Non–Gastrointestinal Tract Associations of *Helicobacter pylori* Infection

What Is the Evidence?

Grigoris I. Leontiadis, MD; Virender K. Sharma, MD; Colin W. Howden, MD

*Helicobacter pylori* infection is linked to conditions of the upper gastrointestinal tract, including peptic ulcer and gastric adenocarcinoma. It has also been associated with a wide variety of non–gastrointestinal tract conditions. However, the evidence in support of *H pylori* infection as a cause of the non–gastrointestinal tract conditions is not widely understood. We reviewed the medical literature for publications and abstracts dealing with putative non–gastrointestinal tract associations of *H pylori* infection. We appraised the level of evidence and applied it to an established set of 9 criteria for determining causation. We found that many studies examining a possible causal relationship have been uncontrolled or inadequately controlled. Studies have often failed to control for socioeconomic status. Studies of treating *H pylori* infection in patients with these disorders have been poorly designed and inappropriately controlled, and therefore add little to the evidence base. Attention should be focused on appropriate testing for and treatment of *H pylori* infection in patients with conditions that are of proven association, notably peptic ulcer disease.

*Helicobacter pylori* has been conclusively linked to different forms of gastritis, as well as to peptic ulcer disease of the stomach and duodenum, gastric adenocarcinoma, and low-grade gastric lymphoma arising from mucosa-associated lymphoid tissue. *Helicobacter pylori* may also have a role in dyspepsia and nonulcer dyspepsia, although this role is currently unresolved.

In view of the excitement and interest generated by the link between *H pylori* and gastric abnormalities, different investigators have sought to determine a role for the infection in a variety of non–gastrointestinal tract disorders. This is despite our current understanding that *H pylori* infection is confined to gastric mucosa. Although the infection is noninvasive, it triggers a marked local inflammatory response and a systemic immune response. *Helicobacter pylori* infection of the stomach could conceivably produce effects elsewhere by altering levels of systemic inflammatory mediators. Our aim is to review critically the evidence that *H pylori* infection causes various other disorders outside the alimentary tract.

Since *H pylori* infection is so common throughout the world, it is not surprising that it has been found in patients with other diagnoses. Such findings may have been because of chance alone. Therefore, assumptions that certain conditions are caused by *H pylori* infection might be spurious; association need not necessarily imply causation. Evidence in support of causation comes in different forms. The strongest evidence comes from randomized, controlled trials, which are seldom available. After those, in decreasing levels of strength, come cohort studies, case-control studies, and case series or single-case reports. Other forms of evidence reviewed herein include experimental studies and observational, cross-sectional studies (controlled or uncontrolled).

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Table 1. Application of 9 Diagnostic Tests for Causes of Certain Non–Gastrointestinal Tract Conditions Proposed to Be Related to Helicobacter pylori Infection*

<table>
<thead>
<tr>
<th>Tests</th>
<th>Coronary Heart Disease</th>
<th>Cerebrovascular Disease</th>
<th>Hypertension</th>
<th>Raynaud Phenomenon</th>
<th>Migraine</th>
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<tr>
<td>Is there evidence from true experiments in humans?</td>
<td>No</td>
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<td>Is the association strong?</td>
<td>No</td>
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<td>Is the association consistent from study to study?</td>
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<td>Is the association specific?</td>
<td>No</td>
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<td>Is the association analogous to a previously proven causal association?</td>
<td>No</td>
<td>No</td>
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* Question mark indicates absence of sufficient evidence for answer.

MATERIALS AND METHODS

We conducted a fully recursive MEDLINE search for published articles dealing with H pylori infection and conditions outside the gastrointestinal tract. We supplemented this with a review of abstracts from recent national and international gastroenterology conferences and conferences specifically devoted to H pylori. We deliberately chose to include abstracts, since research on H pylori is developing rapidly, and we wanted to identify any recent important developments or trends. We reviewed in full those articles published in English. For articles published in other languages, we reviewed an English abstract.

DETERMINING THE PLAUSIBILITY FOR CAUSATION

The following 9 questions were conceived by Sackett et al16 for considering whether a possible association is causal:

1. Is there evidence from true experiments in humans?
2. Is the association strong?
3. Is the association consistent from study to study?
4. Is the temporal relationship correct?
5. Is there a dose-response relationship?
6. Does the association make epidemiological sense?
7. Does the association make biological sense?
8. Is the association specific?
9. Is the association analogous to a previously proven causal association?

These are listed in decreasing order of importance. We have attempted to answer these 9 questions for each of the conditions under review (Table 1). However, when considering a possible role for H pylori infection in a condition outside the gastrointestinal tract, it is not possible to answer each of these questions conclusively. For example, apart from 2 well-described case studies of self-inoculation,17,18 there have been no direct experiments of H pylori infection in humans.

The means of testing for H pylori infection might influence the strength of association with any of the non–gastrointestinal tract conditions under review. Some studies have used highly sensitive and specific means for determining the presence of the infection, such as a carbon-labeled urea breath test (UBT) using carbon 13 or carbon 14. Such tests are highly accurate in determining active H pylori infection.20,21 Other studies have determined H pylori status by serological means. Generally, serological tests have lower sensitivity and specificity than UBT or endoscopic tests; their results may be false-positive in some patients successfully treated for H pylori infection in the past.21,22

It is seldom possible to assess the temporal relationship between the proposed cause (namely, H pylori infection) and the proposed outcome (viz, the non–gastrointestinal tract condition in question). However, our present understanding is that H pylori infection is generally acquired in childhood.23,24,25 Therefore, it might be reasonable to assume that acquisition of the infection would antedate the development of any condition presenting for the first time in adulthood.

It is generally impossible to know if a dose-response relationship exists between H pylori infection and another condition. The diagnosis of H pylori infection is essentially qualitative rather than quantitative. Since the infection is present or absent, its “dose” is unknown. Also, the duration of H pylori infection is usually unknown and cannot otherwise be assessed, although most infections are probably acquired in childhood. We have attempted to evaluate the scientific validity of the biological rationale for any proposed association. However, for many of the putative associations, there is no obvious biological rationale or pathogenetic mechanism.

POSSIBLE MECHANISMS THAT MIGHT EXPLAIN NON–GASTROINTESTINAL TRACT ASSOCIATIONS OF H pylori INFECTION

Helicobacter pylori typically infects and is confined to gastric mucosa. Such mucosa is customarily restricted to the stomach but may also occur elsewhere in the alimentary tract. Heterotopic or metaplastic gastric mucosa infected with H pylori has been documented in the proximal esophagus,23,24 the distal esophagus,25,26 the duodenum,27,28 Meckel diverticulum,29,30 and the rectum.31
Changes in systemic inflammatory mediators could conceivably produce effects elsewhere in the body. 12,33 Helicobacter pylori infection may also be associated with altered coagulation.

**Effects of H pylori Infection on Coagulation**

**Coagulation Factors.** In England, Patel and colleagues32 studied 72 middle-aged white men without a known history of coronary heart disease (CHD). They found a higher mean serum fibrinogen concentration in the men with serological evidence of H pylori infection compared with those who were uninfected (P = .007). In a case-control study of 388 men in England, their group confirmed a significantly raised mean serum fibrinogen concentration associated with H pylori infection.33 In a controlled study of patients recovering from acute myocardial infarction (MI), Rajput-Williams and colleagues34 found a higher mean serum fibrinogen level in their H pylori–infected healthy control subjects than in their noninfected controls (P = .04).

A case-control study involving more than 2000 men and women in Northern Ireland failed to demonstrate any association between H pylori infection and serum fibrinogen or plasma viscosity.35 In a study of patients with dyspepsia in England, no association was found between H pylori status and serum fibrinogen concentration or levels of other coagulation factors, including factors VII:c and VIII:c and von Willebrand factor.36 In 292 patients with CHD, H pylori status was not significantly associated with serum levels of fibrinogen, factor VII or von Willebrand factor.37

In Italy, Bieri and colleagues38 found a significantly higher mean serum fibrinogen level in 64 H pylori–infected patients compared with 66 noninfected patients (P = .04). They also found higher antigen levels of von Willebrand factor in the H pylori–infected group (P < .01). Levels of plasminogen activator inhibitor were no different between H pylori–infected and noninfected patients.

In 300 healthy blood donors from Italy, 53% were seropositive for H pylori infection.39 Levels of fibrinogen were no different between those who were seropositive and seronegative. Those who were seropositive for H pylori had higher concentrations of factor VII:c and prothrombin cleavage fragment. However, these differences disappeared after adjustment for age, sex, and social class.

No significant association was demonstrated between H pylori status and serum fibrinogen levels in almost 1500 male and female patients with CHD in Scotland.40 In a prospective study, Wald et al41 observed 21 520 professional men in England for a mean of 15.6 years. They found no association between H pylori status and serum fibrinogen levels. A recent metaanalysis found no significant association between H pylori status and serum fibrinogen level.42

The best evidence for an association between H pylori infection and hyperfibrinogenemia comes from cross-sectional or case-control studies. However, the association between H pylori infection and increased levels of fibrinogen or other coagulation factors is inconsistent. The largest and most robust studies and a meta-analysis failed to demonstrate any association.

**Platelets.** Increased levels of circulating platelet aggregates were demonstrated in 5 patients with upper gastrointestinal tract complaints who were seropositive for H pylori, compared with 5 similar patients who were seronegative.43 There is no epidemiological evidence of an effect of H pylori infection on platelet function.

**Effects of H pylori Infection on Markers of Systemic Inflammation**

**Leukocyte Counts.** A raised whole blood leukocyte count is associated with an increased risk for CHD.44 Patel et al41 found a significantly higher leukocyte count in 191 middle-aged white men who were seropositive for H pylori infection than in 197 who were seronegative. Karttunen et al45 from Finland studied 96 patients with dyspepsia, of whom 58 were seropositive for H pylori infection. Total whole blood leukocyte counts were significantly higher in the H pylori–positive group, as were absolute counts of lymphocytes and basophils. Three studies30,39,46 and a metaanalysis44 found no association between H pylori status and leukocyte counts.

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**Table:**

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<th>Rosacea</th>
<th>Chronic Urticaria</th>
<th>Iron Deficiency Anemia</th>
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<th>Hyperammonemia</th>
<th>Sudden Infant Death Syndrome</th>
<th>Growth Retardation</th>
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The best evidence of an association between H pylori infection and a raised leukocyte count comes from case-control studies, but is inconsistent. Prospective studies and a meta-analysis do not confirm the effect.

C-reactive Protein and Tumor Necrosis Factor. In a population-based, cross-sectional study of 388 middle-aged, white men in England, H pylori status was one of many variables found to correlate with serum levels of C-reactive protein (CRP). In turn, raised CRP levels were associated with elevated levels of serum fibrinogen, total cholesterol, triglyceride, and glucose. They were negatively associated with high-density lipoprotein (HDL) cholesterol concentration. Concentration of CRP is strongly associated with a propensity to CHD. Serum concentrations of tumor necrosis factor α are positively related to H pylori status. Tumor necrosis factor α is one of the cytokines that regulate CRP production by the liver. Higher circulating levels of soluble tumor necrosis factor receptor I are reported in patients with CHD who are seropositive for H pylori infection.

Helicobacter pylori infection may elevate circulating levels of CRP. However, this is a very nonspecific finding.

Effects of H pylori Infection on Other Risk Factors for Cardiovascular Disease

Cholesterol, Triglyceride, and Glucose Levels. Patel et al found no association between H pylori status and serum levels of cholesterol, triglyceride, apolipoproteins A or B, or glucose. Murray et al found no significant association between H pylori status and levels of total or HDL cholesterol. McDonagh et al found no association between H pylori status and total cholesterol levels.

Scruggs et al studied a large group of asymptomatic, nondiabetic workers in New Zealand. They found no association between H pylori status and levels of total cholesterol, triglyceride, or glucose. Levels of HDL cholesterol were slightly lower in individuals who were seropositive for H pylori infection than in those who were seronegative (mean difference, 0.07 mmol/L [2.7 mg/dL]; P = .03). Infection with H pylori was also associated with a lower HDL cholesterol concentration in a cross-sectional study of the elderly in Finland.

In a Spanish study of 112 patients with CHD admitted to a coronary care unit (CCU), there was no association seen between H pylori status and the presence of hypercholesterolemia or diabetes. In a cross-sectional study of 1756 Danish women, H pylori serological status did not correlate with serum triglyceride or cholesterol levels. In a United States–based study, H pylori serological status was determined in 103 patients undergoing coronary angiography for suspected CHD. Fifty-two patients (50%) were seropositive for H pylori. Serological status was not related to total cholesterol levels or to the presence of diabetes.

Among 91 elderly, dyspeptic patients in Italy, results of gastric histological and rapid urease tests were positive for H pylori infection in 60. There were no significant differences between the patients with positive and negative results with respect to mean levels of glucose, total cholesterol, HDL cholesterol, or triglyceride.

In a nested case-control study, Whincup et al studied 95 middle-aged British men who had survived an MI, 93 who had survived a stroke, and a similar number of matched controls. Helicobacter pylori status was not significantly associated with total cholesterol, HDL cholesterol, or triglyceride levels. However, serum glucose levels were significantly higher in the patients who were seropositive for H pylori (P = .006). In their prospective study of healthy English men, Wald et al found no association between H pylori status and total cholesterol or triglyceride levels.

In South Korea, Kang and colleagues studied 274 patients with suspected CHD who were undergoing coronary angiography. Of these, 64.1% were seropositive for H pylori infection. They found no association between H pylori status and hyperlipidemia or diabetes. However, the same group identified a significantly higher (P = .006) mean serum cholesterol level in association with H pylori infection in a study of 3274 healthy Korean adults. Although statistically significant, this difference was small and unlikely to be clinically meaningful.

The seroprevalence of H pylori infection was 53% in 381 healthy Spanish subjects without a history of peptic ulcer disease or hyperlipidemia. Although the H pylori–infected subjects had a higher mean total serum cholesterol level than those who were not infected, this difference was not apparent after adjustment for age and sex.

A meta-analysis found no significant association between H pylori status and serum cholesterol levels. However, it found a highly statistically significant, although quantitatively small, difference in HDL cholesterol levels (mean difference, −0.032 mmol/L [−1.2 mg/dL]; P < .001) between H pylori–infected and noninfected individuals. It found a small, statistically significant association between H pylori infection and serum or plasma glucose levels (mean difference, 0.14 mmol/L; P < .05), but no association with serum triglyceride levels.

The best evidence of an association between H pylori infection and hypercholesterolemia comes from cross-sectional studies. There is little consistency in results between different studies. The magnitude of effect, if any, is low. There may be a small, negative effect on HDL cholesterol levels.

Homocysteine. A raised serum level of homocysteine is an independent risk factor for CHD. Sung and Sanderson have proposed that H pylori infection predisposes to hyperhomocysteinemia through nutritional deficiencies of folate and vitamins B6 and B12. However, B12 malabsorption might only occur in few infected patients, and only after many years of H pylori infection associated with extensive atrophic gastritis and loss of parietal cell mass. Even then, body stores of vitamin B12 should be sufficient to delay the development of true deficiency for years. There is no particular reason why H pylori infection per se should
be associated with dietary deficiencies of folate or vitamin B6,62
Whincup et al63 found no difference in serum homocysteine levels between 63 H pylori–infected and 55 noninfected individuals without CHD. Saxena et al64 found no significant difference in mean serum homocysteine levels between 122 patients seropositive for H pylori and 98 seronegative patients. Markus and Mendl65 found no association between H pylori status and serum levels of homocysteine or folate in a case-control study of patients with ischemic stroke. Two studies64,65 found a nonsignificant trend toward lower homocysteine levels in association with H pylori infection.

There is no evidence to suggest that H pylori infection causes hyperhomocysteinemia.

Heat-Shock Proteins. Heat-shock protein (hsp) 65 is a stress protein that is expressed in high concentrations in atherosclerotic tissue.66 Immunization of animals with hsp65 can induce atherosclerotic lesions in the absence of hypercholesterolemia. Levels of serum antibodies to hsp65 are significantly higher in patients with carotid atherosclerosis than in matched controls.66 An immune reaction to hsp65 might play a role in the pathogenesis of atherosclerosis.67 As a group, hsp65 have high homology among different species from bacteria to man.66 Helicobacter pylori expresses an hsp65 known as hsp62 that is highly homologous with hsp65 and endogenously produced hsp60.66 Among 136 men consecutively investigated using cardiac catheterization for chest pain or valve abnormalities, there was a highly significant correlation (r = 0.39; P < .001) between the presence of antibodies to hsp65 and H pylori.68 The patients who were seropositive for H pylori had significantly higher levels of antibodies to hsp65 than those who were seronegative.

There may be an association between H pylori infection and the presence of antibodies to hsp65. The relevance of this to the pathogenesis of atherosclerosis is not fully understood.

POSSIBLE DISEASE ASSOCIATIONS WITH H pylori INFECTION

Cardiovascular Disorders

Coronary Heart Disease. Mendall and colleagues69 in England found a 59% seroprevalence of H pylori infection in 111 consecutively white men with established CHD and a 39% seroprevalence in 74 community-based controls (P = .007). After adjustment for socioeconomic status and other cardiovascular risk factors, the odds ratio (OR) for CHD in the presence of H pylori infection was 2.15 (P = .03). However, others thought this association was not causal.70 In a cross-sectional study of a random sample of 388 white men in England, Patel and colleagues31 found an association between H pylori seropositivity and the presence of abnormal results of electrocardiography consistent with underlying CHD (OR = 3.82; P < .01).

In the cross-sectional, population-based study from Northern Ireland by Murray and colleagues,35 there was only a weak association between H pylori status and CHD that did not reach statistical significance (OR = 1.51; P = .10). McDonagh and colleagues40 in Scotland found no significant association between H pylori seropositivity and any measure of CHD among 1428 randomly selected men and women. In Finland, Niemala and colleagues71 performed a case-control study in 116 patients with angiographic evidence of CHD and 116 age- and sex-matched community controls. Seroprevalence of H pylori infection was similar in both groups (64% vs 53%; OR = 1.5). In a nested case-control study in the United Kingdom, Whincup and colleagues46 found a seroprevalence of H pylori infection of 70% in 95 middle-aged men who survived an MI and 57% of 78 age-matched controls (OR = 1.77; P = .03). An analysis of the Eurogast database72 found that deaths due to CHD were negatively correlated with seropositivity for H pylori infection (r = −0.73; P < .05).

Morgano and colleagues72 from Italy studied the seropositivity of H pylori infection in 42 patients admitted to a CCU with acute MI and 198 hospital-based controls. The rates of seroprevalence were 85.7% and 57.1%, respectively. The controls were not well-matched for age, sex, or the absence of cardiac disease. In Spain, Martin-de-Argila and colleagues73 reported a 84.1% seroprevalence of H pylori infection in 101 patients with CHD admitted to the CCU, and a 58.8% prevalence in 68 healthy controls (P < .001) who were not well-matched for age or sex. In a similar study of 112 patients with CHD admitted to the CCU, 81.3% were seropositive for H pylori compared with 63.8% of 53 healthy controls (P < .01) matched roughly for age but not for sex.72

In another poorly controlled study, Ponzetto and colleagues74 reported a seroprevalence of 89% among 27 patients with acute MI and 47% among 619 blood donors (OR = 4.4). Rathbone and colleagues75 performed a case-control study in 342 consecutive patients admitted to a CCU with acute MI and 236 population-based controls. Seroprevalence of H pylori infection was 60.2% in the patients and 55.9% in the controls (age- and sex-stratified OR = 1.05; P = .87). In Italy, Parravicini and colleagues76 performed 13C-UBT on 137 patients with acute MI and 312 healthy blood donors, not well-matched for age. Helicobacter pylori infection was found in 86.1% of the patients and 58.6% of the blood donors, who were younger.

In Germany, Maier and colleagues77 performed a prospective serological study of 87 consecutive patients with known or suspected CHD who were undergoing coronary angiography. The seroprevalence of H pylori infection was no different in those with or without angiographic evidence of CHD (68.4% vs 80.0%; P = .04). Ossei-Gerning77 in England studied 292 patients having coronary angiography for suspected CHD; 204 had angiographic evidence of CHD, and the seroprevalence of H pylori infection in these 204 was 68%. Of the 88 patients without evidence of CHD, the seroprevalence was 50% (P = .003). However, a similar angiographic study of 70 patients in Germany found no significant dif-
ference in rates of *H. pylori* infection, determined using endoscopy, in patients with and without CHD (56% vs 44%; *P* > .05). Furthermore, a study in Korea of 274 patients undergoing coronary angiography for suspected CHD found no difference in *H. pylori* seroprevalence between patients without visible lesions and those with disease in 1, 2, or 3 coronary arteries. In a United States–based angiographic study, *H. pylori* serologic studies were performed in 179 patients with suspected CHD; 121 had angiographic evidence of CHD and 58 did not. Seroprevalence of *H. pylori* infection was 45% in those with CHD and 47% in those without (*P* = .96).

Balaban and colleagues in the United States studied the seroprevalence of *H. pylori* infection in 201 consecutive patients referred for noninvasive cardiac investigation because of suspected CHD. Adjusted ORs for an association with *H. pylori* infection were not significant for CHD (OR = 0.54, *P* = .10) or a previous MI (OR = 2.14; *P* = .10). However, they found a significant relationship between *H. pylori* infection and a history of MI in women (OR = 10.9; *P* = .03), although the sample size was only 34.

In a prospective cohort study of elderly people in Finland, Strandberg and colleagues found no significant association between *H. pylori* seropositivity and evidence of vascular disease. Cardiovascular and total mortality were not related to *H. pylori* status. Similarly, Wald and colleagues in England found no association between *H. pylori* seropositivity and death due to CHD in their prospective study (nested case-control design) of more than 21,000 professional men (OR = 1.06).

The best evidence of an association between *H. pylori* infection and CHD comes from a nested case-control study. Larger prospective studies did not find a significant association. There is no consistent conclusion among different studies. In general, large controlled studies have not confirmed the findings of earlier smaller studies. Those that used appropriate controls were less likely to report a significant association.

Cerebrovascular and Peripheral Vascular Disease. In a nested case-control study, Whincup et al studied results of *H. pylori* serologic testing in 137 middle-aged British men in whom a stroke developed before December 1991 and in 136 age-matched and geographically matched controls. Of the patients with stroke, 93 (67.9%) were seropositive for *H. pylori* compared with 78 (57.4%) of the controls. The OR for stroke associated with *H. pylori* infection was 1.57 (*P* = .07). After adjustment for socioeconomic status, smoking, and blood pressure, the OR was 0.96 (*P* = .92).

In a study of 91 elderly dyspeptic patients in Italy, 60 had results of gastric histological examination and rapid urease testing that were positive for *H. pylori*. All patients underwent echodoppler ultrasonography of extracranial and peripheral arteries. Those with *H. pylori* infection had a similar number of detectable atherosclerotic plaques as the uninfected patients and a similar number of arteries with detectable plaques. The prevalence of concomitant risk factors for atherosclerosis, including hypertension, diabetes, and hypercholesterolemia, was no different between *H. pylori*–infected and noninfected patients.

In a case-control study, *H. pylori* seropositivity was significantly more common in 238 patients with nonhemorrhagic stroke or transient ischemic attack (58.8%) than in a control group of the spouses of 1980 and had normal upper endoscopic results. To look for evidence of *H. pylori* infection, they reexamined gastric mucosal biopsy specimens that had been collected from all patients. They were unable to establish a link between *H. pylori* status and the nature, severity, or progression of dyspeptic symptoms. However, they noticed an unexpected significant association between *H. pylori* infection and hypertension.

Lip et al reported a significantly higher seroprevalence of *H. pylori* infection in patients with hypertension compared with healthy controls. Of 124 hypertensive patients, 85% were seropositive compared with 66% of 38 healthy controls (*P* = .007). The seroprevalence of *H. pylori* infection was not further increased in patients with malignant-phase hypertension.

Whincup et al found a nonsignificant association between *H. pylori* positivity and systolic blood pressure (SBP) in their nested case-control study in England. Mean SBP was 143.7 mm Hg in 78 men with and 138.3 mm Hg in 58 men without *H. pylori* infection (*P* = .06). Mean diastolic blood pressure (DBP) was 81.5 mm Hg in infected and 79.5 mm Hg in noninfected patients (*P* = .37).

At least 7 studies have failed to find an association between *H. pylori* infection and hypertension. A meta-analysis found a statistically significant, although quantitatively small, difference in SBP between *H. pylori*–infected and noninfected individuals (mean difference, 0.9 mm Hg; *P* < .05), but no association between *H. pylori* status and DBP.

The best evidence of an association between *H. pylori* infection
and hypertension comes from a cross-sectional study. No consistent relationship was demonstrated. Most evidence points toward no association.

**Idiopathic Arrhythmia.** In an uncontrolled study, the prevalence of *H pylori* infection among 54 patients with idiopathic arrhythmia was 42%. The rationale for this study was unclear. The prevalence was similar between those with supraventricular and ventricular arrhythmia.

There is no evidence to support an association between *H pylori* infection and idiopathic arrhythmia, and no apparent biological rationale for such an association.

**Raynaud Phenomenon.** Investigators have examined a role of *H pylori* infection in other vascular conditions, based presumably on results of early studies in CHD. In an Italian study, the prevalence of *H pylori* infection using results of $^{13}$C-UBT was 81% in 26 patients with primary Raynaud phenomenon (PRP) and 20% in 10 age- and sex-matched controls. The same group of investigators also studied the effects of treatment of *H pylori* infection on the symptoms of PRP. Of 46 patients with PRP, 36 (78%) were infected with *H pylori* as judged using results of $^{13}$C-UBT. There was no difference in the frequency or severity of attacks of PRP between infected and noninfected patients. The infected patients were treated for *H pylori* infection, and successful eradication was achieved in 30 of 36. Up to 12 weeks after stopping treatment, 5 had complete resolution of the symptom of PRP, and hypertension came from a treatment study is very weak.

**Migraine.** In an Italian study, the prevalence of *H pylori* infection assessed using results of $^{13}$C-UBT was 48% in 225 patients with primary migraine. These patients were treated for *H pylori* infection, and successful eradication was achieved in 84%. Of the patients with successful eradication, 23% had complete resolution of migraine for up to 24 weeks. Patients in whom eradication of *H pylori* infection failed did not improve. This study was not randomized, not blinded, and not appropriately controlled. The same investigators reported a higher prevalence of *H pylori* infection in patients with migraine (47% of 300) than in patients with tension headache (31% of 162; *P* < .05).

There is no obvious biological rationale for an association between *H pylori* infection and migraine. The strongest evidence of such an association is from an uncontrolled case series. Supportive evidence from a treatment study is very weak.

**Endocrine and Metabolic Disorders**

**Diabetes Mellitus.** Since diabetes mellitus may be associated with a variety of upper gastrointestinal tract complaints, investigators have sought to determine whether *H pylori* infection is linked to different forms of diabetes.

In a study from the Netherlands, Oldenburg and colleagues examined the seroprevalence of *H pylori* infection in 45 patients with type 1 diabetes, 98 with type 2 diabetes, and 159 outpatient controls. Seroprevalence was higher in some age groups of diabetic patients. However, the 3 groups were not adequately matched for age or socioeconomic status. Multiple statistical comparisons between groups increased the chance of a type 1 statistical error.

In Italy, Pocecco and colleagues studied the seroprevalence of *H pylori* infection in 69 children and adolescents with type 1 diabetes and 310 age-matched controls without evidence of diabetes or gastrointestinal tract complaints. Controls were matched for age, geographic location, and socioeconomic status. There was a significantly higher seroprevalence in the diabetic patients than the controls (*P* < .001). Among the diabetic patients, *H pylori* infection did not influence diabetic control, insulin dose, height, or weight. In a US-based study, Begue and colleagues studied the prevalence of *H pylori* infection in 69 young diabetic patients (mean age, 11.2 years). Sixty-three of the patients had type 1 diabetes and 6 had type 2. Overall, 16% had serologic evidence of *H pylori* infection that was confirmed with results of UBT. Of the patients with type 1 diabetes, insulin requirements were significantly higher in the infected than in the noninfected patients (*P* = .03). There was a significantly higher mean glycosylated hemoglobin level among infected patients with type 2 diabetes than in the noninfected patients (*P* = .04). However, only 6 patients with type 2 diabetes were included.

In Spain, Martín-de-Argila and colleagues studied the seroprevalence of *H pylori* infection in 101 diabetic patients and 100 controls. Of the patients, 80 had type 1 and 21 had type 2 diabetes. The controls were roughly matched for age. The seroprevalence of infection was not significantly different between diabetic patients and controls. However, patients younger than 24 years and with type 1 diabetes had a higher seroprevalence than age-matched controls (*P* < .05). Among patients older than 24 years and with type 1 diabetes, there was a significantly lower seroprevalence of *H pylori* infection than in age-matched controls (*P* < .05).

Ojetti and colleagues in Italy studied the effects of treating *H pylori* infection on insulin requirements in patients with type 1 diabetes. They recruited 119 patients with type 1 diabetes, 42 of whom had *H pylori* infection determined by a $^{13}$C-UBT. There was no significant difference between infected and noninfected patients regarding mean daily insulin requirements. Of the 42 infected patients, 20 had successful eradication determined by repeated $^{13}$C-UBT. Eradication of *H pylori* infection...
Helicobacter pylori infection did not influence diabetic control.

The best evidence of an association between H pylori infection and thyroid disease comes from case-control studies. There is, however, inconsistency among different studies. There is no substantial evidence that H pylori infection affects diabetic control or insulin requirements.

Thyroiditis. Although there is no obvious link between H pylori and thyroid disease, the infection was found endoscopically in 16 of 30 patients with various autoimmune thyroid disorders and in 16 of 30 control subjects with dyspepsia but without a history of thyroid disease. In a separate study, serologic testing detected H pylori infection in 34 (71%) of 48 women with thyroid disease and antibodies to thyroglobulin and in 16 (48%) of 33 women who served as age-matched controls (P<.05). In infected patients with thyroid disease, levels of antibodies to thyroglobulin were no higher than in uninfected patients. Similarly, H pylori status did not appear to influence levels of thyroid hormones.

The best evidence of an association between H pylori infection and thyroid disease comes from a case-control study. There is no obvious biological rationale for such an association. There is no evidence that H pylori infection influences thyroid function.

Acromegaly. Ten patients with acromegaly who had received octreotide acetate treatment for longer than 2 years complained of a variety of gastrointestinal tract problems. Upper endoscopy was performed in 9 patients, which showed evidence of H pylori infection in 8.

There was histological evidence of gastritis and H pylori infection in 10 of 33 untreated patients with acromegaly. Of patients treated for acromegaly with octreotide, 17 of 36 had evidence of H pylori infection. Of 21 patients studied before and during octreotide therapy, H pylori–related gastritis appeared to have developed in 3.

Helicobacter pylori infection was probably a chance finding in these acromegalic patients. There is no credible evidence of an association between H pylori infection and acromegaly.

Dermatological Disorders

Rosacea. In the past, rosacea may have been erroneously linked to gastritis. However, based on a study published in 1967, gastritis was found in 11 of 18 patients with rosacea compared with 9 of 16 controls, suggesting no such association. An Italian group considered that rosacea and peptic ulcer disease showed seasonal variation, and that rosacea may be ameliorated by some of the antibiotics commonly used to treat H pylori infection, such as metronidazole and tetracycline. In an uncontrolled study, they determined that 85% of 31 patients with rosacea had some evidence of H pylori infection. The investigators then treated 5 patients with rosacea with metronidazole and observed them serologically, reporting a reduction in anti–H pylori IgG levels.

Some dermatologists have greeted the observations of Rebora and colleagues with enthusiasm. Anecdotal case reports suggest improvement in rosacea after systemic antibiotic treatment for H pylori infection. An uncontrolled study from Ireland reported a 95% seroprevalence of H pylori infection in a small group of patients with rosacea. However, 2 controlled studies do not support any association between H pylori infection and rosacea. In the first of these, the seroprevalence of H pylori infection in 94 patients with rosacea was 49%, compared with 53% in a control group of 32 patients with dermatitis. In the second, 27% of 45 patients with rosacea were seropositive for H pylori infection compared with 35% of age-comparable healthy subjects without chronic skin disease.

The proposed biological rationale for an association between H pylori infection and rosacea is weak and probably based on erroneous assumptions. The only evidence of any association is from uncontrolled case series. Studies are inconsistent. Controlled studies of seroprevalence show no association.

Psoriasis. A number of bacterial and fungal pathogens have been proposed as causal for psoriasis. Helicobacter pylori is among the list of putative bacterial agents because of anecdotal case reports of improvement in psoriasis following treatment for this infection. Schneider et al found a seroprevalence of H pylori infection of 46.9% in 32 patients with psoriasis, compared with 53.1% of 32 patients with chronic dermatitis and 35.7% of 14 patients with other forms of skin disease.

In an uncontrolled study of 33 patients with psoriasis and without any history of chronic gastrointestinal tract complaints, the seroprevalence of H pylori infection was 27%. Three patients were treated for H pylori infection without apparent improvement in their psoriasis.

There is no evidence of an association between H pylori infection and psoriasis, and no obvious biological rationale for any association.

Chronic Urticaria. Circulating immune complexes may trigger urticaria. Investigators have considered that H pylori infection might be a source of such complexes. An uncontrolled study of 10 patients with urticaria in Germany found histological evidence of H pylori infection in 8. The authors reported improvement in features of cutaneous urticaria within days of starting treatment for H pylori infection. However, a study of 104 patients was unable to identify an association between H pylori infection and any 1 of 7 varieties of chronic urticaria.

Tebbe and colleagues identified 25 patients with chronic urticaria. They assessed H pylori status by 13C-UBT and serological testing. Of the 25, they found H pylori infection in 17, each of whom was then treated for the infection. Results of repeated 13C-UBT verified eradication of infection in 14. Each of these 14 reported remission (>75% improvement) or partial remission (50%-75% improvement) in symptoms of urticaria for up to 10 weeks.
after treatment. There was no improvement in the 3 patients with failed eradication or in the uninfected patients who did not receive treatment for *H pylori* infection. This study was not randomized or blinded, and it is unclear if the patients were informed of their *H pylori* status or of the success or failure of eradication treatment.

Among 85 patients with chronic urticaria in Austria, 26 were seropositive for *H pylori* infection on results of endoscopy and biopsy.\textsuperscript{115} These patients were then randomized into 1 of 2 groups. Patients received standard treatment, along with ranitidine, for chronic urticaria and placebo or a combination of amoxicillin and metronidazole for *H pylori* infection. Chronic urticaria was unaffected by this relatively ineffective antimicrobial regimen for *H pylori* infection.

In a study from Italy, 22 of 32 consecutive patients with chronic urticaria were infected with *H pylori* as determined by serologic examination and \textsuperscript{13}C-UBT.\textsuperscript{116} The infected patients were randomized to treatment for *H pylori* infection or to no treatment. It is unclear if randomization was blinded or if concealed allocation was used. Despite successful eradication of *H pylori* infection in 10 of the 11 treated patients, their chronic urticaria was not improved. There was no significant difference among the untreated control patients.

In a separate study from Italy, *H pylori* infection was present in 23 of 42 patients with chronic urticaria.\textsuperscript{117} Eighteen patients completed treatment for *H pylori* infection, of whom 16 had successful eradication. Of these, 13 showed an apparent complete resolution of symptoms of chronic urticaria for up to 3 months after treatment. No such improvement was seen in untreated patients. This study was unblinded and not randomized.

There is no obvious biological rationale for an association between *H pylori* infection and urticaria. The best evidence of any association comes from uncontrolled case series. Supportive evidence from studies of treating *H pylori* infection in patients with urticaria is weak.

### Schönlein-Henoch Purpura

Schönlein-Henoch purpura associated with *H pylori* infection has been described in a 21-year-old woman. The condition regressed after initial, unsuccessful treatment for *H pylori* infection but later recurred. After a second course of the same treatment for the infection, the disease again went into clinical remission.\textsuperscript{118}

The only evidence of an association between *H pylori* infection and Schönlein-Henoch purpura is from a single case report with incomplete follow-up.

### Other Dermatological Disorders

In a group of 68 consecutive patients with alopecia areata, the seroprevalence of *H pylori* infection was higher than in age-matched controls.\textsuperscript{119} There are isolated case reports linking *H pylori* infection to atopic dermatitis\textsuperscript{118} and Sweet syndrome.\textsuperscript{110}

The best evidence of an association between *H pylori* infection and alopecia areata is from a case-control study. Evidence of other dermatological conditions is based on individual case reports. A biological rationale for such associations is lacking.

### Rheumatological Disorders

**Rheumatoid Arthritis.** Seventeen of 54 patients with rheumatoid arthritis (RA) had cultures from gastric biopsy specimens that yielded *H pylori*.\textsuperscript{120} Eight of these patients were treated for *H pylori* infection and observed for 18 weeks. Their serum concentrations of anti-*H pylori* IgG fell significantly, but there was no discernible effect of treatment for *H pylori* infection on the course of their RA. The mean titer of anti-*H pylori* antibodies was not different between 14 patients with RA and 24 age-matched controls with chronic pulmonary disease.\textsuperscript{121}

There is no evidence of a causal association between *H pylori* infection and RA, and no biological rationale for any such association.

### Scleroderma

In an uncontrolled study, 5 of 12 patients with scleroderma had evidence of *H pylori* infection on \textsuperscript{13}C-UBT.\textsuperscript{122} Scleroderma did not improve after treatment for *H pylori* infection. The mean titer of anti-*H pylori* antibodies was not different between 11 patients with scleroderma and 24 age-matched controls with chronic pulmonary disease.\textsuperscript{121}

There is no evidence of and no obvious biological rationale for an association between *H pylori* infection and scleroderma.

### Sjögren Syndrome

In the Japanese study already referred to,\textsuperscript{121} the mean titer of anti-*H pylori* antibodies was significantly higher (P<.05) in 7 patients with Sjögren syndrome than in 24 age-matched controls with chronic pulmonary disease.

In an Italian study, *H pylori* infection was present in 71% of 21 patients with primary Sjögren syndrome and 63% of 80 controls with dyspepsia.\textsuperscript{123} In Finland, Collin and colleagues\textsuperscript{124} studied 32 consecutive patients with primary Sjögren syndrome and 64 age- and sex-matched controls using endoscopy. Although atrophic gastritis of the antrum was found more frequently in the patients with Sjögren syndrome (25% vs 4%; P=.01), there was no significant difference in the prevalence of *H pylori* infection (31% vs 39%; P>.05).

There is no evidence of and no obvious biological rationale for an association between *H pylori* infection and Sjögren syndrome.

### Hematological Disorders

**Iron Deficiency Anemia.** Certain bacteria, including *H pylori*, are able to acquire iron from their host.\textsuperscript{125} The elucidation of the genome of *H pylori* identified a number of genes that encode for iron-scavenging functions.\textsuperscript{126} By this mechanism, *H pylori* infection might lead to anemia from iron deficiency without blood loss. *Helicobacter pylori* infection acquired early in life might also lead to iron deficiency in adulthood by producing chronic atrophic gastritis, which impairs the absorption of dietary iron.

Isolated case reports have suggested an association between *H pylori* infection and iron deficiency anemia in children and young adults.\textsuperscript{128-132} In at least 2 of these
iron deficiency anemia was not accompanied by detectable gastrointestinal tract blood loss. In all cases, anemia resolved with successful eradication of *H pylori* infection.

A cross-sectional study of 103 children in Bangladesh aged 6 months to 2 years found a significantly lower (P = .04) mean hemoglobin level in infected than in noninfected children. The anemia was presumed to have been due to iron deficiency.

If the association between iron deficiency anemia and *H pylori* infection is true, it may be confined to children. In a study of more than 2000 adults in Denmark, *H pylori* serologic status did not affect a number of red blood cell indices. The best evidence of an association between *H pylori* infection and iron deficiency anemia comes from a population-based cross-sectional study in children. There is a plausible biological rationale for such an association. Alternatively, *H pylori* infection might simply be a surrogate marker for poverty and malnutrition in childhood.

Autoimmune Thrombocytopenic Purpura. Among 15 patients with autoimmune thrombocytopenic purpura and in whom other causes of thrombocytopenia had been excluded, the prevalence of *H pylori* infection assessed by the 13C-UBT was 67%. The 10 patients with *H pylori* infection were treated for it, and 7 had successful eradication. In these patients, platelet counts increased from a mean of 90 200/mm³ to a mean of 148 800/mm³ (P < .05). Antiplatelet antibodies became undetectable 6 weeks after treatment in 7 patients. In infected patients who were treated for *H pylori* infection but in whom eradication was unsuccessful, there was no change in platelet count or in the levels of antiplatelet antibodies.

The evidence of an association between *H pylori* infection and autoimmune thrombocytopenic purpura is from an uncontrolled case series. Objective evidence from an uncontrolled study of an increase in platelet count following treatment of *H pylori* infection in autoimmune thrombocytopenic purpura should be confirmed prospectively in a randomized controlled trial.

**Hyperammonemia.** Plasma ammonia levels are generally increased in patients with hepatic encephalopathy, although this does not fully explain its clinical manifestations. Hyperammonemia in patients with hepatic encephalopathy is thought to be derived predominantly from bacterial activity in the colon. *Helicobacter pylori* has potent urease activity that may be a source of ammonia in circulating blood. Some investigators have studied the influence of *H pylori* infection on plasma ammonia levels and the risk for hepatic encephalopathy in patients with liver disease.

In a prospective, multicenter, Veterans Affairs–based study, Gubbins and colleagues studied 188 patients with moderate or severe alcoholic hepatitis. Of these, 117 had hepatic encephalopathy. There was a higher seroprevalence of *H pylori* infection in these patients with than in those without encephalopathy (79% vs 62%; P = .01). Using stepwise linear regression, *H pylori* infection was identified as an independent risk factor for hepatic encephalopathy.

Ito and colleagues described 2 patients with recurrent hepatic encephalopathy due to cirrhosis from chronic hepatitis C virus infection. Both had evidence of *H pylori* infection. After successful eradication of infection, plasma ammonia levels were reduced, and hepatic encephalopathy did not recur for at least 5 months. Both patients were subsequently observed for more than 2 years, plasma ammonia levels stayed below those seen before treatment for *H pylori* infection.

In an experimental study in 20 patients with cirrhosis, Plevriss and colleagues determined *H pylori* status by 14C-UBT and administered urea by mouth. Plasma ammonia levels rose in all patients irrespective of *H pylori* status, and there was no difference between the *H pylori*–infected and noninfected patients.

Kirchner and colleagues from Germany studied plasma ammonia levels and the *H pylori* status of 132 patients with cirrhosis, 38 patients with chronic viral hepatitis but without cirrhosis, and 39 age-matched controls. The controls had cardiovascular or cerebrovascular disease but no gastrointestinal tract complaints or evidence of liver disease. Patients with cirrhosis had higher se-ropositivity for *H pylori* infection (81%) than those with chronic viral hepatitis (62%) or controls (54%). However, there was no association between plasma ammonia levels and *H pylori* status.

Miyagi and colleagues in Japan studied 18 patients with cirrhosis and persistent hyperammonemia despite treatment with low-protein diet, kanamycin sulfate, lactulose, and branched-chain amino acids. They divided these 18 patients into 3 groups of 6 patients according to *H pylori* status as assessed endoscopically. One group had diffuse gastric involvement with *H pylori*, the second had more patchy involvement, and the third had no *H pylori* infection. Patients in all 3 groups received treatment for *H pylori* infection. The mean plasma ammonia level was initially reduced in all patients following the standard treatment for hepatic encephalopathy. However, there was a further reduction in plasma ammonia level in the 6 patients with diffuse gastric involvement and *H pylori* infection following eradication treatment. There was no further reduction in plasma ammonia levels in the other groups after similar treatment. In the patients who had diffuse gastric involvement with *H pylori* infection, plasma ammonia levels remained low for up to 12 weeks after eradication treatment.

Llach and colleagues from Spain found no difference in plasma ammonia concentration or in hepatic encephalopathy scores between 32 *H pylori*–infected and 30 noninfected patients with cirrhosis. Furthermore, treatment of *H pylori* infection did not produce any significant change in plasma ammonia concentrations or encephalopathy scores.

Cho and colleagues in South Korea studied levels of ammonia in plasma and gastric juice in 31 patients with cirrhosis and 34 controls. They determined *H pylori* sta-
tus in all patients by serologic examination and endoscopic biopsy. Little information was provided on the control group, but they were not particularly well matched for age. Plasma ammonia levels were higher in the cirrhotic patients than the controls. Levels of ammonia in gastric juice were higher in *H pylori*–infected than in noninfected patients in both groups. *Helicobacter pylori* infection did not affect plasma ammonia concentrations in the patients with cirrhosis.

Among 55 patients with cirrhosis, 37 had clinical or neurophysiologically evident of chronic hepatic encephalopathy. The prevalence of *H pylori* infection determined by gastric mucosal biopsy and rapid urease testing was 67% in the encephalopathic group and 33% in the nonencephalopathic group (*P* = .002). Levels of ammonia in gastric juice were higher in the encephalopathic than in the nonencephalopathic patients (*P* = .05). Plasma ammonia levels were not reported. Seventeen encephalopathic patients, including 13 with and 4 without *H pylori* infection, had treatment with a relatively ineffective regimen for *H pylori* infection. Results of testing for encephalopathy improved in each of the *H pylori*–infected patients. The test results did not change appreciably in the 4 uninfected patients. Eradication of infection was not confirmed.

In an experimental study, Zullo and colleagues from Italy examined the effects of acetohydroxamic acid on plasma ammonia levels in 16 cirrhotic patients. Acetohydroxamic acid is a direct inhibitor of bacterial urease. Eight patients had *H pylori* infection determined by histological examination and a rapid urease test. Plasma ammonia levels did not change after acetohydroxamic acid administration in the 8 patients without *H pylori* infection. However, plasma ammonia concentration at 15 to 30 minutes after acetohydroxamic acid administration fell by a mean of 27% in the 8 patients with *H pylori* infection.

Patients with chronic renal insufficiency have high levels of urea in their gastric lumen. Those with *H pylori* infection might, therefore, have elevated plasma ammonia levels. However, comparison of 9 *H pylori*–infected and 7 noninfected uremic patients found similar plasma and intragastric concentrations of both urea and ammonia.

Observational studies suggest a relationship between *H pylori* infection and raised plasma ammonia levels in patients with chronic liver disease. However, there is inconsistency among different studies. There is a plausible biological rationale for the association (Table 1). Experimental studies investigating the possible association have been inconsistent.

### Miscellaneous Disorders

**Sudden Infant Death Syndrome.** There are some similarities between the epidemiological features of sudden infant death syndrome (SIDS) and those of *H pylori* infection. Both are more common in families of lower socioeconomic status and from nonwhite ethnic groups. Furthermore, the incidence of both appears to be decreasing in parallel. Possible links between *H pylori* infection and SIDS include raised systemic levels of cytokines such as interleukin 1 that may promote fever, immune activation, and deep sleep. Alternatively, *H pylori* might be aspirated from the stomach into the airways, where the generation of ammonia through the action of *H pylori* urease might promote respiratory arrest.

*Helicobacter pylori* was reported at autopsy in the gastric antrum and trachea in 7 infants who died of SIDS. However, the same investigators were subsequently unable to confirm this observation when examining autopsy material from 22 consecutive infants with a postmortem diagnosis of SIDS using histological or polymerase chain reaction testing. In a separate study, polymerase chain reaction testing on antral biopsy specimens from 11 infants who died of SIDS identified *H pylori* in 8 of 9 specimens when it was apparent historically, and in 1 of 2 when it was not. Primary tracheal colonization by *H pylori* without gastric antral involvement has been reported in 3 of 12 infants with SIDS, suggesting possible transmission of *H pylori* by the respiratory route. *Helicobacter pylori* may have been isolated from tracheal secretions of adults in an intensive care unit.

In autopsies of 37 infants with SIDS in 2 metropolitan areas in the United States, there was evidence of gastric antral *H pylori* infection in 20 (54%). Organisms compatible with *H pylori* were identified in tracheal specimens in 22 (59%).

The best evidence of an association between *H pylori* infection and SIDS comes from uncontrolled case series. The temporal relationship for an association is correct, and there is a plausible biological rationale (Table 1). There is unconfirmed evidence of colonization of the upper airways of infants with SIDS by bacterial organisms that may be *H pylori*.

**Growth Retardation in Childhood.** Patel and colleagues studied 554 1-year-old children in Scotland. Of these, 62 had evidence of *H pylori* infection since 7 years of age. On average, these children had grown 1.1 cm less than noninfected children from the ages of 7 through 11 years. Girls had grown 1.6 cm less than their noninfected peers had.

Raymond et al compared 77 French children infected with *H pylori* and 74 age-matched children without the infection. Compared with 23% of the controls, 27% of the infected group were of short stature. Of the children with short stature, there was no evidence of hypoproteinemia or malabsorption.

In a cross-sectional study from southern Italy, 49 of 216 children aged 3 through 14 years were infected with *H pylori* as determined by the $^{13}$C-UBT. Of the 49 infected children, 8 were below the 25th percentile for height, compared with 13 of 167 uninfected children. In the subgroup of children aged 8.5 through 14 years, 8 of 31 infected children were below the 25th percentile for height compared with 8 of 96 uninfected children (*P* = .02).

Oderda and colleagues in Italy found serologic evidence of *H pylori* infection in 20% of 134 con-
sective children with short stature and in 13% of matched controls (P = .19). The authors concluded that *H pylori* infection was not an independent risk factor for short stature in childhood but that low socioeconomic status was of more importance.

In a population-based survey of more than 4700 people in Northern Ireland, the mean height of women older than 25 years who were infected with *H pylori* was 1.6 cm lower than in uninfected women (P < .01 after adjustment for age and socioeconomic status). Among 1756 Danish women in a random sample, those in the upper quartile for height were significantly less likely to be infected with *H pylori* than those in the lower quartile. The likelihood of *H pylori* infection was also related to late menarche, leading the investigators to speculate that an impaired pubertal growth spurt may have explained the finding. The Eurogast Study Group conducted a cross-sectional survey of the seroprevalence of *H pylori* infection in more than 3000 subjects in 2 age groups in various countries. In subjects aged 55 through 64 years, infection with *H pylori* tended to be associated with a low body mass index and short stature. However, this was not statistically significant after adjustment for other variables.

The best evidence of an association between *H pylori* infection and growth retardation in childhood comes from a cohort study. The temporal relationship for any association is correct (Table 1). There is some inconsistency between different studies. *Helicobacter pylori* infection might be a marker for low socioeconomic status and relative malnutrition in childhood.

**Anorexia of Aging.** One report described 3 institutionalized, elderly patients with a variety of medical complaints that included anorexia. Each patient had evidence of *H pylori* infection. Treatment for the infection resulted in improvement in anorexia. Treatment regimens were suboptimal, and eradication of infection was not confirmed. *Helicobacter pylori* infection was not proven as the cause of the anorexia in any of the 3 patients.

There is no evidence of an association between *H pylori* infection and the anorexia of aging.

**COMMENT**

Numerous different conditions have been linked preliminarily to *H pylori* infection. However, many of these associations are based on uncontrolled or inappropriately controlled observations. A biological rationale for an association with *H pylori* infection is often lacking.

Further research on the role of *H pylori* as a possible causal or contributory factor may be warranted for some conditions. Examples might include autoimmune thrombocytopenic purpura and SIDS. However, any such research should be conducted in a responsible, planned, and cautious manner.

Unfortunately, weak evidence of causation by *H pylori* infection in some conditions has already led to poor-quality studies of the effects of treatment for the infection. Sackett has proposed a 5-level system of grading evidence from treatment trials to help determine whether a treatment should be recommended. The highest level of evidence comes from large randomized controlled trials and carries a strong recommendation for adoption of the treatment into routine practice. Studies on the treatment of *H pylori* infection in the conditions reviewed herein have been nonrandomized, unblinded, and uncontrolled or inappropriately controlled. Therefore, these studies present evidence that is, at best, weak. Furthermore, treatment regimens have often been ineffective, and eradication of infection has not been confirmed.

Rather than treating *H pylori* infection in all infected patients identified with a specific diagnosis, it would be of more value to randomize infected patients to receive active or placebo treatment in a double-blinded manner. Only then could investigators adequately assess any effects of treating *H pylori* infection on the underlying condition. Conceivably, antimicrobial therapy might improve 1 of the conditions in question through a mechanism unrelated to eradication of *H pylori* infection. For example, apparent improvement in patients with hepatic encephalopathy after antimicrobial treatment of *H pylori* infection could have been explained by a reduction in levels of colonic bacteria. Therefore, there may be a case for antibiotic treatment, as if for *H pylori* infection, in uninfected patients to eliminate any unrelated, beneficial effect of antimicrobial therapy.

Although *H pylori* infection has been linked to a wide variety of non–gastrointestinal tract conditions, the level of supporting evidence is low (Table 1). Conversely, ample evidence links *H pylori* infection to various conditions of the upper gastrointestinal tract (Table 2). Limited experiments in humans have established a specific and direct relationship with gastritis, with consistent temporality. Although there are no direct experimental data in humans that link *H pylori* infection with peptic ulcer disease, there is a mass of highly consistent and strong circumstantial evidence.

Nested case-control studies and a meta-analysis have established a strong and temporally correct relationship between *H pylori* infection and gastric adenocarcinoma. There is also a strong biological rationale for this association. Similarly, there is a strong, temporally correct association between *H pylori* infection and low-grade gastric lymphoma arising from mucosa-associated lymphoid tissue. However, even in these conditions of the upper gastrointestinal tract, about which there is broad agreement regarding causation by *H pylori*, it is not possible to answer affirmatively all 9 of the questions proposed by Sackett (Table 2).

Demonstration of *H pylori* infection would be unhelpful at present in an individual patient with any of the non–gastrointestinal tract conditions proposed to be associated with it. Since the infection is highly prevalent, it will be found by chance in many patients who seek medical attention for another condition. Demonstrating the infection in a patient with another disorder does not
Table 2. Application of 9 Diagnostic Tests for Causes of Upper Gastrointestinal Tract Conditions Generally Accepted to Be Related to Helicobacter pylori Infection

<table>
<thead>
<tr>
<th>Tests</th>
<th>Gastritis</th>
<th>Peptic Ulcer</th>
<th>Gastric Cancer</th>
<th>Gastric MALT Lymphoma</th>
</tr>
</thead>
<tbody>
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<td>Is there evidence from true experiments in humans?</td>
<td>Yes</td>
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<td>No</td>
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</tr>
<tr>
<td>Is the association strong?</td>
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<td>Is the association consistent from study to study?</td>
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<td>Yes</td>
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<tr>
<td>Is the temporal relationship correct?</td>
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<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Does the association make epidemiological sense?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Does the association make biological sense?</td>
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<tr>
<td>Is the association specific?</td>
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<tr>
<td>Is the association analogous to a previously proven causal association?</td>
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<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* MALT indicates mucosa-associated lymphoid tissue; question mark, absence of sufficient evidence for answer.

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