Concept Paper

Novel Data Analyses Address the African Enigma and Controversies Surrounding the Roles of *Helicobacter pylori* in Peptic Ulcers

Simon Xin Min Dong *

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Novel Data Analyses Address the African Enigma and Controversies Surrounding the Roles of *Helicobacter pylori* in Peptic Ulcers

Simon Xin Min Dong

Research and Development, International Institute of Consciousness Science®, Coquitlam, Vancouver, British Columbia, Canada; simondong@outlook.com

Running title: *Helicobacter pylori* in Peptic Ulcers

Abstract: Currently, peptic ulcers are widely considered an infectious disease caused by *Helicobacter pylori* due to 3 supporting evidences, and this etiology may explain 3 other observations. However, it cannot withstand the challenges of all the 15 major characteristics and the other 75 observations/phenomena of peptic ulcers. To address these challenges, a recently published Complex Causal Relationship with its accompanying methodologies was applied to analyze the existing data. Peptic ulcers are identified as a psychosomatic disease triggered by psychological stress, where *Helicobacter pylori* plays a secondary role in the late phase of ulceration. This new etiology addresses all the characteristics, observations/phenomena, controversies, and mysteries of peptic ulcers in a series of 6 articles. This sixth article focuses on the controversies associated with *Helicobacter pylori*. In-depth analyses find that all the 3 supporting evidences are illusions, and all the 3 explainable observations are misinterpreted, indicating that none of the 15 characteristics and 81 observations/phenomena of peptic ulcers can be elucidated by the etiology based on *Helicobacter pylori*. Moreover, the definitions of 'etiological factor', controversies on *H. pylori*, epidemiological studies, characteristics of the disease, and historical observations suggest 'peptic ulcers are an infectious disease caused by *Helicobacter pylori*' is an illusion and thus, the African enigma, a mystery derived from the illusion, does not exist. Similar illusions widely exist in medical research, resulting in direct interference with the true understanding of diseases. A full understanding of the pathogenesis of peptic ulcers highlights the guiding role of philosophy in life science and medical research.

Keywords: *Helicobacter pylori*; peptic ulcer; etiology; illusion; philosophy; African enigma

Introduction

Peptic ulcers, including gastric and duodenal ulcers, are common and frequently occurring diseases, affecting ~10% of the world population [1]. Over the past 300 years, 13 etiological theories, such as '*No Acid, No Ulcer*' [2], *Nerve Theory* [3], *Psychosomatic Theory* [4], and *Stress Theory* [5], were proposed to explain the pathogenesis of the disease [6]. Although each of these theories could explain a minority of the 15 major characteristics and 81 observations/phenomena of peptic ulcers, they failed to explain the majority of these due to their respective inconsistencies [7]. To date, none of these theories can explain the birth-cohort phenomenon [8] and seasonal variation of peptic ulcers [9], as well as the morphology, predilection sites, relapse, and multiplicity of gastric ulcers [7]. Moreover, the similarities and differences between duodenal and gastric ulcers have never been clarified [2].

The isolation of the bacterium *Helicobacter pylori* (*H. pylori*) in 1982 dramatically changed the concept of peptic ulcers [10]. In 1987, Marshall proposed that peptic ulcers are an infectious disease caused by the infection of *H. pylori* [11]. Currently, it is widely believed that there is a causal relationship between peptic ulcers and *H. pylori* primarily due to 3 supporting evidences [12]. First, most peptic ulcer patients are infected with *H. pylori*, and clinical patients have a higher infection rate than the normal population [13–16]. Second, ulcers are significantly larger in infected rats compared

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to uninfected, and *H. pylori* infection delays ulcer healing, which can be resolved by eliminating the bacterium [17,18]. Third, the elimination of *H. pylori* results in a significant reduction of the ulcer relapse/recurrence rate [15,19,20]. The etiological theory of peptic ulcers based on *H. pylori* infection has been designated as *Theory of H. pylori* [6].

Unfortunately, *Theory of H. pylori* is not superior to any other etiological theory in history but has led to additional controversies and mysteries. To date, how *H. pylori* infection causes peptic ulcers remains elusive [21], and this theory cannot elucidate the roles of gastric acid and NSAIDs in the disease [22,23]. 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, 45 were not associated with *H. pylori* infection [6], making it very difficult for *Theory of H. pylori* to explain the pathogenesis. For example, many patients without *H. pylori* infection also have ulcer lesions. One of the most challenging issues in *Theory of H. pylori* is explaining the ulcer lesions in those uninfected patients. 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 [1,24]. 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 characteristics and 75 of 81 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 of peptic ulcers, 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 [25]. 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 pathway 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 [26]. 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* [27,28]. This new theory identified that peptic ulcers are not an infectious disease caused by *H. pylori*, but a psychosomatic disease triggered by psychological stress [27]. Encouragingly, this etiology can explain all the 15 characteristics and 81 observations/phenomena of peptic ulcers [29]. This etiology also fully addresses all the controversies and mysteries associated with peptic ulcers, such as the birth-cohort phenomenon [30] and seasonal variation [31] of peptic ulcers, and the morphology of gastric ulcers [28], as well as the roles of gastric acid, *H. pylori*, and NSAIDs in the disease [27,28]. The similarities and differences between duodenal and gastric ulcers are also clarified [28]. Due to a limit of words, the data analyses are summarized into a series of 6 articles (Supplementary Table S1). This article is the sixth one, focusing exclusively on addressing the controversies surrounding the roles of *H. pylori* in peptic ulcers, along with the mystery of the African enigma.

Methods

Five steps were taken to address the African enigma and the controversies surrounding the roles of *H. pylori* in peptic ulcers. First, the 3 supporting evidences for 'a causal relationship between *H. pylori* and peptic ulcers' were analyzed in-depth. Second, alternative interpretations were provided for the 3 observations explainable by *Theory of H. pylori.* Third, historical definitions of 'etiological factor' and 'causality' are applied to the roles of *H. pylori* in peptic ulcers. Fourth, controversies on 'a *causal relationship* between *H. pylori* and peptic ulcers' in the literature are briefly reviewed. Lastly, the causal role of *H. pylori* in peptic ulcers is disputed from 3 different angles: epidemiological studies, characteristics, and historical observations/phenomena of the disease.

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Results

Theory of H. pylori could not explain all the 15 major characteristics and 75 of 81 observations/phenomena of peptic ulcers, but has led to additional controversies and mysteries over the past 35 years. In contrast, when *H. pylori* is considered to be a risk factor, rather than an etiological factor, playing a secondary role in only the late phase of peptic ulcerations, *Theory of Nodes* addresses all the characteristics, observations/phenomena, controversies, and mysteries, suggesting 'peptic ulcers are an infectious disease caused by the infection of *H. pylori'* is an illusion in medical research.

1. Data analyses dispute all 3 supporting evidences of *Theory of H. pylori*

In *Theory of Nodes*, *H. pylori* is a local aggressive factor in the stomach and plays a role in only the late phase of peptic ulceration, exacerbating ulcer symptoms, delaying the healing process, and increasing clinical morbidity and mortality rates of peptic ulcers [27,28]. Therefore, 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 patients are excluded from the surveys, causing a much higher infection rate of *H. pylori* among ulcer patients as calculated in Table 1.

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	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 × 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 tend 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%). * This proportion of subclinical patients (H. pylori-negative) is excluded from the calculation of the infection rate of *H. pylori* among ulcer patients.

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 that 'the patients are 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 hyperplasia and hypertrophy of gastrin and parietal cells or the submucosal nodes in the gastric wall, 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 there is a causal relationship between *H. pylori* and peptic ulcers, the infection should account for the lesions in *H. pylori*-negative patients, directly resulting in an insurmountable contradiction.

Third, provided that *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 [32,33]. The high relapse rate might be a result of re-

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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 [15,34,35]. 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 [15,36]. 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% [37]. 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 for duodenal ulcers and the formation of submucous nodes in the gastric wall for gastric ulcers due to psychosomatic factors and psychological stress, which cannot be removed by anti-acid and antibiotic treatments, resulting in 'once an ulcer, always an ulcer' [38,39].

Thus, the 3 supporting evidences for 'peptic ulcers are an infectious disease caused by *H. pylori*' are the direct results of '*H. pylori* is not a cause of peptic ulcers, but a risk factor playing a secondary role in only the late phase of peptic ulcerations'. A higher *H. pylori* infection rate in clinical patients, larger ulcer lesions and delayed healing process after infection, and lower relapse rate after bacterial elimination cannot be used to support 'a causal relationship between *H. pylori* and peptic ulcers'.

2. Alternative interpretations for the 3 observations explainable by *H. pylori*

Out of the 36 observations/phenomena associated with *H. pylori*, excluding the 3 supporting evidences above, 3 other epidemiological observations seem explainable by *Theory of H. pylori*. Interestingly, centering on 'peptic ulcer is a psychosomatic disease triggered by psychological stress', *Theory of Nodes* offers an alternative explanation for each of the 3 observations, further demonstrating the pitfalls of *Theory of H. pylori*.

In a relatively isolated group of Australian Aboriginals, peptic ulcers were rare [40]; in a 2-year study of Pima Indians in North America, no peptic ulcer was found [41]. In contrast, a high percentage (10%) of the Caucasian population in North America developed peptic ulcers during the same time-period [42]. In *Theory of H. pylori*, these two observations were explainable 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 lived in a pastoral culture with less social conflicts, and therefore, led 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, such as financial crisis, unemployment, or interpersonal competition.

In addition, Moshkowitz claimed that the seasonal variation of peptic ulcers might be explainable by the higher frequency of *H. pylori* infection in winter [43]. However, this study was questionable. First, the individuals investigated in this study were not the whole population, but dyspeptic patients, causing non-representative sampling. Second, of all the 702 patients examined, ~50% were not infected, but the seasonal variation in the *H. pylori*-negative patients were not investigated. If the uninfected patients had the same seasonal trends, the higher frequency of *H. pylori* infection in winter could not be used to explain the seasonal variation of peptic ulcers. Third, this study has made an inappropriate analogy comparing peptic ulcers to other communicable infectious diseases, as peptic ulcers are not communicable and not all ulcer patients are infected with *H. pylori*. For all the true infectious diseases, each patient is infected with its respective pathogens, such as AIDS, all the patients are infected with Human Immunodeficiency Virus (HIV). However, in this study ~50% of the symptomatic ulcer patients were not infected with *H. pylori*. Notably, the seasonal changes of *H. pylori* infection were not paralleled with the seasonal variations of peptic ulcers [44,45]. Thus, *H. pylori* infection does not account for the seasonal variation of the disease. In *Theory of Nodes*, the seasonal variation of peptic ulcers is caused by the fluctuation of psychological stress in the population induced by the seasonal changes on the earth [31], and this theory also elucidated all the other epidemiological observations of peptic ulcers, including the birth-cohort phenomenon.

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

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Starting from the statement '*H. pylori* plays a secondary role in only the late phase of peptic ulceration', *Theory of Nodes* elucidated all 36 observations/phenomena of peptic ulcers 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 of a disease be considered an etiological factor of the disease? To answer this question, herein the literatures on the 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 [46]. These criteria have been most frequently cited to identify causal relationships between epidemiological observation and disease [47,48]. 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' [46]. *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 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' [49,50]. When this definition is applied to peptic ulcers, *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' [51]. 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 [18,23,33,52–54]. 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 considered etiological factors' [55], further supporting that *H. pylori* is not an etiological factor of peptic ulcers because the infection of this bacterium 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' or 'causality' do not support Marshal's proposal that '*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*' [2] and *Theory of H. pylori* [6], are in fact not etiological theories, but illusions in peptic ulcer research.

4. 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' [12], or '*H. pylori* is the most important etiological factor for duodenal ulcers [19]' 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 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 roles of *H. pylori* in peptic ulcers with 4 facts [56]: 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. Barry J. Marshall, who discovered the bacterium, drank a concoction made from cultured *H. pylori* in 1984, "expecting to develop, perhaps years later, an ulcer". However,

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he did not develop a peptic ulcer, but suffered from gastritis that could be cured with antibiotics [57]. 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 [58]. Based on these facts, Record and Rubin concluded that *H. pylori* was not a causative agent of peptic ulcers [56].

In 1995, Rauws and Tytgat reviewed evidence that was both supporting and opposing '*H. pylori* is an etiological factor for peptic ulcers' [59]. 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 [60]. 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 [25] 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 [59].

Tovey and Hobsley listed 4 reasons to disprove '*H. pylori* was the primary cause of duodenal ulcers' [61]: 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, BMJ published two 'Head to Head' articles on the association between *H. pylori* and duodenal ulcers [12,62]. Ford and Talley insisted that the association was causal, but Hobsley et al. believed that gastric acid secretion was the key to duodenal ulcers [12,62]. In 2001, Elitsur and Lawrence found that *H. pylori* and NSAIDs were not the primary etiology for peptic ulcers in children [63]. Linda and Ransohoff believed that a causal relationship between *H. pylori* and duodenal ulcers could not be established [64]. In 2013, Kate et al. concluded that acid secretion is the most important cause for duodenal ulcers, often combined with reduced mucosal resistance [65]. *H. pylori* eradication is valuable to the long-term healing, but this does not mean *H. pylori* infection is the initial or primary cause of the duodenal ulcers [65]. Zelickson's clinical observation in 2011 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. Thus, the infection of *H. pylori* was not a predominant etiological factor of peptic ulcer patients [66].

Evidently, existing data has presented a controversial view on the causal relationship between *H. pylori* and peptic ulcers [67]. Numerous studies have questioned Marshall's statement. 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 36 observations/phenomena associated with the bacterium. Moreover, *Theory of Nodes* also elucidated that the hyperplasia and hypertrophy of gastrin and parietal cells [27] or the pre-existing submucous nodes [28] account for other unclear factors or the reduced mucosal resistance in the controversies.

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

Epidemiology is an essential tool to assess risk factors for a disease [68–70]. 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 [8,71], seasonal variation [9], and African enigma [25], 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 [72]. Sonnenberg's mathematical model in 2006 also had evident defects while explaining this phenomena [73]. Many studies attempted to explain the birth-cohort phenomenon by citing the mutation between different strains of *H. pylori*, such as cag- and cag+ [74–

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78]. 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 war, 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 [9] and the African enigma [25]. 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 [44,45], and the infection cannot explain the difference in prevalence of *H. pylori* versus peptic ulcers in Africa, causing the 'African Enigma' [25,59]. In short, *Theory of H. pylori* fails to explain any of the 3 characteristic epidemiological observations of peptic ulcers.

In contrast, *Theory of Nodes* explained all three epidemiological observations based on 'peptic ulcers are a psychosomatic disease triggered by psychological stress, where *Helicobacter pylori* plays a secondary role in only the late phase of ulceration', and verified Susser and Stein's speculation that the mortality rates of peptic ulcers were associated with World War I and the unemployment of the 1930s [30]. It is the psychological stress induced by seasonal changes that account for the seasonal variation of peptic ulcers [31]. Interestingly, the mechanism of the birth-cohort phenomenon presented herein is also applicable to understanding the African enigma: it is not the prevalence of *H. pylori*, but the diverse living environment, political environment, 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 epidemiological illusion, the African enigma [25,59].

In fact, *Theory of H. pylori* cannot explain any of the epidemiological observations. First, despite a high prevalence of *H. pylori* infection, the incidence of peptic ulcers in children is low [63,79]. Second, *H. pylori* prevalence in gastric ulcer patients was less than 50% [52] and in some countries, up to 40% of duodenal ulcer patients are *H. pylori*-negative [61]. Third, ~20% of peptic ulcers in the Polish population were not associated with *H. pylori* infection [18], and in the US, only 27% of symptomatic children with peptic ulcers were *H. pylori*-positive [63]. 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 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. Only those affected by psychological stress become ulcer patients, 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 [52,61]) 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 [63], 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, when peptic ulcers are considered not an infectious disease, but a psychosomatic disease, all the epidemiological observations can be fully understood, further suggesting that *H. pylori* infection is not the cause of the disease.

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

If *H. pylori* is considered an etiological factor in peptic ulcers, then none of the 15 major characteristics of this disease, including the one associated with the bacterium itself, can be fully

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explained. In contrast, when peptic ulcers are considered a psychosomatic disease, all 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 [1,24]. 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 their characteristic 'hole-punch' shape [28].

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 relapse [32,37,87,88]. 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 [28]. 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.

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 usually 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 [1,68]. *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 identifies the similarities and differences between the two diseases [29]. 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

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stomach, but duodenal ulcers are characterized by long-term 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 [60]. *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. Because *H. pylori* is not an etiological factor for peptic ulcers, *Theory of Nodes* believes that animal models for this 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 [17]. All these data support that *H. pylori* infection is not an etiological factor of peptic ulcers.

7. 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, 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 [93]. *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 [94,95]. 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 [8,96]. 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* suggest that peptic ulcers are a '*brain-driven*' event [97,98], and the central noradrenergic system is activated when animals are subject to ulcerogenic stress procedures [97–101]. Gastric ulceration is 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 [100]. Moreover, the amygdala might be the brain site for modulating stress-induced gastric erosions [97,102,103], and manipulation of the central nucleus of the amygdala may produce gastric ulcers [97,102,104,105]. In addition, many peptic ulcer patients

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have psychological symptoms such as anxiety, irritability, depression, or poor appetite [106–108]. 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 [109,110]. Hence, Schwartz's dictum '*No Acid, No Ulcer*' remains true only for duodenal ulcers [111]. 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 [94]. 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 [94], and no consistent hypersecretion of gastric acid was observed after *H. pylori* infection [112,113]. *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 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 [111,114]. In contrast, gastric ulceration is determined not by any of the local aggressive factors in the stomach, such as *H. pylori* or gastric acid, 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 [6]. 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 that 'peptic ulcers are an infectious disease caused by *H. pylori*'.

Discussion

Although *Theory of H. pylori* has been proposed for the past 35 years, the question of how the infection causes peptic ulcers remains elusive. This theory cannot uphold itself against the challenges of the 15 major characteristics and 75 of the 81 observations/phenomena of peptic ulcers, but instead, this has led to more controversies and mysteries. In contrast, when peptic ulcers are studied as a psychosomatic disease triggered by psychological stress, *Theory of Nodes* elucidated 8 observations/phenomena of peptic ulcers in this sixth article (Supplementary Table S2-S6). Together with the other 5 articles of this series, *Theory of Nodes* explicated all 15 major characteristics and 81 observations/phenomena of peptic ulcers and addressed all the controversies and mysteries associated with this disease. All these indicate that peptic ulcers are not an infectious disease caused by *H. pylori*, but a psychosomatic disease triggered by psychological stress. 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*** [11]	***Theory of Nodes*** [27–31]
15 characteristics [6]	**None of the 15 can be explained**	**All the 15 are explained**
Etiology	Peptic ulcers are an infectious disease caused by the infection of *H. pylori* [11].	Peptic ulcers are a psychosomatic disease triggered by psychological stress [27].
Morphology of gastric ulcers [115]	Remains unknown	Explained, the only phenomenon needs to be verified [28].

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Predilection sites of gastric ulcers [116]	Remains unknown	Explained [28].
Relapse and Multiplicity [87,117]	Remains unknown	Explained [28].
Bleeding and Perforation [118]	Remains unknown	Explained [28].
Epidemiology	3 observations/phenomena were used as supporting evidence [15]; it might be able explain the other 3 observations. All the others remain unexplained.	All explained [27–31]. All 3 supporting evidences in *Theory of H. pylori* were identified as illusions, and the other 3 *H. pylori* explainable observations were mis-interpreted in *Theory of H. pylori*.
81 observations/ Phenomenon [6]	**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 [27–31].
45 observations/phenomenon unassociated with *H. pylori*	None can be explained because many patients are *H. pylori*-negative [33,52,53].	All 45 are explained [27–31].
4 Controversies	**None of the 4 is addressed**	**All 4 are addressed clearly**
Roles of *H. pylori*	Controversial [12,56,61,62,65]	Addressed: *H. pylori* is not an etiological factor but plays a secondary role in only the late phase of ulceration [27–29].
Roles of gastric acid	Unknown [12,111]	Addressed [27,28].
Roles of NSAIDs	Unknown [23,54,75,119–122]	Addressed [27,28].
Idiopathic peptic ulcers	Unknown [18,23,54]	Addressed [27,28].
3 Major Mysteries	**None of the 3 is resolved**	**All 3 are resolved clearly.**
Birth-cohort Phenomena [71,123]	Remains a mystery [71,72]	Resolved [30].
Seasonal Variations [9]	Remains a mystery	Resolved [31].
African Enigma [25]	Remains a mystery	Resolved in this article: identified as an illusion due to incorrect etiology.
Similarities and differences between gastric & duodenal ulcers [1,124]	**Remains unknown.**	**Fully illustrated** [28].
Therapy/effect	**Antiacid and antibiotics treatments are the primary therapy; relapse frequently**	**Psychological treatments are the primary therapy; no relapse** [29]**.**

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Conclusions	1. Theory of *H. Pylori* cannot fully explain the pathogenesis of peptic ulcers. 2. *H. Pylori* infection cannot explain all 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* fully explains the pathogenesis of peptic ulcers. 2. This etiology 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 life science and medicine.

Herein, the in-depth data analyses suggests that the three observations used to support 'peptic ulcers are an infectious disease caused by *H. pylori*' are deceiving, and all 3 observations, which seem explainable by *Theory of H. pylori*, has been misinterpreted. Thus, *Theory of H. pylori* is not able to explain any of the 15 major characteristics and 81 observations/phenomena of peptic ulcers. Interestingly, Dr. Marshall drank a concoction made from cultured H. pylori and came down with gastritis that could be cured with antibiotics [125]. Barry Marshall did not develop peptic ulcers as expected, but gastritis only. This brave scientific spirit and behavior also indicate that there is no causal relationship between H. pylori and peptic ulcers, and that 'peptic ulcers are an infectious disease caused by the infection of H. pylori' is an illusion in the field of peptic ulcer research. Compared to *Theory of H. pylori*, the overwhelming advantages of *Theory of Nodes* shown in Table 2 suggests that peptic ulcers are a psychosomatic disease triggered by psychological stress, but they were studied as an infectious disease caused by *H. pylori* over the past 35 years. As a result, little progress has been made in the field of peptic ulcer research. This kind of error may exist widely in the research of almost all diseases. Consequently, so far, no disease has ever 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.

One of the key points in *Theory of Nodes* is that 'peptic ulcers are an infectious disease caused by *H. pylori* [11]' or '*H. pylori* is the most important etiological factor in duodenal ulcers [19]' is an *illusion*, which for more than 3 decades, was direct interference with the true understanding of peptic ulcers 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* [126]. *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 analysis 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 useful 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 surrounding peptic ulcers, such as the birth-cohort phenomenon. 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.

Keeping the concept of *illusion* in mind, elucidating that the African enigma does not actually exist can easily be precipitated. It was called an enigma, because an illusion (incorrect etiology) was employed to explain an observation that *H. pylori* infection is very common in Africa, but the prevalence of peptic ulcers is low and varies regionally [25]. In other words, *H. pylori* infection is in fact not the cause of peptic ulcers, but it was regarded as the cause to elucidate an observation associated with the bacterium, causing this additional mystery/enigma. Similarly, this *illusion* has also

been applied to elucidate many other characteristics and observations/phenomena of peptic ulcers, such as the hypersecretion of gastric acid [127], morphology of gastric ulcers [126], bleeding [128], birth-cohort phenomenon [73] and seasonal variations [43]. Unequivocally, all these efforts failed because they were based on an *illusion*. Thus, the concept '*illusion'* makes it easy to understand why *Theory of H. pylori* could not elucidate all the characteristics and the majority of observations/phenomena of peptic ulcers, and why there were so many controversies and mysteries in peptic ulcer research over the past 35 years.

There have been many examples of *illusion* preventing scientific research from discovering the true cause of phenomena in the history of science. In macro-physics, the earliest concept of 'gravity' was first proposed by the ancient Greek philosopher, Aristotle, more than 2300 years ago [129], but his idea was discredited for 2000 years due to an *illusion* in the field. The apple usually did not fall to the ground vertically as Aristotle's proposal predicted, and more apples fell when it was windy. Thus, it seemed that the wind determined when apples fell and where they landed. The wind is a tangible force, whereas gravity is intangible, making it much easier to believe that the wind drives the apples to fall to the ground. As a result, why the apple always fell to the ground could not be explained until Newton introduced *The Universal Law of Gravitation* in 1687. Newton's law dictates that gravity is the driving force of *the apple falling to the ground*, and the wind plays only a secondary role in this phenomenon, making the branch sway or directly giving the apple an initial horizontal speed. The concept that the wind is the cause of *the apple falling to the ground* is an *illusion*, preventing the acceptance of gravity for more than 2000 years. Further, Einstein's prediction that 'the *Gravitational Redshift of Sirius B* is a visual *illusion*' has also led to massive advancements in the field [130]. Both examples in physics indicate that great achievements in science are usually accompanied by the identifications of *illusions*.

Newton and Einstein identified *illusions* in their respective fields because philosophy was applied to guide their studies. Newton's book in 1687 was entitled *Mathematical Principles of Natural Philosophy* [131], which emphasized the importance of philosophy in scientific research. Einstein also indicated that he should be regarded as a philosopher first [132,133]. Guided by philosophy, both founders of modern science identified *illusions* in their fields while establishing ground-breaking theories. Similar to Newton's and Einstein's theories, *Theory of Nodes* also employed multiple philosophical principles to identify an *illusion* in peptic ulcer research. For example, when the CCR was applied, only the invisible, intangible, and incorporeal psychosomatic factors could be the cause of disease. Since *H. pylori* is not invisible, intangible nor incorporeal, it cannot be considered the cause of any disease, and the etiology of peptic ulcers based on the infection of this bacterium could only be an *illusion*. Only by excluding this *illusion*, could we have a definite etiology to elucidate the pathogenesis of peptic ulcers as demonstrated in *Theory of Nodes*. In addition, *integral perspective* and *historical perspective* contributed to identify this *illusion*. Notably, the CCR, *integral perspective*, and *historical perspective* are philosophical principles, suggesting philosophy plays a central role in *Theory of Nodes* to identify *illusions* and thus, it was not misled by 'peptic ulcers are an infectious disease caused by *H. pylori*'.

To illustrate that life science and medicine must place greater demands on philosophy than physics, herein analogies from fishing in three different types of bodies of water are used. The first body of water is a small and shallow pond, where fish can easily be pinpointed by the naked eye and even caught barehanded. The scientific exploration in macro-science is like fishing in this small and shallow pond. Newton's philosophy played the role of 'the naked eyes' to 'pinpoint' his findings resulting in one universal law, *The Law of Universal Gravitation*, which was sufficient to avoid the *illusion* in macro-science. From the small and shallow pond, we progress to a lake where the water is much deeper and wider, but the fish can still be located with simple tools like buoys and fishing rods. Exploration in micro-science is akin to fishing in a lake. Planck's Quantum Theory and Einstein's Theory of Relativity played the role of 'buoys and fishing rods'. Next, we find ourselves in a boundless and extraordinarily deep ocean. There are concentrated schools of fish in much larger numbers, the variety is much greater, and the fish are much tastier. But here in the ocean, the water is too deep to fish using our naked eyes or with simple tools. The rushing currents and floating objects

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distract from our fishing. To catch the fish in this deep ocean, we need radars to find the schools of fish and to monitor their movement. Explorations in life science and medicine are similar to deep-sea fishing. Metaphorically speaking, the high complexity of life and the human body is 'a boundless and extraordinarily deep ocean', and the large numbers and great varieties of life phenomena and human diseases are 'the massive number of deep ocean fish'. Conceivably, in life science and medicine, many great achievements are awaiting our explorations, but we will inevitably face many dazzling *illusions* (such as 'a causal relationship between *H. pylori* and peptic ulcers'), which may mislead our research or distract our attention like the rushing currents and floating objects during deep-sea fishing. To accurately 'pinpoint and catch' the true causes of life phenomena and human diseases, we will need 'radars', which are tens, hundreds, or even thousands of philosophical principles/concepts as indicated in the book published in 2012, *Philosophical Principles of Life Science* [26]. The three metaphors above indicate that philosophy plays a guiding role in scientific research as our eyes are guiding our daily activities.

However, currently, very few researchers wear both hats as a medical doctor and philosopher. Most medical researchers do not believe that philosophy can play a guiding role in life science and medical studies. The prevalence of 'positivism' has made modern scientists believe that only tangible lab research, clinical observation, or epidemiological survey are scientific research [134], whereas the application of philosophical principles is excluded from their scope [135], causing a strict demarcation between science and philosophy [136]. The concept that philosophy is not practical for scientific research [137], is still the prevailing view today. Given these current circumstances, philosophy is unlikely to guide life science and medical research. Consequently, many studies are being conducted without deliberation while *illusions* like 'a causal relationship between *H. pylori* and peptic ulcers' are interfering with the studies on various life phenomena and human diseases. Inevitably, no disease can be fully understood in modern life science and medicine, which so far, is the case.

Herein, *Theory of Nodes* fully explained the pathogeneses of peptic ulcers for the first time in history because many philosophical principles and concepts were applied to direct the literature review and data analyses, suggesting philosophy could play a guiding role in medical studies. The philosophical principles applied in *Theory of Nodes* could be widely used in the studies on all the other life phenomena and human diseases. I propose that strengthening the construction of philosophical theories should be one of the primary tasks for life science and medical communities in the 21st century and afterwards. Under the guidance of philosophical principles, life science and medicine will be able to avoid the interference from various illusions, thereby elucidating the pathogenesis of numerous human diseases, such as cancer and AIDS.

Conclusion

Based on '*H. pylori* plays a secondary role in only the late phase of peptic ulcerations', all 3 observations supporting 'peptic ulcers are an infectious disease caused by *H. pylori*' are identified as clinical *illusions*, and all 3 observations explainable by *H. pylori* infection were found misinterpreted. Thus, *H. pylori* infection failed to explain any of the 15 major characteristics and 81 observations/phenomena of peptic ulcers. The definitions of 'etiological factor' and 'causality' in history do not support '*H. pylori* is an etiological factor of peptic ulcers', and the existing data has also presented a controversial view on the role of *H. pylori* in peptic ulcers. Moreover, the epidemiological studies, major characteristics of the disease, and historical observations indicate that 'a causal relationship between peptic ulcers and *H. pylori*' is an *illusion* in peptic ulcer research. The identification of this *illusion* is indispensable for a full understanding of the pathogenesis of peptic ulcers, highlighting the guiding roles of philosophy in medical research. The high complexity of life and the human body incurs lots of *illusions*, resulting in the failure of elucidating the pathogenesis of any disease in modern medicine. Philosophy is the eyes/radars of scientific research while implementing and applying philosophy as the guide can effectively identify various illusions in scientific research, thereby significantly accelerating the progress of life science and medicine.

Supplemental Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. The supplemental material includes 6 tables in a PDF document.

Ethics Statement: This study was conducted with integrity, fidelity, honesty, and did not involve any human or animal specimen.

Data Availability Statement: All the supporting data in this article are published papers or books, or in the online supporting information.

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