Concept Paper

‘Peptic Ulcers Are an Infectious Disease Caused by Helicobacter pylori’ Is an Illusion in Medical Research

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Article

"Peptic Ulcers are an Infectious Disease Caused By *Helicobacter Pylori*" is an Illusion in Medical Research

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Abstract: Currently, peptic ulcers are widely studied as an infectious disease caused by *Helicobacter pylori* primarily due to 3 supporting evidences, and this etiology may explain the other 3 observations, but cannot confront the challenges of the 15 major characteristics and the other 75 observations/phenomena of peptic ulcers. To address the challenges, a recently published Complex Causal Relationship with its accompanying methodologies was applied to analyze existing data. Peptic ulcers are identified as a psychosomatic disease triggered by psychological stress, where *Helicobacter pylori* plays a secondary role in only the late phase of ulceration. This new etiology elucidated all the 15 major characteristics and 81 observations/phenomena of peptic ulcers in a series of 6 articles. This sixth article focuses exclusively on the controversies surrounding the role of *Helicobacter pylori* in peptic ulcers. In-depth analyses find that all the 3 evidences supporting "peptic ulcers are an infectious disease caused by *Helicobacter pylori*" are deceiving, and 2 of the 3 explainable observations may have been misinterpreted. Meanwhile, the definitions of 'etiological factor' and 'causality' do not support '*H. pylori* infection is an etiological factor of peptic ulcers', and existing literatures have presented a controversial view on the role of *Helicobacter pylori* in peptic ulcers. Interestingly, if "peptic ulcers are an infectious disease caused by *Helicobacter pylori*" is considered an illusion, all the characteristics of the disease, along with all the clinical, epidemiological, and laboratory observations/phenomena, can be fully understood. This illusion has misguided peptic ulcer research over the past 36 years with little progress in the field, and that may represent a widespread situation in modern medical research, resulting in a direct interference with the true understanding of disease. Evidently, keeping the concept "illusion" in mind may help remove a huge obstacle that impedes medical advance, thereby facilitating the in-depth study of disease.

Keywords: peptic ulcers; pathogenesis; etiology; *Helicobacter pylori*; *illusion*; African enigma; psychosomatic disease; psychological stress

1. Introduction

Over the past 300 years, 13 etiological theories, such as '*No Acid, No Ulcer*' [1], *Nerve Theory* [2], *Psychosomatic Theory* [3], and *Stress Theory* [4], have been proposed to explain the pathogenesis of peptic ulcers [5]. Although each of these theories could explain a minority of the 15 major characteristics and 81 observations/phenomena of the disease [5], they failed to explain the majority of these due to their respective inconsistencies [6]. To date, none of these theories can explain the birth-cohort phenomenon [7] and seasonal variation of peptic ulcers [8], along with the morphology and predilection sites, perforation and bleeding, relapse and multiplicity of gastric ulcers [6]. Moreover, although duodenal and gastric ulcers share much in common, they were found to be epidemiologically, behaviourally, and genetically different two diseases [9,10]. However, the similarities and differences between duodenal and gastric ulcers have never been clarified [1].

The isolation of the bacterium *Helicobacter pylori* (*H. pylori*) in 1982 dramatically changed the concept of peptic ulcers [11]. In 1987, Marshall proposed that peptic ulcers are an infectious disease caused by *H. pylori* [12]. In 1988, Marshall further concluded that "*C[H]. pylori* is the most important etiological factor so far described for duodenal ulcer" [13]. Currently, it is widely believed that there is a causal relationship between *H. pylori* and peptic ulcers primarily due to 3 supporting evidences [14]. First, most peptic ulcer patients are infected with *H. pylori*, and clinical patients have a higher infection rate than the normal population [15–18]. Second, ulcers are significantly larger in infected rats compared to uninfected, and *H. pylori* infection delays ulcer healing, which can be resolved by

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eliminating the bacterium [19,20]. Third, the elimination of *H. pylori* results in a significant reduction of the ulcer relapse rate [13,17,21]. The etiological theory of peptic ulcers based on *H. pylori* infection has been designated as *Theory of H. pylori* [5].

Unfortunately, *Theory of H. pylori* is not superior to any other etiological theory in history but has led to additional controversies [14,22–25] and mysteries. Many researchers have questioned the causal role of *H. pylori* in peptic ulcers, and how *H. pylori* infection causes peptic ulcers has remained elusive [26] for 36 years after Marshall's proposal. This theory cannot identify the roles of gastric acid and NSAIDs in the disease [27,28]. Interestingly, this theory could not explain 30 of the 36 observations/phenomena related to the bacterium itself. Moreover, out of all the 81 observations/phenomena of peptic ulcers, 45 were not associated with *H. pylori* infection [5], making it very difficult for *Theory of H. pylori* to explain the pathogenesis of peptic ulcers. For example, the ulcer lesions in patients without *H. pylori* infection is one of the most challenging issues in *Theory of H. pylori*. In addition, *H. pylori* is omnipresent in the stomach, but gastric ulcers are a sharply circumscribed loss of tissue located primarily in the gastric antrum and lesser curvature, having a characteristic 'punch out' appearance with clean edges, as if it were cut by a knife [10,29]. Thus, *Theory of H. pylori* has fallen into inconsistency when it was applied to explain the morphology and predilection sites of gastric ulcer, as well as all the other characteristics and the majority of observations/phenomena of peptic ulcers. Furthermore, similar to all the other etiological theories in history, *Theory of H. pylori* cannot resolve any one of the epidemiological mysteries, such as the birth-cohort phenomenon and seasonal variation, but directly incur a new mystery of peptic ulcers, the African enigma, which states that *H. pylori* infection is very common in Africa, but the prevalence of peptic ulcers is low and varies regionally [30]. Evidently, the most recent *Theory of H. pylori*, along with all the other 12 etiological theories proposed in modern medical history, failed to explain the pathogeneis of peptic ulcers.

The challenges in current peptic ulcer research suggest that we may have to explore a new path outside of current medicine. Fortunately, in May 2012, a book entitled *Philosophical Principle of Life Science* was published, in which a Complex Causal Relationship (CCR) with its accompanying methodologies, epistemologies, and way of thinking was proposed to understand various life phenomena and human diseases [31]. To test the validity of this CCR, peptic ulcers were selected as a model disease to explain, resulting in the birth of a new etiological theory of peptic ulcers, *Theory of Nodes* [32,33]. This theory integrated the *Psychosomatic Theory* [3] and *Stress Theory* [4] proposed in 1950 into a new etiology of peptic ulcers, where peptic ulcers are not an infectious disease caused by *H. pylori*, but a psychosomatic disease triggered by psychological stress [32]. Encouragingly, this etiology explained all the 15 characteristics and 81 observations/phenomena of peptic ulcers [34], including all the 36 observations/phenomena associated with the bacterium. Moreover, this etiology addressed all the controversies and mysteries related to peptic ulcers, such as the birth-cohort phenomenon [35] and seasonal variation [36], and the morphology and predilection sites [33], as well as the roles of gastric acid, *H. pylori*, and NSAIDs in the disease [32,33]. The similarities and differences between duodenal and gastric ulcers are also clarified [33]. Due to a limit of words, the data analyses are summarized into a series of 6 articles (**Supplementary Table S1**). In the first five articles of the series, 14 major characteristics and 73 observations/phenomena of peptic ulcers, most of which have never been fully understood before, have been explicitly elucidated [32–36]. This analysis is the sixth one of the series, aiming to address the controversies surrounding the role of *H. pylori* in peptic ulcers, along with the mystery of the African enigma.

2. In-depth analyses dispute the 3 supporting evidences of Theory of H. pylori

In *Theory of Nodes*, *H. pylori* is not a cause of peptic ulcers, but a risk factor playing a secondary role in only the late phase of peptic ulceration, exacerbating ulcer symptoms, delaying healing process, and increasing clinical morbidity and mortality rates [32,33]. As a result, patients infected with *H. pylori* are more likely to become clinical patients due to exacerbated symptoms. In contrast, *H. pylori*-negative patients have milder symptoms and are less likely to seek medical attention. This skews the epidemiological surveys because only patients with severe symptoms tend to see doctors and thus, many *H. pylori*-negative subclinical patients are excluded from the surveys, causing a much higher infection rate of *H. pylori* among clinical ulcer patients as calculated in **Table 1**. This analysis

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suggests that "clinical patients have a higher infection rate than the normal population" cannot be used to support "there is a causal relationship between *H. pylori* and peptic ulcers".

Table 1. Clinical patients have higher infection rates due to exacerbated symptom.

	HP^- (100 individuals)	HP^+ (100 individuals)	HP^- & HP^+ (200 individuals)
Actual number of patients	20	20	40
Number of subclinical patients	15*	5*	20*
Number of clinical patients	5**	15**	20**
Clinical morbidity rates	5%	15%	10%
Infection rates of clinical patients = 15 ÷ （5＋15） ＝ 15 ÷ 20[c] × 100% ＝ 75% > *H. pylori* infection rates in the population ＝ 100 ÷ 200 × 100% ＝ 50%			
The infection rate of *H. pylori* in a population is assumed to be 50%, and 100 individuals were analyzed in *H. pylori*-positive and negative groups, respectively. *H. pylori* infection exacerbates the symptoms of peptic ulcers and therefore, infected individuals are more likely to see doctors and become clinical patients (15 vs 5), causing a higher infection rate of *H. pylori* in clinical patients than that in the normal population (75% > 50%). * These subclinical patients (15 + 5 = 20) were excluded from the calculation of the clinical infection rate of *H. pylori*. ** Only clinical patients (5 + 15 = 20) were included in the calculation of the clinical infection rate of *H. pylori*.			

Second, any local aggressive factor in the stomach, such as *H. pylori,* gastric acid, or NSAIDs, may lead to larger ulcer lesions and delay the healing process because they are corrosive to the local tissues. If *H. pylori* is considered an etiological factor, the other two local aggressive factors, gastric acid and NSAIDs, should also be regarded as etiological factors, further causing controversies and challenges in current research. As elucidated by *Theory of Nodes*, removing local aggressive factors via antibiotics or anti-secretary drugs mitigates clinical symptoms and accelerates the ulcer healing process, giving clinical doctors an *illusion* 'the patients were cured'. These treatments may turn 60-80% of clinical patients into sub-clinical patients, but in fact, they are not cured because the real cause, psychosomatic factors and psychological stress, which induce the hyperplasia and hypertrophy of gastrin and parietal cells in the stomach [32] or the submucosal nodes in the gastric wall [33], were not removed. Therefore, larger lesions and delayed healing processes by the infection do not imply that there is a causal relationship between *H. pylori* and peptic ulcers. On the other hand, if peptic ulcers are an infectious disease caused by *H. pylori*, the bacterium should account for the lesions in *H. pylori*-negative patients, directly resulting in an insurmountable contradiction.

Third, provided *H. pylori* infection was the primary cause of peptic ulcers, eradication of the bacterium should be able to prevent the relapse. Unfortunately, despite the successful eradication of *H. pylori*, more than 20% of the patients relapsed [37,38]. The high relapse rate might be a result of re-infection. However, the re-infection of *H. pylori* is rare, as documented with the long-term rates of re-infection as low as 1% per year in Europe and Australia [17,39,40]. With an average follow-up period of one year, a study in the United States found that only 4 of 118 patients (~3.4%) in whom the eradication of *H. pylori* was documented became re-infected [17,41]. In Japan, the re-infection occurred in 15 of 274 patients (5.5%) 6 months after eradication and the annual re-infection rate per year was 2.0% [42]. The re-infection rate is much lower than the relapse rate, indicating that the relapse of peptic ulcers cannot be attributed to the re-infection. Rather, it is other factors that cause the relapse of peptic ulcers. *Theory of Nodes* elucidated that the 'other factors' are the pre-existing hyperplasia and hypertrophy of gastrin and parietal cells in the stomach and the formation of submucous nodes in the gastric wall due to psychosomatic factors and the immediate psychological stress, which cannot be removed by anti-acid and antibiotic treatments, resulting in 'once an ulcer, always an ulcer' [43,44].

Thus, a higher *H. pylori* infection rate in clinical patients, larger ulcer lesions and delayed healing process after infection, and a lower relapse rate after bacterial elimination cannot be used to support "peptic ulcers are an infectious disease caused by *H. pylori*". All the 3 supporting evidences can be explained by "*H. pylori* plays a secondary role in only the late phase of peptic ulcerations, exacerbating clinical symptoms".

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3. Alternative interpretations for two observations explainable by H. pylori

Out of all the 36 observations/phenomena associated with *H. pylori*, excluding the 3 supporting evidences, three other observations are explainable by *Theory of H. pylori*. Starting from "peptic ulcer is a psychosomatic disease triggered by psychological stress", *Theory of Nodes* offers alternative explanations for two of the three observations, further demonstrating the pitfalls of *Theory of H. pylori*.

In a relatively isolated group of Australian Aboriginals, peptic ulcers were rare [45]; in a 2-year study of Pima Indians in North America, no peptic ulcer was found [46]. In contrast, a high percentage (10%) of the Caucasian population in North America developed peptic ulcers during the same time-period [47]. In *Theory of H. pylori*, these two observations can be explained by either no infection or a low infection rate of *H. pylori* in Pima Indians and Australian Aboriginals, or a high infection rate in Caucasians. In contrast, in *Theory of Nodes*, the low morbidity rates of peptic ulcers in Pima Indians and Australian Aboriginals were not because they had a lower *H. pylori* infection rate, but because they were living in a pastoral culture with less social conflicts and therefore, they were leading a less stressful life. The higher percentage of peptic ulcers in the Caucasian population was not because of a high infection rate of *H. pylori*, but because of more conflicts in modern life or civilization, such as financial crisis, unemployment, or interpersonal competition. In addition, *Theory of H. pylori* can explain 'a negative interaction between *H. pylori* and NSAIDs on duodenal ulcers suggests that *H. pylori* reduces the development of ulcers in NSAIDs users (No. 69 in **Supplementary Table S6**)'. However, this observation alone does not indicate that "peptic ulcers are an infectious disease caused by *Helicobacter pylori*".

Hence, of all the 36 observations/phenomena associated with *H. pylori*, *Theory of H. pylori* can explain only 6 (=3+2+1) and falls into inconsistence when it is employed to elucidate all the remaining 30. Unfortunately, none of the 6 explainable observations/phenomena can be used to support "peptic ulcers are an infectious disease caused by *Helicobacter pylori*", suggesting that *Theory of H. pylori* is in fact not supported by any clinical, epidemiological, and laboratory observations/phenomena.

4. Applying historical definition of 'etiological factor' or 'causality' to H. pylori

Starting from "*H. pylori* plays a secondary role in only the late phase of peptic ulceration", *Theory of Nodes* elucidated all the 36 observations/phenomena associated with *H. pylori* within a series of 6 articles, suggesting that it may have identified the role of the bacterium in peptic ulcers. However, this statement raised a new question: can a factor playing a secondary role in only the late phase be considered an etiological factor of the disease? To answer this question, herein the historical definitions of 'etiology' and 'causality' are briefly reviewed and applied to the roles of *H. pylori* in peptic ulcers.

In 1965, Hill proposed 9 criteria to determine causality: strength of the association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogous evidence [48]. These criteria have been most frequently cited to identify causal relationships between potential factors and disease [49,50]. To address the argument above, herein only 'temporality' is applied to the role of *H. pylori* in peptic ulcers. In support of causality, temporality means 'in order for a causal factor to result in an outcome, it must precede the occurrence of the outcome in time' [48]. *H. pylori* infection neither initiates the disease nor precedes the hypersecretion of gastric acid in duodenal ulcers or the formation of submucous nodes in gastric ulcers but plays a secondary role in only the late phase of peptic ulcerations and thus, it is not an etiological factor of the disease.

In 1986, Wulff depicted etiology or causality as 'a linear process where upstream causes represent the etiological factors and the causal intermediates represent the pathological process' [51,52]. When this definition is applied, *H. pylori* is neither an 'upstream cause' nor a causal intermediate but plays a secondary role in only the downstream of the ulceration process. Susser's definition also suggests that "the cause of a disease must precede the effect and occur together with the putative effect" [53]. However, *H. pylori* infection neither precedes the abnormal neurotransmitters supported by innumerable neurological studies on peptic ulcers, nor occurs together with the putative effect as suggested by epidemiological data that ~20% duodenal ulcer patients and ~50% gastric ulcer patients are *H. pylori*-negative [20,28,38,54–56]. Witthöft also proposed that "only causes that directly initiate the disease process (and therefore necessarily temporarily have to precede the onset of the disease) are

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considered etiological factors" [57], further supporting that *H. pylori* is not an etiological factor of peptic ulcers since the infection does not initiate the disease but fortuitously plays a secondary role in only the late phase of the ulceration process.

Therefore, all the existing definitions of 'etiology' and 'causality' do not support "*H. pylori* is an etiological factor of peptic ulcers". Similarly, these definitions are also applicable to gastric acid and NSAIDs. Hence, none of the 3 local aggressive factors in the gastro-duodenum, *H. pylori*, gastric acid, and NSAIDs, is an etiological factor of peptic ulcers; '*No Acid, No Ulcer*' [1] and *Theory of H. pylori* [5], are in fact not etiological theories, but *illusions* in peptic ulcer research.

5. Existing data presented a controversial view on the role of H. pylori

The above analyses indicate that "a causal relationship between *H. pylori* and peptic ulcers" [14], or "*H. pylori* is the most important etiological factor for duodenal ulcers [13]" overstated the roles of *H. pylori* in peptic ulcers. Consequently, studying *H. pylori* as an etiological factor would inevitably lead to controversies, as evidenced by numerous published studies over the past 40 years. In fact, many well-supported controversies on the roles of *H. pylori* in peptic ulcers have been published in multiple peer-reviewed journals.

In 1994, Record and Rubin disputed the causal role of *H. pylori* in peptic ulcers with 4 facts [23]: 1. Not all patients are infected with the bacterium and the infection rate is lower in patients with severe symptoms resulting in complications than in patients with uncomplicated dyspepsia. 2. Epidemiological studies discovered that in most patients, the bacterium is a fortuitous and non-pathogenic agent. 3. Inoculating the bacterium to animals cannot induce ulcerations, and duodenal ulcer patients are known to be hyper-secretors of gastric acid, but the colonization of *H. pylori* induces hypochlorhydria. Notably, Dr. Marshall, who discovered the bacterium, drank a concoction made from cultured *H. pylori* in 1984, "expecting to develop, perhaps years later, an ulcer". However, he did not develop a peptic ulcer, but suffered from gastritis that could be cured with antibiotics [58]. 4. Eradicating the bacterium does not cure the disease. In a follow-up study, 48% of patients relapsed within 6 months of healing after eradicating the bacterium [59]. Based on these facts, Record and Rubin concluded that *H. pylori* was not a causative agent of peptic ulcers [23].

In 1995, Rauws and Tytgat reviewed evidence that was both supporting and opposing "*H. pylori* is an etiological factor for peptic ulcers" [60]. They found that the association between *H. pylori* and ulcer disease was non-specific, since not all ulcer patients were *H. pylori*-positive, and many infected individuals never developed an ulcer. They believed that "most probably, *H. pylori* infection is necessary, but other factors are required for an ulcer to develop". They hypothesized that an increased risk of ulcer with increased density of *H. pylori* infection would strongly support a cause-effect relationship, but only the presence of duodenal ulcers, and not gastric ulcers, was associated with increasing *H. pylori* density [61]. Moreover, if *H. pylori*-induced gastritis is a cause of ulceration, it would be challenging to explain why gastritis is in the stomach, but the ulcer occurs in the duodenum. Furthermore, *H. pylori* infection could not explain the African enigma [30] and why duodenal ulcers had a higher incidence in large cities than in rural areas. Rauws and Tytgat believed that a strong association did not necessarily imply *H. pylori* was the cause of peptic ulcer disease [60].

Tovey and Hobsley listed 4 reasons to disprove "*H. pylori* was the primary cause of duodenal ulcers" [25]: 1. The infection of *H. pylori* is uniformly high in developing countries, but the incidence of duodenal ulcers is remarkably different. 2. In countries with a low infection rate, 30-40% of duodenal ulcer patients are *H. pylori*-negative. 3. *H. pylori* infection could not be detected in some early cases of duodenal ulcers. 4. In duodenal ulcer patients with antral *H. pylori* infection, *H. pylori* is often absent in the duodenum, and a complete eradication of this bacterium could not prevent the relapse of the disease.

There are further data on the controversial role of *H. pylori* in peptic ulcers. In 2009, Ford and Talley insisted that the association was causal, but Hobsley et al. believed that gastric acid secretion was the key to duodenal ulcers [14,22]. In 2001, Elitsur and Lawrence found that *H. pylori* and NSAIDs were not the primary etiology for peptic ulcers in children [62]. Linda and Ransohoff believed that a causal relationship between *H. pylori* and duodenal ulcers could not be established [63]. In 2013, Kate et al. concluded that acid secretion is the most important cause for duodenal ulcers, often combined with reduced mucosal resistance [24]. *H. pylori* eradication is valuable to the long-term healing, but

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this does not mean *H. pylori* infection is the initial or primary cause of the duodenal ulcers [24]. Zelickson's clinical observation found that, of 82 ulcer patients tested, 49 (60%) were *H. pylori*-negative, and of all the 128 patients requiring surgery, only 26% had the infection, suggesting *H. pylori* infection was not a predominant etiological factor of peptic ulcer patients [64].

Evidently, existing data has presented a controversial view on the causal relationship between *H. pylori* and peptic ulcers [65]. In contrast, when *H. pylori* infection is not considered an etiological factor of peptic ulcers, *Theory of Nodes* addressed all the controversies surrounding *H. pylori* and elucidated all the 36 observations/phenomena associated with the bacterium. Significantly, *Theory of Nodes* has elucidated that the hyperplasia and hypertrophy of gastrin and parietal cells in the stomach [32] or the pre-existing submucous nodes in the gastric wall [33] account for other unclear factors or the reduced mucosal resistance in the controversies.

6. Epidemiological studies dispute the causal role of H. pylori in peptic ulcers

Epidemiology is an essential tool to assess risk factors for a disease [66–68]. If there is "a causal relationship between *H. pylori* and peptic ulcers", *Theory of H. pylori* should be able to explain the birth-cohort phenomena [7,69], seasonal variation [8], and African enigma [30], as well as all the other epidemiological observations on peptic ulcers.

The discoverer of the bacterium, Dr. Marshall, could not explain the birth-cohort phenomenon of peptic ulcers by himself [70]. Sonnenberg's mathematical model in 2006 also had evident defects while explaining this phenomena [71]. Other studies attempted to explain the birth-cohort phenomenon by citing the mutation between different strains of *H. pylori*, such as cag- and cag+ [72–76]. However, for this to explain the birth-cohort phenomenon, at the start of the World War I, *H. pylori* would have to mutate to a more virulent strain (cag+) and then upon the resolution of the World War II, revert to a less virulent strain (cag-). This does not follow natural bacterial evolution. Moreover, the birth-cohort phenomenon is not an independent observation that defines peptic ulcers. If the 'mutation theory' is true, then it should explain both the seasonal variation [8] and the African enigma [30]. However, when the 'mutation theory' was used to explain these two phenomena, a fantastic conclusion would have to be drawn: the bacterium mutated back and forth seasonally or regionally. In addition, the seasonal changes of *H. pylori* infection were not in parallel with the seasonal variation of peptic ulcers [77,78], and the infection cannot explain the difference in prevalence of *H. pylori* versus peptic ulcers in Africa, causing the 'African Enigma' [30,60]. In short, *Theory of H. pylori* fails to explain any of the 3 characteristic epidemiological observations of peptic ulcers.

In contrast, based on "peptic ulcers are a psychosomatic disease triggered by psychological stress", *Theory of Nodes* explained all three epidemiological observations. This theory elucidated that the mortality rates of peptic ulcers are parallel with the psychological impacts of multiple environmental factors, which cause the birth-cohort phenomena and seasonal variation by superposition mechanism [35,36]. As per the birth-cohort phenomena, the psychological stress caused by a succession of crucial social events maintained the increased mortality rates from the 1910s to 1940s, whereas the sustained improvements in living environments led to the steady decline of the mortality rates since the early 1950s [35]. Similarly, it is the psychological stress induced by seasonal changes that account for the seasonal variation of peptic ulcers [36]. Interestingly, the mechanism of the birth-cohort phenomenon elucidated by *Theory of Nodes* is also applicable to understanding the African enigma: it is not the prevalence of *H. pylori*, but the diverse living and political environments, social welfare, conflicts, etc. determine the regional difference in the prevalence of peptic ulcers. Thus, *H. pylori* infection is not an etiological factor of peptic ulcers, but it is regarded as an etiological factor by default, resulting in the African enigma [30,60].

In fact, *Theory of H. pylori* cannot explain any one of the epidemiological observations. First, despite a high prevalence of *H. pylori* infection, the incidence of peptic ulcers in children was low [62,79]. Second, *H. pylori* prevalence in gastric ulcer patients was less than 50% [54] and in some countries, up to 40% of duodenal ulcer patients were *H. pylori*-negative [25]. Third, ~20% of peptic ulcers in the Polish population were not associated with *H. pylori* infection [20], and in the US, only 27% of symptomatic children with peptic ulcers were *H. pylori*-positive [62]. Fourth, autopsy reports from three European countries suggested that 20-29% of males and 11%-18% of females had unknowingly suffered from ulcers [80–82]. Finally, duodenal ulcers had higher incidence rates in large cities

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than in rural areas [83,84]. This list further exemplifies the controversies surrounding *H. pylori* as an etiological factor of peptic ulcers.

Theory of Nodes fully addressed all the epidemiological observations. The occurrence of peptic ulcers is not determined by *H. pylori* infection, but by the hyperplasia and hypertrophy of gastrin and parietal cells in stomach or the negative life-view induced by psychosomatic factors in early life [32,33]. Only those affected by psychosomatic factors and psychological stress become ulcer patients [32,33], explaining a high prevalence of *H. pylori* infection, but a low incidence of peptic ulcers. The *H. pylori*-negative gastric and duodenal ulcer patients (50% and 40%, respectively [25,54]) also support the conclusion of *Theory of Nodes* that *H. pylori* is not an etiological factor of peptic ulcers. In addition, only 27% of symptomatic children with peptic ulcers were *H. pylori*-positive [62], indicating ulcers in 73% of younger patients are not associated with the bacterium because they encounter less opportunities of exposure to infection in their short lifetime. From 1900's to 1950's, men were more likely to be the direct participants of social conflicts, such as wars and financial crisis, and they were more likely to bear economical pressures than women, supporting the autopsy findings that a higher percentage of males (20-29%) than females (11%-18%) had unknowingly suffered from ulcers. A more stressful life with highly intensive social competition explains the higher incidence of peptic ulcers in large cities as compared to rural areas.

Therefore, *H. pylori* infection cannot explain any one of the epidemiological observations associated with peptic ulcers. In contrast, if peptic ulcers are considered a psychosomatic disease triggered by psychological stress, all the epidemiological observations and mysteries can be fully understood, further suggesting that *H. pylori* infection is not the cause of the disease.

7. Characteristics of peptic ulcers dispute the causal role of H. pylori in this disease

If *H. pylori* infection is considered an etiological factor of peptic ulcers, none of the 15 major characteristics of this disease, including the one associated with the bacterium itself, can be fully explained. In contrast, when peptic ulcers are considered a psychosomatic disease triggered by psychological stress, all the 15 major characteristics of peptic ulcers, as well as the role of *H. pylori* in the disease, can be fully elucidated.

First, *Theory of H. pylori* cannot explain the predilection sites and morphology of gastric ulcers. The *H. pylori* density was significantly higher in the incisura angularis, which is located not on the gastric antrum, but on the lesser curvature of the stomach [85]. However, gastric ulcers are more likely to occur not in the lesser curvature, but in the gastric antrum. Moreover, since *H. pylori* is omnipresent in the stomach, all regions of the stomach should have the chance to ulcerate, but gastric ulcers have a predilection site in the gastric antrum and lesser curvature, and a characteristic 'punch out' appearance with clean edges, as if it were cut by a knife [10,29]. In contrast, *Theory of Nodes* dictates that the predilection sites of gastric ulcers are determined by the location where the submucosal nodes occur, which is determined by the nerve density in the stomach. Compared to other parts of the stomach, the gastric antrum and lesser curvature have the largest ganglions and the highest density of developed nerve plexus [86]. Thus, they receive more pathogenic nerve impulses from the CNS than other parts of the stomach, thereby becoming the predilection sites of gastric ulcers. The spherical shape of the submucosal nodes gives gastric ulcers a characteristic 'hole-punch' shape [33].

Second, *H. pylori* infection cannot explain the relapse, multiplicity, and self-healing of peptic ulcers. If *H. pylori* was the cause of ulcers, eliminating this bacterium should prevent the relapse, but in fact, numerous data indicates that a complete eradication of the bacterium cannot prevent the relapse [37,42,87,88]. As a result, *Theory of H. pylori* fails to explain '*Once an Ulcer, Always an Ulcer*'. Moreover, *Theory of H. pylori* cannot explain why at times an individual ulcer appears and at other times, they occur in multiples. In *Theory of Nodes*, as long as the negative impacts of psychosomatic factors and psychological stress continue to exist, the relapse of peptic ulcers will be inevitable, resulting in '*Once an Ulcer, Always an Ulcer*'. Thus, it is the relapse and multiplicity of submucous nodes in the gastric wall that determine the relapse and multiplicity of gastric ulcers [33]. The solitude and/or multiplicity of submucous nodes are determined by the local neuroanatomy in the stomach, which may vary individually. In *Theory of Nodes*, peptic ulcers heal automatically via the regeneration of the local tissue, like a wound healing on the skin, but the local aggressive factors, gastric acid, *H. pylori*, and NSAIDs, may delay the healing process.

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Third, *Theory of H. pylori* cannot explain the bleeding and perforation of peptic ulcers. It cannot explain a lower prevalence of *H. pylori* infection in patients with bleeding peptic ulcers [89,90]. A study found that 62% of patients with perforated peptic ulcers were *H. pylori*-positive, but the infection was detected in 87% of ulcer patients without this complication [91]. In *Theory of Nodes*, the bleeding and perforation indicates the patients are severely impacted by psychological stress, causing higher hypersecretion of gastric acid for duodenal ulcers and larger submucous nodes for gastric ulcers. If large blood vessels are close to or within the nodes, they rupture during ulceration, causing bleeding. If the nodes are deep in the serosa, the ulcer will penetrate deep into the serosa, resulting in the perforation of gastric ulcers. In contrast, the patients without the complication of bleeding and perforation are more likely to be subclinical ulcer patients if not infected with *H. pylori*. It is the infection that turns the subclinical ulcer patients into clinical patients. Thus, mildly symptomatic clinic patients are more likely to be infected with the bacterium. In this case, the percentage of *H. pylori*-infected patients without complications is higher than the percentage of *H. pylori*-infected patients with bleeding and perforation.

Fourth, the different etiology, epidemiology and genetics of gastric versus duodenal ulcers indicate that although gastric and duodenal ulcers share some common features, they are two different diseases [10,66]. *Theory of H. pylori* cannot describe the similarities and differences between gastric and duodenal ulcers. In contrast, without taking *H. pylori* infection into consideration, *Theory of Nodes* clearly identified the similarities and differences between the two diseases [34]. Both are a psychosomatic disease triggered by psychological stress due to specific personality traits and/or stressful life events, which lead to abnormal neurotransmitters in the central nervous system and pathogenic nerve impulses to the stomach. However, duodenal and gastric ulcer patients are genetically different individuals in the population. The effector organs of both diseases are the stomach, but duodenal ulcers are characterized by the hypersecretion of gastric acid, whereas gastric ulcers are characterized by immediate formation of submucosal nodes in the gastric wall. Additionally, *Theory of H. pylori* cannot explain why all the stress-induced ulcers in the lab are gastric ulcers, and how chemicals can induce duodenal ulcers in normal rats without the presence of *H. pylori* [92]. In contrast, *Theory of Nodes* elucidates that animal models can only simulate acute stress, which merely causes gastric ulcers, and chemicals interact directly with the effector organs of stress-induced pathogenic nerve impulses, resulting in hypersecretion and eventually, duodenal ulcers. In that case, *H. pylori* is not essential for duodenal ulcerations.

Fifth, many peptic ulcer patients, but not all, were infected with *H. pylori*. As a result, the infection is an important characteristic of this disease and is currently a hot topic in peptic ulcer research. However, *Theory of H. pylori* cannot explain why only the presence of duodenal ulcers was associated with *H. pylori* density, whereas the association between gastric ulcers and *H. pylori* is less clear [61]. *Theory of Nodes* dictates that duodenal ulceration is caused by a superposition of all local aggressive factors in the duodenum. The higher the density of *H. pylori*, the higher the local aggressive intensity that erodes the duodenal bulbs. Therefore, the increasing density of *H. pylori* is associated with the presence of duodenal ulcers. In contrast, gastric ulceration is determined by the formation of submucosal nodes, not the local aggressive factors, leading to the significantly weaker association between gastric ulcers and *H. pylori* infection.

Sixth, since *H. pylori* is not an etiological factor for peptic ulcers, *Theory of Nodes* predicts that animal models for the disease induced by *H. pylori* alone cannot be established. Studies showed that although *H. pylori* infection in rats has been established, the inoculation could induce only mild to moderate mucosal inflammation, and that ulcers could be induced in the oxyntic mucosa of both infected and uninfected rats by exposing the serosal side to acetic acid [19]. Interestingly, Dr. Marshall drank a concoction made from cultured *H. pylori* and came down with gastritis that could be cured with antibiotics [93]. He did not develop peptic ulcers as expected, but gastritis only, also suggesting that the infection of *H. pylori* is not the cause of peptic ulcers.

Historical observations/phenomenon dispute the role of H. pylori in peptic ulcers

Although the 5 major etiological theories in history cannot explain the pathogenesis of peptic ulcers, they were supported by numerous valid clinical, laboratory, and epidemiological observations, and did make important discoveries for this disease. These historical observations/phenomena,

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including those associated with *H. pylori*, can be used to test if there is a causal relationship between *H. pylori* and peptic ulcers.

First, it is challenging for *Theory of H. pylori* to explicate the data originated from both *Psychosomatics Theory* and *Stress Theory*. *Theory of H. pylori* cannot withstand the results from a multi-dimensional case-controlled study in 1986, which discovered a strong association between life events, psychosocial factors and ulcer disease, and ulcer patients exhibited significantly more emotional distress in forms of depression and anxiety [94]. *Theory of H. pylori* also cannot explain why stressful life events frequently precede the onset of ulcer symptoms in both newly diagnosed and chronic ulcer patients, and ulcer symptoms subside after stressful life events are resolved [95,96]. There is also no relationship between *H. pylori* and the crucial social events that occurred in the first half of the 20th century, thought by Susser and Stein to cause the birth-cohort phenomenon of peptic ulcers [7,97]. In contrast, *Theory of Nodes* elucidated that in the pathological process of peptic ulcers, life events/stress occur in the early phase (upstream) of the disease, whereas *H. pylori* is in the late phase (downstream) of disease, exacerbating clinical symptoms. Notably, if *H. pylori* infection is considered an etiological factor of peptic ulcers, none of the observations/phenomena in psychological research can be elucidated.

Second, studies from *Nerve Theory* suggested that peptic ulcers were a '*brain-driven*' event [98,99], and the central noradrenergic system was activated when animals were subject to ulcerogenic stress procedures [98–102]. Gastric ulceration was linked with the enhancement of calcium/calmodulin-dependent catecholamine synthesis in the brain as indicated by the observations that pre-treatment with intraperitoneal EDTA (calcium-chelator) or $CaCl_2$ significantly decreased or increased gastric ulcers induced by cold stress, respectively [101]. Moreover, the amygdala might be the brain site for modulating stress-induced gastric erosions [98,103,104], and manipulation of the central nucleus of the amygdala may produce gastric ulcers [98,103,105,106]. In addition, many peptic ulcer patients have psychological symptoms such as anxiety, irritability, depression, or poor appetite [107–109]. None of these findings can be elucidated by *Theory of H. pylori*. *Theory of Nodes* elucidated that the neurological observations discovered the intermediate phase (midstream) of peptic ulcerations, whereas *H. pylori* infection is in the downstream (late phase). Unequivocally, the midstream neurological process is not caused by the downstream *H. pylori* infection.

Third, duodenal ulcer patients have increased basal and maximal acid secretion, whereas most gastric ulcer patients are normo- or hypo-secretors [110,111]. Hence, Schwartz's dictum '*No Acid, No Ulcer*' remains true only for duodenal ulcers [112]. If *H. pylori* is an etiological factor for peptic ulcers, then *Theory of H. pylori* should be able to explain the differences in gastric acid secretion between duodenal and gastric ulcers. However, *Theory of H. pylori* cannot explain all these clinical findings [95]. If *H. pylori* was the most important etiological factor for duodenal ulcers as stated by Marshall, *H. pylori* infection should account for the hypersecretion of gastric acid, but on the contrary, *H. pylori* infection was found to suppress gastric acid secretion, causing increased pH of gastric juice [95], and no consistent hypersecretion of gastric acid was observed after *H. pylori* infection [113,114]. *Theory of Nodes* fully elucidated the differential relationship of gastric acid in duodenal versus gastric ulcers, which had no causal relationship with *H. pylori* infection. Duodenal ulceration results from the superposition of all local aggressive factors in the gastro-duodenum, where the hypersecretion of gastric acid due to psychosomatic factors in early life determines all the local characteristics of the disease, and this agrees with the findings that duodenal ulcer patients have increased basal and maximal acid secretion [112,115]. In contrast, gastric ulceration is determined not by any of the local aggressive factors in the stomach, such as *H. pylori*, gastric acid, and NSAIDs, but by the formation of submucosal nodes in the gastric wall, and this is supported by the findings that most of gastric ulcer patients are normo- or hypo-secretors.

A comprehensive literature review on peptic ulcers found that the research originated from *Psychosomatics Theory*, *Stress Theory*, *Nerve Theory*, and '*No Acid, No Ulcer*' did make important discoveries on peptic ulcers [5]. Therefore, the historical data from 1900 to 1990 is indispensable for a full understanding of the etiology and pathogenesis of peptic ulcers. However, all these important historical findings were overshadowed by Marshall's proposal "peptic ulcers are an infectious disease caused by *H. pylori*".

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8. The comparative effectiveness research identified an illusion in medicine

The data analyses above suggest that, if peptic ulcers are considered an infectious disease caused by *H. pylori*, none of the 15 major characteristics can be fully understood, and 75 of the 81 observations/phenomena remain elusive. What is more, this etiology has led to more controversies and mysteries than the other etiological theories of the disease. In contrast, if peptic ulcers are considered a psychosomatic disease triggered by psychological stress, all the 15 major characteristics and 81 observations/phenomena can be fully addressed in a series of 6 articles, along with all the controversies and mysteries associated with this disease (**Supplementary Table S1-S6**). This sixth article explained 8 observations/phenomena (**Supplementary Table S5-S6**). A detailed comparison between *Theory of H. pylori* and *Theory of Nodes* is curated into **Table 2**.

Table 2. A comparison between *Theory of H. pylori* and *Theory of Nodes*.

Etiological Theory	***Theory of H. Pylori* [12]**	***Theory of Nodes* [32–36]**
15 major characteristics [5]	**None of the 15 can be explained**	**All the 15 are fully explained**
Etiology	Peptic ulcers are an infectious disease caused by the infection of *H. pylori* [12].	Peptic ulcers are a psychosomatic disease triggered by psychological stress [32].
Morphology of gastric ulcers [116]	Remains unknown	Explained, the only phenomenon needs to be verified [33].
Predilection sites of gastric ulcers [117]	Remains unknown	Explained [33].
Relapse and Multiplicity [87,118]	Remains unknown	Explained [33].
Bleeding and Perforation [119]	Remains unknown	Explained [33].
Epidemiology	3 observations/phenomena were used as supporting evidences [17]; it might be able explain the other 3 observations. All the others remain unexplained.	All explained [32–36]. All 3 supporting evidences in *Theory of H. pylori* were deceiving, and 2 of the other 3 *H. pylori* explainable observations were mis-interpreted in *Theory of H. pylori*.
81 observations/ Phenomenon [5]	**75 of 81 cannot be explained; 45 are unrelated to *H pylori*.**	**All 81 are explained; leaves no observations/phenomena unknown**
36 observations/phenomena associated with *H. pylori*	30 of 36 cannot be explained.	All 36 are explained [32–36].
45 observations/phenomenon not associated with *H. pylori*	None can be explained because many patients are *H. pylori*-negative [38,54,55].	All 45 are explained [32–36].
4 Controversies	**None of the 4 is addressed**	**All 4 are addressed clearly**
Roles of *H. pylori*	Controversial [14,22–25]	Addressed: *H. pylori* is not an etiological factor but plays a secondary role in only the late phase of ulceration [32–34].
Roles of gastric acid	Unknown and controversial [14,112]	Addressed [32,33].
Roles of NSAIDs	Unknown [28,56,73,120–123]	Addressed [32,33].
Idiopathic peptic ulcers	Unknown [20,28,56]	Addressed [32,33].
3 Major Mysteries	**None of the 3 is resolved**	**All 3 are resolved clearly.**
Birth-cohort Phenomena [69,124]	Remains a mystery [69,70]	Resolved [35].
Seasonal Variations [8]	Remains a mystery	Resolved [36].

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African Enigma [30]	Remains a mystery	Resolved in this article: identified as an *illusion* due to incorrect etiology.
Similarities and differences between gastric and duodenal ulcers [9,10]	**Remains unknown.**	**Fully illustrated** [33].
Therapy/effect	**Antiacid and antibiotics treatments are the primary therapy; relapse frequently**	**Psychological treatments are the primary therapy; no relapse** [34]**.**
Summary	1. Theory of *H. Pylori* cannot fully explain the pathogenesis of peptic ulcers. 2. *H. Pylori* infection cannot explain any one of the 15 characteristics and 75 of 81 observations/phenomena of peptic ulcers. 3. Not superior to any other etiological theory in history but has led to more controversies and mysteries.	1. *Theory of Nodes* explained the pathogenesis of peptic ulcers. 2. This etiological theory leaves no characteristics, observations/phenomena, controversies, and mysteries of peptic ulcers unknown. 3. A causal relationship between *H. pylori* and peptic ulcers is a typical *illusion* in modern medicine.

An etiological theory proposing the correct cause should be able to explain all the characteristics and observations/phenomena of the disease [5]. The comparative analysis in **Table 2** suggested that the 15 major characteristics and 81 observations/phenomena of peptic ulcers cannot be fully understood unless the disease is considered a psychosomatic disease triggered by psychological stress as demonstrated in *Theory of Nodes*. The effectiveness suggests that *Theory of Nodes* may have identified the etiology of peptic ulcers, in which *H. pylori* infection is not the cause but was studied as the (primary) cause of the disease. As a result, little progress has been made in peptic ulcer research over the past 36 years, and eradication of the bacterium cannot prevent the relapse [37,42,87,88]. This kind of error may widely exist in the research on almost all diseases. Consequently, so far, no disease has been fully understood in modern medicine. Thus, it is essential to introduce an important concept, *illusion*, to the medical community, wherein an idea, belief, or impression may appear convincing but is in fact misleading and results in misdirection.

If "peptic ulcers are an infectious disease caused by *H. pylori*" is considered an *illusion* in the field, it is easy to understand why *Theory of H. pylori* cannot explain all the 15 major characteristics and the majority of 81 observations/phenomenon but cause more controversies and mysteries. This *illusion* was a direct interference with the true understanding of peptic ulcers for more than 3 decades. First, due to this *illusion*, the real cause of peptic ulcers, proposed by *Psychosomatic Theory* and *Stress Theory* in 1950, was discredited, and the field of research was misdirected to focus on the infection of *H. pylori* [125]. The data analyses in *Theory of Nodes* suggests that *Psychosomatic Theory* and *Stress Theory* could not explain the pathogenesis of peptic ulcers for the past 70 years, primarily because the methodology, epistemology, and way of thinking essential for data analyses have never been established in modern medicine. Second, also due to the *H. pylori illusion*, *Nerve Theory* and *'No Acid, No Ulcer'*, which were proved to have uncovered important intermediate processes for a full understanding of peptic ulcers in *Theory of Nodes*, were also considered outdated in modern medicine. Third, this tunnel vision (*H. pylori illusion*) also resulted in the failure of establishing effective analytical methods to address multiple mysteries, such as the birth-cohort phenomenon and seasonal variation of peptic ulcers. It took an unbiased, comprehensive review of historical studies and novel data analyses guided by a new causal relationship (the CCR) with its accompanying methodologies specific for life science and medicine to develop an integrative theory, *Theory of Nodes*, to fully explain the pathogenesis of peptic ulcers [32–36].

9. Conclusions

The etiology based on *H. pylori* infection cannot explain any of the 15 major characteristics and the majority of 81 observations/phenomena of peptic ulcers but has led to more controversies and mysteries. In contrast, if peptic ulcers are considered a psychosomatic disease triggered by

psychological stress, all the 15 characteristics and 81 observations/phenomena, along with all the controversies and mysteries associated with peptic ulcers, can be fully addressed. The tremendous contrast suggests that peptic ulcers are not an infectious disease caused by *H. pylori*, but a psychosomatic disease triggered by psychological stress. Moreover, the definitions of 'etiological factor' and 'causality' do not support "*H. pylori* is an etiological factor of peptic ulcers", and the existing literatures have also presented a controversial view on the causal role of *H. pylori* in peptic ulcers. Meanwhile, all the epidemiological studies, characteristics of the disease, and historical observations indicate that "peptic ulcers are an infectious disease caused by *H. pylori*" is an illusion, which discredited useful discoveries from other etiological theories in history and misdirected peptic ulcer research to focus on *H. pylori* infection. As a result, very little progress has been made in the field over the past 36 years. The research on all the other diseases might be very similar to peptic ulcer research. Consequently, none of diseases has ever been fully understood in modern medicine, suggesting that medical doctors should always keep the concept "illusion" in mind during research.

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References.

1 Fatović-Ferenčić S: Banić M. No acid, no ulcer: Dragutin (Carl) Schwarz (1868-1917), the man ahead of his time. *Dig Dis* 2011;**29**:507–10. doi:10.1159/000334384
2 von Bergmann G. Ulcus duodeni und vegetatives nerve system. *Berl Klin Wchnscher* 1913;**50**:2374.
3 Wolowitz HM. Oral involvement in peptic ulcer. *J Consult Psychol* 1967;**31**:418–9. doi:10.1037/h0024861
4 Selye H. *The physiology and pathology of exposure to stress*. Oxford, England: : Acta 1950.
5 Dong SXM, Chang CCY, Rowe KJ. A collection of the etiological theories, characteristics, and observations/phenomena of peptic ulcers in existing data. *Data Br* 2018;**19**:1058–67. doi:10.1016/j.dib.2018.05.022
6 Kuang H. *Peptic Ulcer Diseases*. Beijing: : People's Medical Publishing House 1990.
7 Susser M, Stein Z. Civilization and Peptic Ulcer. *Lancet* 1962;**279**:116–9. doi:10.1016/S0140-6736(62)91127-3
8 Sonnenberg A, Wasserman IH, Jacobsen SJ. Monthly variation of hospital admission and mortality of peptic ulcer disease: A reappraisal of ulcer periodicity. *Gastroenterology* 1992;**103**:1192–8. doi:10.1016/0016-5085(92)91503-V
9 Susser M. Peptic Ulcer: Rise and Fall. Christie DA, Tansey EM (eds). Wellcome Witnesses to Twentieth Century Medicine. Vol.14, 2002. London: The Wellcome Trust Centre for the History of Medicine, 2002, £10.00 ISBN: 0-85484-084-2. *Int J Epidemiol* 2003;**32**:674–5. doi:10.1093/ije/dyg194
10 Damon A, Polednak AP. Constitution, genetics, and body form in peptic ulcer: A review. *J Chronic Dis* 1967;**20**:787–802. doi:10.1016/0021-9681(67)90091-4
11 Ciacci C, Mazzacca G. The history of Helicobacter pylori: A reflection on the relationship between the medical community and industry. *Dig Liver Dis* 2006;**38**:778–80. doi:10.1016/j.dld.2006.06.013
12 Marshall BJ. Peptic Ulcer: An Infectious Disease? *Hosp Pract* 1987;**22**:87–96. doi:10.1080/21548331.1987.11703288
13 Marshall BJ, Goodwin CS, Warren JR, *et al*. Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. *Lancet (London, England)* 1988;**2**:1437–42. doi:10.1016/s0140-6736(88)90929-4

14 Hobsley M, Tovey FI, Bardhan KD, *et al.* Does Helicobacter pylori really cause duodenal ulcers? No. *BMJ* 2009;**339**:b2788. doi:10.1136/bmj.b2788

15 Peterson WL. Review article: Helicobacter pylori and peptic ulcer disease. *N Engl J Med* 1991;**324**:1043–8. doi:10.1360/012011953

16 Veldhuyzen van Zanten SJ, Sherman PM. Helicobacter pylori infection as a cause of gastritis, duodenal ulcer, gastric cancer and nonulcer dyspepsia: a systematic overview. *CMAJ* 1994;**150**:177–85.http://www.ncbi.nlm.nih.gov/pubmed/8287340

17 Walsh JH, Peterson WL. The Treatment of Helicobacter pylori Infection in the Management of Peptic Ulcer Disease. *N Engl J Med* 1995;**333**:984–91. doi:10.1056/NEJM199510123331508

18 Graham DY. Helicobacter pylori: its epidemiology and its role in duodenal ulcer disease. *J Gastroenterol Hepatol* 1991;**6**:105–13.http://www.ncbi.nlm.nih.gov/pubmed/1912414

19 Li H, KALIES I, MELLGÅRD B, *et al.* A Rat Model of Chronic Helicobacter pylori Infection: Studies of Epithelial Cell Turnover and Gastric Ulcer Healing. *Scand J Gastroenterol* 1998;**33**:370–8. doi:10.1080/00365529850170991

20 Konturek SJ, Bielanski W, Plonka M, *et al.* Helicobacter pylori, non-steroidal anti-inflammatory drugs and smoking in risk pattern of gastroduodenal ulcers. *Scand J Gastroenterol* 2003;**38**:923–30. doi:10.1080/00365520310004696

21 Rauws EJ, Tytgat GNJ. Helicobacter pylori in duodenal and gastric ulcer disease. *Baillière's Clin Gastroenterol* 1995;**9**:529–47. doi:https://doi.org/10.1016/0950-3528(95)90047-0

22 Ford, Alexander C.; Tally NJ. Head to Head: Does Helicobacter pylori really cause duodenal ulcers? Yes. *BMJ* 2009;**339**:b2784. doi:10.1136/bmj.b2784

23 Record CO, Rubin PC. Controversies in Management: Helicobacter pylori is not the causative agent. *BMJ* 1994;**309**:1571–2. doi:10.1136/bmj.309.6968.1571

24 Kate V, Ananthakrishnan N, Tovey FI. Is Helicobacter pylori Infection the Primary Cause of Duodenal Ulceration or a Secondary Factor? A Review of the Evidence. *Gastroenterol Res Pract* 2013;**2013**:1–8. doi:10.1155/2013/425840

25 Tovey FI, Hobsley M. Review: is Helicobacter pylori the primary cause of duodenal ulceration? *J Gastroenterol Hepatol* 1999;**14**:1053–6. doi:10.1046/j.1440-1746.1999.02005.x

26 Tan VPY, Wong BCY. Helicobacter pylori and gastritis: Untangling a complex relationship 27 years on. *J Gastroenterol Hepatol* 2011;**26**:42–5. doi:10.1111/j.1440-1746.2010.06593.x

27 Musumba C, Pritchard DM, Pirmohamed M. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. *Aliment Pharmacol Ther* 2009;**30**:517–31. doi:10.1111/j.1365-2036.2009.04086.x

28 Gisbert JP, Calvet X. Review article: Helicobacter pylori-negative duodenal ulcer disease. *Aliment Pharmacol Ther* 2009;**30**:791–815. doi:10.1111/j.1365-2036.2009.04105.x

29 Carton J, Daly R, Ramani P. *Clinical Pathology*. Oxford University Press 2007.

30 Holcombe C. Helicobacter pylori: the African enigma. *Gut* 1992;**33**:429–31. doi:10.1136/gut.33.4.429

31 Dong SXM, Chang CCY. *Philosophical Principles of Life Science*. Taipei: : Wunan Culture Enterprise 2012.

32 Dong SXM. The Hyperplasia and Hypertrophy of Gastrin and Parietal Cells Induced by Chronic Stress Explain the Pathogenesis of Duodenal Ulcers. *J Ment Heal Clin Psychol* 2022;**6**:1–12. doi:10.29245/2578-2959/2022/3.1257

33 Xin Min Dong S. A Novel Psychopathological Model Explains the Pathogenesis of Gastric Ulcers. *J Ment Heal Clin Psychol* 2022;**6**:13–24. doi:https://doi.org/10.29245/2578-2959/2022/3.1159

34 Dong SXM. Painting a complete picture of the pathogenesis of peptic ulcers. *Jounral Ment Heal Clin Psychol* 2022;**6**:32–43. doi:10.29245/2578-2959/2022/3.1261

35 Dong SXM. Novel data analysese explain the birth-cohort phenomenon of peptic ulcers. *Preprint* Published Online First: 2023. doi:10.20944/preprints202302.0193.v2

36 Dong SXM. Novel data analyses explain the seasonal variations of peptic ulcers. *Preprint* 2023;:2023020271. doi:10.20944/preprints202302.0271.v2

37 Taskin V, Gurer I, Ozyilkan E, *et al.* Effect of Helicobacter pylori eradication on peptic ulcer disease complicated with outlet obstruction. *Helicobacter* 2000;**5**:38–40.

38 Freston JW. Role of proton pump inhibitors in non-H. pylori-related ulcers. *Aliment Pharmacol Ther* 2001;**15**:2–5. doi:10.1046/j.1365-2036.2001.00114.x

39 Penston JG. Helicobacter pylori eradication–understandable caution but no excuse for inertia. *Aliment Pharmacol Ther* 1994;**8**:369–89.

40 Borody TJ, Cole P, Noonan S, *et al.* Recurrence of duodenal ulcer and Campylobacter pylori infection after eradication. *Med J Aust* 1989;**151**:431–5.

41 Cutler A V, Schubert TT. Long-term Helicobacter pylori recurrence after successful eradication with triple therapy. *Am J Gastroenterol* 1993;**88**:1359–61.

42 Okimoto T, Murakami K, Sato R, *et al.* Is the recurrence of Helicobacter pylori infection after eradication therapy resultant from recrudescence or reinfection, in Japan. *Helicobacter* 2003;**8**:186–91.http://www.ncbi.nlm.nih.gov/pubmed/12752730

43 Katz P. Once an ulcer, always an ulcer? *Am J Gastroenterol* 1994;**89**:808–9.http://www.ncbi.nlm.nih.gov/pubmed/8172163

44 Miller JP, Faragher EB. Relapse of duodenal ulcer: does it matter which drug is used in initial treatment? *BMJ* 1986;**293**:1117–8. doi:10.1136/bmj.293.6555.1117

45 Bateson EM. Duodenal Ulcer-Does it Exist in Australian Aborigines? *Aust N Z J Med* 1976;**6**:545–7. doi:10.1111/j.1445-5994.1976.tb03991.x

46 Hesse FG. Incidence of cholecystitis and other diseases among Pima Indians of Southern Arizona. *J Am Med Assoc* 1959;**170**:1789–90.http://www.ncbi.nlm.nih.gov/pubmed/13672772

47 Sievers ML, Marquis JR. Duodenal Ulcer among Southwestern American Indians. *Gastroenterology* 1962;**42**:566–9. doi:10.1016/S0016-5085(62)80074-2

48 Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965;**58**:295–300.https://linkinghub.elsevier.com/retrieve/pii/S0079742108605629

49 van Reekum R, Streiner DL, Conn DK. Applying Bradford Hill's Criteria for Causation to Neuropsychiatry. *J Neuropsychiatry Clin Neurosci* 2001;**13**:318–25. doi:10.1176/jnp.13.3.318

50 Fedak KM, Bernal A, Capshaw ZA, *et al.* Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015;**12**:14. doi:10.1186/s12982-015-0037-4

51 Wulff HR. Rational Diagnosis and Treatment. *J Med Philos* 1986;**11**:123–34. doi:10.1093/jmp/11.2.123

52 Ross LN. The doctrine of specific etiology. *Biol Philos* 2018;**33**:37. doi:10.1007/s10539-018-9647-x

53 Susser M. What is a Cause and How Do We Know One? A Grammar for Pragmatic Epidemiology. *Am J Epidemiol* 1991;**133**:635–48. doi:10.1093/oxfordjournals.aje.a115939

54 Jones MP. The role of psychosocial factors in peptic ulcer disease: Beyond Helicobacter pylori and NSAIDs. *J Psychosom Res* 2006;**60**:407–12. doi:10.1016/j.jpsychores.2005.08.009

55 Kato S, Nishino Y, Ozawa K, *et al.* The prevalence of Helicobacter pylori in Japanese children with gastritis or peptic ulcer disease. *J Gastroenterol* 2004;**39**:734–8. doi:10.1007/s00535-004-1381-2

56 Iijima K, Kanno T, Koike T, *et al.* Helicobacter pylori-negative, non-steroidal anti-inflammatory drug: Negative idiopathic ulcers in Asia. *World J Gastroenterol* 2014;**20**:706. doi:10.3748/wjg.v20.i3.706

57 Witthöft M. Etiology/Pathogenesis. In: Gellman MD, Turner JR, eds. *Encyclopedia of Behavioral Medicine*. Springer, New York, NY 2013. doi:10.1007/978-1-4419-1005-9_16

58 Wikipedia. Barry Marshall. Wikipedia, Free Encycl. 2020.https://en.wikipedia.org/wiki/Barry_Marshall

59 Porro GB, Lazzaroni M. Campylobacter pylori and ulcer recurrence. *Lancet* 1988;**331**:593.

60 Rauws EAJJ, Tytgat GNJJ. Helicobacter pylori in duodenal and gastric ulcer disease. *Baillieres Clin Gastroenterol* 1995;**9**:529–47. doi:10.1016/0950-3528(95)90047-0

61 Alam K, Schubert TT, Bologna SD, *et al.* Increased Density of Helicobacter pylori on Antral Biopsy is Associated with Severity of Acute and Chronic Inflammation and Likelihood of Duodenal Ulceration. *Am J Gastroenterol* 1992;**87**:424–8.

62 Elitsur Y, Lawrence Z. Non-Helicobacter pylori related duodenal ulcer disease in children. *Helicobacter* 2001;**6**:239–43. doi:10.1046/j.1523-5378.2001.00034.x

63 Linda R, Ransohoff DF. Is helicobacter pylori a cause of duodenal ulcer? A methodologic critique of current evidence. *Am J Med* 1991;**91**:566–72. doi:10.1016/0002-9343(91)90207-E

64 Zelickson MS, Bronder CM, Johnson BL, *et al.* Helicobacter pylori is not the predominant etiology for peptic ulcers requiring operation. *Am Surg* 2011;**77**:1054–60.http://www.ncbi.nlm.nih.gov/pubmed/21944523

65 Scholl R. Peptic ulcer disease and helicobacter pylori: How we know what we know [Article in German]. *Ther Umschau* 2015;**72**:475–80. doi:10.1024/0040-5930/a000703

66 Taylor F. Essential Epidemiology: Principles and Applications. *Int J Epidemiol* 2003;**32**:671–671. doi:10.1093/ije/dyg219

67 Blumenthal U, Fleisher J, Esrey S, *et al.* Epidemiology – a tool for the assessment of risk. In: Bartram LF and J, ed. *Water Quality: Guidelines, Standards and Health.* London, UK.: : IWA Publishing 2001. 135–60.http://discovery.ucl.ac.uk/76470/

68 Jin J, Zhou S, Xu Q, *et al.* Identification of risk factors in epidemiologic study based on ROC curve and network. *Sci Rep* 2017;**7**:46655. doi:10.1038/srep46655

69 Susser M, Stein Z. Civilization and peptic ulcer*. *Int J Epidemiol* 2002;**31**:13–7. doi:10.1093/ije/31.1.13

70 Marshall B. Commentary: Helicobacter as the 'environmental factor' in Susser and Stein's cohort theory of peptic ulcer disease. *Int J Epidemiol* 2002;**31**:21–2. doi:10.1093/ije/31.1.21

71 Sonnenberg A. Causes underlying the birth-cohort phenomenon of peptic ulcer: analysis of mortality data 1911–2000, England and Wales. *Int J Epidemiol* 2006;**35**:1090–7. doi:10.1093/ije/dyl093

72 Graham DY, Yamaoka Y. H. pylori and cagA: Relationships with gastric cancer, duodenal ulcer, and reflux esophagitis and its complications. *Helicobacter* 1998;**3**:145–51. doi:10.1046/j.1523-5378.1998.08031.x

73 Henriksson AE, Edman AC, Nilsson I, *et al.* Helicobacter pylori and the relation to other risk factors in patients with acute bleeding peptic ulcer. *ScandJ Gastroenterol* 1998;**33**:1030–3.

74 Hurlimann S, Dür S, Schwab P, *et al.* Effects of Helicobacter pylori on gastritis, pentagastrin-stimulated gastric acid secretion, and meal-stimulated plasma gastrin release in the absence of peptic ulcer disease. *Am J Gastroenterol* 1998;**93**:1277–85. doi:10.1111/j.1572-0241.1998.409_x.x

75 Yamaoka Y, Kodama T, Kita M, *et al.* Relation between clinical presentation, Helicobacter pylori density, interleukin 1beta and 8 production, and cagA status. *Gut* 1999;**45**:804–11. doi:10.1136/gut.45.6.804

76 Weel JFL, van der Hulst RWM, Gerrits Y, *et al.* The Interrelationship between Cytotoxin-Associated Gene A, Vacuolating Cytotoxin, and Helicobacter pylori-Related Diseases. *J Infect Dis* 1996;**173**:1171–5. doi:10.1093/infdis/173.5.1171

77 Savarino V, Mela GS, Zentilin P, *et al.* Are Duodenal Ulcer Seasonal Fluctuations Paralleled by Seasonal Changes in 24-Hour Gastric Acidity and Helicobacter Pylori Infection? *J Clin Gastroenterol* 1996;**22**:178–81. doi:10.1097/00004836-199604000-00005

78 Raschka C, Schorr W, Koch HJ. Is There Seasonal Periodicity in the Prevalence of Helicobacter Pylori? *Chronobiol Int* 1999;**16**:811–9. doi:10.3109/07420529909016947

79 Oderda G, Vaira D, Holton J, *et al.* Helicobacter pylori in children with peptic ulcer and their families. *Dig Dis Sci* 1991;**36**:572–6. doi:10.1007/BF01297021

80 Watkinson G. The Incidence of Chronic Peptic Ulcer Found at Necropsy: A Study of 20,000 Examinations Performed in Leeds in 1930-49 and in England and Scotland in 1956. *Gut* 1960;**1**:14–30. doi:10.1136/gut.1.1.14

81 Levij IS, Fuente AADELA. A post-mortem study of gastric and duodenal peptic lesions: Part II Correlations with other pathological conditions. *Gut* 1963;**4**:354–9. doi:10.1136/gut.4.4.354

82 Lindström CG. Gastric and Duodenal Peptic Ulcer Disease in a Well-Defined Population: A Prospective Necropsy Study in Malmö, Sweden. *Scand J Gastroenterol* 1978;**13**:139–43. doi:10.3109/00365527809181739

83 van der Merwe CF, te Winkel W. Ten-year observation of peptic ulceration at Ga-Rankuwa Hospital, Pretoria--1979-1988. *S Afr Med J* 1990;**78**:196–9.http://www.ncbi.nlm.nih.gov/pubmed/2200148

84 Moshal MG, Spitaels JM, Robbs J V, *et al.* Eight-year experience with 3392 endoscopically proven duodenal ulcers in Durban, 1972-79. Rise and fall of duodenal ulcers and a theory of changing dietary and social factors. *Gut* 1981;**22**:327–31. doi:10.1136/gut.22.4.327

85 Shi H, Xiong H, Qian W, *et al.* Helicobacter pylori infection progresses proximally associated with pyloric metaplasia in age-dependent tendency: a cross-sectional study. *BMC Gastroenterol* 2018;**18**:158. doi:10.1186/s12876-018-0883-y

86 Smout AJPM, Akkarmans LMA. *Motility of the gastroinal tract*. Beijing, page 18-22: : Science Press 1996.

87 Quan C, Talley NJ. Management of peptic ulcer disease not related to Helicobacter pylori or NSAIDs. *Am J Gastroenterol* 2002;**97**:2950–61. doi:10.1111/j.1572-0241.2002.07068.x

88 Laine L, Hopkins RJ, Girardi LS. Has the impact of Helicobacter pylori therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. *Am J Gastroenterol* 1998;**93**:1409–15. doi:10.1016/S0002-9270(98)00333-5

89 Vaira D, Menegatti M, Miglioli M. What Is the Role of Helicobacter pylori in Complicated Ulcer Disease? *Gastroenterology* 1997;**113**:S78--S84. doi:10.1016/S0016-5085(97)80017-0

90 Gisbert JP, Pajares JM. Review: Helicobacter pylori and bleeding peptic ulcer: what is the prevalence of the infection in patients with this complication? *Scand J Gastroenterol* 2003;**38**:2–9.http://www.ncbi.nlm.nih.gov/pubmed/12608457

91 Gisbert J. Helicobacter pylori and perforated peptic ulcer. Prevalence of the infection and role of non-steroidal anti-inflammatory drugs. *Dig Liver Dis* 2004;**36**:116–20. doi:10.1016/j.dld.2003.10.011

92 Szabo S. Duodenal ulcer disease animal model: cysteamine-induced acute and chronic duodenal ulcer in the Rat. *Am J Pathol* 1978;**93**:273–6.

93 Editors Biography.com. Barry J. Marshall Biography.com. 2014.https://www.biography.com/people/barry-j-marshall-40435 (accessed 10 Dec 2017).

94 Feldman M, Walker P, Green JL, *et al.* Life events stress and psychosocial factors in men with peptic ulcer disease: a multidimensional case-controlled study. *Gastroenterology* 1986;**91**:1370–9. doi:10.1016/0016-5085(86)90189-7

95 Furuta T, Baba S, Takashima M, *et al.* Effect of Helicobacter pylori Infection on Gastric Juice pH. *Scand J Gastroenterol* 1998;**33**:357–63. doi:10.1080/00365529850170973

96 Peters MN, Richardson CT. Stressful Life Events, Acid Hypersecretion, and Ulcer Disease. *Gastroenterology* 1983;**84**:114–9. doi:10.1016/S0016-5085(83)80174-7

97 Smith GD, Susser E. Zena Stein, Mervyn Susser and epidemiology: observation, causation and action. *Int J Epidemiol* 2002;**31**:34–7. doi:10.1093/ije/31.1.34

98 Glavin GB, Murison R, Overmier JB, *et al.* The neurobiology of stress ulcers. *Brain Res Rev* 1991;**16**:301–43. doi:10.1016/0165-0173(91)90012-W

99 Hernandez DE. Neurobiology of brain-gut interactions. Implications for ulcer disease. *Dig Dis Sci* 1989;**34**:1809–16. doi:10.1007/BF01536696

100 Hernandez DE. The Role of Brain Peptides in the Pathogenesis of Experimental Stress Gastric Ulcers. *Ann N Y Acad Sci* 1990;**597**:28–35. doi:10.1111/j.1749-6632.1990.tb16155.x

101 Sutoo D, Akiyama K, Matsui A. Gastric ulcer formation in cold-stressed mice related to a central calcium-dependent-dopamine synthesizing system. *Neurosci Lett* 1998;**249**:9–12. doi:10.1016/S0304-3940(98)00309-7

102 Joëls M, Karst H, Alfarez D, *et al.* Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus. *Stress* 2004;**7**:221–31. doi:10.1080/10253890500070005

103 Henke PG. Attenuation of shock-induced ulcers after lesions in the medial amygdala. *Physiol Behav* 1981;**27**:143–6. doi:10.1016/0031-9384(81)90311-5

104 Tanaka T, Yoshida M, Yokoo H, *et al.* Expression of aggression attenuates both stress-induced gastric ulcer formation and increases in noradrenaline release in the rat amygdala assessed by intracerebral microdialysis. *Pharmacol Biochem Behav* 1998;**59**:27–31.

105 Henke PG. The centromedial amygdala and gastric pathology in rats. *Physiol Behav* 1980;**25**:107–12. doi:10.1016/0031-9384(80)90189-4

106 Henke PG. The amygdala and forced immobilization of rats. *Behav Brain Res* 1985;**16**:19–24. doi:10.1016/0166-4328(85)90078-6

107 Tennant C, Goulston K, Langeluddecke P. Psychological correlates of gastric and duodenal ulcer disease. *Psychol Med* 1986;**16**:365–71. doi:10.1017/S0033291700009193

108 Levenstein S, Prantera C, Scribano ML, *et al.* Psychologic predictors of duodenal ulcer healing. *J Clin Gastroenterol* 1996;**22**:84–9. doi:10.1097/00004836-199603000-00002

109 Magni G, Salmi A, Paterlini A, *et al.* Psychological distress in duodenal ulcer and acute gastroduodenitis. *Dig Dis Sci* 1982;**27**:1081–4. doi:10.1007/BF01391444

110 Cho CH, Lai KH, Ogle CW, *et al.* The role of histamine and serotonin in gastric acid secretion: A comparative study in gastric and duodenal ulcer patients. *J Gastroenterol Hepatol* 1986;**1**:437–42. doi:10.1111/j.1440-1746.1986.tb00131.x

111 Huang JQ, Hunt RH. pH, Healing rate and symptom relief in acid-related diseases. *Yale J Biol Med* 1996;**69**:159–74.https://www.ncbi.nlm.nih.gov/pubmed/9112748

112 Miner P. Review article: relief of symptoms in gastric acid-related diseases--correlation with acid suppression in rabeprazole treatment. *Aliment Pharmacol Ther* 2004;**20 Suppl 6**:20–9. doi:10.1111/j.1365-2036.2004.02162.x

113 Konturek JW, Domschke W. Helicobacter pylori and gastric acid secretion. *Z Gastroenterol* 1999;**37**:187–94.http://www.ncbi.nlm.nih.gov/pubmed/10190251

114 Rademaker JW, Hunt RH. Helicobacter pylori and Gastric Acid Secretion: The Ulcer Link? *Scand J Gastroenterol* 1991;**26**:71–7. doi:10.3109/00365529109098227

115 Blair AJ, Feldman M, Barnett C, *et al.* Detailed comparison of basal and food-stimulated gastric acid secretion rates and serum gastrin concentrations in duodenal ulcer patients and normal subjects. *J Clin Invest* 1987;**79**:582–7. doi:10.1172/JCI112850

116 Boles RS. Modern Medical and Surgical Treatment of Peptic Ulcer: An Appraisal. *J Am Med Assoc* 1948;**136**:528–35. doi:10.1001/jama.1948.02890250016004

117 Malfertheiner P, Chan FKL, McColl KEL. Peptic ulcer disease. *Lancet* 2009;**374**:1449–61. doi:10.1016/S0140-6736(09)60938-7

118 Parsonnet J. Helicobacter pylori: the size of the problem. *Gut* 1998;**43**:S6–9. doi:10.1136/gut.43.2008.S6

119 Chiu PWY. Bleeding peptic ulcers: the current management. *Dig Endosc* 2010;**22 Suppl 1**:S19-21. doi:10.1111/j.1443-1661.2010.00970.x

120 Schmassmann A. Mechanisms of Ulcer Healing and Effects of Nonsteroidal Anti-inflammatory Drugs. *Am J Med* 1998;**104**:43S-51S. doi:10.1016/S0002-9343(97)00211-8

121 Yeomans ND. The ulcer sleuths: The search for the cause of peptic ulcers. *J Gastroenterol Hepatol* 2011;**26**:35–41. doi:10.1111/j.1440-1746.2010.06537.x

122 Hawkey CJ, Wilson I, Naesdal J, *et al.* Influence of sex and Helicobacter pylori on development and healing of gastroduodenal lesions in non-steroidal anti-inflammatory drug users. *Gut* 2002;**51**:344–50. doi:10.1136/gut.51.3.344

123 Malfertheiner P, Megraud F, O'Morain C, *et al.* Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007;**56**:772–81. doi:10.1136/gut.2006.101634

124 Sonnenberg A, Müller H, Pace F. Birth-cohort analysis of peptic ulcer mortality in Europe. *J Chronic Dis* 1985;**38**:309–17. doi:10.1016/0021-9681(85)90077-3

125 Zetterström R. The Nobel Prize in 2005 for the discovery of Helicobacter pylori: Implications for child health. *Acta Paediatr Int J Paediatr* 2006;**95**:3–5. doi:10.1080/08035250500479616

 doi:10.20944/preprints202302.0297.v2