Campylobacter pylori: Addressing the Controversies

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Campylobacter pylori (CP) colonization of the gastroduodenal mucosa is associated with peptic ulcer disease, particularly with duodenal ulcer. The bacterium appears to induce cytopathic changes in epithelial cells lining the stomach, is actively phagocytosed by polymorphonuclear leukocytes, and probably causes the histologic changes of active chronic gastritis. Wheras acid hypersecretion affects only a small proportion of ulcer patients, this type of gastritis affects 95% of duodenal ulcer patients and about 70% of persons with gastric ulcer. This association suggests that the current emphasis on acid reducing therapy for ulcer disease may be replaced by therapy directed at the repair of the mucosal defect present in ulcer patients.

Before *C. pylori* is universally accepted as a serious pathogen, the controversies surrounding gastric colonization by the bacterium need to be addressed. While there is much histological data to indicate a pathogenic role for *C. pylori,* the epidemiology of type B gastritis suggests that the bacterium is a harmless commensal, or at worst, a saprophyte which colonizes damaged gastric mucosa.

The Epidemiology of Type B Gastritis

The epidemiology of Type B gastritis was defined by Scandinavian studies in the 1960s (Kekki et al. 1977), before direct-vision biopsy of the antrum was made possible by the modern fiberoptic gastroduodenoscope. As a result, knowledge of gastritis was based on the examination of biopsy specimens taken from the greater curve of the stomach in acid secreting type mucosa. The antrum was rarely sampled. Moreover, the investigators were more often impressed with the chronic inflammation present, i.e., lymphocytes and plasma cells. The polymorphonuclear leukocytes were less obvious to the researchers, and the epithelial cell changes we now associate with *C. pylori* (Tricottet et al. 1986) passed largely unnoticed.

It is reasonable to assume, nevertheless, that the earlier studies were referring to the same type of gastritis we now associate with *C. pylori,* as expressed in a milder form in body type mucosa. It was found that gastritis was present in about 20% of young adults, and increased with age to affect at least 50% of the population by the age of 60 (Kekki et al. 1977). From these earlier studies we

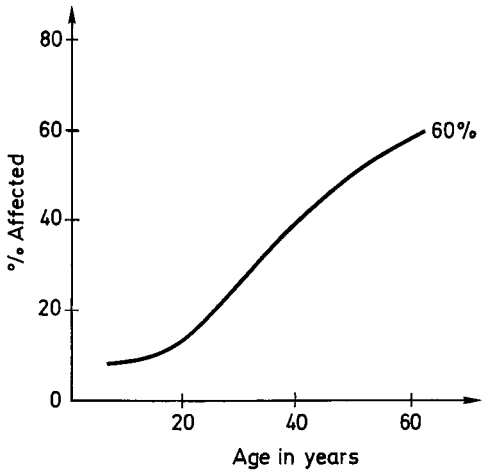

Fig. 1. Epidemiology of type B gastritis (*C. pylori* infection) (Data from Kekki et al. 1977)

can conclude that chronic gastritis is common, increases in frequency with age, and is often asymptomatic (Fig. 1).

Unfortunately, some authors interpreted these findings to mean that chronic gastritis was an inevitable asymptomatic accompaniment of aging and that its association with ulcer disease was mere coincidence. In support of this view were studies such as that of Steer and Colin Jones (1975), which showed that carbenoxolone healed gastric ulcer, while not affecting gastritis. Later it was discovered that cimetidine, a far more effective ulcer healing agent, also healed ulcers without healing the gastritis (McIntyre et al. 1982). The ulcer thus appeared to be a direct consequence of gastric acid secretion rather than of the mucosal inflammation. In addition, there were many asymptomatic persons with type B gastritis who never developed ulcer disease.

Are Type B Gastritis and *C. pylori* Infection the Same Disease?

Recently, *C. pylori* has been added to our evaluation of gastric mucosal histology as a new variable. The bacterium (and/or gastritis) is present in 10%–25% of normal subjects and most of those without *C. pylori* have histologically normal mucosa (Langenberg et al. 1984; Barthel et al. 1986). In my own experience, patients above the age of 70 have normal gastric mucosa unless this infection is present. Furthermore, when elderly persons with *C. pylori*-associated gastritis are treated, the histological changes reverse once the bacterium is eradicated. These observations suggest that chronic gastritis and *C. pylori* infection are very closely related. Type B chronic gastritis is age related only because this infection is more common in elderly persons (Fig. 2).

Epidemiology and Disease Associations of *C. pylori*

In endoscopy populations, the presence of *C. pylori* is almost always accompanied by active chronic gastritis (Hui et al. 1986; Marshall et al. 1987).

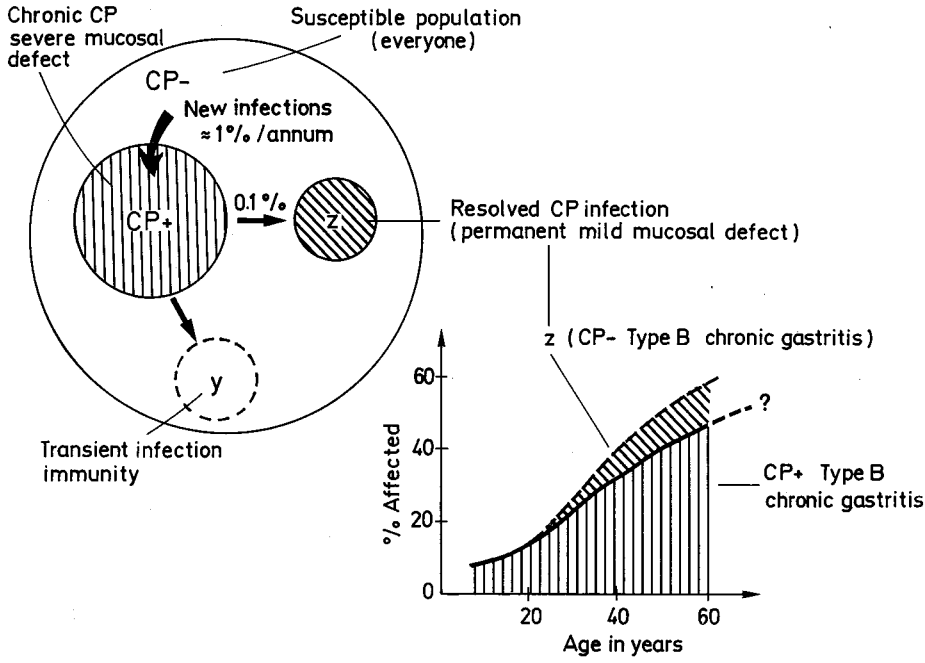

Fig. 2. Type B gastritis explained as *C. pylori* infection. With age, the chance of acquiring chronic *C. pylori* (and of having chronic gastritis) increases. About half the persons who contract the acute infection have a transient episode and may develop immunity (y), the others enter an enlarging pool of persons with chronic gastritis. A small number of persons with chronic infection lose the bacterium, of whom some do not regain a histologically normal mucosa, and remain susceptible to peptic ulcer disease (z)

Tests which detect *C. pylori* may therefore be used to determine the frequency of gastritis in the population. Serological evidence of *C. pylori* infection is present in about 20% of adult blood donors, its occurrence increasing with age. The bacterium, more common in males, is present in 10%–20% of 20 year olds, and infects 40%–50% of persons by age 60. Thus the epidemiology of CP infection corresponds to the known epidemiology of chronic gastritis. Infection appears to be less common than histological gastritis (45% at age 60 vs 55%–60% at age 60), but this could be due to the lower sensitivity of the serological methods. It seems therefore that *C. pylori* infection and type B chronic gastritis affect approximately half of the "normal" population by age 50.

Although reliable data are not available on comparable groups in third world countries, there is evidence to suggest that *C. pylori* infection is widespread there. In India, for example, gastric mucosal urease (a marker for *C. pylori*) was universally present in a series of persons without ulcer disease (Narang et al. 1980). In endoscopy series from Peru (Ramirez-Ramos et al. 1987) and Rwanda (T. Mets, personal communication), the infection was found to be far more common than in equivalent studies in western countries (70% and 93% respectively).

Various Interpretations of the Epidemiological Data

The epidemiological data we have could be explained in two ways. *C. pylori* may have a propensity to affect certain ethnic groups and persons older than 30 years. Alternatively, the infection may be acquired mainly in childhood by fecal-oral spread, in much the same way that *Campylobacter jejuni* is acquired. If the latter hypothesis is correct, then the commonness of the infection in third world countries could be explained as being a result of the poor standards of public hygiene. Similarly, the commonness of the infection in middle aged persons in western countries may be the result of a cohort effect, perhaps from a widespread source of exposure to the bacterium, prevalent 40 years ago. The Second World War caused widespread deterioration in public health standards, soldiers in particular being very common hosts for infectious enteric organisms.

Is *C. pylori* a Public Health Concern?

At this point in time, with so many apparently healthy elderly persons infected, it is difficult to accept that *C. pylori* is a significant pathogen. If aging were the cause of gastritis we would expect to see a gradual transition with age from unchanged to inflamed gastric mucosa. Instead we find only two groups; a group with normal histology and a group with gastritis.

A better appreciation of *C. pylori* as a pathogen may be obtained if we draw the analogy of a tribe of primitive natives 50% of whom have malaria. This could mean that the malaria parasite is a normal commensal, or that malaria is endemic and a major public health problem. In such a population many colonized individuals will be in a state of symbiosis with the parasite. However, the number of such individuals who develop anemia and fever will be greater than in the noninfected persons. In this case asymptomatic persons with malaria are not in an ideal state of health, because statistically, they are at risk of developing the overt disease. Similarly, persons with *C. pylori* infection are not in a state of optimal health, since they are at risk of developing peptic ulcer disease.

C. pylori as a Risk Factor

C. pylori colonization of the stomach is associated with a spectrum of disease ranging from asymptomatic gastritis to peptic ulceration. We can estimate the epidemiology of *C. pylori* associated disease by examining data from both endoscopy studies and serological studies. Serological studies indicate that 20%–25% of the total population has *C. pylori* infection (Marshall et al. 1985a; Eldridge et al. 1985). From postmortem data we know that peptic ulcer occurs in about 8% of persons during their lifetime (Boyd and Wormsley 1985), most of whom can be presumed to have the infection. From endoscopy studies we know that persons who have gastritis but not ulcer (nonulcer dyspepsia [NUD]) are as common as those who have gastritis (*C. pylori*) with ulcer.

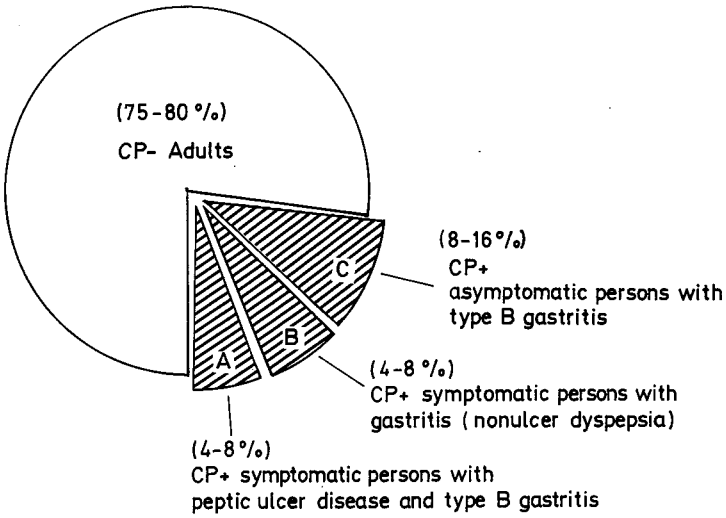

Fig. 3. Epidemiology of *C. pylori:* 20%–25% of adults have *C. pylori* infection and chronic gastritis (estimated from serological and bioptic studies of persons in the normal group). Group A: 8% of the population develops peptic ulcer disease and most of these persons have *C. pylori,* Group B: An equal number of persons (as determined by endoscopy studies of patients) have *C. pylori* but no ulcer (non ulcer dyspepsia). Group C: This leaves 8–12% of the population as persons with asymptomatic *C. pylori* associated gastritis

Combined, all these data show that 25% of adults have *C. pylori* associated gastritis, of which approximately one-third are asymptomatic, one-third have dyspepsia but no ulcer, and one- third have peptic ulcer disease (Fig. 3).

Nearly all cases of peptic ulcer disease occur in the 25% of persons with *C. pylori* infection. This infection thus confers a 20-fold risk of developing peptic ulcer. The risk is acquired with the infection, so that a person with asymptomatic infection presens a threat to noninfected contacts and may be regarded as being a carrier (Goodwin and Armstrong 1986). As the infection is commoner in older persons, grandparents are a potential source of infection.

The Definition of Normality

The presence of *C. pylori* gastritis in about half the population over the age of 60 challenges our concept of gastrointestinal normality in this group. Everyone suffers dyspeptic symptoms at some time, and most people take antacid on occasions, so the definition of normality is an arbitrary one. Two studies have recently addressed this issue. In one study of 292 blood donors who had never been diagnosed as having ulcer disease, normality was defined as corresponding to a person who had not taken antacid in the preceding seven days, and who had never been investigated for dyspepsia with a barium meal or endoscopy. Using a passive hemagglutination test it was found that only 14% of normal donors had serologic evidence of *C. pylori* infection, compared with 28% of the

symptomatic donors ($P = 0.008$) (Marshall et al. 1985a). Recently, Skoglund et al. (1987) reported a similar study of workers at the Procter and Gamble company in Cincinnati, Ohio. In that study a sensitive ELISA method detected *C. pylori* antibody in 46% of the workers who consumed antacids but in only 14% of those who did not. These data suggest that "healthy normal" persons with *C. pylori* infection have more dyspepsia than persons without it. *C. pylori* appears to be a risk factor for dyspepsia. In future gastroenterologic surveys, therefore, control subjects should not include those with *C. pylori* infection.

At recent international meetings, and elsewhere in this publication, evidence has been presented which confirms that *C. pylori* causes gastritis (Marshall et al. 1985b; Morris et al. 1985; Peterson et al. 1987; Lambert et al. 1987). The connection between gastritis and actual peptic ulceration has not yet been established, however.

The pathogenic mechanism whereby *C. pylori* damages the gastric epithelial cells is poorly understood. Recently, Leunk et al. (1987) noted that about 60% of *C. pylori* isolates produce a protein cytotoxin which can be shown to cause vacuolation of intestinal cell lines in vitro. If this toxin is important in vivo, then the ultimate clinical syndrome associated with the bacterium may be more severe when a toxin producing organism is present. Presence or absence of cytotoxin could explain why one person with gastritis is asymptomatic wheras another develops gastric ulcer.

Another finding has been that urease generates ammonia from urea present in the extracellular fluid. Ammonia combines with alphaketoglutarate, and removes this essential substrate from the TCA cycle (Lehninger 1978). For this reason ammonia is toxic to aerobic mammalian cells. Each mole of ammonia produced then requires two moles of ATP to be re-entered into the liver's urea cycle. This urea recycling is a normal gastrointestinal function in ruminants who cannot afford to lose their sparse nitrogen stores in the urine as urea (Cheng et al. 1979). In man, however, dietary nitrogen is plentiful and ammonia generation is a wasteful and sometimes harmful metabolic event. In patients with both uremia and *C. pylori* infection, ammonia generation is likely to be greatly increased, and this would be especially harmful to patients with hepatic impairment.

Gastroenterologists now wonder how common *C. pylori* infection is, and how clinically significant it is. If the bacterium is a pathogen in the subgroup who develop duodenal ulcer (DU) disease (Fig. 4b), then can it be a commensal in a patient with asymptomatic gastritis? Common sense would suggest that it could not be both, yet asymptomatic gastritis is very common and apparently harmless. We do not yet have enough information to answer these questions.

If the benefit of eradicating the bacterium in dyspeptic disease can be shown, study of *C. pylori* infection will become more important. The possibility of reinfection from untreated asymptomatic family members will have to be considered. In addition, the syndromes of acute and chronic *C. pylori* associated gastritis will have to be accurately defined. Unless this is done, inappropriate antibacterial therapy will be used in patients with asymptomatic *C. pylori* infection who in fact have more serious gastrointestinal problems.

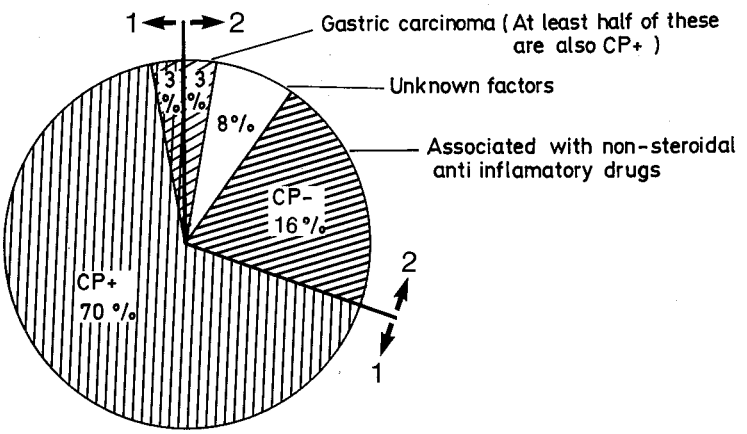

Fig. 4. Disease association with *C. pylori.* **a** Gastric ulcer; **b** duodenal ulcer

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