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REVIEW ARTICLE

Helicobacter pylori and Duodenal Ulcer
Evidence Suggesting Causation

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After the concept of the specificity of infectious diseases was established in the 19th century, Koch's postulates were the reference points used to link an agent and a disease. These postulates state that the agent (1) must be found in patients with the disease only, (2) must be grown outside of the body, (3) when inoculated into a susceptible animal, must cause the same disease, and (4) must be grown from the lesions observed (1). However, Koch himself did not consider these postulates to be rigid criteria. Such was the case for cholera, as there were asymptomatic carriers of this disease. During the 20th century, the discovery of new pathogenic microorganisms, especially viruses, a better knowledge of the immune mechanisms, and the concept of chronic infection have led to the reassessment of Koch's postulates (2).

It is obvious that many recently discovered agents that are considered to be pathogenic do not fit Koch's criteria. Nowadays, the concept of causality encompasses not only infectious diseases but also other diseases, and epidemiology has been the key science in this respect. It has been accepted that six criteria must be considered to define causality. These criteria proposed by Hill in 1965 (3) were used to prove the causal association between cigarette smoking and lung cancer: characteristics of the association (strength, consistency, and specificity), temporal relationship, biological gradient, biological plausibility, effect of an intervention, and coherence of all these data with what is known about the disease. However, none of these criteria is indisputable evidence alone and none can be required as *sine qua non*.

Helicobacter pylori is a newly found bacterium. Its role as an etiological factor of antral gastritis is now well established. An increasing amount of data is now serving to implicate this microorganism in duodenal ulcer disease.

Duodenal ulcer in relation to the bacterium, *Helicobacter pylori*, can be analyzed in the same way as lung cancer in relation to smoking: is there an association or causation?

1. The first characteristic to be considered is the strength of the association. *H. pylori* is found in 90% or more of the cases of duodenal ulcer, and this association is consistent. It has been found in all the studies performed on all the continents. This shows that despite the variety of protocols and techniques used, the same result is found (4–8). On the other hand, in a population known to lack duodenal ulcer (9), *H. pylori* has never been recovered (10). These data refer to some Aborigine tribes in northern Australia that are isolated and have no contact with other people.

Nevertheless, a small number of *H. pylori*-negative duodenal ulcer cases (less than 10%) occurs. They could be due to nonsteroidal antiinflammatory drug consumption or to the Zollinger-Ellison-like syndrome, while some of them could be true *H. pylori*-positive duodenal ulcers but with a false negative diagnosis. Our hypothesis does not apply to these particular cases.

However, the association of *H. pylori* with duodenal ulcer is not specific. *H. pylori* can also be found in subjects with gastric ulcer, nonulcer dyspepsia, and even in asymptomatic subjects (11). This lack of specificity has always been highlighted by the opponents of the infectious theory of duodenal ulcer. How can we explain that so many infected people will never develop an ulcer if *H. pylori* is the cause of duodenal ulcer? This kind of

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situation is, in fact, not uncommon in the field of infectious disease. For example, if we look at what happens during a meningococcal epidemic, most subjects are asymptomatic carriers of the bacteria in their throat, some of them will develop pharyngitis, and only a very small number of the latter group will suffer from meningitis. They all have some degree of pharyngeal inflammation due to *N. meningitidis*. Because of genetic (eg, complement deficiency) and/or environmental factors (eg, irritation by desert winds in the Sahel), some persons will contract meningitis. Meningococcal inflammation in the pharynx is a condition that is necessary but not sufficient. We can postulate that this is also the case with *H. pylori* gastritis in relation to duodenal ulcer with the major difference being that it is a chronic disease evolving over several years. This condition is necessary but not sufficient for the ulcer to develop.

2. The scarce information concerning the temporal relationship between duodenal ulcer and *H. pylori* infection shows that the bacterium is not a contaminant of a preexisting lesion. Sipponen et al gathered data concerning 454 patients endoscoped 10 years earlier. They showed that *H. pylori* gastritis was a major risk factor for duodenal ulcer: among 321 patients with *H. pylori* gastritis at inclusion, 34 developed a duodenal ulcer during the study period versus one out of 133 *H. pylori*-negative patients (12). *H. pylori* happened to be the predecessor of the lesions.

3. The existence of a biological gradient is a good argument for causation. In fact, this aspect has not been extensively studied in the case of the association described. Such a study is difficult to perform on a biopsy specimen because of the patchy distribution of the bacteria. However, a study found a statistically significant higher density of bacteria per square millimeter of antral mucosa in patients with ulcers than in patients without ulcers (13). A global test can preferably be used. Only one study dealt with this problem by comparing the ammonia produced in the gastric juice of patients with duodenal ulcer with the ammonia production of nonulcer dyspepsia patients receiving urea. A statistically significant difference was observed in favor of the duodenal ulcer patients (14), indicating a higher bacterial load on the mucosa of these patients. However, this information was a preliminary report and has not been substantiated by the use of other tests, such as the urea breath test. Using this last test one can theoretically determine the bacterial load in the stomach through the quantity of urease produced. No difference between asymptomatic volunteers and patients with duodenal ulcer disease was found.

4. At the beginning of the *H. pylori* story it was difficult to conceive that a bacterium that infects the stomach antrum could be the cause of an ulcer in the duodenum. An explanation has been found for this incongruity. *H. pylori* has specific binding sites on antral cells (15) and can follow these target cells into areas of gastric metaplasia in the duodenum, generating antral gastritis and duodenitis (16). In fact, gastric metaplasia is also a condition *sine qua non* for duodenal ulcer occurrence. By an unknown mechanism, an unexpected production of serum gastrin is observed after stimulation (17). This would contribute to an increased parietal cell mass and then to a high acid load in the duodenum (18), which is a potential cause of metaplasia. *H. pylori* has potential pathogenic effects that have been demonstrated *in vitro* and could have an impact on the mucous cells: direct action by a cytotoxin (19) and indirect action by hydrolysis of urea-generating cytotoxic ammonia (20, 21). The *in vivo* relevance of these factors is still debatable. *H. pylori* also induces mediators of inflammation (22), which could explain the lesions observed.

5. A strong argument for causation is the effect of interventions. The first attempts to eradicate *H. pylori* were unsuccessful. Progress has been made in this respect. A triple antimicrobial therapy is now well established and was recently recommended by a panel of experts to treat a subgroup of duodenal ulcer patients (23). Rauws and Tytgat (24) and Borody et al (25) applied this therapy to their patients. No duodenal ulcer relapses occurred in patients in whom *H. pylori* was eradicated. This result must be compared to the 60–80% ulcer relapse usually encountered during the year following the first duodenal ulcer crisis treated with anti-H_2. We also performed a similar study with only one duodenal ulcer relapse among 26 patients in whom *H. pylori* was eradicated. *H. pylori* was present again in this patient because of either a relapse or a reinfection.

6. What is the coherence of this theory with what is presently known about duodenal ulcer disease, especially in terms of epidemiological characteristics? The first apparent disagreement is that the prevalence of *H. pylori* is the same in both sexes (11), while classical data on the prevalence of duodenal ulcer disease point to a higher rate in men.

In fact, this last dogma should be reassessed. Kurata recently presented data concerning duodenal ulcer disease deaths in the United States from 1920 to 1985 and showed that, in fact, the death rate has become the same for males and females since 1979. The same was also found for the prevalence rate of ulcer disease in a National Health Interview Survey 1957–1985. Moreover, there is a parallel between the smoking rate in each sex and the duodenal ulcer death rate curve (26). Since men and women have the same rate of *H. pylori* infection in each age group, we can hypothesize that if men and women have the same smoking rate, they will have the same rate of duodenal ulcer, but this remains to be proven. Recent data have indeed shown that smoking could increase the risk of developing an ulcer in subjects with *H. pylori* (27), and it is no longer a risk factor for duodenal ulcer in *H. pylori*-eradicated patients (28).

We do not know what the rate of *H. pylori* infection was in the 19th century. However, it is suspected to have been very high by comparing the living conditions then to those observed today in developing countries (70–90% positivity). The level of hygiene is a good indicator for *H. pylori* infection as it is for any infectious agent. Data concerning ulcer disease show that this disease peaked at the end of the last century. A possible explanation could be that the improvement in hygiene and sanitation that began during the industrialization period would have, as a primary consequence, delayed the age of acquiring *H. pylori* infection. For instance, paralytic poliomyelitis occurred in the 1860s and has been considered to be the result of such a change in hygiene and socioeconomic status, which delays the age of acquiring the infection and leads to a more severe affliction.

Graham has postulated that the same trend could be true for peptic ulcer. When *H. pylori* infection is acquired in infancy, it would eventually lead to gastric carcinoma whereas an infection later in life would be a factor for peptic ulcer (29).

We can postulate that the prevalence rate of *H. pylori* infection has decreased progressively to 40–50% and even more after the introduction of antimicrobial agents in the 1950s. Antibiotics used in monotherapy cannot eradicate the bacteria but can reduce their load and, consequently, the risk of contamination. The global prevalence of duodenal ulcer, estimated by the number of admissions with nonperforated ulcer, has fallen since the middle of this century (30). In fact, a careful analysis performed by Susser shows that the death rate of duodenal ulcer patients was indeed the highest in the generation born around 1890. Moreover, the recession of the flow of duodenal ulcers seems to have begun in young men in the higher social classes (31). This cohort phenomenon is consistent with the hypothesis of the role of *H. pylori* infection in the disease.

In summary, the association between *H. pylori* infection and duodenal ulcer is strong and consistent. The temporal relationship and biological plausibility exist, and eradication has a very positive effect. A coherence with what is known about the evolution of the disease concerning the sex and temporal distribution is present. However, as in most infectious diseases, the infectious agents alone are not sufficient in provoking the disease. Environmental factors (eg, smoking) and probably genetic factors are also important.

It has been recognized for many years that duodenal ulcer is the consequence of an imbalance between the protective and aggressive factors of the mucosa. The hypothesis presented is not contradictory. *H. pylori*-infected mucosa is weakened and allows the main aggressive factor in the stomach, acid, to exert its detrimental effect. The concept of "no acid, no ulcer" is still valid but should be counterbalanced by "no *H. pylori*, no ulcer."

This theory has therapeutic implications since it is now possible to stop the natural history of the disease by administering antimicrobial agents as was illustrated by Goodwin in the "leaking roof" concept (32). It is better to repair your roof (ie, the mucosa) than to stop the rain (ie, the acid production).

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