EDITORIAL

Love in the Time of *Helicobacter*

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There must be a kind of uncertainty principle swimming at the deeper currents of biology—the more there are answers to things, the more we *still* have to understand. It means that for the origins of many diseases we remain unclear even about the 'right' questions. *The one constant*—in biology and in medicine—is that the experiments Nature brings descend by strong, adaptive selection. Accordingly, host-microbe interactions comprise stochastic, dynamic systems. Indeed, we are often surprised at the complexity of infectious disease. We should not be. No matter how well we understand the 'root', *a priori* it is not possible to deduce the existence of the forest fire. A very relevant example is human gastric invasion by *Helicobacter pylori*. The microbe, its adaptation as commensal and frequent pathogen, as well as the host's adaptive, inflammatory response—the functions of the genomes of both organisms —are steeped in complexity, often emergent in a surprising but troubling way: gastric carcinoma. *H. pylori* as a cause of gastric ulceration, much less gastric cancer, was long and manifestly resisted by the medical community.

Déjà vu? We may have arrived at a similar precipice thanks to one more *Helicobacter* (or Helicobacters), which could be etiologic in complex enterohepatic disease, at least in mice. The report of a new animal model for human disease has been chosen as an Annual Best Paper for studies appearing in *Experimental Biology and Medicine* in the year 2001 (1). The article by Shomer, Dangeler, Schrenzeil, Whary, and their co-authors raises attention to *Helicobacter* in complex, elusive murine disorders of blaring immunopathogenesis, including inflammatory bowel disease (IBD) and cholangiohepatitis (CH). The authors have described one of the urease-negative Helicobacters previously believed non-pathogenic. These days we will no longer so casually approach *Helicobacter* and disease? This speaks to the originality and importance of the report by Shomer and colleagues, who explored *Helicobacter*, their own strain (MIT 96-100), in both SCID (T and B cell deficient) and immunocompetent mice, identifying the organism as etiologic in IBD and CH, in A/J mice.

Shomer and co-workers were careful to re-isolate their *Helicobacter* from the diseased host (Koch's postulates!), performed ultra-structural studies, sequenced 16S rRNA genes, placed the organism phylogenetically, and described immunologic parameters of disease. By the quality of their results, in the A/J mouse *Helicobacter* is now a redoubtable cause of severe IBD and CH, of probable Th1 (pro-inflammatory) immunologic character. The study attaches potential relevance to findings of novel *Helicobacter* species in human bile in chronic cholangitis and within the liver in some hepatocellular carcinomas. Thanks to the merits of a well composed study, we can anticipate continued development of some of the 'right' questions for human IBD and CH-like disease.

These developments are exciting because IBD and CH-like diseases in humans remain frankly confusing. When the pathogenesis of these diseases in humans is finally clarified, if Helicobacters are marked as relevant pathogens, we might hope for vaccines to resist several serious and often devastating diseases, immunologic and neoplastic alike. Such a development would comprise a major development in preventive medicine. In the meantime, Shomer et al., and many other investigators, will need continued perspicacity. Just as starters, why doesn't the immune response eradicate murine *Helicobacter* infection? Are murine IBD and CH the product of molecular mimicry (immunologic cross reaction between microbe and host)? What are the opportunities for vaccination?

At the least the study by Shomer and colleagues presents a generic model for IBD and CH, likely useful for approaching elements of immunopathogenesis and therapies in enterohepatic disease. Under the best of fortunes, this model might help to locate *Helicobacter* to the usual suspects among forms of IBD and CH-like disease in humans. Beyond, the authors may enjoy the opportunity to witness rules governing emergence of autoimmune character out of immunologic complexity. Where it climbs the slopes of uncertainty, science can transport to places of satisfaction (enamoration?). In reading Shomer and colleagues' description of murine IBD and CH, and the surprise of another immunopathogenic *Helicobacter*, we are reminded of the pleasure, within science, of pursuit and discovery.

1) Shomer, NH, Dangler, CA, Schrenzel, MD, Whary, MT, Xu, S, Feng, Y, Paster, BJ, Dewhirst, FE, Fox, JG. Cholangiohepatitis and inflammatory bowel disease induced by a novel urease-negative *Helicobacter* species in A/J and Tac:ICR:Ha*scid*fRF mice. Exp Bio Med 226:420-428,2001