**Helicobacter pylori** but not High Salt Induces Gastric Intraepithelial Neoplasia in B6129 Mice

Arlin B. Rogers,^1^ Nancy S. Taylor,^1^ Mark T. Whary,^1^ Erinn D. Stefanich,^1^ Timothy C. Wang,^2^ and James G. Fox^1^

^1^Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts and ^2^Division of Digestive and Liver Diseases, College of Physicians and Surgeons, Columbia University, New York, New York

**Abstract**

*Helicobacter pylori* is responsible for most human stomach cancers. Gastric cancer also is overrepresented in populations consuming high-salt diets. Attempts to test the hypothesis that high salt promotes *H. pylori* carcinogenesis have been hindered by the lack of a wild-type mouse model. Based on pilot observations of unexpectedly early gastric adenocarcinoma in C57BL/6 × 129S6/SvEv (B6129) mice infected with *Helicobacter felis*, we conducted a study to characterize *H. pylori* infection in these mice and to determine whether high salt promotes tumorigenesis. Male and female mice were gavaged with *H. pylori* Sydney strain-1 or vehicle only and divided into four groups based on infection status and maintenance on a basal (0.25%) or high (7.5%) salt diet. In uninfected mice, the high-salt diet enhanced proliferation and marginally increased parietal cell mucous metaplasia with oxyntic atrophy. Lesions in *H. pylori* infected mice without regard to diet or gender were of equivalent severity and characterized by progressive gastritis, oxyntic atrophy, hyperplasia, intestinal metaplasia, and dysplasia. Infected mice on the high-salt diet exhibited a shift in antimicrobial humoral immunity from a Th1 to a Th2 pattern, accompanied by significantly higher colonization and a qualitative increase in infiltrating eosinophils. No mice developed anti-parietal cell antibodies suggestive of autoimmune gastritis. At 15 months of age infected mice in both dietary cohorts exhibited high-grade dysplasia consistent with gastric intraepithelial neoplasia. In summary, we report for the first time *H. pylori*-induced gastric intraepithelial neoplasia in a wild-type mouse model and show no additive effect of high-salt ingestion on tumor progression. (Cancer Res 2005; 65(23): 10709-15)

**Introduction**

*Helicobacter pylori*, a WHO class I carcinogen, is responsible for most human gastric cancers (1, 2). Stomach tumors are the second leading cause of human cancer deaths (3). In addition to *H. pylori* infection, dietary factors, including deficiencies of vitamin C and E and high intake of salt and nitrates, have been linked epidemiologically to an increased risk of stomach cancer (4). An association between high-salt ingestion and gastric cancer has been suspected since the 1960s (5). Both inherently salty foods and those cured in salt for preservation have been implicated in this process (4). The European Cancer Prevention and INTERSALT Cooperative Research Group showed in a multinational study an association between urinary sodium concentration (a surrogate marker of salt ingestion) and gastric cancer risk (6). A prospective study in Japan reported a dose-dependent association between self-reported salt ingestion and risk of stomach cancer among middle-aged men but not women; however, the correlation weakened when stratified by geographic region (7). Based on epidemiologic evidence, a Joint WHO/FAO Expert Consultation concluded that high-salt intake “probably increase(s) the risk of stomach cancer” (8). Because of significant geographic overlap among *H. pylori* endemicity, high-salt diet, and gastric cancer as is found in the Far East, some investigators have postulated that high salt may act cooperatively with *H. pylori* to promote stomach cancer (9). However, direct proof for this hypothesis is lacking.

Mouse models have been used experimentally to test the potential relationship between high-salt intake and *H. pylori* infection (10, 11). However, to date, no such study has found evidence of an additive or synergistic promotional effect between gastric *Helicobacter* infection and high salt. For example, in a previous report from our group, C57BL/6 mice infected with *H. pylori* Sydney strain-1 (S11) for 4 months, and maintained on a high-salt diet, exhibited higher gastric urease activity, serum gastrin, foveolar hyperplasia, and colonization levels than did those on a basal diet; however, no meaningful effect of salt on gastric inflammation or oxyntic atrophy scores was observed (11). A critical limitation of mouse models is that to date, there has been no identified wild-type (WT) strain susceptible to *H. pylori*-induced gastric carcinoma. Infection of inbred mice with *H. pylori* results in gastritis ranging in severity from mild in the BALB/c strain to moderately severe in the C57BL/6 (12). Because of the need for better mouse models of *H. pylori* carcinogenesis, we were intrigued by the observation of earlier-than-expected gastric carcinoma in a pilot study of *Helicobacter felis* infection in C57BL/6 × 129S6/SvEv (B6129) mice (8 months after inoculation versus 13 months in C57BL/6 mice).^3^ Based on these preliminary observations, we undertook the present study to address two questions: (a) Can *H. pylori* induce gastric neoplasia in WT B6129 mice? and (b) Will a high-salt diet promote tumorigenesis?

**Materials and Methods**

**Animals and study design.** We carried out replicate experiments using C57BL/6 × 129S6/SvEv mice from different sources. The first study employed multigenerationally intercrossed C57BL/6 × 129S6/SvEv (B6c129S) mice (*n* = 52) maintained in our in-house colony. Mice in our colony are viral antibody-free for 11 murine viruses and negative for enteric *Helicobacter* spp., *Salmonella* spp., and *Citrobacter rodentium*, as well as endoparasites and ectoparasites. Because the relative strain contribution

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^3^ A.B. Rogers and J.G. Fox, unpublished data.
from the original C57BL/6 and 129Sv/Ev parents inherited by individual mice in this colony was unknown, we repeated the experiments using 66 male and 66 female B6129F1 mice purchased from Taconic Farms (Germantown, NY). For both experiments, animals were divided into four groups: (a) sham-inoculated mice maintained on a basal (0.25%) salt diet (Special Formulation Lab Diet, Purina Mills, Richmond, IN); (b) sham-inoculated mice fed a high-salt (7.5%) diet; (c) H. pylori–infected mice on the basal diet; or (d) H. pylori–infected mice on the high-salt diet. At 8 weeks of age, mice were gavaged with 10⁶ colony-forming units (CFU) of H. pylori SS1 or broth only (0.2 mL) every other day for a total of three doses. Mice were housed at four to five per microisolator cage on hardwood shavings on a 12-hour day/night cycle with constant humidity and temperature control. At 6, 12, or 15 months of age, mice were necropsied following euthanasia by CO₂ inhalation. From the combined experiments, 54 mice were evaluated at 6, 52 at 12, and 62 at 15 months of age. Twelve of the 180 original mice (86 females and 94 males) were excluded from analysis due to unrelated conditions. All mice were maintained in compliance with the USPHS Policy on Humane Care and Use of Laboratory Animals in a facility certified by the Association for the Assessment and Accreditation of Laboratory Animal Care. Protocols were approved by the Massachusetts Institute of Technology Committee on Animal Care.

Helicobacter pylori quantitative culture. For assessment of H. pylori colonization levels by quantitative culture, aseptically collected gastric corpus and antrum specimens from mice at 6 and 15 months were weighed, homogenized, plated onto selective medium, and incubated under microaerobic conditions at 37°C for 2 to 5 days as previously described (11). Helicobacter growth was confirmed morphologically by phase microscopy and Gram stain, and biochemically by urease, catalase, and oxidase.

Table 1. Murine gastric histopathology scoring paradigm

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score</th>
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<tbody>
<tr>
<td>Inflammation</td>
<td></td>
</tr>
<tr>
<td>Patchy infiltration of mixed leukocytes in mucosa and/or submucosa. Add 0.5 for significant granulocytes.</td>
<td>Multifocal-to-coalescing leukocyte infiltration not extending below submucosa</td>
</tr>
<tr>
<td>Epithelial defects</td>
<td></td>
</tr>
<tr>
<td>Rare dilated glands and/or attenuated epithelium</td>
<td>Frequent dilated glands, some large, surface epithelial &quot;tattering&quot;</td>
</tr>
<tr>
<td>Hyalinosis Red refractile droplets and crystals: Ym1/ Ym2 (34)</td>
<td>Slightly increased surface epithelial red glassy (hyalin) intracytoplasmic droplets in cardia</td>
</tr>
<tr>
<td>Mucous metaplasia*</td>
<td>Rare small foci in corpus</td>
</tr>
<tr>
<td>oxyntic gland atrophy</td>
<td>&gt;50% chief cell loss, &lt;25% parietal cell loss</td>
</tr>
<tr>
<td>Foveolar hyperplasia</td>
<td>&gt;1.5× normal isthmus length</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>Rare small foci, usually near cardia</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Focal, irregularly shaped gastric glands (analogous to colonic aberrant crypt foci) including elongated, slit, trident, and back-to-back forms.</td>
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*Foamy change (resembling Brunner’s glands) predominantly affecting parietal cells, with PAS+ and Alcian blue+ mucins.
†Foveolar columnar heightening, globoid cells with PAS/Alcian blue+ mucins (often mixed), ≥ brush border, or goblet cells.
The specific detection of IgG1 and IgG2c, respectively (BD PharMingen, San Diego, CA). Extravidin peroxidase (Sigma) at 1:2,000 was followed by 2.2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diaminomium salt (ABTS substrate, KPL, Gaithersburg, MD) for color development. Absorbance development at 405/592 nm was recorded by an ELISA plate reader (Dynatech MR7000, Dynatech Laboratories, Inc., Chantilly, VA). Results were reported as mean absorbance from triplicate measurements at a sample dilution of 1:100. Total serum IgG1 and IgG concentrations were measured using commercial kits (Bethyl Laboratories, Montgomery, TX). Titers were compared for statistical purposes as described above.

**Histopathology.** At necropsy, the stomach and proximal duodenum were removed and incised along the greater curvature. Linear gastric strips from the lesser curvature extending from the squamocolumnar junction through proximal duodenum were fixed overnight in 10% neutral-buffered formalin, routinely processed and embedded, cut at 4 μm, and stained with H&E. A comparative pathologist (A.B.R.) blinded to treatment groups scored gastric lesions on an ascending scale from 0 to 4 using the criteria outlined in Table 1. Defining characteristics for dysplasia and gastric intraepithelial neoplasia (GIN) were adapted from consensus guidelines on murine models of intestinal cancer (13). Mean lesion scores were compared by Kruskal-Wallis non-parametric one-way ANOVA.

**Special stains, immunohistochemistry, and proliferation index.** Selected tissues from infected and control animals were characterized with special stains and immunohistochemistry. Acidic (intestinal type) mucus were shown with pH 2.5 Alcian blue followed by periodic acid-Schiff (PAS) to stain remaining neutral (gastric type) mucus. Apoptosis was shown by caspase-3 immunohistochemistry using a rabbit polyclonal antibody specific for the cleaved (activated) isoform (Cell Signaling Technologies, Beverly, MA). Cell proliferation labeling indices (LI) were determined by Ki-67 immunohistochemistry using the ABK kit (DAKO, Carpinteria, CA) as described previously (10). From representative male and female mice in each of the four groups, labeled nuclei from 10 well-oriented proximal corpus glands per animal were counted in a blinded fashion. Statistics were done as described for colonization and serology.

**Results**

High salt increased *Helicobacter pylori* colonization and altered antibody responses. *H. pylori*-infected B6129 mice on the high-salt diet maintained significantly higher gastric bacterial burdens than did animals on the basal diet, in agreement with our previous observations in C57BL/6 mice (11). Mean *H. pylori* colonization in mice on the basal diet was 9,474 ± 4,798 CFU/mg stomach, whereas bacterial load in mice on the high-salt diet was 70,579 ± 15,863 CFU/mg (P < 0.0001). Moreover, colonization dropped significantly between 6 and 15 months in mice on the basal diet but increased in mice on the high-salt diet (Fig. 1). In mice on the basal diet, the decline in bacterial burden was especially marked in the corpus. In both dietary cohorts, *H. pylori* colonization of the corpus was roughly equivalent to that of the antrum.

**Figure 1.** *H. pylori* colonization of the gastric corpus and antrum as determined by quantitative culture in mice on a basal versus high-salt diet at 6 and 15 months of age. Mice on the high-salt diet had significantly greater colonization at both time points (P < 0.05). Note the statistically significant decrease in bacterial burden in mice on the basal diet between 6 and 15 months versus a slight increase over the same timeframe in mice on the high-salt diet. In both dietary cohorts, bacterial levels were equivalent between the corpus and antrum at 6 months but slightly higher in the antrum at 15 months.

**Figure 2.** Circulating anti-*H. pylori* IgG titers in male and female 15-month-old mice as determined by ELISA. A, note increased levels of the Th1-associated antibody IgG2c in *H. pylori*-infected mice on the basal diet (group 3) compared with the high-salt diet (group 4). B, Th2-associated antibody IgG1 is significantly higher in infected mice on the high-salt diet. C, anti-*H. pylori* Th1/Th2-type antibody ratio is significantly higher in infected mice on the basal diet, consistent with a Th2 shift in mice on the high-salt diet. Anti-*H. pylori* titers in uninfected mice (groups 1 and 2) were below the lower threshold of significance (dashed horizontal line).
antrum at 6 months, but antral levels were significantly increased relative to the corpus at 15 months (Fig. 1). There were no consistent differences in colonization between genders (data not shown). Stomach tissue from sham-inoculated mice was negative for *H. pylori* in culture.

We did serology on mice 15 months of age for *H. pylori*–specific IgG2c (Th1) and IgG1 (Th2) antibodies (14). Only infected mice (groups 3 and 4) developed significant antibody titers against *H. pylori* (Fig. 2). There were no significant gender differences within groups, although infected females on the high-salt diet exhibited slightly higher titers than males on the same diet (Fig. 2). However, diet had a major effect on anti-*H. pylori* IgG2c/IgG1 ratio. Mean IgG2c antibody titer was nearly 50% higher in infected mice on the standard basal versus high-salt diet (absorbance, 1.5 versus 1.1, respectively; *P* = 0.002). Conversely, mean IgG1 titer was significantly higher in mice on the high-salt diet (absorbance, 0.5 versus 0.2; *P* = 0.003). The net result was a dramatic increase in Th2/Th1 anti-*H. pylori* antibody ratio in mice on the high-salt diet (*P* < 0.0001). We found no significant differences between groups for total (as opposed to *H. pylori* specific) serum IgG1 and IgE concentrations nor did we detect serum anti-parietal cell antibodies by immunohistochemistry (data not shown). Thus, we found no systemic or parietal cell-specific serologic evidence of autoimmunity or hypersensitivity induction attributable to *H. pylori* infection or high-salt gastric injury, either alone or in combination.

**Helicobacter pylori** infection was the predominant disease determinant. Histopathologic scores stratified by group were essentially identical between B6129F1 and B6;129S mice (data not shown); therefore, data from both experiments were combined. The generic strain designation assigned to the combined groups of mice was B6129. In sham-inoculated B6129 mice on the high-salt diet (group 2), there was a very slight increase in inflammation, oxyntic atrophy, mucous metaplasia, and hyperplasia scores consistent with mild atrophic gastritis at 6 and 12 months compared with uninfected mice on the basal diet (group 1; Fig. 3). However, because these mild changes occurred sporadically in both groups, there was no statistically significant difference between them. For all lesion criteria except hyalinosis and mucous metaplasia (data not shown), statistically significant increases (*P* < 0.05) were evident in *H. pylori*–infected mice (groups 3 and 4) at 15 months compared with uninfected mice (Fig. 3). Inflammation, epithelial defects, and oxyntic atrophy scores reached significantly higher levels by 6 months, and hyperplasia, intestinal metaplasia, and dysplasia were significantly increased by 12 months (Fig. 3). Interestingly, except for mucous metaplasia, mean lesion grades were slightly higher for mice on the basal diet (group 3) than for mice on the high-salt diet (group 4; Fig. 3). These differences were not statistically significant.

**Helicobacter pylori**–infected B6129 mice developed gastric intraepithelial neoplasia. Compared with histologically normal mice (Fig. 4A–B), mice with mucous metaplasia secreted mixed acidic intestinal-type and neutral gastric-type mucus (Fig. 4C–D). Infected mice on both diets developed chronic active gastritis, oxyntic atrophy, hyperplasia, intestinal metaplasia, and dysplasia, recapitulating Correa’s multistage model of *H. pylori* carcinogenesis (15). By 12 months of age, mice infected with *H. pylori* exhibited severe gastritis and epithelial changes, including glandular ectasia and mineralization, surface irregularities, marked hyperplasia, and early dysplasia with glandular distortion and pleomorphism (Fig. 4E–F). Although not quantified, there was a subjective increase in the proportion of infiltrating eosinophils in mice on the high-salt diet. In some mice, there was complete oxyntic atrophy with surface epithelial proliferation, inflammation, and fibrosis (Fig. 4G). Intestinal metaplasia (incomplete or type II) was manifested by columnar elongation of foveolar epithelium interspersed with rare goblet cells (Fig. 4H; ref. 16). By 15 months, B6129 mice in both dietary cohorts developed *H. pylori*–associated high-grade dysplasia consistent with GIN (13). Dysplastic changes were characterized by marked surface epithelial hyperplasia, absence of oxyntic cells, disorganization and branching of glands, loss of columnar glandular orientation, cell stratification, pleomorphism and atypia, and nuclear changes, including anisokaryosis, loss of basal polarity.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Gastric histopathology scores for all mice at 6, 12, and 15 months based on the criteria outlined in Table 1. Compared with uninfected mice on the basal diet (group 1) or high-salt diet (group 2), *H. pylori*–infected mice on either the basal (group 3) or high-salt (group 4) diet had significantly higher mean scores for inflammation, epithelial defects, and oxyntic atrophy by 6 months, and for hyperplasia, intestinal metaplasia, and dysplasia by 12 months that persisted to the end of the study. There were no statistically significant differences between groups for hyalinosis or mucous metaplasia (data not shown).
vesicular (euchromatic) chromatin pattern, and increased mitotic figures with occasional bizarre forms (Fig. 4I-L). In some mice, there was glandular herniation into the muscularis mucosae (Fig. 4J). However, invasion of neoplastic glands into the submucosa or lymphatics was not observed. Goblet dysplasia characterized by disorderly stratification of cells expanded by large cytoplasmic mucus vacuoles with nuclear margination (somewhat resembling signet ring cells) was evident multifocally (Fig. 4M; ref. 16). Intestinal metaplasia was confirmed by the demonstration of acidic and mixed mucins within apical cytoplasmic droplets, and on the surface of atypical cells by pH 2.5 Alcian blue/PAS stain (Fig. 4N).

Helicobacter pylori infection simultaneously up-regulated epithelial proliferation and apoptosis. In dysplastic regions, high rates of intercurrent apoptosis and proliferation were shown by immunohistochemistry. Lumens of ectatic glands contained many caspase-3+ epithelial cells, whereas epithelial lining cells of the same glands exhibited a high rate of proliferation as shown by nuclear Ki-67 immunoreactivity (Fig. 4O-P). We rarely detected caspase-3+ cells within the gastric mucosa, probably because of rapid phagocytic removal by neighboring viable cells. To quantitatively compare proliferation differences, we determined the Ki-67 LI for representative mice at 12 months from each of the four groups. In uninfected mice, the high-salt diet resulted in a moderate but statistically significant (P = 0.003) increase in proliferation (Fig. 5). As expected, H. pylori infection significantly increased Ki-67 LI in mice on either diet compared with uninfected controls (Fig. 5; P < 0.001). In contrast to observations in uninfected mice, however, H. pylori–infected mice on the high-salt diet had a lower proliferation index than that of mice on the basal diet (P < 0.001). Taken together, these data are in agreement with our previous study in INS-GAS mice indicating that up-regulated proliferation and not down-regulated apoptosis is the primary mechanism of foveolar hyperplasia in H. pylori–infected mice (10).
Discussion

*H. pylori* infection is now recognized as the single greatest risk factor for human gastric cancer (17). High-salt ingestion has been proposed to increase the risk of stomach carcinoma as well (7). However, in contrast to *H. pylori* infection, which increases the risk of stomach cancer up to 10×, epidemiologic associations between high-salt and gastric tumors are less consistent and rarely raise the adjusted odds ratio above 2 (18). Thus, although *H. pylori* has been designated a class I carcinogen (1), a Joint WHO/FAO Expert Consultation could only conclude that high-salt ingestion “probably increase(s) the risk of stomach cancer” (8). Indeed, a prospective study in the United States found no association between self-reported seasoning of food with salt and subsequent risk of stomach cancer, whereas food salting was significantly associated with high blood pressure (19). Thus, the hypothesis that high-salt ingestion promotes gastric cancer remains controversial.

In the present study, B6129 mice infected with *H. pylori* developed chronic active gastritis and, by 15 months of age, high-grade dysplasia consistent with GIN (13). Neither we nor others have observed this high degree of gastric dysplasia by 15 months in gastritis-susceptible inbred C57BL/6 mice following infection with *H. pylori* (20). B6129 mice fed a high-salt diet showed a shift in anti-*H. pylori* humoral immunity from a Th1 to a Th2 phenotype. This humoral immunity shift is not specific to B6129 mice. Our group observed a similar increase in Th2-associated IgG1 relative to Th1-associated IgG2a in *H. pylori*-infected INS-GAS mice on a FVB background (10). However, the salt-associated shift in humoral immunity to a Th2 pattern seemed to be *H. pylori* specific. We found no increase in total IgG1 or IgE consistent with hypersensitivity nor did we detect anti-parietal cell antibodies suggestive of autoimmune gastritis. Further studies will be needed to determine whether antibody responses reflect cell-mediated immunity within the gastric mucosa. For example, in contrast to previous work from our group showing that a Th2-invoking helminth infection may reduce the risk of *Helicobacter*-induced gastric cancer (21), we found no protective effect of the high-salt diet on dysplastic progression. Direct chemical injury to a gastric mucosa already impaired by *Helicobacter*-induced gastritis may offset any beneficial effect from the salt-induced humoral immunity shift. Moreover, innate immunity plays a critical role in *H. pylori* infection. For example, the cyclooxygenase-2/prostaglandin E synthase pathway was shown to be a critical mediator of proinflammatory and tumorigenic phenotypes in the murine gastric mucosa, both in transgenic mice and in *Helicobacter* infection models (22).

The most frequently studied animal models of *H. pylori* infection are the Mongolian gerbil and the mouse (23–25). Gerbils infected with *H. pylori* develop an antral gastritis/duodenitis that mimics the ulcerogenic form of the human disease (26). Unlike mice but similar to humans, the bacterial cag pathogenicity island seems to be a critical disease determinant in gerbils (27). The gerbil model should prove highly useful towards addressing questions specifically related to cagA and other *H. pylori* virulence determinants in vivo. Our group showed previously in gerbils that high dietary salt alone provoked oxyntic atrophy and foveolar hyperplasia (28). Moreover, others have shown a synergistic promoting effect of *H. pylori* and high salt on N-methyl-N-nitrosurea (MNU)–initiated gastric cancer in the gerbil model (29). However, chemical initiation required to induce cancer, as no tumors developed in gerbils untreated with MNU regardless of *H. pylori* infection status or diet. Thus, to date, the gerbil model has failed to show a contribution of high salt in the promotion of gastric tumorigenesis in the absence of chemical initiation. Importantly, pathogenic gastric *Helicobacter* spp. in both gerbils and mice reproduce Correa’s histologic progression of inflammation, oxyntic atrophy, epithelial hyperplasia, intestinal metaplasia, and dysplasia/cancer (30), attesting to their appropriateness as models of human disease.

In contrast to the antral-predominant disease seen in the Mongolian gerbil, stomach lesions in mice infected with gastric *Helicobacter* spp. are usually most severe in the cardia and corpus (25). Corpus gastritis and parietal cell mucous metaplasia contribute to the sometimes severe atrophic gastritis observed in murine models (11). C57BL/6 mice infected with *H. pylori* SS1 for 4 months and maintained on a high-salt diet exhibited higher gastric urease activity, serum gastrin, bacterial colonization, and foveolar proliferation levels than did those on a basal diet; however, no meaningful effect of salt on gastric inflammation or oxyntic atrophy scores was observed (11). High salt likewise increased foveolar proliferation in uninjected but not infected mice in the present study. Thus, induction of proliferation in the absence of dysplasia does not seem to increase the risk of carcinogenesis in this model. In agreement with this concept, *H. pylori* infection was shown to induce DNA damage in Big Blue mice (containing a chromogen-inducible lambda phage transgene for *in vitro* mutation quantitation), but no increase in mutation frequency was evident in animals fed a high-salt diet (31).

To our knowledge, this is the first report of *H. pylori*–induced gastric intraepithelial neoplasia in any wild-type mouse model. In agreement with a previous study using INS-GAS mice on a FVB background (10), we observed no promotional effect of high salt on *H. pylori* tumorigenesis in B6129 mice. Wild-type and genetically engineered mice on a 129S background are used widely in inflammatory bowel disease studies due to their high susceptibility to bacterial-induced colitis and cancer (25). Additional work will be required to determine whether inbred 129S mice are susceptible to
H. pylori–induced gastric tumorigenesis, or whether the combined contribution of C57BL/6 and 129Sv/Ev parental strains was necessary to induce GIN in the present study. Whereas *H. felis* infection results in stomach cancer in C57BL/6 and other susceptible strains of mice (32), to date, the only published murine model of gastric carcinogenesis due to *H. pylori* is the INS-GAS mouse (10, 33). INS-GAS mice are transfected with a humanized gastrin transgene linked to a rat insulin promoter and develop constitutive hypergastrinemia and gastric cancer within 7 months of *H. pylori* infection. However, previous work from our group showed that *H. pylori*–infected INS-GAS mice fed a high-salt diet exhibited no increase in tumor progression over those fed the basal diet. Indeed, in agreement with our present study, gastritis and dysplasia scores in INS-GAS mice on the high-salt diet were slightly lower than those for mice on the basal diet, although like the present study, those differences were not statistically significant (10). As is the case with humans, male INS-GAS mice infected with *H. pylori* were more susceptible to tumorigenic progression than females (10), in contrast to the present study in B6129 mice that high-salt ingestion in this model neither promotes nor prevents tumorigenesis. The B6129 mouse model provides a new opportunity to study *H. pylori* carcinogenesis in vivo.

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References


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