REVIEW

The non-*H pylori* helicobacters: their expanding role in gastrointestinal and systemic diseases

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Gut 2002;**50**:273–283

The number of species in the genus *Helicobacter* has rapidly expanded over the past decade. The genus now includes at least 24 formally named species as well as numerous other helicobacters awaiting formal naming. This review highlights the expanding role that other helicobacters, although not as well known as *H pylori*, play in gastrointestinal and systemic disease in humans.

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Accepted for publication
30 August 2001

The number of species in the genus *Helicobacter* has rapidly expanded during the past decade. Today, at least 24 formally named helicobacters have been identified and an additional 35 or more novel helicobacters await formal naming. Of the gastric helicobacters, *Helicobacter pylori* is the best known and the most important in terms of global impact on human disease. However, two other gastric helicobacters, *H heilmannii* and *H felis,* are associated with gastric disease in humans and are worthy of discussion.[1 2] Nineteen named species colonise the lower intestinal tract of animals, many of which also colonise humans (table 1). These helicobacters which naturally colonise the intestinal crypts and are often associated with diarrhoea, can cause bacteraemia and systemic disease including colonisation of the biliary tract and induction of cholecystitis and hepatitis (and in some cases hepatic cancer). Immunocompromised hosts are particularly susceptible to these microaerobic organisms.[3–7] Eight of these enterohepatic helicobacters (*H canis*, *H pullorum*, *H cinaedi*, *H fennelliae*, *H canadensis*, *H winghamensis*, *H westmeadi*, and *H rappini*) have been isolated from diarrhoeic and/or bacteraemic humans (table 2). Some of the species may also have zoonotic potential. *H heilmannii* and *H felis* are associated with gastritis in a variety of animals, including humans. *H pullorum* has been isolated from humans and poultry, *H canis* from dogs, cats, and humans, *H cinaedi* from humans, non-human primates, dogs, and hamsters, and "*H rappini*" from dogs, cats, mice, humans, and non-human primates. The purpose of this review is to highlight the expanding role that other helicobacters, although not as well known as *H pylori*, play in gastrointestinal and systemic disease in humans.

HISTORICAL PERSPECTIVE

Early descriptions of the non-*H pylori* gastric organisms: *H felis, H heilmannii (bizzozeronii), "Flexispira rappini"*

Gastric spiral shaped microorganisms have been noted in animals and humans for more than a century. Rappin in 1881 and Bizzozero in 1893 are credited with the first observations of gastric spiral shaped bacteria in animals. Salomon in 1896 reported spiral organisms in the stomachs of dogs, cats, and the brown Norway rat, but none in humans, monkeys, cattle, pigs, mice, pigeons, or crows.[8] Others recorded 100% prevalence of spiral organisms in the stomachs of dogs, cats, and rhesus monkeys. Because many of the helicobacters observed in the stomachs of animals have been isolated only recently, earlier papers describing these bacteria were based on morphological criteria. Three morphological forms of these organisms were reported in dogs by Lockard and Boler.[9] All three of these morphologically distinct organisms are now known to be *Helicobacter* spp by 16S rRNA analysis and the early descriptions provided by these authors have been useful for identifying and studying similar gastric bacteria in animals and humans.

Lockard type 1 (now known as "*H rappini*" taxa) is a bacterium entwined with periplasmic fibres which appear to cover the entire surface of the organism (fig 1).[9] Bryner *et al* isolated a similar organism from aborted ovine fetuses and classified the organism as "*Flexispira rappini*".[10] It is now known that this organism is a *Helicobacter* species. "*Flexispira rappini*" experimentally produces abortion in guinea pigs and sheep as well as hepatitis in aborted fetuses. It has also been isolated from the intestines of a variety of animals and humans.[10 11] Lockard bacterium type 2 also has periplasmic fibres but they are sparsely distributed on the organism and can appear singly or in groups of two, three, or four. This bacterium, which measures 0.4×5–10 μm, has been cultured from the stomachs of cats, dogs, and humans and has been named *H felis*.[12] The third morphologically distinct organism, type 3, is the bacteria most commonly seen in animal stomachs (dogs, cats, non-human primates, cheetahs, swine) and occasionally in human stomachs. This bacterium, although very tightly spiralled, does not have periplasmic fibres. The organism has been given various names—"*Gastrospirillum hominis*", "*H heilmannii*" and most recently has been cultured from dogs and named *H bizzozeronii* (fig 2).[13 14] This bacterium measures 0.3×5–10 μm and

Abbreviations: PCR, polymerase chain reaction; CLOs, campylobacter-like organisms; HLOs helicobacter-like organisms; CDT, cytolethal distending toxin; RFLP, restriction fragment length polymorphism; HIV, human immunodeficiency virus; XLA, X linked agammaglobulinaemia; PSC, primary sclerosing cholangitis.

Table 1 Characteristics which differentiate non-gastric *Helicobacter* species

Taxon	Catalase production	Nitrate reduction	Alkaline phosphatase hydrolysis	Urease	Indoxyl acetate hydrolysis	γ Glutamyl transpeptidase	Growth at 42°C	Growth with 1% glycine	Susceptibility to		Peri-plasmic fibres	No of flagella	Distribution of flagella	G+C content (mol%)
									Nalidixic acid (30 μg disc)	Cephalothin (30 μg disc)				
H canadensis	+	+	–	–	+	–	+	+	R	R	–	2	Bipolar	ND
H rodentium	+	+	–	–	–	–	+	+	R	R	–	2	Bipolar	ND
H pullorum	+	+	–	–	–	ND	+	ND	R	S	–	1	Monopolar	34–35
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 rappini"	+	–	–	+	ND	+	+	–	R	R	+	10–20	Bipolar	34
H cinaedi	+	+	–	–	–	–	–	+	S	I	–	1–2	Bipolar	37–38
H westmeadii	+	+	+	–	ND	ND	–	ND	+	–	–	1	Bipolar	ND
H pametensis	+	+	+	–	–	–	+	+	S	S	–	2	Bipolar	38
H winghamensis	–	–	–	–	+	ND	–	ND	S	S	–	1–2	Bipolar	ND
H mesocricetorum	+	+	+	–	ND	–	ND	–	S	R	–	2	Bipolar	ND
H aurati	+	–	–	+	+	+	+	–	S	R	+	7–10	Bipolar	ND
H typhlonius	+	+/–	–	–	–	–	+	+	S	R	–	1	Bipolar	ND
H cholecystus	+	+	–	–	–	–	+	+	I	R	–	2	Bipolar	ND
H trogontum	+	+	–	+	ND	+	+	ND	R	R	+	5–7	Bipolar	ND

+, positive reaction; –, negative reaction; S, susceptible; R, resistant; I, intermediate; ND, not determined; G+C,guanine plus cytosine.

has 10–20 sheathed flagella at both ends of the cell. *Helicobacter* spp have also been cultured from the stomachs of ferrets, non-human primates, cheetahs, dolphins, whales, and mink.

Early descriptions of enterohepatic *Helicobacter* spp

Spiral motile bacteria have evolved to inhabit the mucus of the intestinal crypts. The best known of these spiral microaerobic organisms is *Campylobacter jejuni*. We now recognise that the intestinal crypts of a variety of animals, as well as humans, are also the natural reservoir of many members of the genus *Helicobacter*. In early studies on lower bowel flora of rodents, Davis *et al*, using electron microscopy, described what is now known as distinct species of helicobacters. The most clearly recognisable form (fusiform to spiral and entwined by periplasmic fibres) belonged to the diverse taxa of "*H rappini*" which includes *H bilis* and *H trogontum* (fig 3).[4 11] Indeed, organisms with this same morphology have been noted by electron microscopy in the bowel of humans and the inflamed colon of cotton top tamarins suffering from ulcerative colitis.[15 16]

Members of the second type that was commonly noted by electron microscopy resembled campylobacters but were longer and had bipolar sheathed flagella. These were most likely representative of several species of human as well as rodent helicobacters with this morphology—for example, *H hepaticus* (fig 4), *H typhloclonus,* or those with unsheathed flagella—being consistent with the morphology of *H rodentium*. Rodent helicobacters, particularly *H hepaticus* and *H bilis*, which persistently colonise their hosts, have been linked to both chronic hepatic and intestinal disease and are increasingly being used in mouse models to understand the pathogenesis of *Helicobacter* induced gastrointestinal disease.[3 4 17]

ISOLATION OF FASTIDIOUS ENTEROHEPATIC AND NON-*H PYLORI* GASTRIC *HELICOBACTER* SPP

Many hospital laboratories may have difficulty in isolating enteric helicobacters. Because of the slow growth of helicobacters under microaerobic conditions, an accurate diagnosis is unlikely if blood culture procedures which rely on visual detection of the culture media are utilised.[18 19] Dark field microscopy or use of acridine orange staining of blood culture media, rather than Gram staining, increases the likelihood of visualising the organism.

Selective antibiotic media are routinely used if faecal specimens are being processed. However, several strains of both *H cinaedi* and *H fennelliae* are inhibited by concentrations of cephalothin and cetazolin used frequently in selective media for isolation of enteric microaerobic bacteria.[19] Alternatively, recovery is facilitated by passing faecal homogenates through a 0.45 μm filter.[20] *H cinaedi* and *H fennelliae* can grow under anaerobic conditions but this anaerobic growth may be only under laboratory conditions where the organisms have adapted to the controlled anaerobic environment. For the best recovery of enterohepatic helicobacters, faecal or intestinal biopsy samples should be placed in 20% glycerol medium for transportation. Higher H_2 levels (5–10%) are required for optimal enteric *Helicobacter* spp isolation. Unfortunately, this atmosphere is not available in the commercially available diagnostic kits used for *Campylobacter* isolation.

It also has been suggested by several investigators that the true prevalence of *H pullorum* in both chickens and as a purported cause of gastroenteritis in humans may be under reported because of the difficulties associated with isolation and species identification.[21] *H pullorum* is sensitive to polymyxin which is used in Skirrow selective media for isolation of CLOs; its use for isolation of *H pullorum* is therefore not warranted. Like many helicobacters, *H pullorum* is inert in most biochemical tests commonly used in diagnostic laboratories and even when isolated on bacterial media may be easily

Table 2 Non-*Helicobacter pylori* helicobacters isolated from humans (as of 2001)

Species	Other hosts	Primary site	Other sites	References
*"H rappini"**	Sheep, dog, mice	Intestine	Blood (humans); liver (sheep); stomach (dogs)	9, 56, 60, 82, 124
*H canis**	Dog, cat	Intestine	Blood (humans); liver (dog)	24, 52–54
*H cinaedi**	Hamster, rhesus monkey, dog	Intestine	Blood, soft tissue, joints (humans); liver (monkey)	20, 40–44
H fennelliae	Dog, macaque	Intestine	Blood	18, 37, 38
*H pullorum**	Chicken	Intestine	Liver (chicken)	61, 62
H canadensis	NR**	Intestine	NR	33
H westmeadii	NR	NR	Blood	76
H winghamensis	NR	Intestine	NR	66
*"H heilmannii"**	Dogs, cats, monkeys, cheetahs, wild rats, swine	Stomach	NR	1, 9, 95, 96
*H felis**	Dogs, cats, cheetahs	Stomach	NR	2, 118

*Some data suggest zoonotic potential.
NR, not recorded.

misidentified (table 1). For example, it can not be distinguished from *Campylobacter coli* except by its lack of indoxyl acetate, and is indistinguishable from *C lari* except for its lack of tolerance to 2% NaCl and sensitivity to nalidixic acid. One report describes the use of fatty acid profiles to differentiate *H pullorum* from *C lari*.[22]

Current identification of multiple species of microaerobic bacteria in faeces poses a particular challenge, especially when these microaerobes grow on similar media in comparable atmospheric conditions. Primary isolation of *Campylobacter* spp may be misleading because *Helicobacter* spp may be present in smaller numbers, and grow at a slower rate than *Campylobacter* spp. Their similar phenotypic traits and biochemical profiles also complicate a diagnosis. Accurate diagnosis of mixed infections with these bacteria may require diagnostic laboratories to incorporate polymerase chain reaction (PCR) based assays using *Helicobacter* and *Campylobacter* genus and species specific primers. This recommendation is supported by a recent study which reported improved sensitivity for PCR compared with conventional culture techniques in identifying mixed infections of *Campylobacter* spp in human cases of gastroenteritis.[23] Using genus specific *Campylobacter* and *Helicobacter* PCR assays should allow discrimination between the two species.[24] Other authors have also strongly recommended that species specific PCR assays based on 16S rRNA genes be used for definitive diagnosis.[25 26]

Investigators in South Africa have established a protocol to allow primary isolation of multiple species of *Campylobacter* and *Helicobacter* from individual diarrhoeic children. The technique uses selective filtration; the filtrates are placed onto antibiotic free blood agar plates, and incubated in an H_2 enriched atmosphere.[27 28]

> "Investigators in South Africa have established a protocol to allow primary isolation of multiple species of *Campylobacter* and *Helicobacter* from individual diarrhoeic children"

The authors not only documented an increase in the number of CLOs and helicobacter-like organisms (HLOs) isolated but they were able to culture *C upsaliensis* for the first time. They also reported a 16.2% prevalence of multiple species of CLOs based on primary isolation, biochemical characterisation, and serological confirmation. The authors frequently recovered between two and five CLOs and HLOs from one stool sample,

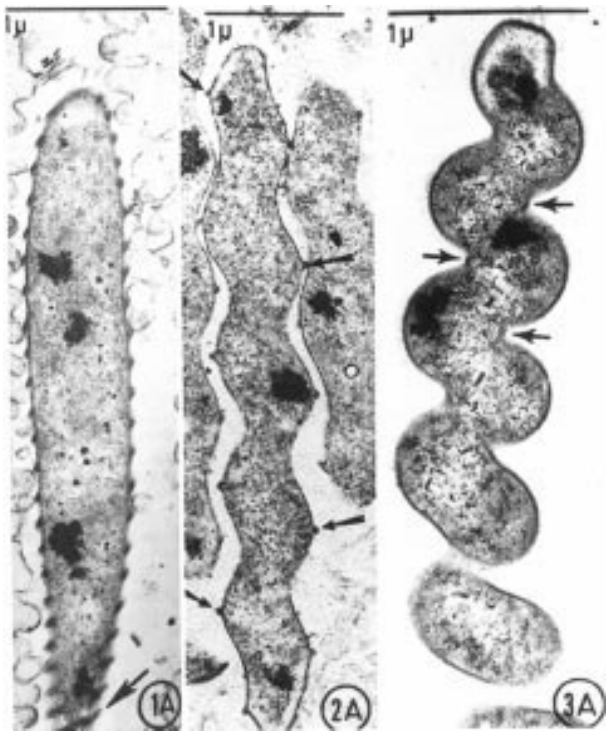

Figure 1 Collage of the original photomicrographs taken from Lockard and Boler[9] of bacteria seen by electron microscopy in the dog stomach. Reprinted with permission of the *American Journal of Veterinary Research*.

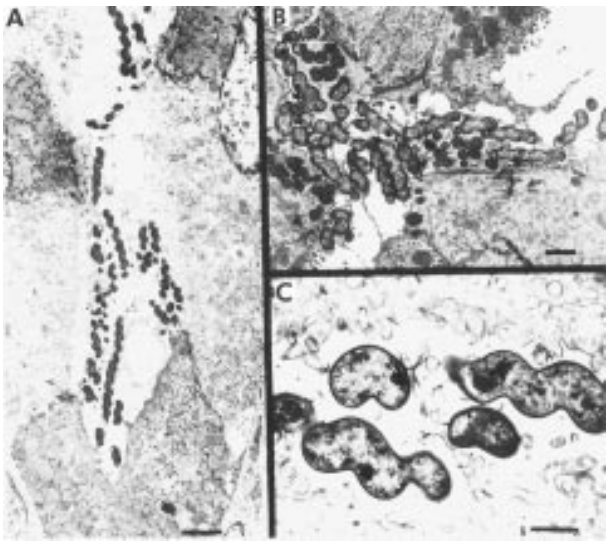

Figure 2 Transmission electron micrograph of gastric tissue from a cat showing large numbers of tight helix shaped bacteria resembling "*Helicobacter heilmannii*" in the gastric pits (A, B) and in close proximity to parietal cells (C). Bars =2, 1, and 0.5 μm in (A), (B), and (C), respectively. Reprinted from the *Journal of Clinical Microbiology* with permission from the author.[95]

Figure 3 Scanning electron micrograph of "*Helicobacter rappini*" in the colon of a mouse. Also notice bacterium in the background with the morphology of *H hepatitis* (courtesy of DB Schauer).

Figure 4 Negatively stained preparation of *Helicobacter hepaticus* isolated from the caecum of a mouse. Typical cell with a single subterminal flagellum at either end (bar=500 nm) (courtesy of the author).

with *C jejuni* (with different serotypes), *C coli*, *C upsaliensis*, *H fennelliae*, and *H cinaedi* being commonly isolated.[27] Mixed CLO and HLO infections were also recently reported in cats using PCR based methods.[24]

Direct PCR of faecal samples as well as other body fluids for diagnosis of enteric helicobacters has been hampered by the presence of inhibitory substances. To circumvent these difficulties, a screening technique for detecting *Helicobacter* spp in rodents was developed whereby reproducible PCR results are obtained following a simple and quick purification protocol.[29] In this technique, bacteria are released from the faecal material by treatment with PVPP, an agent used to isolate bacteria from soil. The best results with the PVPP treated samples were obtained at 4°C with efficacy of the PCR reaction decreasing when the treatment was performed at higher temperatures, probably reflecting increased release of inhibitors at higher temperatures. As reported in other laboratories, addition of a Chelex 100 treatment enhanced the final PCR reaction.[30 31] The use of a new commercially available QIAamp Tissue Kit (Qiagen, Inc., Chatsworth, California, USA) for DNA extraction from faecal samples has also proved extremely useful in detection of enteric helicobacters by PCR.[32] Routine use of PCR techniques on human stool may prove useful as an adjunct for diagnosis for these fastidious microaerophiles. More recently, several enteric helicobacters have been assayed for cytolethal distending toxin (CDT). Its presence or absence as determined by PCR, cytopathic effect on cell cultures, and flow cytometry may assist in distinguishing among closely related species—for example, *H pullorum* from *H canadensis*.[33–36]

Gastric *Helicobacter* spp require special environmental and cultural conditions for their growth. The organisms are thermophilic, grow at 37°C, and growth on chocolate or blood agar takes up to five days. The organisms do not grow under aerobic or anaerobic conditions and achieve optimum growth in a high humidity with microaerobic conditions (5% CO_2, 90% N_2, 5% H_2). To date, however, isolation of these gastric helicobacters, *H felis* and *H bizzozeronii* (except for one isolate from a human), has been successful only in dogs and cats.

HELICOBACTER ASSOCIATED DIARRHOEA

H cinaedi

In 1984, a group of microaerobic CLOs were isolated from rectal swabs of male homosexuals suffering from protocolitis and enteritis.[37 38] These bacteria could be broadly classified into three major DNA homology groups. One of these was *H cinaedi*, previously classified as *C cinaedi* (CLO-1A) (table 2). The second CLO2 was named *C fennelliae,* and the third still unnamed organism was classified as CLO3.[39] Although *H cinaedi* has been primarily recovered from immunocompromised individuals, the organism has also been isolated from diarrhoeic faeces of chronic alcoholics, immunocompetent males and females, and children.[40 41] For example, Tee *et al* isolated nine strains of apparent enteric helicobacters from faecal cultures of over 1000 patients with gastroenteritis; three were classified biochemically and by DNA/DNA hybridisation as *H cinaedi*.[42]

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In an attempt to understand the pathogenesis of *H cinaedi* and *H fennelliae* infection, pigtailed macaques (*Macaca nemestrina*) were experimentally challenged by the oral route with the organisms.[43] Both *H cinaedi* and *H fennelliae* caused bacteraemia, diarrhoea, and focal colonic lesions. One of five monkeys infected with *H fennelliae* also had acute proctitis and *H cinaedi* induced lymphoid hyperplasia.[43] We have recently isolated *H cinaedi* from an inflamed colon, mesenteric lymph node, and liver of a rhesus monkey.[44] This case highlights the ability of enteric helicobacters to translocate across the intestinal epithelia. Isolation of other novel helicobacters from inflamed colons of monkeys is also consistent with the increasing recognition of enteric helicobacters in children with gastroenteritis who reside in developing countries.[27 45 46]

Zoonotic potential

Since *H cinaedi* has been isolated from normal intestinal flora of hamsters, it has been suggested that pet hamsters serve as a reservoir for transmission to humans (table 2).[20 47] This fastidious microaerophile was recovered from blood of a neonate with septicaemia and meningitis.[40] The mother of the neonate had cared for pet hamsters during the first two trimesters of

her pregnancy.[40] The mother had a diarrhoeal illness during the third trimester of pregnancy; the newborn was likely to have been infected during the birthing process although this was not proved. Further studies are needed to confirm the zoonotic risk of handling *H cinaedi* infected hamsters.[20] Also of interest is the isolation, based on cellular fatty acid and identification analysis, of *H cinaedi* from the faeces of dogs and a cat.[19] In a recent case of *H cinaedi* associated arthritis, the patient occasionally worked with cows and farm animals.[48] *H cinaedi* was also recently isolated from the colon and liver of a rhesus monkey with colitis and hepatitis.[44]

H fennelliae

Like *H cinaedi*, *H fennelliae*, previously known as *C fennelliae*, was first isolated from rectal swabs of homosexuals with chronic diarrhoea and proctitis.[37 38] However, unlike *H cinaedi*, this enteric helicobacter does not often cause bacteraemia in adults.[49 50]

Zoonotic potential

Although *H fennelliae* has been identified in the faeces of a dog and macaque, no direct evidence of zoonotic transmission has been reported.[19]

H canis

A *H fennelliae*-like organism was isolated from the faeces of a child suffering from gastroenteritis.[51] *H canis* has also been isolated from bacteraemic humans.[39 52] The bacteria were distinguished from *H fennelliae* by their ability to grow at 42°C, failure to produce catalase, and marked tolerance to bile. Morphologically, the bipolar sheathed flagella of *H canis* are similar to those in *H cinaedi* and *H fennelliae*, and are useful in characterising the organism as a helicobacter.

Zoonotic potential

The same bacteria were isolated from faeces of normal and diarrhoeic dogs and were classified, based on 16S rRNA sequencing, as a novel helicobacter and named *H canis*.[53] It has been isolated from a colony of cats with endemic diarrhoea and from clinically normal cats.[24 54] Our laboratory has also identified *H canis* based on 16S rRNA data from the liver of a puppy diagnosed as having an active multifocal hepatitis.[52] Additional investigations will be required to ascertain whether *H canis* in dogs and cats constitutes a potential reservoir for zoonotic transmission to humans. The fact that other microaerophilic bacteria—for example, *Campylobacter jejuni*—are associated with zoonotic transmission to humans, especially children handling young puppies and kittens, strengthens the argument that dogs and cats may be responsible for zoonotic infection of helicobacters.[53] It is also important to note that both helicobacters (including *H canis*) and campylobacters can be isolated from diarrhoeic faeces of individual pet animals and humans; careful diagnostic efforts are therefore needed to properly identify mixed infections with these microaerobic bacteria.[27 54]

"*H rappini*" (*Flexispira rappini*)

Based on our recent 16S rRNA analysis of numerous "*H rappini*" strains from multiple sources, these organisms are members of at least 10 species of closely related "*H rappini*" taxa.[55] "*H rappini*" was first reported in two humans with chronic diarrhoea and their pets.[56] A novel *Helicobacter* sp isolated from cotton top tamarins with chronic diarrhoea also belongs to the *H rappini* taxa.[46] Bacteria of this morphology by electron microscopy have also been noted in rat enterocytes[57] and more recently in the colon of normal mice, or enterocytes and lamina propria of mice experimentally infected with *Serpulina dysenteriae*.[11 58]

Zoonotic potential

Identical "*H rappini*" strains have been isolated from the faeces of both dogs and their owners, and the occurrence of *H rappini* was associated with cellulitis following a cat scratch. The latter case may simply reflect the fact that the patient had *H rappini* colonisation of his bowel and that the organism gained access to the blood via translocation. However, there is an apparent likelihood of zoonotic transmission with this organism.[56 59 60]

H pullorum

Novel helicobacters, named *H pullorum*, isolated from caeca of normal chickens, the livers and intestinal contents of chickens with hepatitis, and faeces of humans with gastroenteritis have been characterised biochemically, by DNA hybridisation, and by 16S rRNA sequencing.[61] This bacterium is urease negative and can be distinguished from most other helicobacters by lack of sheathed flagella. Like *H hepaticus, H canis*, and *H bilis* (all three capable of colonising the liver), *H pullorum* is tolerant to bile. The potential of *H pullorum* to cause serious gastrointestinal disease is evidenced by isolation of the organism from a young woman and a young man, both of whom suffered from chronic diarrhoea of one month's duration.[62] The young man also had elevated liver enzymes, which although not proved, may have been induced by invasion of the liver by *H pullorum* in a manner similar to the organism's ability to cause hepatitis in chickens. Since then, *H pullorum* associated gastroenteritis has been increasingly recognised in both Europe and North America.[26 63]

Cytotoxic activity in a member of the CDT family of bacterial toxins has been reported in a number of enterohepatic helicobacters, including *H pullorum*.[34 36] CDT activity is characterised by the appearance of cellular distension, cytoskeletal abnormalities, G_2/M cell cycle arrest, and cytolethality in cultured cell lines treated with bacterial culture supernatants or sonicates of bacteria expressing the toxin.[34 36] Although the mode of action of enterohepatic helicobacter CDT on eukaryotic cells is unknown, it was recently shown that bacterial CDT induced cell cycle arrest in *Escherichia coli*, and *C jejuni* was associated with a DNase activity intrinsic to the CDTB polypeptide. This toxin may play a role in the pathogenesis of enterohepatic disease by targeting lymphocytes and causing cell cycle arrest.[64 65]

Zoonotic potential

H pullorum is isolated from faeces and liver of chickens. Given that chickens are major zoonotic reservoirs of *C jejuni* in humans, it is probable that chickens infected with *H pullorum* could also be responsible for infection in humans.[61] Also, because of the difficulty of differentiating campylobacters from helicobacters by routine biochemistry tests, campylobacter related infections due to eating undercooked poultry may indeed on occasion be misdiagnosed.

> "It is probable that chickens infected with *H pullorum* could also be responsible for infection in humans"

Further molecular characterisation may indicate that the isolates were *H pullorum*. This needs to be confirmed in additional studies.

H canadensis

Numerous helicobacter isolates cultured from diarrhoeic patients in Canada were recently analysed.[26] These bacteria had been previously characterised biochemically, by restriction fragment length polymorphism (RFLP) (*Alu*I, HhaI), and by fatty acid analysis as *H pullorum*. However, four of the isolates varied biochemically from *H pullorum* by their inability to hydrolyse indoxyl acetate and their resistance to nalidixic acid. Using complete 16S rRNA analysis we determined that

these four strains clustered near *H pullorum* but had a sequence difference of greater than 2% and therefore represent a novel helicobacter, *H canadensis*.[33] This novel helicobacter could also be distinguished from *H pullorum* by RFLP using *Apa*LI and the lack of CDT.[33 35] This finding highlights the importance of careful molecular analysis in addition to standard biochemical tests in speciating the increasing number of *Helicobacter* spp isolated from humans and animals.

H winghamensis

From 1997 to 1999, five isolates of CLOs were identified from three Canadian patients that were exhibiting symptoms of gastroenteritis, including fever, stomach malaise, and diarrhoea. The organisms were catalase, urease, alkaline phosphatase, and nitrate negative but oxidase and indoxyl acetate positive. Complete 16S rRNA sequence analysis grouped these organisms within the *Helicobacter* genus and also differentiated them from previously identified *Helicobacter* spp. The closest relative by phylogenetic analysis was "*H rappini*", taxon 1. Electron microscopy illustrated that these isolates had 1–2 bipolar flagella; however, the periplasmic fibres characteristic of *H rappini* were not observed. The isolates also lacked a flagellar sheath, a trait shared with four other helicobacters, *H canadensis*, *H pullorum*, *H rodentium*, and *H mesocricatorum*.[66]

HELICOBACTER ASSOCIATED BACTERAEMIA, CELLULITIS, AND ARTHRITIS

H cinaedi

H cinaedi has been isolated from the blood (sometimes on a recurrent basis) of homosexual patients with human immunodeficiency virus (HIV) as well as children and adult females.[40 41 49 67–72] It is also interesting to note that *H cinaedi* can cause bacteraemia in immunocompetent adults and children with and without diarrhoea.[41]

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H cinaedi was also isolated from the blood of experimentally infected macaques receiving an oral inoculum of *H cinaedi*.[43] In a retrospective study of 23 patients with *H cinaedi* associated illness, 22 had the organism isolated from blood using an automated blood culture system where a slightly elevated growth index was noted.[18] This study also described a new *H cinaedi* associated syndrome, consisting of bacteraemia and fever accompanied by leucocytosis and thrombocytopenia. Recurrent cellulitis and/or arthritis are also noted in a high percentage of *H cinaedi* infected immunocompromised patients.[18 73]

In the study by Burman *et al*, four of seven patients with bacteraemia had a variety of skin lesions, including cellulitis, erythema nodosum, and erythematous plaques.[73] In contrast, others noted that in *H cinaedi* bacteraemic cases, cellulitis may be atypical; in 9/23 cases the cellulitis was characterised as brown or copper coloured skin without the associated heat typical of inflammation.[18] In isolated cases, cellulitis can develop into lymphoedema.[72]

Antimicrobial in vitro testing of 22 strains of *H cinaedi* provide the clinician with a variety of antibiotics to use in treating infected patients.[74] Tetracycline and various aminoglycosides appear to be effective in treating infections with *H cinaedi*. Apparent relapses of *H cinaedi* bacteraemia in patients treated with ciprofloxicin (despite its previous use to successfully treat *H cinaedi* infection) and the occurrence of in vitro resistance of *H cinaedi* isolates to ciprofloxicin, suggest that this antibiotic should be used with caution.[18 19 74 75]

"H westmeadii"

In 1997, a novel helicobacter, *H westmeadii*, was cultured from the blood of two HIV infected patients.[76] "*H westmeadii*", although morphologically and biochemically similar to *H cinaedi*, was previously distinguished by its ability to hydrolyse hippurate and grow anaerobically. Also, the authors stated that results of ribotyping, fatty acid analysis, and 16S rRNA ribosomal sequences made it distinctly different from *H cinaedi* and *H fennelliae*. By electron microscopy, there is little morphological difference between *H cinaedi*, *H fennelliae*, and *H westmeadii*, all having single sheathed polar flagella. *H cinaedi* and *H fennelliae* are longer (2.5–5 μm) and thicker (0.5–1 μm) than *H westmeadii* which are 1.5–2 μm×0.5 μm in diameter. Vandamme *et al* raises the question of whether *H westmeadi* is a separate species or a junior synonym of *H cinaedi*. They based their results on numerical analysis of whole cell protein electrophoresis, extensive biochemical analysis, and semiquantitative DNA-DNA hybridisation experiments.[77]

One HIV infected individual who had "*H westmeadi*" bacteraemia was admitted because of pyrexia and neutropenia following chemotherapy. His medications on admission consisted of dapsone (100 mg daily), fluconazole (400 mg daily), and acyclovir (200 mg twice daily). After recovery of a Gram negative rod from his blood, he was treated empirically with tricarcillin-clauvlamate and tobramycin. His fever subsided and his leucocyte count became elevated. However, he died 11 months later with advanced Kaposi's sarcoma. In the second bacteraemic patient, there was a previous history of being HIV positive and having related diseases, including oral candidiasis, diarrhoea, and weight loss. He was subsequently admitted with a four week history of cellulitis in the right leg. He had "*H westmeadi*" isolated from a blood culture and was treated with penicillin and flucloxacillin without clinical improvement. He developed a maculopapular rash and oral candidiasis; his treatment was changed to cephalothin, to which he initially responded. He later developed recurrent lesions on both legs which resolved with time; however, the patient died several months later of HIV related illness.[76]

H fennelliae

H fennelliae has been isolated from a bacteraemic child with leukaemia[78] and was responsible for septic shock in a non HIV-infected heterosexual patient.[79] However, this patient was undoubtedly immunocompromised because of liver cirrhosis and diabetes mellitus, as well as pre-existing disseminated fungal infections. One HIV seropositive patient, suffering from successive bacteraemia, had both *H cinaedi* and *H fennelliae* isolated from his blood at different times.[49] These patients also have diarrhoea concurrent with the isolation of *H fennelliae* from their blood.

Non-standardised in vitro testing suggest that *H fennelliae* is susceptible to a variety of antibiotics including ciprofloxacin, doxycycline, gentamicin, rifampin, and sulphamethoxazole.[74] Intravenous chloramphenicol has also been used to treat bacteraemic patients.[49]

> "Non-standardised in vitro testing suggests that *H fennelliae* is susceptible to a variety of antibiotics"

One patient with *H fennelliae* bacteraemia responded clinically to intravenous ampicillin-sulbactam and ceftazidine followed by ampicillin-sulbactam. The patient remained well at follow up, six months after being discharged from hospital.[79]

H rappini

Isolation of *H rappini* from the blood of experimentally infected guinea pigs 1.5 weeks after inoculation indicates the ability of these organisms to cause bacteraemia.[10] Also, the observation of translocation of *H rappini*-like organisms in enterocytes of cotton top tamarins with ulcerative colitis or

mice coinfected with *Serpulena hyodysentereae* supports this viewpoint.[15 58] *Helicobacter rappini*-like organisms were recently isolated from a nine year old bacteraemic child with pneumonia.[80] The organism was grown in a paediatric bottle (BACT/Alert Microbial detection system Organon Technika). The child was successfully treated with erythromycin. Also, "*H rappini*" was isolated on two occasions from the blood of an HIV negative 65 year old febrile patient undergoing haemodialysis for end stage renal disease.[60] He had a history of chronic pancreatitis due to alcoholism and also had secondary diabetes which required insulin therapy. Two months prior to the septic episode with "*H rappini*", the patient had suffered from cellulitis, secondary to a cat scratch.

> "*Helicobacter rappini*-like organisms were recently isolated from a nine year old bacteraemic child with pneumonia"

The strains were recovered from aerobic blood culture media (Bactec Plus Aerobic/F) but not from anaerobic culture media (Bactec Anaerobic/F). By whole protein numerical analysis and biochemical characteristics, the organism was indistinguishable from the LMG 8738 strain (ATCC 43879) first described by Archer and colleagues.[56] "*H rappini*" from this patient was >99% similar by 16S rRNA analysis to that of "*H rappini*" strain ATCC 43966.[60] The "*H rappini*" recovered from the patient with end stage renal disease and alcoholism appeared by in vitro criteria (using inhibition zones of >30 mm around antibiotic discs) to be more sensitive to antibiotics than the Archer strain.[56] The strain was susceptible to ceftriaxone, meropenem, erythromycin, clindamycin, clarithromycin, doxycycline, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, and metronidazole. This "*H rappini*" strain was considered to be resistant to penicillin G and cefazolin because no zone of growth inhibition was observed. Susceptibility to ampicillin and co-trimoxazole appeared to be decreased (inhibition zone diameters of 28 and 22 mm, respectively).[60] These results were consistent with the clinical failure in this patient when treated with co-trimoxazole and clinical cure when treated with meropenem.

Recurrent *H rappini* associated bacteraemia over a period of several months, despite several courses of antibiotics, has also been noted in two patients with prolonged cellulitis and X linked agammaglobulinaemia (XLA).[81 82] Both of the *H rappini*-like organisms in the XLA patients, by DNA-DNA hybridisations, were 81% related to each other but only <70% to "*H rappini*" (ATCC strain 43966). In both patients the organism was grown in aerobic paediatric BacTAlert (Organon Teknika Corp, Durham, North Carolina, USA) blood culture media. It was then successfully subcultured using microaerobic conditions that included H_2. The use of phase contrast microscopy of blood culture to observe the characteristic darting motility as well as acridine orange staining of these bacteria proved very helpful for selecting conditions for incubation of subcultures.[81 82]

> "Recurrent *H rappini* associated bacteraemia over a period of several months, despite several courses of antibiotics, has also been noted in two patients with prolonged cellulitis and X linked agammaglobulinaemia"

The first XLA patient was 36 years old when he had "*H rappini*" isolated from his blood on multiple occasions. He had XLA diagnosed at age four years and was treated with intramuscular gamma globulin until age 32 years. At age 34 years he developed leg swelling, fever, night sweats, and anorexia. The "cold" cellulitis progressed to a woody appearing skin lesion suggestive of lymphatic obstruction. In this case, in vitro antibiotic testing using E test strips indicated that "*H rappini*" were resistant to ampicillin, azithromycin, ceftriaxone, chloramphenicol, ciprofloxacin, and clindamycin.[82] The organism was sensitive to imipenem, metronidazole, minocycline, and rifampin and showed intermediate sensitivity to doxycycline. Based on these findings, the patient was initially treated with doxycycline and metronidazole with noted clinical improvement of the cellulitis. Blood cultures remained positive however, and treatment was changed to oral amoxcillin-clavulanic acid, minocycline, and rifampin.[82] Initial improvement was again noted but recurrence of symptoms followed. Intravenous gentamicin and imipenem were then initiated and continued for five months which achieved resolution of systemic infection and negative follow up on blood cultures.[82] In the second case of XLA, the patient had a history of this disease since he was six months old. He had been diagnosed as having pyoderma granulosum with non-healing skin ulcers and swelling of the leg at age 17 years. At age 18 years, he developed pyrexia and was treated with intravenous gentamicin, metronidazole, and vancomycin. The fever resolved and the skin ulcers healed, but after treatment was terminated the lesions recurred. At age 21 years, with no improvement in clinical signs, blood samples were taken and "*H rappini*"-like organisms were cultured on several occasions. The patient was also determined to have osteomyelitis by magnetic resonance imaging. Surgical bone debridement of the femur, tibia, and calcaneous of the opposite leg was performed; culture of these sites also grew "*H rappini*"-like organisms. Treatment with intravenous imipenem and gentamicin led to initial resolution of the fever and macular rash with gradual improvement in the ulcers. Gentamicin was discontinued (because of hearing loss) and replaced by intravenous meropenum. After nine months of intravenous antibiotics, the ulcers substantially improved and therapy was stopped. These two cases of XLA highlight the apparent susceptibility to *H rappini*-like infections due to a B cell (humoral) immunodeficiency with resultant intravascular and intralymphatic infections.

ENTEROHEPATIC HELICOBACTERS: DO THEY CAUSE HEPATOBILIARY DISEASE IN HUMANS?

Several *Helicobacter* spp colonise the livers of animals and induce hepatitis.[3 4 17 44 52] As a result, several recent studies have been undertaken to determine whether *Helicobacter* spp are associated with cholecystitis and other hepatobiliary diseases in humans. Cancer of the gall bladder is the number one cause of cancer mortality in Chilean women. The incidence of this gall bladder tumour vary widely on a worldwide basis, being approximately 30 times higher in high risk than in low risk populations, suggesting that environmental factors such as infectious microorganisms, carcinogens, and nutrition play a role in its pathogenesis and in some cases liver tumours.

> "Several recent studies have been undertaken to determine whether *Helicobacter* spp are associated with cholecystitis and other hepatobiliary diseases in humans"

In one study, bile or resected gall bladder tissue from 46 Chileans with chronic cholecystitis undergoing cholecystectomy were cultured for *Helicobacter* spp and subjected to PCR analysis using *Helicobacter* specific 16S ribosomal RNA primers.[83] Recovery of *Helicobacter* spp from frozen specimens was unsuccessful. However, by PCR analysis, 13/23 bile samples and 9/23 gall bladder tissues were positive for *Helicobacter* spp. Eight of the *Helicobacter* specific PCR amplicons were sequenced and subjected to phylogenetic analysis. Five sequences represented strains of *H bilis*, two strains of "*H rappini*" (ATCC 49317), and one strain of *H pullorum*. These data

support an association of bile resistant *Helicobacter* spp with gall bladder disease.[83]

Subsequently, Rudi and colleagues[84] showed that *Helicobacter* spp were not detected by PCR in bile from German patients with biliary diseases. Germany has a low incidence of bile duct and gall bladder cancer, and so they assumed that the discrepancy between their results and those of Fox and colleagues[83] could be explained by regional differences in the distribution of bile resistant *Helicobacter* species.

Primary sclerosing cholangitis (PSC) is another chronic cholestatic liver disease of unknown aetiology. Pathological lesions consist of persistent inflammation with destruction and fibrosis of intrahepatic and extrahepatic bile ducts. The high correlation of PSC and ulcerative colitis has raised the hypothesis that chronic portal bacteraemia may initiate inflammation and promote subsequent hepatobiliary damage. A study was therefore undertaken to ascertain whether *Helicobacter* spp known to cause hepatobiliary disease in animals were present in PSC patients.[85] Liver biopsies and bile were obtained from eight patients with PSC. Trypticase soy agar with 5% sheep blood, TVP, and CVA medium were used for *Helicobacter* spp isolation. The primers chosen for PCR amplification recognised conserved regions of the 16S rRNA specific for all known *Helicobacter* spp and produced an amplified product of 1220 bp. For confirmation of the PCR amplified fragment, Southern blot hybridisation was performed with a *Helicobacter* specific PCR generated probe. Although *Helicobacter* spp were not cultured, they were identified by PCR amplification and Southern hybridisation using a *Helicobacter* specific probe in five of eight patients.[85] In three of these patients, a 1200 bp PCR amplified product was successfully cloned and sequenced. Analysis of the sequences indicated high homology to the 16S rRNA sequences of a cluster of *Helicobacter* spp previously isolated from animals—that is, *H rodentium*, *H rappini*, and *H pullorum*.[85]

> "The difficulty in obtaining gall bladder and liver tissues from selected populations highlights the need for non-invasive serological assays to determine the prevalence of hepatic *Helicobacter* organisms in various biliary and hepatic diseases of humans"

Nilsson *et al* have recently found *Helicobacter* spp (including *H pylori*) using *Helicobacter* spp specific PCR in the livers of PSC patients as well as in patients with primary biliary cirrhosis, another idiopathic biliary disease.[86] Bile and liver samples were PCR positive for *Helicobacter* DNA in nearly half of 24 patients with primary biliary cirrhosis and PSC. Interestingly, *Helicobacter* spp were not identified in control patient livers or in patients with non-cholestatic liver disease. The difficulty in obtaining gall bladder and liver tissues from selected populations highlights the need for non-invasive serological assays to determine the prevalence of hepatic *Helicobacter* organisms in various biliary and hepatic diseases of humans. Nilsson *et al* also reported an immunoblot assay to discriminate between *H pylori*, *H hepaticus*, and *H bilis* infections in humans. Cross reacting antibodies as well as *H hepaticus* specific antibodies were detected in serum samples from patients with various liver diseases.[87] These authors concluded that sera IgG antibodies to *H hepaticus* were present in 56 of 144 (39%) patients with chronic liver diseases, including six of 30 patients with PSC.[87] However, sera antibody to *H hepaticus* in diseased patients was not increased compared with healthy blood donors. They also noted that seroconversion to *H pylori* was frequently noted but there was no clear association of *H pylori* seroreactivity to a specific disease category. A study of Mexican patients with gall stone disease found only a low prevalence of helicobacters in gall bladder epithelium by immunohistochemistry (1/95) and PCR (1/32).[88]

In France, investigators cited the presence of *Helicobacter* spp DNA in liver tissue in eight of eight patients with primary liver carcinoma whereas *Helicobacter* DNA was found in only one control case (1/8) without liver disease.[89] Others in Sweden have identified *Helicobacter* spp DNA in liver cancer cases.[90]

Since bile acids, intestinal acids, and highly charged mucin components are strong inhibitors of the PCR reaction, all of these studies have to be interpreted with caution until methods to safely remove or neutralise the effect of these inhibitors in bile, bile tract, and liver biopsies have been developed. To date, none of these studies have been able to culture *Helicobacter* from bile or liver. Further studies using specific and sensitive detection methods are needed to ascertain the association of *Helicobacter* infection with hepatobiliary diseases in different populations.

NON-*H PYLORI* GASTRIC HELICOBACTERS ISOLATED FROM HUMANS

"*H heilmannii*" (*Gastrospirillum hominis*)

Of the known gastric *Helicobacter* spp, "*H heilmannii*" has the largest number of known mammalian hosts. These gastric HLOs have commonly been observed microscopically in the stomachs of dogs, cats, cheetahs, swine, wild rats, various species of non-human primates, and in a small percentage of humans with gastritis.[1 2 91–96] Characterisation of these bacteria has relied on 16S rRNA analysis because of the inability to grow the organisms on artificial media. Maintenance of bacteria in the laboratory, other than in a frozen state, has relied on preparation of these gastric spirals in the stomachs of mice.[8] Recently however, investigators from Finland have been able to culture a large spiral bacteria from gastric biopsies of dogs.[14] They have named the organism *H bizzozeronii* in honour of the Italian pathologist who was one of the first scientists credited with the observation of these organisms in the stomach of mammals.[14] For in vitro growth, the organism required a fresh moist medium containing antibiotics, a microaerobic environment, and a 5–10 day incubation period.[14 97] A case report of isolation of a *H heilmannii*-like organism was also reported in a human with gastritis.[98] This isolate was susceptible to amoxicillin, metronidazole, and tetracycline.

A diagnosis of humans infected with *H heilmannii*, first observed and reported in three humans in 1987, has been made on morphological grounds by a variety of authors assessing human gastric biopsies.[1 13 91 99–102] The frequency of occurrence is between 0.25% and 0.60% depending on the study. However, as many as 6% of patients in Thailand and China have been reported to be infected with "*H heilmannii*".[103 104]

> "*H heilmannii* is located in the deep part of the gastric pits of human patients whereas *H pylori* colonises more frequently the mucus layer of surface epithelia"

Heilmann and Borchard[1] examined 15 180 gastric biopsies and observed the gastric helicobacter in 39 German patients, 34 of whom had a chronic active gastritis, and the remaining five had a chronic gastritis consisting of a lymphoplasmacytic inflammation. *H heilmannii* is located in the deep part of the gastric pits of human patients whereas *H pylori* colonises more frequently the mucus layer of surface epithelia. The gastric HLOs can also invade parietal cells in a manner similar to gastric HLO in other mammals. Pathologists have also systematically compared the histology of "*H heilmannii*" and *H pylori* in a large group of patients.[105] A total of 202 patients with "*H heilmannii*" infection were compared with an equal number of *H pylori* infected individuals. "*H heilmannii*" associated gastritis was more mild compared with *H pylori* gastritis cases.[105] In the Heilmann study, 34 of the 39 patients complained of upper abdominal discomfort. Other reports indicate that patients infected with gastric HLOs can have intermittent epigastric pain, and occasional bleeding is noted from peptic

ulcers.[1 102 106–111] These helicobacters can persist in humans for years, and presumably the same is true for other mammals.

"*H heilmannii*" has also been associated with primary gastric low grade lymphoma in humans.[100 112] Similar to *H pylori* associated lymphoma, clinical remission of the lymphoma was noted in five patients after antibiotic eradication of the gastric helicobacter.[100 113 114]

> "*H heilmannii* has also been associated with primary gastric low grade lymphoma in humans"

Eradication of "*H heilmannii*" by antimicrobial therapy has also resulted in the resolution of gastritis and peptic ulcer disease.[1 99 115] "*H heilmannii*" infections have been successfully treated with bismuth alone and with combination therapies that included metronidazole or amoxicillin.[1 98 99]

Zoonotic potential

Because "*H heilmannii*" ("*H bizzozeronii*") and to a lesser extent *H felis* colonise a small percentage of humans with gastritis, and no environmental source for these bacteria has been recognised, pets have been implicated in zoonotic transmission of the organisms. Using a questionnaire, 125 German patients infected with gastric HLOs provided information regarding animal contact. Of these, 70.3% had contact with one or more animals (compared with 37% in the "normal" population). More than a threefold preponderance of male over female patients with gastric HLOs was recorded.[91] In addition to dogs and cats as potential zoonotic hosts of these gastric helicobacters, swine may also be a source of infection to humans.[116]

In one report of "*H heilmannii*" infection, the household had two cats; a gastric biopsy from one cat indicated it was infected with gastric spiral organisms with similar morphology to that depicted in the child's stomach.[101] In another report, a pet cat and its owner had "*H heilmannii*" identified in their gastric mucosa. The authors noted that each of the *H heilmannni* strains had a 580 bp region of the ureB gene that were identical.[117]

Another study closely links the occurrence of gastric HLOs infection with exposure to companion animals.[101] A 12 year old girl after moving to a farm (with various domestic animals, including dogs), developed an 18 month history of epigastric pain, nausea, vomiting, and anorexia. Treatment with H_2 blockers did not relieve symptoms in the girl. An antral lymphonodular hyperplasia was noted at endoscopy and histologically an active chronic gastritis associated with "*H heilmannii*" was present in the gastric biopsy.[101] Institution of various anti-*Helicobacter* antimicrobial treatment—for example, amoxicillin and omeprazole for six weeks and metronidazole for 12 weeks—resulted in clinical improvement, but the symptoms in the girl returned shortly after treatment was ceased. This history suggested reinfection, and her two dogs (one asymptomatic, the other with a long history of vomiting) were endoscoped. The symptomatic dog which frequently licked the face of the girl had an active chronic gastritis associated with large numbers of "*H heilmannii*". The asymptomatic dog also had a mild gastritis associated with fewer "*H heilmannii*". The girl and the two dogs were simultaneously placed on a six week course of amoxicillin and bismuth. The symptoms in the dog resolved and endoscopy showed resolution of the gastritis. The girl's symptoms increased while on therapy and omeprazole (60 mg/day) was given. The girl remained symptom free three months after therapy. This case study suggests that the dog was the source of infection but without DNA fingerprinting of the "*H heilmannii*" strains to confirm identity, the causal association is only suggestive. Nevertheless, eradication of the gastritis in the dogs apparently prevented subsequent relapse in the girl.[101]

H felis

Lee *et al* isolated a tightly coiled spiral organism from the gastric mucosa of cats in 1988.[2] The bacterium had tufts of bipolar sheathed flagella and a body entwined with periplasmic fibres, which usually occurred in pairs.[2] The bacteria were urease, catalase, and oxidase positive, typical biochemical features of other gastric helicobacters. In subsequent studies using 16S rRNA sequencing analysis and further biochemical characterisation, the organism was named *H felis*.[12] Gastric spiral bacteria with similar morphology (based on electron microscopy) have also been identified in the stomachs of dogs, cheetahs, swine, non-human primates, and wild rats.[9 92] The organism is infrequently observed in human gastric biopsies in the gastric tissue of humans.[118] Interestingly, BALB/c mice infected with *H felis* develop a lymphoma-like gastric lesion which if treated with antimicrobials reduces the development of these gastric lesions.[119] Also, the recent observation that *H felis* infection in INS/GAS transgenic C57/BL mice induces gastric cancer adds credence to isolated case reports of "*H heilmannii*" associated gastric carcinoma.[120–122] Coinfection with *H felis* and "*H heilmannii*" is often observed in animals and perhaps in humans as well. Indeed, it is impossible to distinguish the two organisms histologically by light microscopy.

Zoonotic potential

In one case study, a researcher performing physiological studies with cat stomachs developed an acute gastritis, presumably caused by *H felis* based on electron microscopy.[118] Similar gastric spiral bacteria were shown in gastric mucosa of cats being used by this scientist. The gastritis observed in *H felis* infected dogs and cats is similar to that observed with "*H heilmannii*".

CONCLUSION

Over the past 20 years, the genus *Helicobacter* has evolved rapidly due to isolation of novel species from a wide range of animals and humans. The genus now includes at least 24 formally named species as well as numerous other helicobacters not formally named. Nineteen of these formally named helicobacters are found in the intestinal mucus of animals, eight in humans, and two in birds.

> "Infection with *Helicobacter* spp and their associated diseases in numerous hosts allow us the means to assess pathogenic mechanisms"

Many of these helicobacters can also colonise the biliary tract of the liver and induce hepatitis (and in some cases hepatic cancer) or cause bacteraemia and systemic disease in immunocompromised hosts.[3 4 17 123 124] Discovery of these helicobacters provides the scientific community with an excellent opportunity to study and better understand the finely balanced ecological relationship between these bacteria which persistently colonise the gastrointestinal tract and their effect on the host.

Infection with *Helicobacter* spp and their associated diseases in numerous hosts allow us the means to assess pathogenic mechanisms. In vivo models are also being used to develop various therapeutic and prophylactic modalities to eradicate or prevent helicobacter induced gastrointestinal disease in humans. In addition, it is important to study the epidemiology of helicobacters and their zoonotic potential as well as to identify novel *Helicobacter* spp and their possible associations with what are currently poorly defined disease syndromes.

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