**INTRODUCTION**

The principal cause of death in the Western world is cardiovascular diseases, the majority of which are coronary heart disease or cerebrovascular disease with a pathogenic mechanism of atherothrombosis.1

In recent years, a theory of «response to the lesion» has been proposed as the inductor mechanism for atherothrombosis; basically this theory states that inflammatory and immunological processes triggered by viral or bacterial infections are the underlying cause of the atherosclerotic process.2-4 In fact, there is scientific evidence supports this theory with regard to *Chlamydia pneumoniae*,5 *Chlamydia TWAR*,6 and cytomegalovirus7 such as, for example, the finding on PCR or immunofluorescence of *Chlamydia pneumoniae* and *Chlamydia TWAR* in atheromatous plaques by PCR, immunocytochemistry, and electron microscope.5 A relationship has been observed between dental infections and coronary cardiopathy,8 as has a co-
relation between cardiovascular risk factors and markers for inflammatory processes. \(^9\) \(^{10}\) **Helicobacter pylori** has also been associated with the genesis of coronary cardiopathy \(^{11}\) \(^{13}\) and cerebrovascular disease. \(^{14}\)

**Helicobacter pylori**

*Helicobacter pylori* is a gram-negative microaerophilic bacillus; it requires an atmosphere of 5% O\(_2\) and 5% to 10% CO\(_2\). Its morphology is heterogeneous in that it can take a helicoidal, spiral, or curved shape, with 2 to 6 flagella; nevertheless, in aged cultures it tends to present in coccoid form. It measures 0.5 mm to 1.0 mm in diameter by 2.5 mm to 5.0 mm long. It is characterized by the production of a urease that, via the production of ammonia, creates a microenvironment with a pH greater than that of gastric mucous, allowing it to survive. Culturing *helicobacter pylori* is somewhat difficult as it requires a longer incubation period than the majority of bacteria (5 days instead of 24 hours), and enriched culture mediums must be used. \(^{15}\) \(^{17}\)

*H. pylori* is a bacterium that occurs worldwide, with a prevalence that varies according to the socioeconomic conditions of the population being studied. It is considered the etiopathogenic agent of both benign and malignant gastro duodenal disease, based principally on the fact that eradication of the bacteria is associated with the scarring of peptic ulcers, disappearance of gastritis, decrease in recidive ulcers, improvement in dyspeptic symptomatology, and regression of low-grade MALT lymphoma. In fact, it has been classified as a type 1 carcinogen by the World Health Organization (WHO). \(^{18}\) \(^{21}\) *H. pylori* has also been isolated in bile and biliary vescicles. \(^{22}\) In addition, as mentioned above, in recent years it has been proposed that *H. pylori* has a role in the atherothrombotic process; the evidence for this is analyzed below.

**Association between H. pylori infection and cardiovascular disease**

The study of the association of *H. pylori* with cardiovascular disease (coronary cardiopathy and ischemic cerebrovascular disease) has been undertaken by different investigators:

**Case-control epidemiological studies**

These reveal, by the detection of antibodies, a greater prevalence of infection by *H. pylori* in patients with coronary cardiopathy \(^{12}\) and in patients with cerebrovascular ischemia; nevertheless, there are studies with the opposite results, such as the investigation carried out by Rengström et al. \(^{23}\) A study by Pasceri et al \(^{13}\) revealed a greater prevalence of infection by strains of *H. pylori* cagA+ in patients with coronary cardiopathy vs a control group, while the prevalence of infection by strains of cagA- did not reveal differences between the patients and the control group. This would explain the contradictory results obtained by other authors.

**Studies of the correlation between the seroprevalence of H. pylori and cardiovascular risk factors**

There are factors that increase the risk of atherothrombosis, such as an elevation of plasma fibrinogen and coagulation factor VII, an increase in reactive protein C synthesis, hypercholesterolemia, and hypertriglycercidemia. There are also with contradictory results in this respect. Niemèla et al \(^{24}\) found significant differences between triglyceride and HDL values among seropositive and seronegative subjects vs *H. pylori*. Rengström et al \(^{25}\) did not observe significant differences in plasma fibrinogen, cholesterol, or triglyceride levels among seropositive and seronegative patients. Nevertheless, Patel et al \(^{10}\) found a significant increase in fibrinogen in seropositive patients, but did not find differences in the plasma cholesterol or triglyceride values, parameters that are elevated in some gram-negative infections. \(^{7}\) Blood coagulation factor VII has also been studied, but no significant differences have been found among patients seropositive for *H. pylori* with regard to those who were seronegative. \(^{25}\) \(^{26}\)

**Studies of the correlation of the seroprevalence of H. pylori and markers of inflammatory processes**

There is growing evidence that inflammation plays an etiopathogenic role in atherosclerosis and that some markers of inflammation are associated with a greater risk of coronary cardiopathy or a worse prognosis, such as reactive protein C, \(^{27}\) white blood cell count, \(^{28}\) plasma fibrinogen, \(^{25}\) \(^{28}\) or the presence of heat shock proteins (hsp). \(^{29}\) Upon comparison of patients seropositive for *H. pylori* with seronegative patients, Patel et al \(^{10}\) \(^{28}\) found a significant elevation in the white blood cell count; Birnie et al detected an hsp increase \(^{60}/\) \(^{65}\), \(^{30}\) and the elevation of reactive protein C has been associated with a worse prognosis in patients with unstable angina or recent myocardial infarction. \(^{27}\) There have also been studies of the association of coronary cardiopathy with TNF-α values, another marker for inflammation, but statistically significant differences have not been detected. \(^{25}\)

**Presence of H. pylori in atheromatous plaques**

Studies have been performed using the polymerase chain reaction (PCR) to ADN detector of *H. pylori* in the tissues analyzed. These studies, in addition to

---

Rev Esp Cardiol 2002;55(6):652-6 653
being few in number (only 2 groups of investigators have presented results) are contradictory. Cunningham et al found the presence of *H. pylori* in atheromatous plaques (First European Congress of Chemotherapy), while Blasi et al, in a study carried out on surgical samples of aortic aneurysms, could not identify the presence of *H. pylori* in any of the 51 samples, in spite of the fact that 47 of the patients were seropositive for the bacteria. On the other hand, it is known that bacteria that resists serum, or the lytic activity of its serum complement, survive longer in the bloodstream, allowing it to colonize other areas of the organism. In this respect, *H. pylori* is susceptible to the bactericidal activity of human serum (principally due to the activation of the alternate pathway of the complement), and there is variation in the union of the different strains to C3, making its survival in the bloodstream unlikely.

**Pathogenic mechanisms**

Based on the existing scientific evidence, various mechanisms have been proposed to explain the association of infection by *H. pylori* with cardiovascular disease.

**Inflammatory response**

A low-grade chronic inflammatory response is produced, provoking the atherogenic process via changes in some cardiovascular risk factors, such as coagulation and lipid factors, with liberation of fibrinogen, reactive protein C, TNF-α, and interleukine 6 (IL-6), in addition to an increase in the white blood cell count, which would induce a prothrombotic state. In adults, *H. pylori* induces an active chronic inflammatory process with the presence of neutrophils, T lymphocytes, B lymphocytes, and plasma cells; in other words, it produces a response that is as much cellular as it is humeral. The specific cellular response is characterized by being mounted by T helper 1 lymphocytes, causing an increase in the liberation of cytokines, especially IL-1, IL-6, IL-8, TNF-α and interferon γ. The capability of inducing cytokines differs among the strains of *H. pylori*, with the cagA+ strains being observed to produce the most intense liberation and a greater variety of cytokines. On the other hand, it has also been observed that soluble extracts of *H. pylori* promote plaque aggregation in the microcirculation of gastric mucous.

**Modification of blood lipids**

Infection by *H. pylori* induces an elevation of cholesterol and triglyceride levels with a decrease in HDL cholesterol, contributing to the development of dyslipidemia, a known cardiovascular risk factor.

**Formation of oxidants**

Some authors propose that the formation of oxidants is also important, as it has been observed that antioxidants decrease in patients with *H. pylori*, which may cause lipid peroxidation and thus atherogenesis, as oxidation of low density lipoproteins (LDL) is 1 of the fundamental steps in the atherogenic process.

**Crossed reactivity with anti heat shock protein (hsp) antibodies**

Another theory is that of anti hsp antibodies with crossed reactivity, as *H. pylori* produces hsp of 60 kDa with a high degree of sequence homology with the human 60 kDa hsp expressed by the endothelium.

**Hyperhomocysteinemia**

Hyperhomocysteinemia is a new cardiovascular risk factor, as it has been observed that an elevation in homocysteine values is associated with an increase in cardiovascular risk. In this respect, in patients with chronic gastritis (generally caused by *H. pylori* infection) it can produce a decrease in the absorption of vitamin B12 and folate, causing secondary hyperhomocysteinemia.

**Socioeconomic level**

There are studies that demonstrate a greater prevalence of coronary cardiopathy and cardiovascular events in people at lower socioeconomic levels. However, it has been proposed that infection by *H. pylori* would only be a marker of socioeconomic level, as it is lower in infected patients than in non-infected patients, similar to what is observed in a comparison of cardiopath vs non-cardiopaths.

In summary, an etiopathogenic relationship between various chronic diseases and microorganism infections has been found, whether it occurs via direct pathogenic mechanisms or the immune response of the host against the microorganism. *H. pylori*, give its widespread distribution in the world population and the high incidence of gastro duodenal disease, is 1 of the most important microorganisms associated with illness that were previously considered to have a non-infectious etiology. With respect to the association of this bacterium with coronary cardiopathy, the existing scientific evidence suggests that infection by *H. pylori* contributes to the genesis, progression, and severity of cardiovascular disease, although it is unlikely that it triggers cardiovascular disease on its own. Ultimately, it is the balance between the factors that favor cardiovascular disease and the host’s protective factors that will determine the course of each individual, but perhaps in the future we should carry out treatment to eradicate...
H. pylori in those patients at greater cardiovascular risk, as we now do with weight reduction, a decrease in the consumption of fat, and smoking cessation, among others.

ACKNOWLEDGEMENT

We would like to express our gratitude to Prof. Jorge Roa, of the Departamento de Fisiología, Universidad de Concepción, Chile, for his constant support and encouragement during the preparation of this manuscript, to Laboratorios Andrómaco for their collaboration through the Proyecto Apertus 2000, and to Laboratorios Recalcine for their help with the compilation of bibliographic references that were not available in Chile.

REFERENCES