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HELICOBACTER PYLORI AND CANCER: PARADIGMS FOR MICROBIAL ROLES IN CANCER ETIOLOGY

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In 1982, Helicobacter pylori was first isolated from the human stomach, which has led to a revolution in thinking about gastrointestinal diseases. However, medical scientists had observed these organisms in the stomach 100 years earlier, and there now is a broad body of evidence that H. pylori are ancient and indigenous to humans.

However, it is now clear that H. pylori have been gradually disappearing from humans, concomitant with changing socioeconomic conditions and antibiotic usage. As a result, with large numbers of H. pylori-positive or –negative individuals, we now can ascertain the consequences of its presence (or absence). It has become evident that the presence of H. pylori substantially increases risk for development of adenocarcinomas of the (non-cardia) stomach, as well as peptic ulcer disease. Studies of histopathology as well as animal models support the causative role of H. pylori in gastric neoplasia. However, all H. pylori strains are not equivalent in their virulence. For example, strains with an intact cag island as part of its chromosomal DNA are associated with enhanced risk of (non-cardia) gastric adenocarcinoma as well as peptic ulcer disease.

While H. pylori has been disappearing, relatively new diseases affecting the esophagus have become more prominent. Is there any relationship between these entities (gastro-esophageal reflux disease, Barrett's esophagus, and adenocarcinoma of the esophagus) and the disappearance of H. pylori? Over the past seven years, we and others have performed studies that indicate such a role. This work shows that gastric colonization with H. pylori, especially cag-positive strains is protective against these illnesses. The mechanisms appear to involve, at least, the phenomenon that H. pylori persistence lowers gastric acidity. For perhaps the first time in human history and pre-history, there are large numbers of individuals reaching the age of 40 without H. pylori colonization, who have high levels of gastric acidity, washing the "unprotected" esophagus.

Thus, in its presence or absence, H. pylori affects risk of two important neoplasms of the gastrointestinal tract. In addition to the direct implications of these phenomena, the role of

H. pylori can be viewed as a paradigm for the behavior of persistent indigenous organisms in the etiology of neoplasia. A model in which our commensal organisms are components of our normal physiology may help our understanding of neoplasia, degenerative diseases, and aging.

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