Extradigestive manifestations of *Helicobacter pylori* gastric infection

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Summary
In the past year, several studies have been carried out on the association between *Helicobacter pylori* infection and a miscellany of extradigestive diseases, such as cardiovascular, immunological, and various other pathologies. In particular, a higher prevalence of *H pylori* infection in patients affected by ischaemic heart disease has been described and there is growing evidence for an association between *H pylori* and some autoimmune diseases. Moreover, recent studies have shown that various helicobacter species have been detected in human bile; if confirmed, this finding could revise the diagnostic and therapeutic approach to diseases of the biliary tract.

Introduction

It has long been known that some infectious agents which affect specific areas of the body may also have systemic sequelae. A typical example of this phenomenon is infection by β haemolytic streptococcus group A, a frequent determinant of acute or chronic tonsillitis, which can also lead to rheumatic fever, cardiac inflammation, glomerulonephritis, and neurological involvement.[1] It has been shown that the extrapharyngeal manifestations of the infection are caused by cross mimicry between bacterial and host antigens.[1]

H pylori is one of the most frequent causes of gastrointestinal infections worldwide; it is known that the immunological response elicited by the bacterium is an important determinant of gastric mucosal damage.[2] In particular, the production of large amounts of various proinflammatory substances, such as cytokines, eicosanoids, and proteins of the acute phase follows gastric colonisation by *H pylori* (fig 1).[2] It has also been shown that there is cross mimicry between some bacterial and host antigens which may be responsible, at least in part, for the mucosal damage during the infection.[3] On the basis of these observations, some authors have also investigated the role of *H pylori* as a pathogenic determinant of some extragastroduodenal idiopathic diseases, such as cardiovascular, immunological, skin, liver, biliary tract, and various other disorders, in which an inexplicable increase in cytokines or an autoimmune trait has been involved in the pathogenesis.

Vascular diseases

ISCHAEMIC HEART DISEASE

Over the past 20 years, several studies carried out on the pathogenesis of peripheral vascular diseases have found that diabetes, hyperlipaemia, hypertension, and smoking are important risk factors for the development of atherosclerosis and have made the development of therapeutic approaches for the control of these pathologies possible. Recently, attention has been focused on the possible pathogenic mechanisms involved in the development of atherosclerosis through an association with infectious diseases. Various studies have found that the presence of a chronic infection by some microbial species could act as a risk factor in vascular diseases. In particular, several epidemiological studies have been carried out on the association between ischaemic heart disease (IHD) and *H pylori* infection.[4–11] In spite of this large number of studies, however, whether the association is causal or occasional is still unclear. Since the first report in 1994, at least 25 epidemiological studies have been published on the association between *H pylori* antibody titre and IHD. In all studies, however, potential confounding factors, such as low socioeconomic status, seem to be strongly associated both with *H pylori* infection and coronary heart disease. The failure to make appropriate adjustments for potential confounding factors could lead to spurious associations of infection with coronary heart disease. In fact, most of the studies in which controls were opportunistically recruited and not adjusted for confounding factors reported a strong association. Conversely, studies that tried to reduce the effects of selection bias by adjusting for potential confounding factors and by random sampling of controls from roughly the same population tended to report weak associations.[12] On balance, studies performed to date do not show a strong association, but they do vary in their results and are consistent with a 10–20% excess risk. Whether or not residual confounding explains such a weak association is open to debate.

With regard to the pathogenic mechanisms proposed in order to link *H pylori* with IHD, it is of special interest to note that the "infectious hypothesis" has long been supported to explain IHD occurrence. Micro-organisms, such as chlamydia, cytomegalovirus, or other herpes viruses, have been proposed as potential determinants of coronary atheroma.[13 14] It has also been shown that immunological mechanisms are implicated in the pathogenesis of atherosclerosis and that there is a relation between serum cytokine concentration and coronary heart disease.[15] Increased serum

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Abbreviations used in this paper: IHD; ischaemic heart disease; IL, interleukin; TNF, tumour necrosis factor; ICVD, ischaemic cerebrovascular disease; MALT, mucosa associated lymphoid tissue.

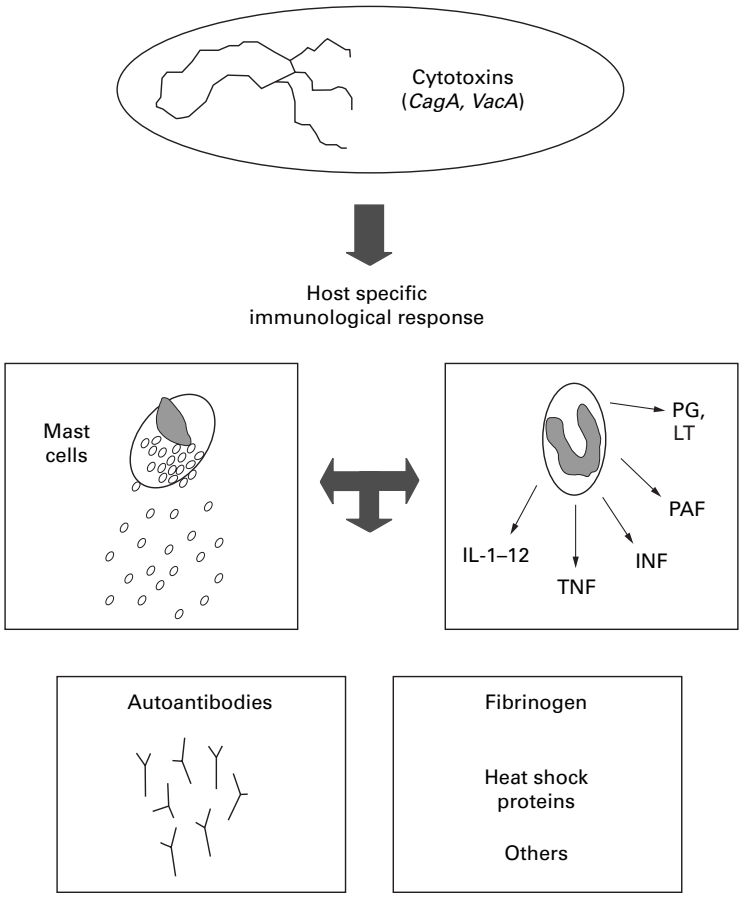

Figure 1 Schematic representation of the substances released by the immune system following gastric colonisation by Helicobacter pylori. TNF, tumour necrosis factor; PAF, platelet activating factor; LT, leukotriene; PG, prostaglandin; IL, interleukin; INF, interferon.

concentrations of interleukin (IL) 6 and tumour necrosis factor (TNF) α in particular show a linear correlation with some cardiovascular risk factors[15]; and cytokines, such as IL-6 and TNF-α, or other phlogosis mediators promote release of some acute phase proteins, such as fibrinogen or C-reactive protein.[2] Furthermore, cytokines may amplify the inflammatory response through other mechanisms, as shown in table 1. No definitive data are available on the role of *H pylori* in influencing the systemic inflammatory response. However, as raised concentrations of cytokines or phlogosis mediators are predictive of a higher risk of acute IHD events,[16] and many of these proteins could be released as a result of *H pylori* gastric colonisation,[2] a link with IHD is likely. Furthermore, as *cagA* positive strains cause greater release of cytokines by gastric epithelial cells,[17] a recent study which showed a significantly higher prevalence of *H pylori cagA* positive strains in patients affected by IHD than in matched controls, is of interest.[6] Considering the peculiar ability of these strains to stimulate greater release of cytokines by the inflammatory cells, the authors concluded that only some cytotoxic *H pylori* strains could be associated with IHD.[6] If confirmed, this association with more cytotoxic strains could be extremely important in answering concerns over residual confounding factors such as social class. Other proposed mechanisms that may influence IHD by means of *H pylori* are the development of cross mimicry between endothelial and bacterial antigens, such as heat shock proteins, and the development of a procoagulant status as a result of the infection.[18]

ISCHAEMIC CEREBROVASCULAR DISORDERS

Few studies are available. A recent report shows that *H pylori* infection affects patients with ischaemic cerebrovascular disease (ICVD) more frequently than controls.[19] Moreover, as the study reported that infected patients show a mean carotid stenosis greater than uninfected subjects, the authors concluded that *H pylori* infection may act, at least in part, by increasing atherosclerosis.[19] In addition to the mechanisms already proposed for the relation between *H pylori* and IHD, another reason that could explain the association could be the reduction of gastric absorption of folate caused by the infection, a well known risk factor for ischaemic vascular disease.[8] The lack of well designed prospective studies able to show a causal relation between *H pylori* infection and ICVD, however, still does not make it possible to assess the validity of the association.

FUNCTIONAL VASCULAR DISORDERS

As the release of large amounts of various proinflammatory and vasoactive substances (such as cytokines, eicosanoids, and acute phase proteins) follows gastric colonisation by

Table 1 Action of cytokines released during the acute phase response to infection

Cytokine	*Actions*
IL-1	Increase in T lymphocyte (TL) and B lymphocyte (BL) proliferation; IL-2 receptor expression; activation of natural killer cells (NK); increase in expression of cyclooxygenase and lipoxygenase; endogenous pyrogen production; action on central nervous system and endocrine system
IL-2	Stimulation of TL proliferation and differentiation; increase in cytolytic action of NK; stimulation of killer cell proliferation and antibody release by BL
IL-6	Stimulation of haemopoietic cell maturation and BL/TL proliferation and differentation; increase in acute phase protein production by hepatocytes; endogenous pyrogen production
IL-7	Stimulation of BL/TL proliferation; increase in monocyte and macrophage action
IL-8	Chemotactic action for neutrophils, TL, and basophils; increase in lysosomal enzyme release by neutrophils; stimulation of neutrophil and monocyte adhesion to endothelial cells, and LTB_4 release by neutrophils
IL-10	Chemotactic action for monocytes and TL; increase in TL adhesion to endothelial cells
IL-12	Increase in CTL, NK, and macrophage cytolytic action; increase in haemopoietic cell, NK, and TL proliferation; increase in IFN-γ production by TL; inhibition of IgE production by BL
TNF-α	Increase in expression of growth factors, cytokines, cellular receptors, acute phase proteins; endogenous pyrogen production
IFN-γ	Increase in expression of MHC class I and class II on the surface of macrophages; antitumour and antiviral action; stimulation of macrophage action
LTC_4	Increase in vessel permeability and slowing of microcirculation blood flow; increase in endothelial adhesion of neutrophils; inhibition of cellular turnover
PAF	Platelet activation

IL, interleukin; TNF, tumour necrosis factor; IFN, interferon; LTC_4, leukotriene C_4; PAF, platelet activating factor; LTB_4, leukotriene B_4; CTL, cytotoxic T lymphocytes.

H pylori, the bacterium may be involved in some functional vascular disorders. It has been shown that *H pylori* infection is common in two typical functional vascular disorders such as primary Raynaud's phenomenon and idiopathic migraine. Furthermore, in both cases *H pylori* eradication resulted in a significant improvement in the clinical manifestation of the disease.[20 21] Controlled eradication studies, however, still need to be performed and the exact sequence of events that could link *H pylori* infection to functional vascular diseases remains to be shown.

Immunological diseases

Several clinical observations suggest a role for *H pylori* infection in various immunological disorders. Some reports have shown healing of some autoimmune diseases (such as Henoch-Schönlein purpura, Sjögren's syndrome, and autoimmune thrombocytopenia) after eradication of *H pylori*.[22–25] Furthermore, the observation of complete disappearance of some cases of extragastric mucosa associated lymphoid tissue (MALT) lymphoma, such as those localised to the salivary gland, small intestine, and rectum, following treatment for *H pylori* infection, is of special interest.[26–28]

Although no definitive data are available on the pathogenesis of these phenomena, it has been shown that antibodies against *H pylori* may react with some extragastric tissues, such as glomerular capillary walls, ductal cells of the salivary gland, and renal tubular cells.[29 30] Similar mechanisms have been suggested to link *H pylori* infection with some acute immune polyneuropathies in which there is a molecular mimicry between *Campylobacter jejuni* lipopolysaccharides and GM1 ganglioside.[31] On the basis of these observations, it is hypothesised that an antigenic similarity between *H pylori* and host antigens could be responsible for autoimmunity in some infected patients. Further studies are required to clarify this.

Skin diseases

Some studies have suggested a link between idiopathic chronic urticaria and *H pylori* infection.[32–34] A recent study in particular showed a significant decrease in the typical symptoms of urticaria, such as wheals, erythema, and pruritus after eradication of *H pylori*.[33] The reasons behind the phenomenon, however, are unknown. Probably, an increase in mast cell degranulation, which could be induced by peculiar *H pylori* cytotoxic strains, may act as a trigger in subjects with an individual susceptibility to develop urticaria.

Acne rosacea and alopecia areata have also been associated with *H pylori* infection.[35–37] Discordant and not definitive data, however, are available on these topics.

Liver and biliary tract

Recently, a higher prevalence of *H pylori* infection has been described in patients with liver cirrhosis than in age and sex matched controls.[38] Further studies, however, are necessary in order to verify whether the association is causal or occasional. Furthermore, it is unclear whether the association has a clear pathological significance as the available data show no relation between *H pylori* infection status and severity of the liver disease.[39] However, the fact that infected patients have higher blood concentrations of ammonia and that eradication of the bacterium results in a significant reduction, is interesting.[40]

A possible link between *H pylori* infection and some diseases of the biliary tract has been hypothesised. In particular, a recent study showed both the presence of *H pylori* sequences in bile samples, and a homology between sequences of CagA protein and those of aminopeptidase N, a well known substance capable of inducing cholesterol aggregation.[41] However, whether *H pylori* is associated with cholelithiasis is not known. Finally, there is emerging evidence of a possible role of other helicobacter species, such as *H bilis* and *H pullorum*, in the pathogenesis of chronic cholecystitis.[42]

Other extragastroduodenal diseases

H pylori infection is reported to be more highly prevalent in patients with sideropenic anaemia compared with healthy controls.[43] Furthermore, several case reports showed the resolution of chronic idiopathic sideropenia following eradication of *H pylori*.[44–46] The mechanisms behind this phenomenon, however, are still unclear. It is plausible to speculate that direct use of iron by the bacterium or impairment of iron absorption through the release of iron binding substances, such as lactoferrin or siderophores, may lead to sideropenia in some infected patients.[44 47]

Low growth rate and sudden infant death are other diseases that have been associated with *H pylori* infection.[48–50] Data, however, are conflicting and well designed controlled studies are required to clarify the existence of a causal association.

Conclusions

As peculiar *H pylori* cytotoxic strains may induce a local chronic release of cytokines, or vasoactive or procoagulant substances by the immune cells in susceptible subjects, several studies have been designed to assess a role of *H pylori* infection in some extragastric idiopathic diseases. Available epidemiological data are conflicting because of the presence of several confounding factors (socioeconomic status and geographical location, time of acquisition of the infection, presence of different bacterial strains, previous antimicrobial therapy, presence of concominant infections) which may influence the results of these studies. However, as *H pylori* eradication often leads to the disappearance of or an improvement in some extradigestive pathologies, further well designed in vitro, epidemiological, and controlled intervention studies, with special reference to *cagA* status of infecting strains, are needed in order to identify whether and by which molecular mechanisms *H pylori* may cause extragastric manifestations.

1 Bisno AL. Group A streptococcal infections and acute rheumatic fever. *N Engl J Med* 1991;**325**:783–93.
2 Bamford KB, Andersen L. Host response. *Curr Opin Gastroenterol* 1997;**13**(suppl 1):25–30.
3 Negrini R, Savio A, Poiesi C, *et al*. Antigenic mimicry between H. pylori and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology* 1996;**111**:655–65.
4 Mendall MA, Goggin PM, Molineaux N, *et al*. Relation of Helicobacter pylori infection and coronary heart disease. *Br Heart J* 1994;**71**:437–9.
5 Ossei-Gerning N, Moayyedi P, Smith S, *et al*. Helicobacter pylori infection is related to atheroma in patients undergoing coronary angiography. *Cardiovasc Res* 1997;**35**:120–4.
6 Pasceri V, Cammarota G, Patti G, *et al*. Association of virulent Helicobacter pylori strains with ischemic heart disease. *Circulation* 1998;**97**:1675–9.
7 Laurila A, Bloigu A, Nayha S, *et al*. Chlamydia pneumoniae and Helicobacter pylori infections in Sami and Finnish reindeer herders. *Int J Circumpolar Health* 1997;**56**:70–5.
8 Markle HV. Coronary artery disease associated with Helicobacter pylori infection is at least partially due to inadequate folate status. *Med Hypotheses* 1997;**49**:289–92.
9 Ossewaarde JM, Feskens EJ, De Vries A, *et al*. Chlamydia pneumoniae is a risk factor for coronary heart disease in symptom-free elderly men, but Helicobacter pylori and cytomegalovirus are not. *Epidemiol Infect* 1998;**120**:93–9.
10 Wald NJ, Law MR, Morris KJ, *et al*. Helicobacter pylori infection and mortality from ischaemic heart disease: negative result from a large, prospective study. *BMJ* 1997;**315**: 1199–201.
11 Strandberg TE, Tilvis RS, Vuoristo M, *et al*. Prospective study of Helicobacter pylori seropositivity and cardiovascular diseases in a general elderly population. *BMJ* 1997;**314**:1317–18.
12 Danesh J, Appleby P. Persistent infection and vascular disease: a systematic review. *Exp Opin Invest Drugs* 1998;**7**: 691–713.
13 Burch GE. Viruses and arteriosclerosis. *Am Heart J* 1974;**87**:407–12.
14 Saikku P, Mattila K, Nieminen MS, *et al*. Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. *Lancet* 1988;ii:983–6.
15 Mendall MA, Patel P, Asante M, *et al*. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart* 1997;**78**:273–7.
16 Ridker PM, Cushman M, Stampfer MS, *et al*. Inflammation, aspirin and the risk of cardiovascular diseases in apparently healthy men. *N Engl J Med* 1997;**336**:973–9.
17 Atherton J, Covacci A. Pathogenic properties of Helicobacter pylori. *Curr Opin Gastroenterol* 1997;**13**(suppl 1):20–4.
18 Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? *Lancet* 1997;**350**:430–6.
19 Markus HS, Mendall MA. Helicobacter pylori infection: a risk factor for ischaemic cerebrovascular disease and carotid atheroma. *J Neurol Neurosurg Psychiatry* 1998;**64**: 104–7.
20 Gasbarrini A, Massari I, Serricchio M, *et al*. Helicobacter pylori and Raynaud phenomenon. *Gastroenterology International* 1997;**10**(suppl 1):18–19.
21 Gasbarrini A, De Luca A, Fiore G, *et al*. Beneficial effects of Helicobacter pylori eradication on migraine. *Hepatogastroenterology* 1998;**21**:765–70.
22 Machet L, Vaillant L, Machet MC, *et al*. Schönlein-Henoch purpura associated with gastric Helicobacter pylori infection. *Dermatology* 1997;**194**:86.
23 Reinauer S, Megahed M, Goerz G, *et al*. Schönlein-Henoch purpura associated with gastric Helicobacter pylori infection. *J Am Acad Dermatol* 1995;**33**:876–9.
24 Figura N, Giordano N, Burroni D, *et al*. Sjögren's syndrome and Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 1994;**6**:321–2.
25 Gasbarrini A, Franceschi F, Tartaglione R, *et al*. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. *Lancet* 1998;**352**:878.
26 Alkan S, Karcher DS, Newman MA, *et al*. Regression of salivary MALT lymphoma after treatment for Helicobacter pylori. *Lancet* 1996;**348**:268–9.
27 Fishbach W, Tacke W, Greiner A, *et al*. Regression of immunoproliferative small intestinal disease after eradication of Helicobacter pylori. *Lancet* 1997;**349**:31–2.
28 Matsumoto T, Iida M, Shimizu M. Regression of mucosa-associated lymphoid-tissue lymphoma of rectum after eradication of Helicobacter pylori. *Lancet* 1997;**350**:115–16.
29 Ko GH, Park HB, Shin MK, *et al*. Monoclonal antibodies against Helicobacter pylori cross-react with human tissue. *Helicobacter* 1997;**2**:210–15.
30 Nagashima R, Maeda K, Yuda F, *et al*. Helicobacter pylori antigen in the glomeruli of patients with membranous nephropathy. *Virchows Arch* 1997;**431**:235–9.
31 Nevo Y, Pestronk A. Acute immune polyneuropathies: correlations of serum antibodies to Campylobacter jejuni and Helicobacter pylori with anti-GM1 antibodies and clinical patterns of disease. *J Infect Dis* 1997;**176**(suppl 2):S154–6.
32 Rebora A, Drago F, Parodi A. May Helicobacter pylori be important for dermatologists? *Dermatology* 1995;**191**:6–8.
33 Di Campli C, Gasbarrini A, Nucera E, *et al*. Beneficial effects of Helicobacter pylori eradication on idiopathic chronic urticaria. *Dig Dis Sci* 1998;**43**:1226–9.
34 Tebbe B, Geilen CC, Schulzke JD, *et al*. Helicobacter pylori infection and chronic urticaria. *J Am Acad Dermatol* 1996; **34**:685–6.
35 Mindel JS, Rosemberg EW. Is Helicobacter pylori of interest to ophthalmologists? *Ophthalmology* 1997;**104**:1729–30.
36 Sharma VK, Lynn A, Kaminski M, *et al* A study of the prevalence of Helicobacter pylori infection and other markers of upper gastrointestinal tract disease in patients with rosacea. *Am J Gastroenterol* 1998;**93**:220–2.
37 Tosti A, Pretolani S, Figura N, *et al*. Helicobacter pylori and skin diseases. *Gastroenterology International* 1997;**10**(suppl 1):37–9.
38 Siringo S, Vaira D, Menegatti M, *et al*. High prevalence of Helicobacter pylori in liver cirrhosis. Relationship with clinical and endoscopic features and the risk of peptic ulcer. *Dig Dis Sci* 1997;**42**:2024–30.
39 Farinati F, De Bona M, Floreani A, *et al*. Helicobacter pylori and the liver: any relationship? *Ital J Gastroenterol Hepatol* 1998;**30**:124–8.
40 Miyaji H, Ito S, Azuma T, *et al*. Effects of Helicobacter pylori eradication therapy on hyperammonaemia in patients with liver cirrhosis. *Gut* 1997;**40**:726–30.
41 Figura N, Cetta F, Angelico M, *et al*. Most Helicobacter pylori-infected patients have specific antibodies, and some also have H. pylori antigens and genomic material in bile. Is it a risk factor for gallstone formation? *Dig Dis Sci* 1998;**43**: 854–62.
42 Fox JG, Dewhirst FE, Shen Z, *et al*. Hepatic Helicobacter species identified in bile and gallbladder tissue from Chileans with chronic cholecystitis. *Gastroenterology* 1998; **114**:755–63.
43 Franceschi F, Gasbarrini A, Ricerca BM, *et al*. High prevalence of H. pylori infection in patients affected by idiopathic sideropenic anemia [abstract]. *Gut* 1998; **43**(suppl 2):A106.
44 Dufour C, Brisigotti M, Fabretti G, *et al*. Helicobacter pylori gastric infection and sideropenic refractory anemia. *J Pediatr Gastroenterol Nutr* 1993;**17**:225–7.
45 Marignani M, Angeletti S, Bordi C, *et al*. Reversal of long-standing iron deficiency anaemia after eradication of Helicobacter pylori infection. *Scand J Gastroenterol* 1997; **32**:617–22.
46 Carnicer J, Badia R, Argemì J. Helicobacter pylori gastritis and sideropenic refractory anemia. *J Pediatr Gastroenterol Nutr* 1997;**25**:441.
47 Nakao K, Imoto I, Gabazza EC, *et al*. Gastric juice levels of lactoferrin and Helicobacter pylori infection. *Scand J Gastroenterol* 1997;**32**:530–4.
48 Perri F, Pastore M, Leandro G, *et al*. Helicobacter pylori infection and growth delay in older children. *Arch Dis Child* 1997;**77**:46–9.
49 Vaira D, Menegatti M, Salardi S, *et al*. Helicobacter pylori and diminished growth in children: is it simply a marker of deprivation? *Ital J Gastroenterol Hepatol* 1998;**30**:129–33.
50 Pattison CP, Marshall BJ. Proposed link between Helicobacter pylori and sudden infant death syndrome. *Med Hypotheses* 1997;**49**:365–9.