicobacter* species, with a predominance of 19-carbon cyclopropane fatty acid and tetradecanoic acid (198).

Epizootiology. It is now apparent that the many descriptions of pleomorphic spiral bacteria in the stomachs of dogs and cats (92, 255, 257, 353, 404, 417, 418) represent multiple species that often can be distinguished by 16S rRNA sequence analysis or DNA-DNA hybridization. These include, as well as *H. felis*, several other organisms discussed below such as *H. bizzozeronii*, *H. salomonis*, and "*H. heilmannii*." Still other isolates that may be novel species remain unnamed (96). The combination of enzyme-linked immunosorbent assay and immunoblotting detected *Helicobacter* infection with 95.6% sensitivity and 79.8% specificity in dogs (378), but efforts to specifically detect *H. felis* were less successful (351). Therefore, there are no seroepidemiologic studies which examine the prevalence of *H. felis*. Nevertheless, despite its name, *H. felis* is apparently not the most common *Helicobacter* species in cats and dogs. In six studies that collectively cultured gastric biopsy specimens from 147 cats and 85 dogs, one *H. felis* strain was isolated from a cat and only four strains were identified in dogs (96, 197, 298, 303, 315, 427). Even with modified culture conditions that appear more effective than those used previously, *H. felis* was cultivated from only 3 of 22 cats and 8 of 95 dogs (220). Most animals were colonized by organisms that resembled "*H. heilmannii*" and could not be cultivated. Human infection with *H. felis* has been reported rarely (168, 237), apparently as a zoonosis, but no environmental or other host reservoir is known.

Surprisingly, *H. pylori* has also been isolated from domestic cats obtained from a single commercial breeder (193). The gastric mucosa of the infected cats was characterized histologically by moderate to severe lymphoplasmacytic follicular infiltrates, predominantly in the gastric antrum, where bacterial colonization was greatest (194). The histology of naturally infected cats was reproduced by experimental inoculation of specific-pathogen-free animals with feline- and human-derived *H. pylori* (137). Although initially these data raised the possibility that *H. pylori* in humans may be a zoonosis, this conclusion is not supported by seroepidemiologic data (14, 416) or by studies of gastric *Helicobacter* species in domestic pet cats (14, 298, 303, 416). Natural *H. pylori* infection in cats appears to be restricted to animals obtained from a particular commercial breeder, and infection was probably acquired as an anthroponosis.

Clinical significance. Much as was true of the early descriptions of *H. pylori* infection in humans, the clinical significance of gastric *Helicobacter* infection in dogs and cats has been difficult to determine. Most studies find that between 50 and 100% of cats and dogs are infected with *Helicobacter*. There is no convincing evidence that infection is associated with clinical symptoms such as chronic vomiting or inappetence, nor is there typically a clear association between infection and histologic gastritis (96, 116, 169, 197, 200, 202, 203, 298, 303, 314, 315, 321, 353, 377, 417, 418, 427). However, in many studies the animals are incompletely described, there are no controls, and the bacteria are only characterized by urease assay or routine histologic testing. Since animals may be infected with more than one species of *Helicobacter* that are urease positive and that are indistinguishable on light microscopy, the pathogenic role of *H. felis* is difficult to determine from these observational studies. Experimental infection of *H. felis* in 7-day-old gnotobiotic dogs resulted in seroconversion and large numbers of lymphoid nodules throughout the gastric mucosa, as well as a mild diffuse lymphocytic infiltrate (247). Similar nodules described previously as components of the normal microscopic anatomy of the dog stomach may also have been a result of *H. felis* infection (1). Control animals had no evidence of infection or lymphoid nodules at necropsy. However, when 4-month-old specific-pathogen-free dogs were infected with the same strain of *H. felis*, the results were very different (363). Mild gastritis and lymphoid follicles were found in both infected and uninfected dogs. There was no correlation between the number of organisms and the intensity of inflammation, nor did infection produce alterations in gastric pH, acid output, or plasma gastrin. The different results in these two studies probably reflect host differences, such as alterations in gastric acidity or immune response with age, or differences between specific-pathogen-free and gnotobiotic animals. Experimental inoculation of specific-pathogen-free cats with *H. felis* induced lymphoid follicular hyperplasia but only mild gastritis (364). There was no accompanying up regulation of antral mucosal interleukin-1α (IL-1α), IL-1β, or tumor necrosis factor alpha, nor were there changes in gastric secretory function.

Virulence determinants and other characterized genes. The *H. felis* urease is composed of A and B subunits, which are 73.5 and 88.2% identical, respectively, to the corresponding polypeptides from *H. pylori* (117, 181). One presumes that urease is required for *H. felis* colonization, but efforts at genetic manipulation have been largely unsuccessful. Recently, the flagellin genes from *H. felis* (*flaA* and *flaB*) were cloned and isogenic mutants were generated by electroporation (224). Transformation efficiency was low relative to what is typically seen with *H. pylori* or *H. mustelae*, and mutants could be obtained only using plate-grown bacteria. Both *flaA* and *flaB* mutants showed truncated flagella and were poorly motile in vitro, and the *flaA* mutant was unable to colonize gastric mucosa in the mouse model. This result differs from that with *H. mustelae*, in which mutation in a single flagellin gene reduces but does not abolish colonization. Unlike *H. mustelae*, *H. felis* is found exclusively in the mucus layer and is not attached to the gastric epithelium (348); it has been speculated that any impairment of motility may therefore eliminate colonization (224).

The *cagA* and *vacA* genes appear to be absent from *H. felis* (283). The only other sequences from *H. felis* that have been published to date are for a P-type ATPase encoded by the *copAP* operon (24) and for a nearby open reading frame with homology to the *E. coli ftsH* gene encoding an ATP-dependent metalloprotease (273). Both have closely related homologs in *H. pylori*.

Development of the rodent model. *H. felis* readily colonizes mice, with the same gastric tropism seen with *H. pylori* in humans (77, 134, 244). Infection typically predominates in the gastric antrum but, interestingly, is accompanied by a largely mononuclear cell inflammatory response that is more prominent in the corpus (134, 281, 341). The difference in the anatomic locations of the infection and the inflammation has led to the suggestion that *H. felis* in mice may stimulate an autoimmune response to gastric tissue (341). A similar mechanism has been proposed for *H. pylori* gastritis in humans based on molecular mimicry between bacterial LPS and host Le antigens (15). As inflammation progresses into atrophic gastritis, substantial reduction in bacterial colonization of the gastric antrum may develop (341). This can also be produced, along with increased colonization of the corpus, by treatment of *H. felis*-infected mice with the proton pump inhibitor omeprazole (64). These findings suggest that local acid production may be important in the distribution of *H. felis* in the mouse stomach. Unlike *H. pylori* in humans, *H. felis* in the mouse does not attach intimately to gastric epithelial cells, nor does it produce a prominent polymorphonuclear infiltrate.

H. felis infection of the rat has also been used as a model of *H. pylori* infection. Although limited reagents and lack of genetically characterized strains make the rat less attractive than the mouse in general, the similarity in gastric physiology between the rat and human may make it more useful for some studies. *H. felis* infection in the gnotobiotic rat is localized to the gastric antrum, causes a predominantly mononuclear cell infiltrate, and is accompanied by a transient IgM and sustained IgG antibody response (152). In one study with conventional rats, neither *H. felis* nor "*H. heilmannii*" (see below) induced significant gastritis (63). Since these rats also showed no changes in gastrin and acid output, it was concluded that the inflammatory response, rather than direct bacterial effects, is probably responsible for changes in gastric physiology induced by *H. pylori* in humans. A more direct test of this hypothesis might utilize isogenic strains of *H. felis* or *H. pylori* that differ in the extent of the inflammatory response, in order to avoid comparisons across different animal hosts and bacterial species.

With the successful introduction of *H. pylori* into mice (261) and the availability of the *H. pylori* genome (395), future work will probably rely more on the *H. pylori* mouse model than on *H. felis*. Nevertheless, the *H. felis* rodent model has produced significant results that further our understanding of *Helicobacter* pathogenesis.

(i) Atrophic gastritis, lymphoma, and gastric cancer. Atrophic gastritis (thought to be the histologic precursor lesion to gastric adenocarcinoma) and gastric MALT lymphoma associated with *H. pylori* infection in humans (56, 435) have also been observed in mice infected with *H. felis* (239). In an initial study of conventional mice experimentally infected with *H. felis* CS1, atrophic changes in the gastric corpus developed 48 weeks after inoculation and progressively increased over the subsequent 24 weeks (241). Uninoculated animals developed less extensive atrophy, but the results were difficult to interpret because animals in both groups developed coinfection with *Helicobacter muridarum*, an organism that normally colonizes the small and large bowel of rodents. However, subsequent inoculation of specific-pathogen-free mice with *H. felis* confirmed the development of corpus atrophy without coinfection by *H. muridarum* (341). Long-term infection of specific-pathogen-free mice with *H. felis* can also produce lesions that resemble human gastric B-cell MALT lymphoma (109). Antibiotic treatment of *H. felis* in chronically infected mice reduces the development of gastric MALT lymphoma (108). This suggests that the lymphoma is antigen dependent, at least while it remains low grade, in much the same fashion as *H. pylori*-associated gastric MALT lymphoma in humans (211, 335). Elegant studies with insulin-gastrin (INS-GAS) transgenic mice also suggest that *H. felis* infection acts synergistically with chronic hypergastrinemia to produce parietal cell loss and development of gastric cancer (410). Further studies with transgenic mice, as well as the recently described *H. pylori* gerbil model (383), will probably contribute significantly to our understanding of the relationship between *Helicobacter* infection and gastric malignancy.

(ii) Therapy. The *H. felis* mouse model has been promoted as a preclinical tool for evaluation of novel antimicrobial therapy for *H. pylori* infection. In general, the results obtained by treatment of *H. felis* in the mouse model mimic the outcome of human clinical trials investigating the treatment of *H. pylori* (78, 206, 233, 367). However, given the relative ease of performing human clinical studies, hundreds of which have now been completed (403), and the development of the *H. pylori* mouse model, it seems unlikely that the *H. felis* mouse model will play an important role in efficacy studies of novel *H. pylori* therapies.

(iii) Mechanisms of inflammation and atrophy. The nature of the host response is an important factor in *Helicobacter*-associated diseases. Infection with *H. felis* in several inbred strains of mice (C57BL/6, C3H/He, and SJL) produces severe gastritis, while in other strains (BALB/c, CBA) the inflammatory response is much less marked (283, 341). F_1 hybrids of the CBA mouse crossed with strains that develop severe gastritis maintained the mild inflammation phenotype of the CBA parent (384). Thus, low inflammation was a dominant response which might in part reflect immune suppression rather than a genetic defect. It has also been proposed that increased proliferation and apoptosis seen in the C57BL/6 mice may be related to the lack of secretory phospholipase A_2 ($sPLA_2$), which is encoded by the *Mom1* locus responsible for variability in the number of polyps in mice with multiple intestinal neoplasia (411). SV129 mice are also $sPLA_2^{-/-}$ and show similarly severe pathologic changes in response to *H. felis* infection, while BALB/c and C3H/HeJ mice are $sPLA_2^{+/+}$ and have less inflammation. The decrease in gastric $sPLA_2$ levels after infection of C57BL/6 mice with *H. felis* is also consistent with the role of $sPLA_2$ in maintaining gastric differentiation (254). However, since these studies were not performed on congenic strains, other genes may also be involved. For example, C3H/HeJ mice have a defect in responsiveness to LPS that also contributes to reduced atrophic gastritis (342). Genes of the major histocompatibility complex probably also contribute to individual differences described in mouse strains (283).

Genetically well-characterized mice have recently been exploited to extend our understanding of *Helicobacter*-induced gastric inflammation. *H. felis* infection in C.B-17 mice with severe combined immunodeficiency (SCID mice) produces an inflammatory response that does not differ from that seen in immunocompetent controls (31). However, infection of T-cell-

deficient C57BL/6 mice with *H. felis* results in minimal gastritis compared with infection of B-cell-deficient and wild-type C57BL/6 mice (338). The difference between these results is probably due to the host strain, since the C.B-17 SCID mouse is in a BALB/c background, which does not develop extensive gastric pathologic changes. Host adaptive immunity is therefore likely to be involved in the development of *Helicobacter* gastritis (106). IL-6-deficient mice do not show any difference in the mucosal IgA response to *H. felis* infection or to local immunization, which is unexpected in view of the presumed role of IL-6 in the terminal differentiation of IgA-producing B cells (41). Presumably the IL-6 defect can be compensated by production of other cytokines. Inoculation of *H. felis* into mice deficient in the anti-inflammatory cytokine IL-10 results in a markedly increased mononuclear cell inflammation that progresses to loss of parietal and chief cells (28). This severe gastritis is probably an exaggeration of the normal Th1-type immune response that occurs after infection with *H. pylori* and *H. felis* (18, 266, 281). It may result from loss of IL-10 regulation of the host response to LPS (27) and is consistent with the observation that C3H/HeJ mice, which are not responsive to LPS, do not develop atrophic gastritis with chronic *H. felis* infection (342). IL-10 knockout mice infected with *H. felis* also show increased gastric epithelial cell proliferation and loss of normal differentiation, which is seen in a milder form in p53 hemizygous transgenic mice (153). Surprisingly, *H. felis* infection of mice with truncation of the *Apc* gene (a tumor suppressor involved in colorectal carcinogenesis) causes decreases in inflammation, serum IgG levels, and epithelial cell proliferation (144).

(iv) Vaccine development. The limitations of current *H. pylori* therapies have prompted interest in the development of vaccines for both treatment and primary prevention. Although natural infection with *H. pylori* induces specific IgG and IgA that do not prevent initial colonization or subsequent reinfection, the results of considerable work suggest that it may be possible to prevent *Helicobacter* infection by immunization. Much of this work has utilized the *H. felis* mouse model. Orogastric immunization of mice with an *H. felis* sonic extract together with cholera toxin produces a significant antibody response in serum and gastric secretions (62) that is associated with protection after challenge with *H. felis*, often with 90 to 100% efficacy (33, 51, 61, 118–120, 240, 316, 328, 352). *H. pylori* sonic extract plus cholera toxin also protects against challenge with *H. felis*, although less effectively (240, 280). Studies of particular antigens suggest that protection against *H. felis* infection in the mouse model can be achieved with *H. pylori* urease holoenzyme or its B subunit (112, 118, 250, 280, 297, 316), catalase (329), and the GroES and GroEL homologs, HspA and HspB, respectively (119). Similar vaccine efficacy has also been described in the *H. pylori* mouse model by immunization with *H. pylori* cytotoxin (VacA), a protein associated with cytotoxin expression (CagA), catalase, and urease (58, 170, 179, 261, 262, 329).

However, some recent studies with mice and with more relevant animal models such as the pig and rhesus monkey suggest that when careful quantitative colony counts are performed, current vaccine formulations yield 1 to 2 log unit reductions in *H. pylori* colonies but do not provide sterilizing immunity (107, 188, 231, 249). The clinical significance of such quantitative reductions is unknown. Furthermore, protection may be more difficult to achieve in animals naturally infected with *Helicobacter*. When ferrets naturally infected with *H. mustelae* were immunized with *H. pylori* urease, colonization was eliminated in only 30% of animals (60). Immunization of uninfected ferret kits with *H. mustelae* lysate, together with the adjuvant muramyl dipeptide, was also ineffective at primary prevention (422). These disappointing results may be attributed to many variables in addition to the fact that *H. mustelae* naturally infects the ferret. For example, there are limited data on optimal adjuvant and dosage conditions in the ferret, and there may be significant differences between the important epitopes on *H. mustelae* and *H. pylori* urease. However, a study with rhesus monkeys found that after immunization with *H. pylori* urease plus *E. coli* heat-labile enterotoxin, an estimated 31% of animals were protected from natural infection with *H. pylori*, compared with 7% protected by administration of placebo plus heat-labile enterotoxin (90). Although the difference between the groups was statistically significant, the results are difficult to interpret because the initial absence of *H. pylori* infection was documented only by serologic testing, which is not sensitive for the detection of recent infection. More recently, a study with specific-pathogen-free rhesus monkeys found no evidence that urease vaccination could prevent *H. pylori* infection or reduce bacterial colony counts after experimental challenge (368). These results raise concern that protection of an animal from a *Helicobacter* species with which it is naturally colonized may be more difficult than protection from an ecologically irrelevant species.

The availability of the *H. pylori* genome (6, 395) now permits the evaluation of numerous recombinant vaccine candidates, which should probably first be evaluated in the *H. pylori* mouse model and then, if effective, be studied in nonhuman primates. Vaccines that are effective in primary prevention may also be useful for therapeutic immunization (57, 170), which may be increasingly important as antibiotic-resistant strains of *H. pylori* become more prevalent. *H. pylori* and *H. felis* in the mouse model will also continue to be useful in our attempts to better understand mechanisms of immunity. Some evidence suggests that the pathologic changes associated with natural infection may be due predominantly to a Th1 cell-mediated immune response while protection following immunization may be associated with a Th2 response (119, 281, 282, 343). However, this may be an oversimplification. The density of *H. felis* colonization in mice can be substantially reduced by infecting them with a replication-defective adenovirus. This effect was dependent on the presence of gamma interferon and IL-12, which are Th1 cytokines (222). Others have also recently shown that protection from *H. pylori* colonization in the mouse model can be achieved by systemic vaccination that induces either a Th1- or Th2-type cytokine response (32). The relative importance of IgG and IgA antibodies remains controversial (120, 250), although recent work with B-cell knockout mice suggests that antibody responses to urease are not required for protection in the mouse model (113).

Helicobacter bizzozeronii and *Helicobacter salomonis*

Large gastric spiral bacteria, which resemble those seen by early investigators and described most clearly by Lockard and

Boler (257), were recently cultivated (195, 219) and named after Bizzozero (30) and Salomon (344). Both organisms were isolated from dogs by using culture techniques that differed only modestly from those used by other investigators, particularly in using brain heart infusion rather than brucella broth, cultivation for up to 12 days, careful attention to keeping plates moist, and cultivation only of biopsy specimens that were rapidly urease positive. *H. bizzozeronii*, which is indistinguishable morphologically from the Lockard type 3 bacterium and from "*H. heilmannii*," is typically 5 to 10 μm long and 0.3 μm wide, with bipolar sheathed flagella (Fig. 3). *H. salomonis* is usually somewhat smaller (5 to 7 by 0.8 to 1.2 μm) and less tightly coiled, a morphology similar to that originally published by Weber and Schmittdiel (418) but not described by Lockard and Boler. The 16S rRNA sequences from these bacteria are approximately 99% similar to one another and to that from the closely related *H. felis*. Restriction fragment length polymorphism (RFLP) analysis suggests that the 23S rDNA genes are also closely related (218). However, distinct species occasionally have 16S rRNA genes that are virtually identical (133). In this case, DNA-DNA hybridization studies show clearly that *H. bizzozeronii* and *H. salomonis* are each genetically homogeneous and distinct from one another, as well as from other canine and feline gastric *Helicobacter* species. Pulsed-field gel electrophoresis suggests that there is more heterogeneity among strains of *H. bizzozeronii* than among strains of *H. salomonis* (196), although this result will require replication with a larger number of strains.

Cultivation of *Helicobacter* species from dogs and cats has been typically unsuccessful, despite microscopic and DNA evidence of *Helicobacter* (96, 298, 303, 427). When the culture methods used originally to isolate *H. bizzozeronii* and *H. salomonis* were applied to specimens from a group of dogs and cats, the results showed that the seemingly subtle modifications in culture methods were probably important (220). Cultures of specimens from 48 (51%) of 95 dogs and 3 (14%) of 22 cats were positive, which was considerably greater than the 0 to 10% that has recently been reported (96, 298, 303, 427). Approximately half the positive cultures from dogs yielded *H. bizzozeronii*. The remainder were about evenly divided between *H. felis* and *H. salomonis*, with "*Helicobacter* sp. flexispira" (see "Enterohepatic *Helicobacter* species" below) cultivated in two dogs. The three positive cultures in cats were all *H. felis*. *H. bizzozeronii*, *H. salomonis*, and *H. felis* were difficult to distinguish unequivocally by using morphology, bacteriology, routine biochemistry, or 16S rRNA sequence analysis. However, numerical analysis of whole-cell-protein electrophoresis results and calculation of percent similarity yielded clusters that best corresponded to the three different species.

"Helicobacter heilmannii"

In 1987 a novel gram-negative spiral bacterium was found in gastric biopsy specimens from three patients, although in retrospect the organism may have been the same as that described in humans many years earlier (235). It was easily distinguished from *H. pylori* by virtue of its larger size, more tightly coiled morphology, and failure to grow in microaerobic culture (72). Although it was recognized early that the organism closely resembled bacteria seen in a variety of other mammals, it was nevertheless tentatively assigned a new genus and species designation, "*Gastrospirillum hominis*," which reflected its occurrence in humans (271). The initial observation was quickly confirmed by numerous other case reports that described similar organisms in small numbers of patients (2, 5, 38, 85, 95, 121, 122, 124, 204, 213, 284, 289, 307, 385, 426, 428, 430; L. Mazzucchelli, Letter, Dig. Dis. Sci. **40:**1463, 1995).

Taxonomy and nomenclature. In vitro cultivation of this large gastric spiral bacterium remains elusive, but inoculation of mice and rats with gastric homogenates from infected humans and nonhuman primates permitted cultures to be maintained in vivo (77, 243). Mouse gastric tissue infected with organisms from two human patients was then used as a DNA template to amplify and sequence bacterial 16S rRNA genes, a technology that is now commonplace for the identification of uncultivated bacteria (347). The results confirmed early speculation based on antibody cross-reactivity (242) that the large gastric spiral organism originally designated "*Gastrospirillum hominis*" was actually a new species of *Helicobacter* that is most closely related to *H. felis* (371). The bacterium was tentatively designated "*Helicobacter heilmannii*" (371), after Konrad Heilmann, a German histopathologist who at the time had described the largest series of cases and who died prematurely shortly after its publication (201).

Unexpectedly, however, the 16S rRNA sequences from two different patient isolates of the large gastric spiral bacterium differed by 3.5%, which is sufficient to consider these organisms different species. We originally referred to these as "*Gastrospirillum hominis*" ("*H. heilmannii*" 1) and "*Gastrospirillum hominis*" ("*H. heilmannii*" 2) (371). The 16S rRNA sequence from what was recently described as the first culturable example of "*H. heilmannii*" (7, 205) is between 98.2 and 98.4% identical to sequences from *H. felis*, *H. bizzozeronii*, and *H. salomonis*. Since this organism was cultivated, it should be possible to perform DNA-DNA hybridization to confirm its species identity, but it is probably not the same as "*H. heilmannii*" 1. We have also reported recently one nearly complete and nine partial 16S rRNA sequences that were amplified from bacteria in the stomachs of healthy cats (303). These sequences are very similar but not identical to sequences from *H. felis*, *H. salomonis*, *H. bizzozeronii*, and "*H. heilmannii*" 2, all of which are closely related by 16S rRNA sequence analysis. Sequence comparison using urease or other genes may provide additional discrimination beyond 16S rRNA (50).

What, then, should we call uncultivated gastric bacteria that are urease positive and have the morphology of gastrospirillum? Both "*Gastrospirillum*" and "*hominis*" are inappropriate because these bacteria clearly belong in the *Helicobacter* genus and because humans are not typically the natural host. A recent proposal addressed the confusion created by the proliferation of new taxa invoked for uncultivated bacteria that are defined by limited data, such as 16S rRNA sequence. It was suggested that the usual binomial species designations be replaced with a new category, *Candidatus* (L., a candidate), followed by a descriptive epithet (295, 296). Following this suggestion, the designation "*Candidatus* Helicobacter suis" was proposed based on the identification in swine of a gastrospirillum which had a 16S rRNA gene that was 99.5% identical to that from "*H. heilmannii*" type 1 (67, 326). However, organisms with virtually identical 16S rRNA sequences have also been

commonly found in rhesus monkeys and other nonhuman primates, as well as in additional human patients (288; J. V. Solnick and J. O'Rourke, unpublished observations). Since the host range of this organism appears broad, the epithet "suis" may not be appropriate. The designation "*H. heilmannii*" is in common use, appropriately pays tribute to an early worker in the field, and avoids the implication that the organism has a restricted host range. Although current published data do not yet satisfy the criteria recently proposed for assignment of "*H. heilmannii*" to *Candidatus* status (75), ongoing experiments are likely to do so. We therefore propose that the designation "*H. heilmannii*" be applied to what was previously called "*H. heilmannii*" type 1 and to closely related bacteria. Newly observed uncultivated bacteria with a gastrospirillum morphology, but with a 16S rRNA sequence that is about 98% or more similar to *H. felis*, might be referred to as a member of the "*H. felis* species group" (303) or as "*H. felis*-like." This would apply to what we have previously called "*H. heilmannii*" type 2. "*H. heilmannii*"-like may also be used descriptively in the absence of genetic information, with the understanding that it may obscure species differences that will be apparent when 16S rRNA sequence or better cultivation methods are available.

Microbiology. The morphology of "*H. heilmannii*" is similar to that of *H. felis*, but periplasmic fibers are absent. The organism is 4 to 10 μm in length and 0.5 to 0.8 μm in diameter and has four to eight tight spirals (Fig. 3). There are typically 6 to 10 tufts of bipolar flagella. "*H. heilmannii*" is well visualized and distinguished from *H. pylori* by light microscopic examination of paraffin sections stained with hematoxylin and eosin or Warthin-Starry silver stain. Surprisingly, a recent report found that *H. pylori* can be induced to assume the morphology of "*H. heilmannii*" by being grown in brucella broth with 1% cyclodextrin rather than on blood agar (115). Since 16S rDNA sequences amplified from tissue infected with an "*H. heilmannii*"-like organism do not typically resemble *H. pylori*, it is unlikely that this observation is often relevant in vivo, but further study is warranted.

Several case reports indicated that a urease assay on tissue infected with "*H. heilmannii*" was negative, or slow to develop, which suggested that the urease of "*H. heilmannii*" might be quite different from that of other gastric *Helicobacter* species. However, PCR and DNA sequencing using degenerate primers based on *H. pylori* sequences showed that the "*H. heilmannii*" urease is composed of two subunits of approximately 26 and 62 kDa, which are 82 and 92% identical at the amino acid level to the corresponding UreA and UreB, respectively, from *H. felis* (372). The urea breath test has been used in animals to detect "*H. heilmannii*" (299, 369), and it is likely that a small percentage of humans with a positive urea breath test are infected with "*H. heilmannii*" and not *H. pylori*. Immunization with recombinant "*H. heilmannii*" urease has recently been shown to protect mice from infection with "*H. heilmannii*" and *H. felis*, but protection was accompanied by increased corpus atrophy. The possible role of residual undetected infection in promoting atrophy in the immunized animals (112) could be addressed by studying the effects of antibiotic therapy on atrophy in immunized animals. Beyond the ultrastructure and presence of the typical *Helicobacter* urease, little is known about the microbiology of this uncultivated organism.

Host range and epidemiology. The prevalence of infection with "*H. heilmannii*"-like organisms in humans is less than 0.5% among patients presenting for upper gastrointestinal endoscopy (124, 201, 271, 289), although it is reportedly as high as 6% in China and Thailand (425, 429). This latter observation requires confirmation by studies in other developing countries. In contrast to the low prevalence in humans, infection is very common in dogs (96, 427), cats (298, 303, 427), pigs (20, 326), and nonhuman primates (88, 91, 369). Recent studies also suggest that "*H. heilmannii*"-like organisms may infect wild urban rats (173) and both small and large exotic felids (104, 217, 227, 228). Thus, unlike the host range restriction of many *Helicobacter* species, such as *H. pylori* in humans and other primates, *H. felis* in cats and dogs, and *H. mustelae* in ferrets, "*H. heilmannii*"-like organisms are widely distributed in the animal kingdom. To date, "*H. heilmannii*" infection has been confirmed by 16S rDNA sequence analysis (rather than morphology alone) only in humans (371), pigs (70, 326), and nonhuman primates (Solnick and O'Rourke, unpublished), although it seems likely that it will be identified in other hosts.

Since "*H. heilmannii*" is common in animals, it has often been suggested that "*H. heilmannii*" infection in humans may be a zoonosis. "*H. heilmannii*" observed in a child morphologically resembled bacteria which were seen in the stomachs of her pet dogs (394). A human patient and his pet cat have also been documented to harbor "*H. heilmannii*" strains, which may have been the same organism since they had 580 bp of identical sequence from the ureB gene (79). Neither of these observations conclusively documents zoonotic transmission, since "*H. heilmannii*"-like bacteria are common in dogs and cats and the *ureB* gene is highly conserved. However, these findings are consistent with recent data which suggest that compared to patients infected with *H. pylori*, those infected with "*H. heilmannii*" are significantly more likely to report contact with a variety of animals, particularly dogs, cats, pigs, and cattle (272). If, as seems likely, "*H. heilmannii*" infection in humans is a zoonosis, the organism may be poorly adapted to the human gastric environment, since infection of humans is rare despite frequent contact with domestic animals. Alternatively, *H. pylori* may be simply better adapted to humans and may also protect against subsequent infection with "*H. heilmannii*," since dual infections are rarely seen.

Histopathology. The histopathology of "*H. heilmannii*"-like infection in humans was described for 39 cases in the first large series reported by Heilmann (201) and more recently in a study that compared 202 patients with "*H. heilmannii*" infection to 202 matched controls infected with *H. pylori* (376). Compared with *H. pylori*, "*H. heilmannii*" infection in humans is more often focal, with fewer organisms, and is often restricted to the gastric antrum. "*H. heilmannii*" is typically found in the mucus layer above surface epithelial cells and does not show the intimate adherence and pedestal formation often seen with *H. pylori*. Organisms may also be found deep in the lumen of the gastric glands and within parietal cells. Gastritis, while present, is much less marked in patients infected with "*H. heilmannii*" than in those infected with *H. pylori* (376, 425). The relatively mild inflammatory response to natural infection with "*H. heilmannii*"-like organisms has also been found in cats (303), dogs (96), and nonhuman primates (91, 369). However, the elevation of acid output in rhesus monkeys infected with

"*H. heilmannii*" suggests that, despite the minimal inflammatory response, the organism does alter the host gastric physiology (91).

Domestic swine may also be naturally infected with "*H. heilmannii*," with a prevalence of about 10% when evaluated by histologic testing (185, 277, 278, 327) but as high as 50 to 60% when evaluated by the more sensitive mouse inoculation assay (276, 326). Infection is associated with mononuclear inflammation and lymphoid follicles in the pylorus. Natural infection is also associated with gastric ulcer of the pars esophagea, a nonglandular area of stratified squamous epithelium that extends from the esophagus into the stomach (326, 431). When examined by mouse inoculation of gastric contents from swine, "*H. heilmannii*" was found in 20 (100%) of 20 pigs with ulcers and in 27 (90%) of 30 pigs with preulcer lesions but in only 7 (35%) of 35 pigs with macroscopically normal pars esophagea. This association is potentially important, since gastric ulcers in farmed pigs cause up to 2.5% of animals to die of gastrointestinal hemorrhage before slaughter. However, recent experimental inoculation of gnotobiotic piglets with "*H. heilmannii*," originally isolated from cheetahs and maintained in vivo in the mouse, did not reproduce the gastroesophageal ulcers seen in naturally infected animals (234). Furthermore, while gastritis was seen in experimentally inoculated animals, it occurred only in the gastric fundus, while in naturally infected animals gastritis has been observed in the pylorus. Since "*H. heilmannii*" is poorly characterized, these discrepancies may be due to strain differences or perhaps to host variables, such as the age at which infection occurs. It may also simply be that gastric ulcers in swine are not caused by "*H. heilmannii*," which is not the first microorganism to be found in association with ulceration of the pars esophagea (386).

Although laboratory rodents are not naturally colonized with "*H. heilmannii*," they can be readily infected experimentally. Human-derived "*H. heilmannii*" in the conventional Quackenbush Swiss mouse produced a mononuclear and polymorphonuclear gastritis, which progressed to gastric atrophy beginning 48 weeks after infection (241). Inoculation of "*H. heilmannii*" from pigs into Wistar rats or CFW(LOB) axenic mice resulted in a mild to moderate mononuclear infiltrate, predominantly in the gastric antrum (274, 292). In contrast, BALB/c mice infected with "*H. heilmannii*" derived from cheetahs with severe gastritis developed an initially mild lymphocytic and lymphofollicular inflammation, which progressed to severe gastritis with ulceration after 6 months (102). Kittens could also be infected with cheetah-derived "*H. heilmannii*," but the inflammation was mild and did not progress over an 11-month observation period (103). Thus, while the differences in histopathologic changes seen with experimental "*H. heilmannii*" infection may be partially related to bacterial differences, particularly since the inoculum is poorly characterized, host factors are also clearly important.

Clinical considerations. Although inflammation in humans infected with "*H. heilmannii*" is less severe than in humans infected with *H. pylori*, gastritis is nevertheless always present. Furthermore, human infection with "*H. heilmannii*" has been documented in association with acute and chronic gastrointestinal symptoms (2, 4, 85, 204, 289, 307, 385, 428), which in some cases have resolved with effective therapy, and in association with gastric pathologic responses, including ulcer, adenocarcinoma, and lymphoma (38, 68, 332, 430). Recently, remission of gastric MALT lymphoma was described after treatment of "*H. heilmannii*" infection in five patients, a phenomenon that is well known in *H. pylori*-associated gastric MALT lymphoma (288). Two of the five patients from whom bacterial 16S rRNA sequence was available were infected with an organism that was 99.3% identical to "*H. heilmannii*" (type 1), although only 172 bp were sequenced and the region of the 16S rRNA gene was not specified. Not surprisingly, "*H. heilmannii*" infection also occurs in asymptomatic individuals (268), which is also the case for, and in fact is typical of, infection with *H. pylori* (83). Whether "*H. heilmannii*" infection causes gastrointestinal symptoms and gastric pathologic changes is difficult to determine because of its low prevalence. However, it is probably prudent to use the same guidelines for when and how to treat "*H. heilmannii*" infection that have been proposed for infection with *H. pylori* (13, 93). Touch cytologic testing performed by rolling a gastric biopsy specimen onto a glass slide and staining it with modified Giemsa or Gram stain may be more sensitive than biopsy (67, 69). Treatment of "*H. heilmannii*"-like organisms in dogs and cats appears to be relatively ineffective, which may be consistent with their role as members of the normal flora (55, 299).

Helicobacter acinonychis

Chronic gastritis is widespread among captive cheetahs in zoological parks and is a significant clinical problem (293). Investigation of cheetahs with chronic vomiting revealed two kinds of gastric spiral bacteria (105). One could not be cultivated and resembled "*H. heilmannii*," although periplasmic fibers were sometimes present. The other was morphologically and biochemically similar to *H. pylori* but somewhat smaller (0.3 by 1.5 to 2.0 μm) and with a G+C content of 30% rather than the 39% that is typical for *H. pylori*. Analysis of the 16S rRNA gene from the cultivated organism showed that it was most closely related to *H. pylori* (97.4% similar), and the name *H. acinonyx* was proposed (97), recently changed to *H. acinonychis* (399). Bacteria isolated from two Sumatran tigers killed because of age-related disability also appears to be *H. acinonychis* (349).

H. acinonychis appears to be more closely associated with gastritis in cheetahs than does the "*H. heilmannii*"-like organism. Animals infected with *H. acinonychis* with or without the "*H. heilmannii*"-like organism typically have severe lymphoplasmacytic gastritis with scattered neutrophils and lymphoid follicles, sometimes accompanied by gross thickening of the gastric rugae, erosions, and punctate hemorrhages. In contrast, animals infected with the "*H. heilmannii*"-like organisms alone sometimes have only minimal gastritis (104, 408). However, the pathogenic role of *H. acinonychis* in cheetahs is unproven. Antibiotic treatment of *H. acinonychis* was reported to provide symptomatic relief from vomiting, anorexia, and weight loss in three cheetahs without clearing the infection (408). Interestingly, the gastritis seen in captive cheetahs is not found in wild cheetahs, although infection with gastric spiral organisms is nearly always present in both (392). Whether this is related to differences in the bacterial species infecting captive and wild animals or to host variables such as stress of captivity remains to be determined. Further studies of therapy and experimental

inoculation will be required to determine if *H. acinonychis* plays a role in clinical and histologic gastritis in cheetahs, although such studies face obvious logistical difficulties.

Little is known about possible virulence genes in *H. acinonychis*. One presumes that urease, flagella, and perhaps other documented virulence factors in other *Helicobacter* species are important. The *H. acinonychis* homologue (*hxaA*) of a putative *H. pylori* adhesin (*hpaA*) is probably not an adhesin, since later work has shown that HpaA is in fact a flagellar sheath protein that is not involved in attachment (114, 223, 311).

Helicobacter nemestrinae

An organism isolated from the pigtailed macaque (*Macaca nemestrina*) was reported to differ from *H. pylori* by virtue of its growth at 42°C and its cellular fatty acid profile (42). Studies of DNA-DNA hybridization and 16S rDNA also suggested that it was a novel species most closely related to *H. pylori*. Surprisingly, the G+C content was only 24%, much lower than those of all known *Helicobacter* species, which prompted a reappraisal by two groups. The results suggest that *H. nemestrinae* (ATCC 49396) may in fact be identical to *H. pylori*. Repeat determination of the 16S rDNA sequence (F. Dewhirst, personal communication) showed that it is 99.5% identical to human *H. pylori* and 100% identical to *H. pylori* isolated from the rhesus macaque (84). Repeat analysis of DNA base composition indicates that *H. nemestrinae* (ATCC 49396) is 39% G+C (identical to *H. pylori*) and that the protein profile is also consistent with *H. pylori* (P. Vandamme, personal communication). Confirmation must await publication of these results.

"*Helicobacter suncus*"

Cultures from the stomach of house musk shrews (*Suncus murinus*) with chronic gastritis yielded a gram-negative, urease-positive bacterium whose 16S rRNA sequence is most closely related to that from a *Helicobacter* organism isolated from birds. The name "*H. suncus*" has been proposed (182) but not validated. The organism has been described as having an interesting tendency to occur predominantly in a coccoid or coccobacillary form in vitro, with about 1% of cells appearing fusiform, while in vivo only fusiform bacteria are seen.

Candidatus Helicobacter bovis

Urease-positive bacteria resembling *Helicobacter* have been observed in histologic sections of the bovine abomasum (40, 187, 199), which is the true glandular stomach in ruminants. Infection may be associated with a lymphocytic and plasmacytic infiltrate. Although efforts to cultivate these organisms have been unsuccessful, sequence analysis of 16S rDNA amplified from abomasal tissue suggests that they represent a novel *Helicobacter* species (Table 3; Fig. 6), which has recently been designated *Candidatus* Helicobacter bovis (71). It is unknown whether *Candidatus* H. bovis infection is related to abomasal ulcers in cattle that were previously attributed to diet and stress due to illness or weather (186).

Other Gastric Bacteria

With the exception of occasional transient colonization by enteric bacteria, only *Helicobacter* species are generally known to infect the human stomach. However, a urease-positive coccoid organism has recently been cultivated from gastric biopsy specimens obtained from Korean patients (252). Biochemical analysis of the urease from this bacterium showed that kinetic parameters, relative abundance, and subunit composition are similar to those of *Helicobacter* urease (251). Preliminary taxonomic classification by fatty acid composition and biochemical analysis suggested that the organism was related to *Staphylococcus*. The 16S rDNA sequence from this organism is essentially identical to that from *S. saprophyticus* and also very similar (<1% different) to those from the closely related species *S. xylosus* and *S. cohnii*. (D. H. Calhoun, personal communication). The prevalence and clinical significance of gastric colonization with this bacterium are unknown.

ENTEROHEPATIC *HELICOBACTER* SPECIES

In addition to the gastric spiral-shaped bacteria, there is an equally diverse group of *Helicobacter* species that have been identified in the intestinal tract and/or the liver of humans, other mammals, and birds (Table 4). These enterohepatic *Helicobacter* species (EHS) do not normally colonize the gastric mucosa but do have features of ultrastructure and physiology in common with the gastric *Helicobacter* species (Table 2). The EHS were first recognized in laboratory rodents, where they are highly prevalent in most inbred strains and outbred stocks. Consequently, the EHS have been considered a component of the resident microbiota, or normal flora. It is now clear that some, and perhaps all, of the EHS have the ability to cause disease in normal, immunocompetent rodents. A growing number of EHS have also been reported to be associated with gastroenteritis, hepatitis, and other disease states in humans and in other animal species. The significance of the EHS in human disease and the true prevalence of these organisms in human populations remain to be determined. Nonetheless, the potential importance of these emerging pathogens cannot be overlooked.

Early Morphologic Observations

The surface mucus gel layer and the contiguous mucus deep in the crypts represents the interface between the host epithelium and the lumen of the gastrointestinal tract. Early studies characterizing the resident microbiota in the gut of laboratory rodents led to the discovery of a diverse population of spiral-shaped bacteria uniquely adapted to thrive in this transitional zone. These early studies, which utilized transmission electron microscopy rather than culture and isolation, described two morphologic types of organisms, both of which are now known to be EHS. Members of the first group superficially resemble *Campylobacter* species but are longer and have a single polar flagellum at each end (Fig. 7). Members of the second group, which includes the Lockard type 1 organism, have periplasmic fibers that wrap helically around the body of the bacterium as well as bipolar tufts of sheathed flagella (Fig. 1). Because of the periplasmic fibers, these organisms have a cross-hatched appearance in negative-stain preparations (Fig. 1A) but appear barber pole-like in longitudinal sections and scalloped in oblique sections in transmission electron micrographs (Fig. 1B). In studies that characterized the patterns of bacterial colonization of the large intestines of laboratory rodents, Davis

TABLE 4. Enterohepatic *Helicobacter* taxa

Taxon	Natural host	Strain	GenBank 16S rRNA accession no.	Reference
H. bilis	Mouse, dog, human	ATCC 51630^T	U18766	161
H. canis	Dog, human	ATCC 5140^T	L13464	375
H. cinaedi	Human, hamster	ATCC 35683^T	M88150	397
H. cholecystus	Hamster	ATCC 700242^T	U46129	162
H. fennelliae	Human	ATCC 35684^T	M88154	397
H. hepaticus	Mouse	FRED1	L39122	23
H. muridarum	Mouse, rat	ATCC 49282^T	M80205	248
H. pamntenis	Bird, swine	ATCC 51478^T	M88147	76
H. pullorum	Chicken, human	ATCC 51801^T	L36141	374
"*H. canadensis*"	Human	NLEP 16143	AF262037	140
H. rodentium	Mouse	ATCC 700285^T	U96296	356
H. trogontum	Rat	ATCC 700114^T	U65103	275
"*H. typhlonicus*"	Mouse	MU96-1^T	AF061104	164
"*H. mesocricetorum*"	Hamster	MU97-1514^T	AF072471	362
"*Helicobacter* sp. flexispira" taxon 5	Sheep, dog, human, mouse	ATCC 43966	M88137	74
"*H. mainz*"	Human	ATCC 51800	X81028	210
"*H. westmeadii*"	Human	NA[a]	U44756	398
Helicobacter sp. cottontop	Cottontop tamarin	NA	AF107494	345

[a] NA, not available.

et al. identified both morphologic types of organisms in the mucus of the cecum and colon (65, 66). The bacteria could be found during the first week of life, and they remained on the apical surface of the intestinal epithelium and packed deep in the crypts throughout the life of the animals. Bacteria seen by electron microscopy in early studies of "intestinal spirochetosis" in dogs and rats were also probably *Helicobacter* species (238).

Perhaps because their ultrastructure is less remarkable, the early literature contains fewer reports of the simple spiral-shaped organisms than of the organisms with periplasmic fibers. Nonetheless, the simple spiral-shaped, organisms have been isolated from a variety of mammals, including humans (*H. cinaedi*, *H. fennelliae*, and *H. canis*), and rodents (*H. hepaticus*, *H. rodentium*, and *H. cholecystus*), as well as from birds (*H. pametensis* and *H. pullorum*). The distinction between these organisms and the organisms with periplasmic fibers has a morphologic basis only; no comparable phylogenetic dichotomy has been recognized (Fig. 6). On the other hand, the presence of periplasmic fibers has facilitated the recognition of members of the second group of EHS in a variety of locations. Spiral-shaped bacteria with periplasmic fibers were observed free in the cytoplasm of enterocytes as well as deeper in the lamina propria of mice following treatment with nitrogen mustard (192). Such treatment results in a generalized loss of epithelial integrity, but it is interesting that the EHS were the only organisms found to invade under these conditions. The abundance of these organisms in the mucus deep in the crypts of the ileum and their proximity to the apical surface of the epithelial cells lining the crypts may account, at least in part, for these observations. Erlandsen and Chase exploited the ultrastructural characteristics of these organisms to ascertain the fate of bacteria following phagocytosis from the crypts by differentiated enterocytes in the ileum of untreated rats (111). Davis et al. also noted the occasional penetration of EHS into the epithelium of the rat cecum (66). More recently, invasion into the lamina propria of the cecum by EHS in mice following challenge with the spirochete *Serpulina hyodysenteriae* has been reported (212). The significance of cell entry and/or tissue invasion by EHS and the conditions under which these events take place have not been fully elucidated. Tissue invasion may be a prerequisite for or a consequence of *Helicobacter*-associated disease in the gastrointestinal tract. It may also play a role in bacterial translocation to the liver and/or into the systemic circulation, either as a primary event or secondary to other disease states.

The fact that many investigators have encountered EHS with periplasmic fibers in the gastrointestinal tracts of laboratory rodents no doubt reflects the frequency with which these animals are used in biomedical research. Bacteria with the same morphology have also been isolated from the gastrointestinal tracts of other mammals, including dogs, cats, nonhuman primates, and humans ("*Helicobacter* sp. flexispira" and *H. bilis*). The complete range of host species from which these organisms can be isolated is not known. It may be that such bacteria can flourish wherever a mucus-rich interface between epithelial cells and the lumen of an alimentary tract is found. Certainly, the observation of bacteria that appear morphologically indistinguishable from EHS in the hindgut of *Periplaneta americana*, the American cockroach (39), suggests that the distribution of these microbes is very wide indeed.

Helicobacter hepaticus

Historical perspective. In autumn 1992, pathologists at the National Cancer Institute-Fredrick Cancer Research and Development Center recognized that male A/JCr mice serving as saline-injected controls in a long-term chemical carcinogenesis assay had a higher than expected incidence of liver tumors (415). Historically, hepatocellular tumors were found in male mice of this inbred strain with an incidence of approximately 1% at 15 months of age or older. However, evaluation of tissue from animals euthanized between August and October 1992 revealed liver tumors in 3 of 6 mice, and in December 1992 liver tumors were found in 11 of 12 mice (415). All of the animals with liver tumors also had chronic active hepatitis. At the time, contamination with an environmental chemical was suspected as the cause of the hepatocellular tumors and the

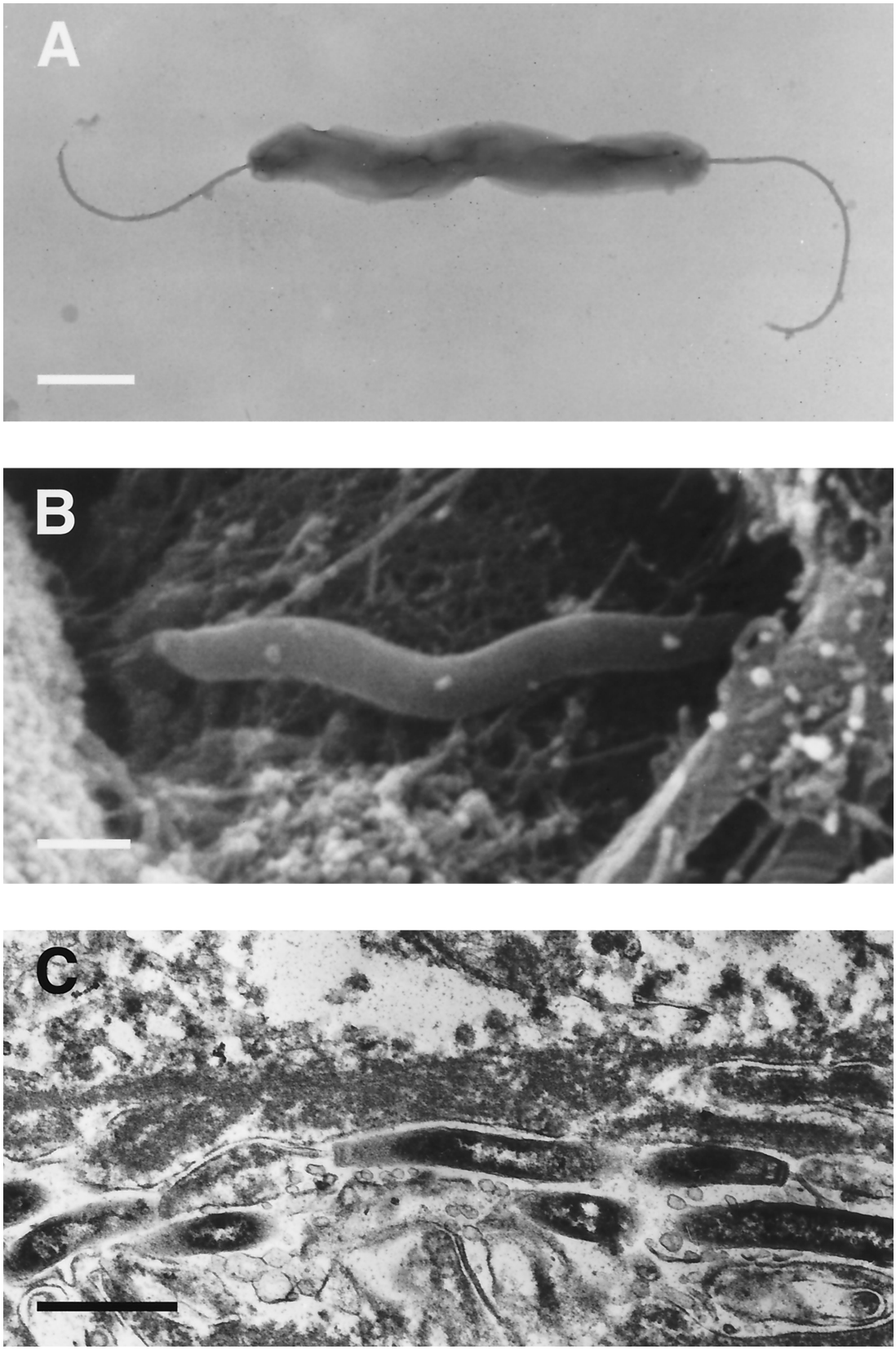

FIG. 7. (A and B) Negatively stained preparation (A) and transmission electron micrograph (B) of *H. hepaticus* show the absence of periplasmic fibers and the single bipolar flagella. (C) Transmission electron micrograph of a liver section in a mouse reveals *H. hepaticus* in a bile canaliculus. Panel C is reprinted from reference 253 with permission from the American Society for Microbiology. Bars, 0.5 μm.

hepatitis, but extensive analyses of food, bedding, and water proved negative (415). An environmental toxin seemed even less likely when it was discovered that mice in the breeding colony, housed in a separate facility, also had hepatic lesions. Hepatitis was worse in males than in females and was documented in A/JCr, C3H/HeNCr, SJL/NCr, BALB/cAnNCr, and SCID/NCr mice but not in C57BL/6NCr mice (415). A/J mice without hepatitis were obtained from a commercial vendor, and when the disease was shown to be transmissible by inoculating these animals with homogenates of liver from affected A/JCr mice, the search for an infectious agent was intensified. Using Steiner's silver impregnation as a special stain, spiral-shaped bacteria were found in bile canaliculi and gallbladders of affected mice (415). It was then that microaerobic culture and isolation was performed on liver tissue and on cecal and colonic mucosal scrapings (146).

Culture and isolation. Fox et al. succeeded in isolating *H. hepaticus* from the liver and cecal and colonic mucosa of mice with chronic active hepatitis (146). After a 3- to 7-day incubation under anaerobic or microaerobic conditions, but not in ambient O_2, the organism grew as a spreading film on solid media supplemented with serum or blood. The organism is a simple spiral 1.5 to 5 μm long and 0.2 to 0.3 μm in diameter, with a single-sheathed flagellum at each end but without periplasmic fibers (Fig. 7). *H. hepaticus* exhibits catalase, urease, and oxidase activities, and it grows at 37°C but not at 42 or 25°C (Table 2). Nucleotide sequence determination of the 16S rRNA gene shows that *H. hepaticus* is a distinct species of *Helicobacter* most closely related to *H. muridarum* (23, 146). *H. hepaticus* is probably the best characterized of the EHS. It is now known to cause chronic active hepatitis and typhlitis in many susceptible strains and stocks of mice (154, 412, 415), hepatocellular tumors in male A/J (154, 415) and B6C3F1 (189) mice, and inflammatory bowel disease in a variety of mouse lines with altered immune functions (48, 236, 253, 407, 413). Infection with *H. hepaticus* is highly prevalent in laboratory mouse colonies (355), but the organism has not been isolated from other host species to date. In immunocompetent mice, there are no clinical signs of disease and no obvious reduction in breeding efficiency. Thus, many investigators may not be aware that their mice are infected with *H. hepaticus*.

Pathology. In naturally infected A/JCr mice, *H. hepaticus* causes focal nonsuppurative necrotizing hepatitis that progresses to chronic active hepatitis characterized by oval cell hyperplasia, cholangitis, and minimal necrosis (154, 412). Males have liver lesions that develop earlier and are more severe than those in females. The basis for the increased susceptibility in males is not understood. Most animals have no gross pathologic lesions in the liver, but severely affected mice may have yellow to white foci and/or a prominent reticular pattern in one or more liver lobes (154, 412). Microscopically, focal lesions can be seen as early as 1 month of age (412). These areas of hepatic necrosis and inflammation become multifocal and may coalesce by 3 to 6 months of age (154). With time, oval cell hyperplasia and lymphoplasmacytic infiltration of surrounding bile ducts and portal veins become prominent (154, 412). The most chronic lesions, seen after 8 months of age, include bile duct hyperplasia in many portal areas, cytomegaly and karyomegaly of hepatocytes, and intranuclear pseudoinclusions (154, 412). Hepatocellular necrosis becomes less prominent at this stage. Between 12 and 18 months of age, most male mice go on to develop preneoplastic nodular hyperplasia and hepatocellular tumors (154, 412). Chronic active hepatitis leading to hepatocellular neoplasia was also observed in germ-free female Swiss Webster mice following experimental infection with *H. hepaticus*, clearly establishing the organism as a murine pathogen (160).

Carcinogenesis and a confounding factor in risk assessment. More recently, *H. hepaticus* infection has also been shown to be associated with hepatic neoplasia in B6C3F1 mice used for carcinogenesis testing by the National Toxicology Program (155, 189). Unfortunately, several 2-year carcinogenesis studies were confounded by the presence of hepatocellular tumors and hepatic hemangiosarcoma in control male mice. It is of interest that genetic susceptibility to *Helicobacter* hepatitis and hepatic neoplasia appears to have a dominant pattern of inheritance, since B6C3F1 mice are produced by interbreeding susceptible C3H and resistant C57BL/6 strains of mice. A genetic role in susceptibility to inflammation from *H. hepaticus* is also suggested by studies with recombinant inbred AXB mice that are derived from matings between C57BL/6 and susceptible A/J mice (214). The mechanism by which *H. hepaticus* infection leads to hepatic neoplasia remains poorly understood. No evidence of mutations in *ras* or in the *p53* tumor suppressor gene was found in liver tumors taken from A/JCr mice infected with *H. hepaticus* (366). The absence of *p53* mutations is consistent with earlier findings, but activating mutations in the H-*ras* oncogene are characteristic of chemically initiated murine liver tumors. The absence of mutations in *H. hepaticus*-associated liver tumors suggests that the mechanism of *H. hepaticus* carcinogenesis may not involve genotoxic damage (49). Instead, the enhanced rate of hepatocyte proliferation and apoptosis seen in affected mice may influence hepatocarcinogenesis by acting as a tumor promoter (80, 154, 304). *H. hepaticus* infection also results in oxidative stress in the liver, as evidenced by elevated levels of 8-hydroxydeoxyguanosine (8-oxo-dG) found in affected male A/JCr mice (365). Reactive oxygen species and reactive nitrogen species may also contribute to hepatocarcinogenesis in *H. hepaticus* infection.

Inflammatory bowel disease. *H. hepaticus* organisms seen with Steiner stain in the liver are present in bile canaliculi but not within hepatocytes. This was confirmed by transmission electron microscopy (154, 412) (Fig. 7C). Bacteria are also found in the gallbladder and in large numbers on the surface epithelium in the intestine and deep in the crypts, particularly in the cecum (154, 415). Indeed, *H. hepaticus* is found earlier and more consistently in the intestine than in the liver, indicating that this is the primary site of colonization (154). In the intestines of immunocompetent mice, *H. hepaticus* infection causes mild inflammation and epithelial hyperplasia that is typically seen as a relatively late change (160, 421). In contrast, *H. hepaticus* infection in immunodeficient nude and SCID mice is associated with marked typhlitis, colitis, and proctitis, often with a high incidence of rectal prolapse (253, 339, 413). Similar lesions have been associated with *H. hepaticus* infection in lines of targeted gene mutant mice (knockout mice) that have been used as models of idiopathic inflammatory bowel disease (IBD) (128). Furthermore, experimental infection with *H. hepaticus* has been shown to be sufficient to induce IBD-like lesions in SCID mice reconstituted with naive $CD4^+$

CD45RB^{high} T cells (48), as well as in IL-10-deficient mice (236) and Rag-2-deficient mice (407). Some controversy remains about the exact role of *H. hepaticus* infection in the etiopathogenesis of IBD in various knockout mouse models. Nonetheless, it is now clear that *H. hepaticus* infection can cause severe intestinal inflammation that resembles Crohn's disease and ulcerative colitis in knockout mice that have a dysregulated immune response.

Bacterial pathogenesis. The mechanism by which *H. hepaticus* causes hepatic and intestinal disease remains poorly understood. Infected mice develop persistent humoral and mucosal immune responses that are not protective (154, 256, 412, 421). Both chronic active hepatitis in A/JCr mice and IBD in IL-10 knockout and Rag-2 knockout mice are associated with a Th1 immune response, which is characterized by high levels of gamma interferon and the presence of activated macrophages (236, 407, 421). *H. hepaticus* and HSP70 share cross-reactive epitopes, and it has been suggested that autoimmunity could play a role in disease pathogenesis (414). A novel toxin activity has been identified in *H. hepaticus* that causes vacuole formation in a murine liver cell line, resulting in a granular appearance of the affected cells (388). This granulating cytotoxin is a heat-labile secreted protein with a native molecular mass of >100 kDa that is distinct from the vacuolating cytotoxin of *H. pylori*. More recently, Young et al. have identified three genes encoding cytolethal distending toxin (CDT) and CDT activity in *H. hepaticus* (433). *H. hepaticus* CDT causes cell cycle arrest in HeLa cells and is closely related to the CDT of *Campylobacter* species (323). Genetic and phenotypic evidence of CDT has also been found in, *H. bilis*, *H. canis*, and *H. pullorum* (52, 432). The role of these toxins in *H. hepaticus* pathogenesis remains to be determined.

Diagnosis and treatment. *H. hepaticus* can be isolated from the livers of animals with hepatitis (146). However, it is more consistently recovered from the intestinal tract (154). This is particularly true in C57BL/6 mice that are resistant to hepatic disease. Sensitive isolation procedures typically include incubation on a selective medium and/or passage through a 0.45-μm-pore-size filter to enrich for *H. hepaticus* organisms (355). Although reliable in the hands of an experienced microbiologist, these procedures are tedious and require days to weeks for successful culture and isolation. PCR provides more rapid results and greater sensitivity. Several PCR methods have been described, including *H. hepaticus*-specific amplification with primers complementary to regions in the 16S rRNA gene (355) and a PCR-RFLP that also amplifies a portion of the 16S rRNA gene (334). Shen et al. have described a second PCR-RFLP method that specifically amplifies a portion of the *H. hepaticus* urease structural genes *ureAB* and then allows genotyping to be performed (357). Serodiagnosis of *H. hepaticus* infection by enzyme-linked immunosorbent assay using a membrane preparation as antigen has also been described (256). With regard to treatment, several antibiotic regimens have been described for eradication of *H. hepaticus* (129, 130, 339), but treatment failures do occur. Rederivation of genetically characterized mice by constructing the strain in *Helicobacter*-free recipient mice may be a more reliable method for the elimination of this pervasive murine pathogen.

Helicobacter cinaedi and *Helicobacter fennelliae*

First identified as *Campylobacter* species, *H. cinaedi* and *H. fennelliae* are simple spiral-shaped organisms that resemble *H. hepaticus* morphologically (Fig. 7) but do not produce urease. Totten et al. isolated these organisms from rectal swabs taken from homosexual men (397). Over 30 isolates of *H. cinaedi* (from the Latin for "of a homosexual") were recovered from asymptomatic individuals and individuals with proctitis, proctocolitis, or enteritis. Another six isolates, all recovered from patients with clinical signs, were shown to comprise a distinct species and were named *H. fennelliae* after Cynthia Fennell, the technologist who first isolated the organism. A lone isolate from a symptomatic individual was designated *Campylobacter*-like organism 3 (CLO-3) and has still not been named (397). Additional isolates of *H. cinaedi* from dogs, cats, and Syrian hamsters were shown by DNA-DNA hybridization to belong to a single species (226). Although the hamsters from which *H. cinaedi* was isolated appeared healthy (167), experimental inoculation of infant pigtailed macaques (*M. nemestrina*) with *H. cinaedi* or *H. fennelliae* caused diarrhea and bacteremia (125). Indeed, although *H. cinaedi* has been documented as a cause of acute diarrhea in otherwise healthy individuals (390), bacteremia without gastroenteritis has been more frequently associated with *H. cinaedi* and *H. fennelliae* infection in patients immunocompromised due to AIDS (53, 259, 300, 340) or other underlying conditions (207). These infections can also manifest as cellulitis or septic arthritis (45). Interestingly, *H. cinaedi* has also been isolated from the blood of immunocompetent children and adults with and without diarrhea (405) and in one case from a neonate with bacteremia and meningitis whose mother had cared for pet hamsters during pregnancy (308). Thus, these organisms—like *Campylobacter fetus* and *C. hyointestinalis*, which are typically associated with disease in farm animals—cause invasive disease as well as gastroenteritis in humans, particularly those with underlying immunosuppression such as that caused by AIDS.

Helicobacter canis

A separate group of isolates originally designated CLOs were recovered from the feces of dogs with or without diarrhea. These isolates morphologically resemble *H. hepaticus* but grow at 42 as well as 37°C and do not exhibit urease activity. On the basis of DNA-DNA hybridization and 16S rRNA sequencing, these strains were shown to comprise a distinct species that was named *H. canis* (375). *H. canis* has also been isolated from the feces of a 5 1/2-year-old boy with gastroenteritis (47) and from the liver of a 2-month-old puppy suffering from multifocal necrotizing hepatitis (147). More recently, *H. canis* has been isolated from Asian leopard cat-domestic cat hybrids (Bengal cats) with a 6-month history of episodic diarrhea (126). However, because the cats were infected with other potential enteric pathogens, including *Campylobacter helveticus*, and because *H. canis* was also isolated from cats without diarrhea, the pathogenic potential of this organism in cats remains unclear. Further studies are needed to determine whether *H. canis* is a cause of hepatic disease as well as gastroenteritis in carnivores such as dogs and cats, as well as in humans.

Helicobacter pametensis, *Helicobacter pullorum*, and "*Helicobacter canadensis*"

H. pametensis and *H. pullorum* both infect birds and mammals. *H. pametensis* was first isolated from the feces of wild birds and a domestic pig near the Pamet River on Cape Cod, Mass. (354). Six isolates of *H. pametensis* from gulls, terns, and the pig were characterized by 16S rRNA gene sequencing and found to represent a single, distinct species (76). In addition, other *Helicobacter* species were isolated from terns and from a house sparrow. These *Helicobacter* species were designated *Helicobacter* sp. Bird-B and *Helicobacter* sp. Bird-C, respectively (76). They have not yet been named. *H. pametensis* has also been isolated from the stomach of a cat coinfected with "*H. heilmannii*" (298). *H. pullorum* was designated a separate species on the basis of 16S rRNA gene sequencing (374). Isolates were recovered from the ceca of subclinically infected broiler chickens, from the livers and intestinal contents of laying hens with vibrionic hepatitis, and from humans with gastroenteritis (374). One individual, in addition to having diarrhea, developed elevated liver enzyme levels and hepatomegaly (46). There is clearly a potential for zoonotic food-borne transmission of *H. pullorum* to humans, as is known to occur with *Campylobacter* species. While both *H. pametensis* and *H. pullorum* are urease negative and grow readily at 42 as well as 37°C, they can be distinguished by the fact that *H. pametensis* has sheathed flagella but *H. pullorum* does not (374). Importantly, *H. pullorum* does not grow on campylobacter selective medium containing polymyxin B; it grows well on blood agar supplemented with cefoperazone, vancomycin, and amphotericin B (17, 374). Recently, four isolates cultured from Canadian patients with diarrhea, which were originally classified as *H. pullorum*, were shown by 16S rRNA sequence to represent a novel species, designated "*H. canadensis*" (140). Whether "*H. canadensis*" has an avian reservoir and is acquired by humans as a zoonosis has not yet been determined.

Helicobacter cholecystus

Franklin et al. isolated a novel *Helicobacter* species from the gallbladder of Syrian hamsters affected with cholangiofibrosis and centrilobular pancreatitis (162). This organism is called *H. cholecystus*, and it is somewhat morphologically distinct from the other simple spiral-shaped *Helicobacter* species. *H. cholecystus* has a rod-shaped protoplasmic cylinder and a single polar, sheathed flagellum, but it does not have periplasmic fibers. It is urease negative and grows at 42°C.

Helicobacter rodentium

H. rodentium is also a urease-negative, spiral-shaped organism that grows well at 42 as well as 37°C (356). Like *H. pullorum*, *H. rodentium* has unsheathed flagella. This organism was first isolated from subclinically infected laboratory mice. Subsequently, Shomer et al. reported an outbreak of diarrhea in a colony of SCID mice carrying mutations in the *p53* tumor suppressor gene that were coinfected with *H. rodentium* and *H. bilis* (359). The true pathogenic potential of *H. rodentium* in immunodeficient and immunocompetent mice remains to be determined.

"*Helicobacter mesocricetorum*"

The most recently described *Helicobacter* species, "*H. mesocricetorum*," is a urease-negative bacterium (362) isolated from fecal pellets of asymptomatic Syrian hamsters (*Mesocricetus auratus*). It is closely related to *H. rodentium* and *H. pullorum*, which share the somewhat unusual property among *Helicobacter* species of having unsheathed flagella. Histologic evaluation of the gastrointestinal tracts of "*H. mesocricetorum*"-infected hamsters revealed no pathologic changes, and thus this bacterium is probably commensal. Whether "*H. mesocricetorum*" can be transmitted to humans as a zoonosis, like *H. cholecystis* and *H. cinaedi*, which also infect hamsters, is unknown.

"*Helicobacter typhlonicus*"

Fox et al. isolated a novel species from *H. hepaticus*-free IL-10-deficient mice with IBD (149). IL-10-deficient mice experimentally infected with this organism developed typhlocolitis and proctitis by 4 months postinoculation, demonstrating the ability of this EHS to cause disease. Although the infected IL-10-deficient mice had focal hepatic granulomatous inflammation and mild cholangitis, no bacterial organisms were seen in the liver. In SCID mice experimentally infected with this organism, there was mild to moderate proliferative typhlitis at 4 months postinoculation, while experimentally infected A/JCr mice had minimal to mild typhlitis 6 months postinoculation. Shortly after this publication appeared, Franklin et al. cultivated from the feces of BALB/c mice an EHS that was identical to that described by Fox et al., and the designation "*H. typhlonicus*" was proposed (164). Pathologic changes similar to those reported by Fox et al. were seen in SCID mice experimentally inoculated with "*H. typhlonicus*" (164).

Other Urease-Negative *Helicobacter* Species without Periplasmic Fibers

In addition to these 11 formally or provisionally named species, other EHS without periplasmic fibers have been described. "*H. mainz*" was isolated from the blood and joint fluid of an AIDS patient with septic arthritis (210) and from the blood of two other AIDS patients with bacteremia (123). Provisionally named after Mainz, Germany, the city where they were first isolated, these isolates have a 16S rRNA gene sequence that is 97.7% similar to *H. fennelliae*. Thus, it is not clear if "*H. mainz*" can truly be considered a distinct species. Likewise, "*H. westmeadii*" was isolated from the blood of two AIDS patients with bacteremia and provisionally named after Westmead, New South Wales, Australia (398). Because these isolates have a 16S rRNA gene sequence that is very similar to that of *H. cinaedi* (Table 3), they, too, may not represent distinct species. More recently, a similar organism was isolated by Weir et al. from the blood of an AIDS patient (420). The definitive classification of this isolate also remains to be determined.

Foley et al. have described an organism that was identified in the intestine of a kitten with diarrhea (127). This organism was provisionally named "*H. colifelis*" and was found to have a 16S rRNA gene sequence 98.3% similar to *H. canis*. Because the organism was not successfully cultured, it is difficult to determine if it represents a novel EHS. Its association with diarrhea

is also not proven, because inoculation of infected feces did not produce diarrhea in specific-pathogen-free cats, although the feces was positive by PCR using primers specific for the *Helicobacter* genus.

Helicobacter muridarum

Historical perspective. Phillips and Lee succeeded in isolating the first EHS in 1983 by inoculating blood- or serum-enriched media with mucosal scrapings from the intestines of conventional Wistar rats and BALB/c mice almost 10 years before it would be formally named as a *Helicobacter* species (322). The isolates grew slowly, spreading as a thin film after a few days of incubation at 37°C, even on media containing 3% agar. The growth requirements of the isolates were reminiscent of the in vivo niche in which they thrived. Like *Campylobacter* species, they required a reduced partial pressure of O_2 and an increased partial pressure of CO_2. These microaerobic conditions could be produced by equilibrating evacuated jars with a bottled gas mixture or with anaerobic gas generator envelopes, without the use of catalyst so as not to remove residual O_2. The isolates also required media with surface moisture for optimal growth. Plates that had been predried to remove surface condensation did not generally support growth, but biphasic conditions, with broth over a layer of solid medium, were well suited for culture of these organisms. In pure culture, the isolates were found to be spiral shaped and gram negative. Like the organisms seen by Davis et al. (66) and Erlandsen and Chase (111) by electron microscopy, the isolates were 0.5 to 0.6 μm in diameter and 3.5 to 5 μm long. They had two to three spiral turns, periplasmic fibers, and bipolar tufts of sheathed flagella. Nucleotide sequence determination of 16S rRNA eventually confirmed what growth requirements, ultrastructure, and biochemical characteristics had suggested: *H. muridarum* is a separate species in the genus *Helicobacter* (248).

Epidemiology. Based on microscopic observations of *H. muridarum* in the intestinal crypts of conventional rats and mice, Phillips and Lee found that the ileum had a higher density of colonization than did the cecum or the colon (322). However, when gnotobiotic animals were experimentally inoculated with pure cultures of the organism, few of the ileal crypts in rats and none of the ileal crypts in mice contained spirals. Instead, the cecum, and to a lesser extent the colon, was found to contain the highest density of organisms. This suggests that in the absence of competing microbiota, the large intestine, and the cecum in particular, is the primary site of colonization by *H. muridarum*. In something of a contrast to what was found by Erlandsen and Chase in normal rats (111), Phillips and Lee observed bacteria free in the cytoplasm of epithelial cells lining the crypts of the gnotobiotic rats and mice but not in the conventional animals. The cells containing these bacteria appeared damaged, containing numerous vacuoles, swollen mitochondria, and diffuse cytoplasm (322). It is apparent that *H. muridarum* can invade the intestinal mucosa of rodents, and its presence there is associated with cellular degeneration. The circumstances under which this tissue invasion takes place, and the ultimate fate of the invading bacteria, have still not been elucidated.

Pathology. It has also been noted that *H. muridarum* can colonize the stomachs of mice, where it is associated with inflammatory lesions. Queiroz et al. described gastritis, characterized by a mixed-cell infiltrate, that varied from mild to severe in 6- to 8-week-old BALB/c mice (325). *H. muridarum* infection in the stomach and the associated gastritis were found in over half of the mouse colonies examined. However, the prevalence within a given colony varied from 5 to 100%. All of the mice examined by Queiroz et al. were found to have *H. muridarum* in the cecum, and most of the animals had the bacteria in the ileum as well, although no inflammation was observed at these sites. In some mouse colonies, occasional gastric colonization with *H. muridarum* occurs spontaneously in older animals, presumably as a consequence of reduced parietal cell mass (136). It has also been reported that when mice enzootically infected with *H. muridarum* in the lower bowel are experimentally challenged with gastric *Helicobacter* species, or simply as the mice age, *H. muridarum* can take advantage of the altered gastric milieu, displace the gastric spirals, and persistently colonize the stomach (241). In the study by Queiroz et al., the mice were young and had not been experimentally inoculated with another *Helicobacter* species. Details of the process by which hypochlorhydria and/or perturbations of the indigenous gastric microbiota lead to colonization of the stomach by EHS remain to be determined. However, the potential confounding influence of the EHS on in vivo studies of gastric *Helicobacter* species should not be ignored.

Helicobacter sp. flexispira ("*Flexispira rappini*")

Nomenclature. A heterogeneous group of organisms that are all ultrastructurally identical to the Lockard type 1 organism has been given the provisional name "*Flexispira rappini*" (43). This name has never been validated (215) and is therefore parenthetical. The species name is eponymous for Rappin, who in 1881 described spiral organisms in mucosal scrapings taken from the gastric mucosa of dogs. The generic name *Flexispira* should be abandoned in favor of *Helicobacter*, since several studies have shown that these organisms are members of this taxon (136, 145, 161, 248, 346). Recent data suggest that what has been called "*Flexispira rappini*" represents at least 10 different *Helicobacter* taxa (74), including the two named species *H. bilis* (161) and *H. trogontum* (275). Thus, as is the case for "*H. heilmannii*," multiple different species are morphologically indistinguishable. Members of the remaining eight species have been isolated from many sources (Table 5), including aborted sheep fetuses (59, 230), humans with or without diarrhea (337, 373, 391, 420), dogs (99, 220, 337), and apparently healthy laboratory mice (346). Most recently, they have been isolated from patients with bacteremia and from cottontop tamarins with colitis (345, 346). However, none of the flexispira taxa contain enough phenotypically and genotypically characterized strains to be formally named "*Helicobacter rappini*." Therefore, we have adopted the suggestion of Dewhirst et al. that these organisms be collectively referred to as *Helicobacter* sp. flexispira (or as flexispira-like for brevity), with a specific taxon designation number applied when appropriate (74).

Historical perspective. Organisms fitting the description of *Helicobacter* sp. flexispira were first isolated from late-term-aborted sheep fetuses by Kirkbride et al. (230). The fetal lambs had focal hepatic necrosis that was suggestive of *Campylobacter* infection. However, culture of fetal liver, lung, and abomasal

TABLE 5. Examples of isolates comprising *Helicobacter* sp. flexispira

Source	Strain	Other designations	GenBank 16S rRNA accession no.	Reference
47-year-old-man with diarrhea (case 1)	ATCC 43879	CCUG 23435, SLH-38264, LMG 8738, NADC 1937	M88138	337
16-yr-old asymptomatic girl (case 1)	ATCC 49309	NADC 1939	NA[a]	337
5-mo-old puppy (case 1)	ATCC 49308	NADC 1938	NA	337
40-yr-old man with diarrhea (case 2)	ATCC 43880	SLH-14020, LMG 8457	NA	337
Aborted sheep fetus	ATCC 43966	NADC 1893	M88137	230
Canine feces	ATCC 49317	NADC2016	AF047851	C.E. Gates and C. A. Kirkbride, unpublished
Mouse feces	DBS59		L12765	346
9-yr-old girl with bacteremia and pneumonia	FH 9702248		AF034135	391
65-yr-old immunocompromised man with bacteremia	H1353		AF118017	373
36-yr-old immunocompromised man with recurrent bacteremia	CDC-H69		AF118807	420

[a] NA, not available.

contents yielded *Helicobacter* sp. flexispira after 1 week of incubation on blood agar under an atmosphere of 80% N_2, 10% CO_2, and 10% H_2 at 37°C (230). Koch's postulates were fulfilled by producing abortion in a small percentage of pregnant ewes inoculated intravenously with *Helicobacter* sp. flexispira (229). Bryner et al. went on to show that intraperitoneal inoculation of pregnant guinea pigs caused abortion featuring suppurative placentitis and splenitis (44). The organism was cultured from heart blood at necropsy of the guinea pigs 11 days after inoculation, suggesting persistent bacteremia. Characterization of this isolate demonstrated that it was positive for catalase, oxidase, and urease activities (16). Pure cultures of isolates that were catalase, oxidase, and urease negative were recovered from the placenta, liver, and abomasal contents of aborted lambs in Britain (59), but these isolates were not extensively characterized.

Human infection and disease. Two cases of chronic diarrhea apparently caused by *Helicobacter* sp. flexispira in adults have also been described by Romero et al. (337). The first was in a 47-year-old man with a 1-month history of nonbloody diarrhea, fever, headache, and lower abdominal pain. The organism was also recovered from his asymptomatic 16-year-old daughter and from a subclinically infected 5-month-old female puppy in the household. The second case was in a 40-year-old man with a 2-month history of nonbloody diarrhea without fever. This individual had no known contact with animals. Both patients were successfully treated with erythromycin. These strains were shown to differ from Kirkbride's ovine isolate by the lack of catalase activity and by exhibiting a more rapid urease reaction (16). An essentially identical strain was isolated from the ileum and cecum of healthy outbred mice (346). The nucleotide sequence of a partial 16S rRNA gene fragment from the murine isolate was shown to be over 99% similar to that of the human isolate and that of the ovine isolate (346), indicating that these organisms are all closely related. They also appear to have the potential to cause zoonotic infections.

Two cases of bacteremia caused by *Helicobacter* sp. flexispira have also been reported. The first was in a 9-year-old girl with a 5-day history of fever, productive cough, and malaise (391). A blood sample obtained at the time she was diagnosed with pneumonia yielded a pure culture of a strain that was oxidase positive but catalase and urease negative. This isolate was shown by 16S rRNA nucleotide sequence determination to be most closely related to an ovine isolate of *Helicobacter* sp. flexispira. The second case was in a 65-year-old man undergoing hemodialysis for end-stage renal failure (373). The patient also had a history of pancreatitis due to alcoholism with secondary diabetes mellitus and severe peripheral vascular disease. A few days after initiation of hemodialysis through a Hickman catheter, he developed bacteremia. A strain that was oxidase and urease positive but catalase negative was isolated from a blood culture. The patient was treated successfully with intravenous vancomycin and amikacin, but 3 weeks later he developed recurrent fever, dyspnea, and a productive cough. The same strain was again isolated from blood cultures and was shown to have a 16S rRNA gene sequence that was 99.6% similar to that of the urease-negative strain isolated from the pediatric patient (391). Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of total bacterial proteins from this isolate also showed a pattern virtually indistinguishable from that of the *Helicobacter* sp. flexispira isolate described by Romero et al. (337). More recently, a flexispira-like organism was isolated from the blood of a patient with X-linked agammaglobulinemia suffering from persistent bacteremia (419). The organism was positive for catalase, oxidase, and urease and was found to be closely related to Romero's human isolate and Kirkbride's ovine isolate by 16S rRNA gene sequence determination. Surprisingly, DNA-DNA hybridization studies indicated that these organisms were only 24 to 37% related, and conclusive identification of this isolate remains to be performed (419).

Other host species. Other examples of flexispira-like organisms have been isolated from the stomachs of healthy dogs from a commercial supplier of random-source animals (96) and the stomachs of pet dogs which presented for gastrointestinal signs or for euthanasia (220). In the study by Eaton et al. (96), pure cultures of gastric *Helicobacter* species were isolated from 6 of 54 dogs. Two of the isolates had a flexispira-like morphology and were urease positive and catalase negative. The nucleotide sequence of the 16S rRNA gene from one of these isolates indicated that it was a distinct species, while the other isolate was an *H. bilis* strain (see below). In the study by Jalava et al. (220), gastric *Helicobacter* species were isolated from 48 of 95 dogs. Two of the isolates were reported to be *Helicobacter* sp. flexispira based on their morphology. The strains were

both catalase positive, and one had urease activity while the other was urease negative. Total bacterial protein profiles indicated that the two strains were similar to one another but sufficiently different from the isolate described by Romero et al. to be members of a distinct species (220). More recently, Saunders et al. reported that a novel *Helicobacter* species could be isolated from cottontop tamarins, a species of New World monkey that develops ulcerative colitis and colon cancer (345). This *Helicobacter* species is morphologically flexispira-like and exhibits oxidase and catalase activities but is urease negative. Nucleotide sequence determination of the 16S rRNA gene from this organism indicated that it is a separate species.

Helicobacter bilis

Mice. First identified in aged, inbred mice with chronic hepatitis, *H. bilis* is a distinct species that also has an "*H. rappini*"-like, or Lockard type 1, ultrastructure (161). Fox et al. recovered *H. bilis* from the livers and intestines of subclinically infected C57BL/6, CBA/CA, DBA/2, and BALB/c mice between 19 and 27 months of age. The isolates grew at 42 as well as 37°C and exhibited catalase, oxidase, and urease activities (Table 2). Growth was observed in the presence of bile at concentrations of up to 20%. Nucleotide sequence determination of the 16S rRNA genes from these isolates unambiguously identified *H. bilis* as a separate species (161). Infection with *H. bilis* has also been associated with typhlocolitis and diarrhea in immunodeficient rodents, The first case report described dual infection with *H. bilis* and *H. rodentium*, as described in an earlier section of this review (359). The affected animals were SCID mice and had germ line mutations in the *p53* tumor suppressor gene. These animals were a combination of C57BL/6 and 129/Sv crossed with a C.B-17 genetic background, and they developed epizootic diarrhea associated with hyperplastic typhlocolitis. Younger animals, in particular, had marked thickening of the colon with dramatic crypt elongation and bloody mucoid diarrhea (359). The only liver lesions seen in these young animals were consistent with septicemia. One adult female SCID mouse also developed diarrhea and rectal prolapse. It is not clear if the high morbidity described in this case report was due to the dual infection, to the virulence of the *H. bilis* strain, or to some other predisposing factor(s).

Two groups have fulfilled Koch's postulates with *H. bilis* in SCID mice. Shomer et al. used intraperitoneal injection to experimentally inoculate defined-flora outbred ICR SCID mice with the *H. bilis* type strain (360). Franklin et al. orally inoculated inbred C.B-17 SCID mice with a different strain of *H. bilis* (163). Defined-flora SCID mice, which have a microbiota composed entirely of eight species of anaerobic bacteria (the altered Schaedler's flora) (73), developed a hyperplastic typhlocolitis. Some of the experimentally inoculated mice developed diarrhea, but at 7 weeks postinoculation, which was the conclusion of the study, there was no evidence of hepatitis (360). Conversely, the orally inoculated C.B-17 SCID mice with a conventional microbiota did not exhibit clinical signs of disease. By 3 months postinoculation, the animals had hyperplastic typhlitis and more mild lesions in the proximal colon (163). Male mice also developed chronic active hepatitis by 3 months postinoculation; liver lesions were seen in the female mice at 6 and 9 months postinoculation.

Rats. *H. bilis* has also been isolated from outbred athymic nude rats with typhlitis (190). These animals, some of which exhibited mild diarrhea, had hyperplastic typhlitis with or without colonic inflammation. The 5- to 8-month-old male rats did not have any significant lesions in the stomach or in the liver. The *H. bilis* isolate was inoculated by intraperitoneal injection into *Helicobacter*-free 2-month-old male outbred nude rats (190). These animals lost weight, and some developed watery diarrhea 2 to 3 months postinoculation. All of the experimentally inoculated rats developed hyperplastic typhlocolitis that was seen as early as 1 month postinoculation. None of these animals developed any significant lesions in the stomach or in the liver.

Host range. Like *Helicobacter* sp. flexispira, *H. bilis* may be transmitted between host species and cause zoonotic infections. As mentioned above, a *Helicobacter* isolate from the stomach of a random-source laboratory dog was identified as *H. bilis* by 16S rRNA gene sequencing (96). Sequencing of PCR-amplified 16S rRNA gene fragments has also been used to show that *H. bilis* can infect the gallbladders of humans with chronic cholecystitis (145). A total of 9 of 23 gallbladders and 13 of 23 bile samples taken from Chilean patients undergoing cholecystectomy were PCR positive for *Helicobacter* species (145). Although culture and isolation was also attempted, no *Helicobacter* organisms were recovered from the samples. The complete nucleotide sequences of eight of the amplicons were determined. Five of these were found to be *H. bilis* (145). Two of the amplicons were *Helicobacter* sp. flexispira with a high degree of similarity to the 16S rRNA gene sequence of the isolates described by Romero et al. (337). One additional amplicon was found to be *H. pullorum*. Establishing a causal relationship between *H. bilis* infection and human diseases, including chronic cholecystitis and biliary cancer—for which the Chilean population is at high risk—will require further studies. Nonetheless, it seems likely that *H. bilis*-associated diseases are not limited to laboratory rats and mice. In unpublished studies mentioned previously (145), *H. bilis* has also been isolated from the stomach and the cecum of gerbils and from the feces of cats.

Helicobacter trogontum

A *Helicobacter* species that seemed essentially identical to *H. bilis* was isolated from the colonic mucosa of Holtzman and Wistar rats by Mendes et al. (275). Like *H. bilis*, *H. trogontum* grew at 42 as well as 37°C but not at 25°C. The isolates were also positive for urease, catalase, and oxidase activities (Table 2). Despite these phenotypic similarities, nucleotide sequence determination of 16S rRNA gene fragments from *H. trogontum* showed that it differed from that of *H. bilis* by 3.9% and from that of Kirkbride's ovine *Helicobacter* sp. rappini isolate by 4.3% (275). Thus, *H. trogontum* is a distinct species. Experimental inoculation of gnotobiotic outbred mice resulted in primarily cecal colonization, with fewer organisms in the colon, at 3 weeks postinoculation (291). Transmission electron microscopy revealed that, like *H. muridarum*, *H. trogontum* invaded enterocytes in the cecum of gnotobiotic mice, where it was found free in the cytoplasm. An organism with an ultrastructure indistinguishable from *H. trogontum* was seen in the common bile ducts of rats experimentally inoculated with the liver fluke,

Fasciola hepatica (132). Since the organism was not cultured, it is not clear if these rats were infected with *H. trogontum*, *H. bilis*, or another member of the *Helicobacter* sp. rappini group. It remains to be determined if *H. trogontum* can colonize the liver of rats and if rats are susceptible to *Helicobacter*-associated hepatitis.

HELICOBACTER PATHOGENESIS: AN ECOLOGICAL PERSPECTIVE

Bacterial colonization of the gastrointestinal tract of humans and other animals has been a subject of study for decades. It has long been known that the colon and, to a lesser extent, the small bowel are populated with a complex microbial ecosystem made up largely of anaerobic bacteria which thrive in the highly reduced environment of the bowel. What has become clear over the last 20 years is that the stomachs of humans and a wide range of other animals also have a microbial ecology that consists primarily of one or more urease-producing *Helicobacter* species. Furthermore, *Helicobacter* species are commonly present as a part of the enteric and hepatobiliary biota in humans and a variety of other animals. In short, members of the *Helicobacter* genus are ubiquitous colonizers of the enteric mucosal surface, which forms a critical interface between an organism and its environment.

The present consideration of multiple *Helicobacter* species in a wide range of hosts provides a broad view of the question that has been repeatedly asked: Are these bacteria pathogens? Even as the National Institutes of Health consensus statement was published in 1994, recommending antibiotic therapy for patients with *H. pylori* infection and peptic ulcer (12), it was recognized that *H. pylori* was a "slow bacterium" (36), "almost normal flora" (245), and that "in a world of black and white *Helicobacter pylori* is gray" (35). Emerging evidence suggests that while *H. pylori* infection can cause duodenal ulcer and gastric cancer, it may also protect against diseases such as adenocarcinoma of the proximal stomach and lower esophagus, which suggests a commensal or in fact symbiotic host-parasite interaction. Thus, the relationship between *H. pylori* and human health and disease is probably complex and dynamic, as described recently in a thoughtful review by Blaser (34).

Examination of the broader range of *Helicobacter* infections emphasizes the perspective that these bacteria often do not have a clearly pathogenic relationship with their host. However, there are important caveats. First, there are exceptions, such as *H. cinaedi* and *H. fennelliae*, which clearly produce disease in a primate model and have been found to be associated with human disease. Second, clinical disease can be absent while pathologic changes are profound. For example, *H. hepaticus* causes a chronic active hepatitis and hepatocellular tumors in many strains of immunocompetent mice, even though the animals appear to be clinically fit. In contrast, "*H. heilmannii*" appears to cause minimal inflammation in nonhuman primates and other natural hosts, as do the multiple *Helicobacter* species that infect dogs and cats. Third, we have very limited knowledge of the prevalence and natural history of many *Helicobacter* infections as they occur in nature in nonhumans. Fourth, it should be remembered that the association between disease and *H. pylori* infection in humans is based on long-term case-control and treatment studies, which utilized very large sample sizes and long-term follow-up that are often impractical in other hosts. If experimental inoculation of *H. pylori* were performed in humans, it would probably be difficult to show clinical disease without decades of observation on large numbers of individuals. We suspect that the occurrence of disease in a minority of humans infected with *H. pylori* is not unique but, rather, represents a "an overstepping of the line by one side or the other, a biological misinterpretation of borders" (393) that can sometimes be found in other interactions between *Helicobacter* species and their natural hosts. Finally, the relationship between disease and *Helicobacter* infection is often host specific. This pertains not only to an immunocompromised host, such as IBD in SCID or IL-10-deficient mice infected with *H. hepaticus*, but also to infection with a *Helicobacter* species not normally present in a given host. The potential importance of this should not be underestimated, since many emerging human infectious diseases represent transmission of agents that are harmless and enzootic in their natural host, such as *Borrelia burgdorferi*, the agent of Lyme disease. We should keep in mind that enteric infections such as acute diarrheal disease are commonly due to unrecognized pathogens. Since *Helicobacter* probably would not be identified by the cultivation methods routinely applied to cases of human diarrheal disease, its contribution remains unknown. Regardless of whether these *Helicobacter* species cause disease in their natural host, they provide an important resource to better understand gastric and enterohepatic diseases in humans.

RECOMMENDATIONS AND CONCLUSIONS

Currently there are 20 formally named species comprising the genus *Helicobacter* (one of which, *Candidatus* Helicobacter suis, is likely to be changed to *Candidatus* Helicobacter heilmannii). Additional species have been provisionally named but not yet validated, and still others have been isolated but not yet named. The genus *Helicobacter* will continue to grow at a brisk pace, and it would not surprise us if novel species not discussed here are described before this article goes to press. Consequently, some basic recommendations are in order. First, it bears repeating that identification—and thus, the ability to recognize *Helicobacter* species in the etiopathogenesis of disease—is dependent on good classification. Minimal standards for the description of new *Helicobacter* species are still in development (75). Nonetheless, the Subcommittee on the Taxonomy of *Campylobacter* and Related Bacteria (of the International Committee on Systematic Bacteriology) did agree that such minimal standards should be based on a minimum number of 5 to 10 strains per taxon (215). Along these lines, there are several good examples of *Helicobacter* species that have not been named due to insufficient numbers of isolates but have been sufficiently well described in the literature to permit their recognition in a clinical setting. Certainly not every novel *Helicobacter* species should be named, even provisionally, when first isolated. Sufficient characterization should be performed to ensure the validity of the taxon. For the cultured *Helicobacter* species, this should include a combination of 16S rDNA sequencing, DNA-DNA hybridization, protein profiling, cellular fatty acid profiling, and biochemical characterization. Characterization of uncultivated species is obviously more limited

and relies largely on 16S rDNA sequence comparison, which can sometimes be misleading when sequences are very closely related. While not every method can or should be used for every novel *Helicobacter* species, a polyphasic approach is clearly in order (406).

For the uncultured *Helicobacter* species, important advances have been made by using PCR-based methods and by conducting monoassociation studies with gnotobiotic rodents. However, successful culture and isolation of these organisms will confer a degree of clarity to their taxonomy that currently is out of reach. While some groups are achieving greater and greater success in culturing these fastidious organisms, even the more hardy *Helicobacter* species can pose a challenge to the microbiologist whose only experience with the genus is *H. pylori*. These *Helicobacter* species require special conditions for growth. They require a microaerobic environment, which can be achieved with a commercial gas generator envelope, but many grow better under an atmosphere of 5 to 10% hydrogen (such as is provided in a bottle gas mixture), and in fact some of the EHS will not grow at all with commercial gas generator systems. These *Helicobacter* species also grow slowly, and contaminating enteric microbiota that are present in the lower bowel or transiently in the gastric compartment can overgrow them. Worse still, thermophilic *Campylobacter* species may be inadvertently cocultured with these *Helicobacter* species, and they are similar enough to make isolation quite difficult. Selective media can be used, but it is important to keep in mind that some *Helicobacter* species are sensitive to the common antimicrobial agents incorporated into commercial *Campylobacter* media. Finally, some of these *Helicobacter* species seem to require surface moisture on solid media for growth. Freshly poured plates are typically better than plates that have been predried, and—contrary to typical good microbiologic technique—the plates should be incubated with the lid uppermost. Some of these organisms simply fail to grow as discrete colonies but, rather, form a fine spreading film that may go unrecognized as bacterial growth by the casual observer. Additional recommendations about culture technique for *Helicobacter* species can be found in the excellent review by Fox and Lee (151).

The true extent of ecological niches occupied by species of *Helicobacter* is not yet known. Neither has the full spectrum of disease syndromes that are associated with *Helicobacter* infections been defined. Only by developing new and improved molecular diagnostic techniques and by optimizing culture and isolation methods will we develop a more complete understanding of the *Helicobacter* genus. As progress is made in this area, it will also become important to increase our understanding of the mechanisms of pathogenesis that characterize these organisms. Certainly, some features of *H. pylori* pathogenesis will be shared by the other gastric *Helicobacter* species, as well as by the enterohepatic *Helicobacter* species. However, there will be some important differences as well. It seems likely that future studies on *H. pylori* and the other members of the *Helicobacter* genus will benefit from comparative analyses of these organisms. This is all the more true, given the genomic database that has become available for *H. pylori*. Similar advances in genomic sequencing of *Campylobacter* species will also provide valuable insights into the biology of spiral-shaped bacteria that inhabit mucus gel layers. Certainly, our understanding and our appreciation of *H. pylori* and its role in our gastric microenvironment have grown in the past decade. By taking advantage of these genomic resources and some of the recently developed tools for genetic manipulation of *Helicobacter* species in the coming years, we may also gain new perspectives on the intricate coexistence that we and our diverse spiral-shaped microbiota maintain in health and in disease.

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