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Chronic *Helicobacter* Infection of the Human Liver and Bile Are Common and May Trigger Autoimmune Disease

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After the rapid decline of leptospirosis as a cause of bacterial hepatitis and jaundice in Eastern Europe before the mid-20th century, research on viral hepatitis has exploded. It seems likely that continuing discovery of "new viruses" has delayed the search for new fastidious microbes as possible initiating causes of chronic human liver disease. However, the discovery of important new intestinal pathogens such as *Campylobacter jejuni* as a dominating cause of diarrhea in humans, and *Helicobacter pylori* as the dominating cause of chronic gastritis worldwide, has encouraged studies in various animal species as well. Today more than 20 *Helicobacter* species are well defined and isolated from the stomach, intestine, and liver of rodents and other animals. Several of these species have also been detected in extragastric specimens from humans with chronic infection and malignant diseases [1,2]. The recent discovery that two bile-tolerant species, *H. bilis* and *H. hepaticus*, cause chronic hepatitis in mice prompted studies for these and other gastric, usually bile-tolerant species, like *H. pylori* and intestinal bile-resistant organisms such as *H. cineadi* and *H. pullorum*, first classified as new *Campylobacter* species [3–5]. Avenaud *et al*. [6] detected a new species, *Helicobacter* "liver," with close similarity to *H. pylori* in liver tissue of patients with malignant liver disease, later confirmed by us [7].

Some of these species cause acute and chronic infections, primarily in patients with HIV–AIDS and other immunosuppressive states. Interestingly, recent studies in interleukin-10 knockout and SCID mice show that these immunodeficient mice commonly develop chronic colitis and possibly chronic hepatitis as well [1,8]. Such a syndrome was first described in the past year in rhesus monkeys, and it may thus exist in other primates, including humans [9]. One new *Helicobacter* species was also described recently in a semiprimate, the cotton-top tamarin, with chronic inflammatory bowel disease (IBD)–like colitis [10]. The first report that *H. hepaticus* and *H. bilis* cause chronic cholangitis and biliary disease came from Chile with a proposal of a zoonotic transmission from rodents, and possibly other existing reservoirs [11]. This report encouraged studies on the possible role of these and other fastidious microorganisms of such putative animal pathogens in primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) [3,5]. Together, these results, and a first report on *Helicobacter* detection by polymerase chain reaction (PCR) in cholangiocarcinoma that developed in PSC patients and patients with other liver cancers [12], suggest that more extensive systemic studies are needed. It seems likely that adaptation to gastric bile reflux may select for various gastric and intestinal *Helicobacter* species and other microaerophilic microbes to invade the biliary tract and human liver by 1) an ascending infection or 2) transport by bloodborne macrophages similar to the situation in chronic salmonellosis in animals and humans.

However, the continuous discovery of nonculturable new species such as *H. suis* (previously *H. heilmannii*) strongly suggests that PCR-based as well as immunodiagnostic methods should be developed to study these infections and their relation to ulcerative colitis and other forms of IBD, MB Sjögren syndrome, and possibly other autoimmune diseases. The development of specific serology for *H. pullorum* indicates that intestinal infections with this pathogen may be common in Scandinavia (Wadström T, Unpublished results), and that a search for other emerging foodborne pathogens such as *Arcobacter* species should be performed based on recent congress reports suggesting these microbes as possible new human liver pathogens. Moreover, animal models to study these infections should be developed, and further attempts to cultivate the organisms from liver specimens in naturally and experimentally infected animals should be performed.

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