The Hyperplasia and Hypertrophy of Gastrin and Parietal Cells Induced by Chronic Stress Explain the Pathogenesis of Duodenal Ulcers

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Abstract

Peptic ulcers, including duodenal and gastric ulcers, are currently studied as an infectious disease caused by Helicobacter pylori. However, this etiology cannot elucidate the major characteristics and observations/phenomena of the disease, as well as the roles of gastric acid and NSAIDs. Additionally, many patients with severe ulcer symptoms have no infection, suggesting bacterial eradication cannot prevent relapses in all ulcer patients. To address these challenges, a recently published Complex Causal Relationship with its accompanying methodologies was applied to analyze the existing data. Peptic ulcers were identified as a psychosomatic disease triggered by psychological stress, where Helicobacter pylori plays a secondary role in only the late phase of ulceration. An integration of five major etiological theories in history illustrated the entire pathogenesis of peptic ulcers, which addressed all the characteristics, observations/phenomena, controversies, and mysteries of the disease in a series of 6 articles. This first article focuses on the pathogenesis of duodenal ulcers. The hyperplasia and hypertrophy of gastrin and parietal cells induced by chronic stress potentiate the individual’s response to immediate stress, resulting in the hypersecretion of gastric acid and eventually, duodenal ulceration. This psychopathological mechanism resolved all the controversies associated with Helicobacter pylori and explicitly elucidated 7 characteristics of duodenal ulcers, as well as 42 observations/phenomena. The roles of gastric acid, Helicobacter pylori, and NSAIDs in duodenal ulcers were also identified. The effectiveness validated the etiology of duodenal ulcers identified by the Complex Causal Relationship, indicating stress management is essential for a complete cure of the disease without relapse.

Introduction

Peptic ulcer disease, including duodenal and gastric ulcers, is a serious medical condition in the upper gastrointestinal tract, affecting ~10% of the world population. Over the centuries, 13 etiological theories, such as 'No Acid, No Ulcer' (1910), Nerve Theory (1913), Psychosomatic Theory (1950), and Stress Theory (1950), have been proposed to explain its pathogenesis. Although each of these theories could explain some characteristics and observations/phenomena of peptic ulcers, they failed to explain the majority of these due to their respectively challenging inconsistencies.

In 1987, Marshall proposed that peptic ulcers are an infectious disease caused by the infection of Helicobacter pylori (H. pylori). This etiological theory has been designated as Theory of H. pylori. However, this theory is not superior to any other theory in history, but has led to additional controversies and challenges in the field. It cannot explain most of the 15 characteristics and 81 observations/phenomena of peptic ulcers, including 30 of the 36 observations/...
phenomena associated with the bacterium itself. For example, provided *H. pylori* is the cause of peptic ulcers, all patients should have the infection, but ulcers in 20–40% patients are idiopathic\(^{14,15}\), indicating not all patients are infected. Interestingly, many patients with severe ulcer symptoms have no infection\(^{13,16}\), suggesting that bacterial eradication cannot prevent the relapse in these patients\(^17\). Moreover, how the infection leads to ulceration remains unknown and the roles of gastric acid and Non-steroidal Anti-inflammatory Drugs (NSAIDs) in the disease have never been elucidated\(^{15,18}\), thus exemplifying the pitfalls of this theory. Furthermore, this etiology cannot elucidate the birth-cohort phenomenon, seasonal variation, and African enigma of peptic ulcers, as well as the morphology and predilection sites of gastric ulcer.

The progress on all other diseases is similar to peptic ulcers. To date, no disease has been fully understood. To address these challenges, I investigated the successful, historical, scientific research in fields outside the scope of medical science and found inspirations from the realm of physics. Newton established the first causal relationship in 1687 in his *Law of Universal Gravitation*, and Einstein established the second causal relationship in 1905 in his *Mass-energy Equation*. The two historic universal causal relationships allowed major progress to be made in macro- and micro-physics, respectively. The successes in physics suggest that establishing a universal causal relationship for life science and medicine may be essential to understand life phenomena and human diseases.

In May 2012, a new causal relationship, the Complex Causal Relationship (CCR), was proposed for life science and medicine\(^{19}\). The CCR can be explained by drawing a parallel to Newton’s *Law of Universal Gravitation* or Einstein’s *Mass-energy Equation*. In both historic causal relationships, Newton and Einstein considered two essences of their research subjects: the visible, tangible, and corporeal MASS, which was defined as the Concrete Essence; and the invisible, intangible, and incorporeal Force or Energy, which was defined as the Abstract Essence.

In physics, the apple falls to the ground due to its Abstract Essence, Force, and electrons transition to new orbitals due to absorption or release of the Abstract Essence, Energy. The CCR dictates that, similar to the research subjects in physics, the human body also has both Concrete Essence and Abstract Essence, and the human body suffers from various diseases due to its Abstract Essence\(^{19}\). However, the Abstract Essence of the human body has rarely been investigated in modern medicine.

I hypothesize that taking the Abstract Essence of the human body into consideration may allow us gain unprecedented insights into any disease. To test this hypothesis, peptic ulcers were selected as a model disease, and the CCR with its accompanying methodologies was applied to analyze the existing data. Encouragingly, the data analyses can address all the controversies, mysteries, characteristics, and observations/phenomena of peptic ulcers. Due to a limit of words, the data analyses were summarized into a series of 6 articles (Supplementary Table S1). This article is the first one, focusing on the pathogenesis of duodenal ulcers. Notably, numerous historical studies, especially those from 1900 to 1990, are extremely valuable for a full understanding of the pathogenesis of peptic ulcers.

**Methods**

Four steps were taken to analyze the existing data. First, the CCR served as a benchmark to pinpoint the etiology of peptic ulcers from the 13 theories in history. Second, the application of a novel methodological concept, Integral Perspective\(^{19}\), integrated 5 major etiological theories into one single theory. Third, another novel methodological concept, Superposition Mechanism\(^{19}\), was employed to explain the clinical, epidemiological, and laboratory observations of duodenal ulcers. Lastly, the roles of gastric acid, *H. pylori*, and NSAIDs in duodenal ulcers were elucidated.

**Results**

A definite etiology with effective analytical methods is required for a full understanding of disease. Herein the application of the CCR with its accompanying methodologies helped to achieve this goal. Fortunately, modern medicine has accumulated enough empirical data for data analyses.

**The Application of the CCR Identified the Etiology of Peptic Ulcers**

The CCR dictates that although the Abstract Essence of the human body is invisible, intangible, and incorporeal, it is the driving force of life phenomena and human diseases, indicating that the early phase of any disease is an abstract process. Based on this concept, out of all the 13 etiological theories\(^6\), only *Psychosomatic Theory* and *Stress Theory* suggested invisible, intangible, and incorporeal causes for peptic ulcers as shown in Table 1. Both theories were supported by numerous data from clinical and epidemiological observations\(^5,20–22\), and were demonstrated reproducible\(^23–30\). *Psychosomatic Theory* focuses more on the impact of mental health related to past life experiences, whereas *Stress Theory* concentrates on the influence of current life events. When combining the two theories, I elucidate that psychosomatic factor makes the individual susceptible to current psychological stress, leading to peptic ulcers. Concisely, a combination of the two etiological theories suggests that peptic ulcers are a psychosomatic disease triggered by psychological stress.

Ford and Talley insisted that there is a causal relationship between *H. pylori* and duodenal ulcers\(^6\), whereas Hobsley believed that gastric acid plays a more important role
Table 1: Five major etiological theories of peptic ulcers in history

<table>
<thead>
<tr>
<th>Etiological Theories</th>
<th>Founder &amp; Year</th>
<th>Repeat Example</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No Acid, No Ulcer</td>
<td>Dragutin (Carl) Schwartz, 1910</td>
<td>P. Miner, 2004</td>
<td>The hypersecretion of gastric acid is the cause of peptic ulcers.</td>
</tr>
<tr>
<td>4. Stress Theory</td>
<td>Hans Selye, 1950</td>
<td>Michael P. Jones, 2006</td>
<td>Stress induced by personality traits, and social and natural events is the cause of peptic ulcers.</td>
</tr>
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b. The etiological theory based on the infection of H. pylori was designated as Theory of H. pylori.

than H. pylori in the disease. Currently, NSAIDs are also considered a cause of peptic ulcers. However, H. pylori, gastric acid, and NSAIDs are not invisible, intangible, and incorporeal and thus, none of the 3 concrete factors match the standard set by the CCR to be the cause of disease. This explains why the etiologies based on H. pylori, gastric acid, or NSAIDs cannot explain the pathogenesis of peptic ulcers, despite supports from clinical or epidemiological observations. In fact, the hypersecretion of gastric acid may not be a cause but an effect of psychological stress, as observed in clinical patients. Additionally, there are 30-40% idiopathic (H. pylori-negative and non-NSAIDs user) ulcer patients, also suggesting that neither H. pylori nor NSAIDs is the cause of peptic ulcers.

Integrating Five Major Etiological Theories in History into One Single Theory

Next, the 13 etiological theories in history were further examined. Five of them have been studied in more details and were supported by numerous clinical, epidemiological, and laboratory data (Table 1). Interestingly, each of the five major theories focused on only one area of the human body. For example, Nerve Theory only focused on abnormal neurotransmitters in the brain, ‘No Acid, No Ulcer’ was solely concerned with the hypersecretion of gastric acid, and Theory of H. pylori concentrated exclusively on bacterial infection in the upper digestive tract.

Newton’s Law of Universal Gravitation suggests that due to the abstract essence of the apple and the earth, Force, the two objects are not independent entities but an ‘inseparable integrity’. Similarly, the CCR suggests that, due to the abstract essence of the human body, all the individual organs are not independent pieces, but an ‘inseparable integrity’. This concept is termed ‘integral perspective’, which indicates that integrating the five major theories on peptic ulcers into one single theory may gain unprecedented insights into the disease. Excitingly, an integration of the five major theories, Psychosomatic Theory, Stress Theory, Nerve Theory, ‘No Acid, No Ulcer’, and Theory of H. pylori (Table 1) did paint a complete picture of the pathogenesis of peptic ulcers, including the early, intermediate, and late phases of peptic ulcerations. Psychosomatic Theory and Stress Theory illustrate the early phase of peptic ulcers, in which abstract psychosomatic factors and psychological stress initiate the disease. Nerve Theory bridges the gap between the early and the late phases of peptic ulcerations, uncovering the consequences of psychological stress that aberrant nerve impulses are transmitted to the stomach, resulting in the hypersecretion of gastric acid in duodenal ulcer, or the pathological lesions in gastric ulcer. The late phase of peptic ulceration is a corrosive process caused by local aggressive factors in the stomach as described in ‘No Acid, No Ulcer’ and Theory of H. pylori. For ease of narration, the new theory originated from the integration is termed Theory of Nodes. More details on how this term is derived will be given in the second article of the series on the pathogenesis of gastric ulcer

The Pathogenesis of Duodenal Ulcer

Theory of Nodes divides the entire process of duodenal ulceration into early, intermediate, and late phases. The mechanism of gastric acid hypersecretion is the key pathological process to elucidate all the clinical, epidemiological, and laboratory observations/phenomena of duodenal ulcers, as well as the roles of gastric acid, H. pylori, and NSAIDs in the disease. Notably, each of the three phases described herein is supported by a large amount of existing data.

Early phase: the hyperplasia and hypertrophy of gastrin and parietal cells

In Theory of Nodes, hereditary predisposition determines that psychosomatic factors, such as hypochondriasis, a negative perception of life events, dependency,
lowered self-confidence, make a portion of individuals in the population more susceptible to environmental factors than others. Existing data discovered a positive correlation between stressful occupations and duodenal ulcers, and duodenal ulcers were associated with bad habits, poor lifestyle, laborious work, unhealthy environment, and long-term emotional distress. These findings suggest that the early phase of duodenal ulcer is a long-term/chronic pathophysiological process. Life in large cities is more competitive and stressful than in rural areas, explained the higher incidence of duodenal ulcers in large cities. Psychosomatic factors or chronic stressors constantly provoke the neurotransmitter release in the central nervous system and thus, duodenal ulcers are a ‘brain-driven event’ often accompanied by psychological disturbances such as anxiety, neuroticism, depression, somatization, or poor appetite.

Constant and prolonged releases of neurotransmitters in the central nervous system lead to an extremely complex pathophysiological process, in which distinct neural networks regulate the functions of multiple peripheral organs, resulting in the hyperplasia and hypertrophy of gastrin and parietal cells in the stomach. Existing data suggests that at least four pathways are involved in this chronic process (Figure 1): 1. Bad habits in eating, drinking, and smoking or long-term drug usage cause local chronic stress in the stomach. For example, drinking a large volume of water immediately after lunch significantly lowers the concentration of gastric acid. The increased pH is constantly sensed and regulated by the enteric nervous system, causing increased parietal cell mass and hyperplasia of gastrin cells. 2. Vagus nerves play a key role in gastric secretion; tensions, emotional strains, and competitive efforts of modern life result in hypertonus in the vagus nerves. The hyperplasia of gastrin cells was observed after bilateral truncal vagotomy, indicating brain-gut axis may induce the hyperplasia of gastrin cells due to vagus nerve dysfunction. 3. Prolonged exposure to stress activates the hypothalamus-pituitary-adrenal (HPA) axis, causing the hyperplasia and hypertrophy of adrenaline and the

Figure 1: Chronic stress induces hyperplasia and hypertrophy of gastrin and parietal cells. Multiple pathways are involved in the hyperplasia and hypertrophy of gastrin and parietal cells. (a) Local stress in the stomach induced by bad habits or long-term drug use is sensed and regulated by the enteric nervous system, causing hyperplasia and hypertrophy of gastrin and parietal cells via a negative feedback loop. (b) Chronic stress leads to vagus nerve dysfunction via the brain-gut axis, resulting in the hyperplasia of gastrin cells. (c) Prolonged exposure to stress activates the HPA axis, inducing the hyperplasia and hypertrophy of adrenaline. The subsequent high level of corticosteroids causes hyperplasia and hypertrophy of gastrin and parietal cells. (d) Chronic stress induces the hyperplasia and hypertrophy of gastrin and parietal cells via the parathyroid-hormone axis. (e) There might be other unknown or unchecked pathways. Pathways a, b, c, d, and e lead to the hyperplasia and hypertrophy of gastrin and parietal cells in the early phase. (f) Due to the hyperplasia and hypertrophy of gastrin and parietal cells, the perception of stress triggers the hypersecretion of gastric acid in the intermediate phase. (g) The hypersecretion of gastric acid, along with H. pylori, NSAIDs, and other local aggressive factors, results in duodenal ulcerations in the late phase.
subsequent high level of hormones from adrenaline may induce the hyperplasia and hypertrophy of gastrin and parietal cells (Figure 1c). Chronic stress may induce hyperplasia and hypertrophy of parathyroid glands, which were also reported to be associated with duodenal ulcer. In addition, a birth-cohort study found that the trends for duodenal ulcers were similar to gastric ulcers but followed ~5 years behind

In Theory of Nodes, the pathways to induce the hyperplasia and hypertrophy of gastrin and parietal cells vary individually due to heredity and past life experiences, and the degrees of hyperplasia and hypertrophy to induce duodenal ulcers range from mild, moderate, to severe, which is associated with the local aggressive factors in the gastroduodenum, especially the infection of *H. pylori*.

*Late phase: symptomatic ulcer*

The late phase of duodenal ulcer is a corrosive process caused by local aggressive factors, including gastric acid and *H. pylori*, mechanical abrasion, and chemical erosion from medications such as NSAIDs (Figure 1g). Some researchers believed that peptic ulceration is not an infectious process, but a corrosive one. In Theory of Nodes, the hypersecretion of gastric acid is unrelated to any of the local aggressive factors in the stomach, but potentiated by the hyperplasia and hypertrophy of gastrin and parietal cells and triggered by psychological stress due to personality traits or life events. Thus, the hypersecretion of gastric acid is an intermediate process of duodenal ulceration, suggesting it is not a cause of duodenal ulcers, but an effect of psychological stress. Nevertheless, the hypersecretion of gastric acid is the determinant aggressive factor in the stomach in the late phase of duodenal ulceration, governing multiple characteristics of this disease, especially the observations related to *H. pylori* and NSAIDs. The pain relief after the gastric acid is buffered or neutralized with alkali or food further reveals the important role of gastric acid in duodenal ulcers.

For individuals with severe hyperplasia and hypertrophy of gastrin and parietal cells, the hypersecretion of gastric acid alone is sufficient to induce duodenal ulcers. In that case, neither *H. pylori* infection nor NSAIDs usage is essential for ulceration. Therefore, duodenal ulcer may occur in the absence of *H. pylori* and/or NSAIDs, leading to idiopathic(*H. pylori*-negative and non-NSAIDs user) ulcer patients. Administering cysteamine or propionitrile, which effectively stimulates the hypersecretion of gastric acid, can induce acute and chronic duodenal ulcer in normal rats, whereas inoculation of *H. pylori* alone cannot, further indicating that gastric acid plays a more important role than *H. pylori* in duodenal ulcers. Gastric acid, *H. pylori*, and NSAIDs play a role in only the late phase of ulceration, suggesting duodenal ulcer is not initiated by any of the 3 local aggressive factors. Unequivocally, none of them is an etiological factor of the disease.
The Superposition of Local Aggressive Factors in the Gastro-duodenum

Most of the controversies on peptic ulcers concentrate on the late phase of ulceration, especially on the roles of H. pylori, gastric acid and NSAIDs. To further understand the late phase of duodenal ulceration, herein the existing data on all known local aggressive factors in the stomach was analyzed. Interestingly, the local aggressive factors were studied as separate entities in modern medicine, and they have never been considered a combinatorial force to corrupt the mucosa. The concept of integral perspective dictates that a pathological process is usually caused by an individual aggressive factor, but by multiple factors based on Superposition Mechanism, which takes into account that factors with commonalities can have additive effects. Existing data indicates that the hypersecretion of gastric acid is a determinant factor in the late phase of duodenal ulceration, but all the other local aggressive factors also contribute to the corrosive intensity, ultimately resulting in duodenal ulceration when the total corrosive intensity exceeds the resistance of duodenal mucosa. Therefore, it is the total sum of corrosive intensities from all local aggressive factors acting on duodenal bulb that leads to the characteristic erosive appearance of duodenal ulcers. To illustrate the Superposition Mechanism, herein 21 hypothetical cases with different local aggressive factors that may lead to ulceration were generated in Figure 2. These hypothetical cases are a summary of data from epidemiological and clinical studies.

In Figure 2, Case A demonstrates an H. pylori-negative healthy individual who has normo-secretion and suffers no damage ($D_{\mu}=0$). This is the baseline for normal, healthy individuals. Case B represents the most common situation for individuals with normo-secretion and H. pylori infection. Although they suffer damage from the H. pylori infection, the $\Sigma D_{\mu}$ value does not reach the lowest threshold, $D_{\mu_{\text{min}}}$, meaning the individuals do not suffer from ulceration. Cases C, D, E and F are H. pylori-negative examples where different degrees of hypersecretion determine the $\Sigma D_{\mu}$ value. Case C does not ulcerate ($\Sigma D_{\mu}<D_{\mu_{\text{min}}}$), Case D

![Figure 2. The superposition mechanism of local aggressive factors in duodenal ulceration.](image)

The data in the graph is representative of different hypothetical situations where local aggressive factors create an additive effect that may lead to ulceration. The hypersecretion of gastric acid is a determinant factor in duodenal ulceration, but all the other local aggressive factors are also involved. The corrosive intensity caused by an aggressive factor was defined as Damage Unit ($D_{\mu}$), and the total sum of corrosive intensities of each case ($\Sigma D_{\mu}$) is calculated individually by the formula: $\Sigma D_{\mu} = D_{\mu_{\text{Gastric Acid}}} + D_{\mu_{H. pylori}} + D_{\mu_{NSAIDs}} + D_{\mu_{Corrosive Medications}}$. Due to distinct genetic backgrounds and life experiences, the susceptibility of duodenal mucosa varies individually. Accordingly, each individual has her/his own threshold of ulceration. Therefore, a theoretical range between $D_{\mu_{\text{min}}}$ and $D_{\mu_{\text{max}}}$ was set as the threshold of ulceration. $\Sigma D_{\mu}$ values per individual case below $D_{\mu_{\text{min}}}$ (dash line) will not result in ulceration, $\Sigma D_{\mu}$ values above $D_{\mu_{\text{max}}}$ (solid line) will result in ulceration, and $\Sigma D_{\mu}$ values within the range may or may not result in ulceration. When the $\Sigma D_{\mu}$ value falls between $D_{\mu_{\text{min}}}$ and $D_{\mu_{\text{max}}}$, even though some individuals have the same $\Sigma D_{\mu}$ value, the one whose duodenal mucosa is more susceptible to the local aggressive factors is more likely to ulcerate. *Indicates cases of ulceration.
ulcerates because $D_{H_{max}} < \Sigma D_{H} < D_{H_{max}}$ and Case F has high-range hypersecretion ($\Sigma D_{H} > D_{H_{max}}$), which results in ulceration. Although Case E has the same $\Sigma D_{H}$ as Case D ($\Sigma D_{H}=\Sigma D_{H}$), Case E does not ulcerate because her/his duodenal bulb mucosa is less susceptible than Case D.

Cases G and H give examples of patients with similar $\Sigma D_{H}$ values due to corrosive intensity from superposition of both low-range hypersecretion of gastric acid and $H. pylori$ infection. Both cases are within the range for potential ulceration, however, the individuals in Cases G and H have different mucosal susceptibility; therefore, Case G progresses to ulceration whereas Case H does not. Case I represents the $\Sigma D_{H}$ value for hypothetical $H. pylori$-positive patients with mid-range hypersecretion. Although the corrosive intensity of acid alone does not overcome the individual’s mucosal resistance to ulceration, with the addition of the damage from $H. pylori$ the $\Sigma D_{H}$ value surpasses $D_{H_{max}}$ and therefore, the patient suffers ulceration. Case J is an example of $H. pylori$-positive patients with high-range hypersecretion. With or without the damage from $H. pylori$, the hypersecretion exceeds $D_{H_{max}}$ resulting in ulceration. Case K illustrates normo-secretion with NSAIDs use, wherein the $\Sigma D_{H}$ value does not reach $D_{H_{max}}$. The damage from the NSAIDs alone is not enough to cause ulceration. Cases L and M represent the additive damage of low-range hypersecretion and NSAIDs usage. In both cases, the damage from the gastric acid alone does not reach $D_{H_{min}}$ but with the addition of the corrosive intensity from NSAIDs, the $\Sigma D_{H}$ enters the threshold for potential ulceration. However, only Case L ulcerates because her/his duodenal mucosa is more susceptible to local aggressive factors than Case M. Case N is an example of the additive damage of mid-range hypersecretion and NSAIDs usage, but in this case, the patient ulcerates because $D_{H_{Gastric Acid}} + D_{H_{NSAIDs}} > D_{H_{max}}$.

Cases O and P illustrate $H. pylori$-positive individuals with low-range hypersecretion and NSAIDs usage, wherein $D_{H_{min}} < \Sigma D_{H} < D_{H_{max}}$. However, only Case O ulcerates because this individual is more susceptible than Case P. Case Q represents the $\Sigma D_{H}$ value for $H. pylori$-positive, NSAIDs using patients with mid-range hypersecretion. Although the corrosive intensity of the hypersecretion of gastric acid alone is less than $D_{H_{max}}$, the addition of the damage from $H. pylori$ and NSAIDs causes the $\Sigma D_{H}$ value to surpass $D_{H_{max}}$ and the patient suffers ulceration. Notably, $H. pylori$ may upregulate the expression of COX-2 and subsequently results in the biosynthesis of gastroprotective prostaglandin, which in turn offsets the corrosive intensity of NSAIDs and thus is conducive to the healing of NSAIDs-induced ulcers68,72, causing ‘$H. pylori$ infection reduces the development of ulcers in NSAIDs users’44. Case R represents the $\Sigma D_{H}$ value from high-range hypersecretion, $H. pylori$ infection, and NSAIDs usage, whereas the corrosive intensity of the acid alone surpasses $D_{H_{min}}$ and causes ulceration. In this case, the $\Sigma D_{H}$ values from $H. pylori$ and NSAIDs do not significantly contribute to the ulceration process. Case S illustrates normo-secretion with $H. pylori$ infection and NSAIDs use, wherein the $\Sigma D_{H}$ value does not reach $D_{H_{min}}$. The damage from $H. pylori$ and NSAIDs is not enough to cause ulceration. Cases T and U show similar situations with very low-range hypersecretion, $H. pylori$ infection, and corrosive medications. In these cases, corrosive medication usage, such as chemotherapy drugs, exerts damage on the duodenal bulb causing the $\Sigma D_{H}$ value to enter the ulceration threshold. Case T ulcerates, but Case U does not due to different susceptibility.

In summary, cases A, B, C, K, and S have $\Sigma D_{H}$ values that are less than $D_{H_{min}}$ and do not ulcerate. Cases F, I, J, N, Q, and R are duodenal ulcer patients because their $\Sigma D_{H}$ values surpass $D_{H_{max}}$. Cases D, G, L, O, and T have $\Sigma D_{H}$ values within the threshold range for ulceration and they ulcerate due to their susceptibility to local aggressive factors. Cases E, H, M, P, and U also have $\Sigma D_{H}$ values within the threshold range for ulceration, but they do not ulcerate because the corrosive intensity cannot overcome their individual resistance to local aggressive factors. Cases C, G, H, L, M, O, P, T, and U have mild degree of hyperplasia and hypertrophy of gastrin and parietal cells, Cases D, E, I, N, and Q, have moderate degree of hyperplasia and hypertrophy, and Cases F, J, and R have severe hyperplasia and hypertrophy, which account for the different levels of gastric acid hypersecretion in these cases.

The Roles of Gastric Acid, $H. pylori$, and NSAIDs in Duodenal Ulcerations

Figure 2 can elucidate all the observations/phenomena related to gastric acid, $H. pylori$, NSAIDs and other medications in duodenal ulcers. Since each of the 3 local aggressive factors partially contributes to the corrosive intensity and duodenal ulceration is caused by the total corrosive intensity, the higher density of $H. pylori$, the higher total corrosive intensity. As a result, $H. pylori$ infection exacerbates clinical symptoms and increases the clinical morbidity/mortality rates of the disease, and so does the NSAIDs usage. In contrast, the eradication of $H. pylori$ decreases the total corrosive intensity, causing mitigated symptoms, lowered morbidity/mortality and the rates of re-bleeding in ulcer patients. Cases B to J explain why $H. pylori$ density is associated with the morbidity rate of duodenal ulcers44 and Cases K to R explain that duodenal ulcers in $H. pylori$-negative patients are presumably due to NSAIDs72. Without the hypersecretion of gastric acid, the corrosive intensity caused by either $H. pylori$ or NSAIDs could not reach the threshold of ulceration. Therefore, $H. pylori$-positive patients and NSAIDs users require the hypersecretion of gastric acid to progress to duodenal ulcers68, indicating $H. pylori$ infection is not ‘the most
important etiological factor of duodenal ulcers, but second to the hypersecretion of gastric acid. For individuals with mild or moderate hyperplasia and hypertrophy of gastrin and parietal cells, *H. pylori* infection and/or NSAIDs usage significantly increase the corrosive intensities. As a result, although the hypersecretions of gastric acid in those individuals are not enough to induce duodenal ulcers independently, they still suffer from duodenal ulcers because the total sum of corrosive intensities reaches the threshold of ulceration. All these analyses suggest that neither *H. pylori* infection nor NSAIDs usage is essential for ulceration and they both are not the cause of duodenal ulcers. They play a secondary role in only the late phase of ulceration and thus, *H. pylori* strains such as CagA, VacA, and SecA, cannot explain the higher prevalence of duodenal ulcers.

Case B is applicable to most *H. pylori*-infected individuals, but only those also impacted by the hypersecretions of gastric acid due to psychological stress (Case G) will have the chance to become ulcer patients. This explains in spite of a high prevalence of *H. pylori* infection worldwide, the incidence of duodenal ulcer disease is low. The variation of ulcer prevalence is due to different social environments, as shown in the birth-cohort phenomenon. Comparing Cases C and G demonstrates that the morbidity of duodenal ulcers is increased in *H. pylori*-infected individuals. Contrasting Cases D and G or F and I illustrates the conclusion from a study in Northern Italy and Denmark that ' *H. pylori*-negative duodenal ulcers were associated with a poorer prognosis mainly because of a higher rate of ulcer and symptom relapse. To reach the ulceration threshold without the corrosive intensity from *H. pylori*, the hypersecretion of gastric acid needs to be higher in *H. pylori*-negative patients. The higher hypersecretion in Cases D and F indicates more severe negative impacts from psychosocial stress than in Cases G and I. Additionally, the damage from *H. pylori* can be relieved by antibiotics, as in Cases G and I, decreasing the corrosive intensity in these patients, whereas Cases D and F cannot achieve the same therapeutic effect. Therefore, there is a poorer prognosis and a higher relapse rate in *H. pylori*-negative patients. Cases D and F were caused simply by the hypersecretion of gastric acid due to psychological stress, which explain 20–40% of patients with idiopathic ulcers and the eradication of *H. pylori* cannot prevent the relapse of these cases.

Bleeding suggests that the patients are more likely to have severe hyperplasia and hypertrophy of parietal and gastrin cells and they are seriously impacted by stress as illustrated by Cases F. In that case, *H. pylori* infection is not essential to reach the threshold for ulceration. In contrast, non-bleeding ulcer suggests the patients are more likely to be slightly impacted by stress with mild hyperplasia and hypertrophy as Case G, and *H. pylori* infection is essential to reach the threshold for ulceration. As a result, bleeding ulcer patients are more likely to be *H. pylori* negative and non-bleeding patients are more likely to be *H. pylori* positive, causing 'the prevalence of *H. pylori* in patients with bleeding ulcers may be 15–20% lower than in patients with non-bleeding ulcer'. Clinical patients suffer the relapses of ulcers because neither anti-secretory nor anti-*H. pylori* therapy is an etiological treatment and the hyperplasia and hypertrophy of parietal and gastrin cells, as well as the impact of stress, have not been eliminated. The pre-existing hyperplasia and hypertrophy and the perception of stress from time to time, resulting in 'once an ulcer, always an ulcer'. Moreover, Figure 2 indicates that the classification of duodenal ulcers into three categories, *H. pylori*-related, NSAIDs-related, and non-*H. pylori/non-NSAIDs*-related, overlooked the determinant factor in duodenal ulceration, the hypersecretion of gastric acid.

Figure 2 further suggests that gastric acid is the primary local aggressive factor in the late phase of duodenal ulcers and *H. pylori* is a secondary contributor to this process, as indicated by Cases D, F, L, and N where ulceration occurs without *H. pylori*. These four cases support the finding that in some countries, 30-40% of duodenal ulcer patients were *H. pylori*-negative and explain a clinical observation 'up to 35% of 387 infected patients failed to respond to standard anti-*H. pylori* therapy'. Other clinical trials also found that the most common therapies, including proton pump inhibitors plus two antibiotics, were unsuccessful in more than 20% of patients, and in a routine clinical setting, the unsuccessful treatment rate was even greater. In addition, together with Cases J and R, these cases exemplify that etiological factors other than *H. pylori* play a significant role in duodenal ulcers because there is a 20% relapse rate within six months despite successful eradication of *H. pylori*. Cases J and R also explain that many duodenal ulcers are falsely attributed to *H. pylori* infection because the majority of the damage in these cases comes from the hypersecretion of gastric acid. Furthermore, the eradication of *H. pylori* would effectively cure the patients without recurrence in Cases G and I, which are representative of most clinical patients. However, the eradication of *H. pylori* would not prevent the relapse in *H. pylori*-negative Cases D and F, or in *H. pylori*-positive Cases J and R, where the damage caused by the bacterium was not a determinant factor in ulceration. The hypersecretion of gastric acid in Cases J and R suggests the patients were severely impacted by stress and may result in bleeding. In these two cases, *H. pylori* eradication were not likely to prevent the relapse. It is more common to identify cases similar to Cases G and I in clinical patients, whereas Cases D, F, J and R occur less frequently, which explains the dramatic decrease of relapse after *H. pylori* eradication.
Discussion

Although 13 theories have been proposed, the pathogenesis of duodenal ulcer remains elusive. Guided by the CCR with its accompanying methodologies, Theory of Nodes pinpointed the etiology of peptic ulcers from historical data and proposed a psychopathological mechanism, which elucidated 7 characteristics and 42 observations/phenomena of duodenal ulcer (Supplementary Table S2-S6). Unequivocally, a full understanding of the pathogenesis is indispensable for the development of strategies for a complete cure of the disease without relapse. Herein it is the application of the CCR with its accompanying methodologies that garners Theory of Nodes unprecedented insights into duodenal ulcers.

The psychopathological mechanism elucidated herein indicates that duodenal ulcer is a chronic disease associated with the individual’s life experiences/daily behaviors, and multiple psycho-neuro-endocrine organs are involved. Thus, stress-induced duodenal ulcer is hardly reproduced in animal models due to short lifespans. This mechanism also elucidated that the crux of duodenal ulcer issue is the hyperplasia and hypertrophy of gastrin and parietal cells induced by chronic stress. Therefore, neither anti-acid nor anti-H. pylori treatments can prevent the relapse of the disease, whereas stress management is essential for a complete cure without relapse. Based on the mechanism elucidated herein, Theory of Nodes recommends two levels of stress management for duodenal ulcer disease prevention. At the individual level, healthy habits and lifestyles improve both physical and mental well-being. To reduce stress from daily life, an individual should try her/his best to maintain harmonious family, social, and working environments. At the societal level, creating a positive and healthy environment is extremely important to cultivate healthy dispositions. This requires governments to lead and participate on all levels by fulfilling their administrative roles and promoting the harmonies of social, natural, and working environments to their citizens. These efforts will maximally reduce the chronic stress induced by social competitions and conflicts. Eventually, the morbidity and mortality rates of peptic ulcers may decrease to a minimal level.

Apparently, the pathogenesis of duodenal ulcers has never been fully understood before, primarily because a universal CCR has yet to be established and therefore, there is no benchmark for etiological factors. Consequently, modern medical doctors changed their research direction from time to time, resulting in the 13 etiological theories over the centuries. In that case, it was not surprising that the 3 local aggressive factors, gastric acid, H. pylori, and NSAIDs, were considered etiological factors one after another, causing multiple controversies and mysteries in peptic ulcer research. In contrast, guided by the CCR, Theory of Nodes pinpointed the cause of peptic ulcers from historical data, and combined Psychosomatic Theory and Stress Theory into a complete etiology of the disease. This new etiology elucidated that all the 3 local aggressive factors are not etiological factors, but risk factors playing a role in only the late phase of the disease. As a result, 7 characteristics and 42 observations/phenomena of duodenal ulcers, most of which have never been understood before, were explicitly elucidated. The effectiveness indicates that Theory of Nodes may have definitely identified the etiology of duodenal ulcers for the first time in history. Obviously, without the CCR, modern research on all other diseases is similar to the peptic ulcer research and thus, to this day, no disease has been fully explained and the majority of diseases, such as cancer and AIDS, remain incurable. Herein the first application of the CCR identified the etiology of a model disease, suggesting it may be widely applied to identify the etiology of any disease.

Although Psychosomatic Theory and Stress Theory have discovered the real cause of peptic ulcers for 70 years, they still could not explain the pathogenesis of peptic ulcers. Theory of Nodes demonstrated that the methodological concepts derived from the CCR, Integral Perspective and Superposition Mechanism, are indispensable for the data analyses. Without the two concepts, much invaluable historical data is deemed outdated and remains unanalyzed in modern medicine. For example, the discovery of H. pylori overshadowed all the other 4 major etiological theories in history, Psychosomatic Theory, Stress Theory, Nerve Theory, and ‘No Acid, No Ulcer’. Interestingly, the application of Integral Perspective in Theory of Nodes pulled all these 4 theories from the shadow as each of them did make important discoveries and proved useful for a full understanding of duodenal ulcers. In addition, Superposition Mechanism superposed the corrosive effects of the local aggressive factors into a combinatorial force, thereby elucidating all the clinical, epidemiological, and laboratory observations of duodenal ulcers, as well as the roles of gastric acid, H. pylori, and NSAIDs in the disease. The research on all other diseases is in the same scenario, indicating that the wide application of these methodological concepts may allow us gain unprecedented insights for any disease.

Conclusion

Duodenal ulcer is a psychosomatic disease triggered by psychological stress, where gastric acid, H. pylori, and NSAIDs play a role in only the late phase of ulcerations, exacerbating clinical symptoms and increasing morbidity/mortality rates. The hyperplasia and hypertrophy of parietal and gastrin cells in the stomach induced by chronic stress potentiate the individual’s response to psychological stress, resulting in the hypersecretion of gastric acid and eventually, duodenal ulceration. This psychopathological mechanism elucidated
7 characteristics and 42 observations/phenomena of duodenal ulcers, suggesting stress management is essential for a complete cure of the disease without relapse. The validity showcased herein indicates that the CCR with its accompanying methodologies may be applied to understand the pathogenesis of any disease, potentially leading to novel insights into the disease.

Acknowledgements

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Conflict of Interest

The author has no conflict of interest to declare.

Ethics Statement

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

Funding Statement

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Data Availability Statement

All the supporting data in this article are published papers or books, or in the supplementary materials.

Supplementary Materials

The supplementary materials include 6 tables in a PDF document.

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References


Supplementary Materials

The Hyperplasia and Hypertrophy of Gastrin and Parietal Cells Induced by Chronic Stress Explain the Pathogenesis of Duodenal Ulcers

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Table S1: List of 6 articles to explain all the 15 characteristics and 81 observations/phenomena of peptic ulcers

<table>
<thead>
<tr>
<th>Article</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1*</td>
<td>The Hyperplasia and Hypertrophy of Gastrin and Parietal Cells Induced by Chronic Stress Explain the Pathogenesis of Duodenal Ulcers</td>
</tr>
<tr>
<td>A2</td>
<td>A Novel Psychopathological Model Explains the Pathogenesis of Gastric Ulcers</td>
</tr>
<tr>
<td>A3</td>
<td>Painting a Complete Picture of the Pathogenesis of Peptic Ulcers</td>
</tr>
<tr>
<td>A4</td>
<td>Novel Data Analyses Explain the Birth-Cohort Phenomenon of Peptic Ulcers</td>
</tr>
<tr>
<td>A5</td>
<td>Novel Data Analyses Explain the Seasonal Variation of Peptic Ulcers</td>
</tr>
<tr>
<td>A6</td>
<td>Novel Data Analyses Address the African Enigma and the Controversies Surrounding the Roles of Helicobacter Pylori in Peptic Ulcers</td>
</tr>
</tbody>
</table>

Note: 1. A1: Article 1. 2. * This Article. 3. The 6 articles altogether explained all of the 15 major characteristics and 81 observations/phenomena of peptic ulcers. 4. The order and titles of articles might be modified during publication process.

Table S2: Index of 7 elucidated characteristics of peptic ulcers

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
<th>Explanation in the Article</th>
<th>Article, Page, Column &amp; Line #</th>
</tr>
</thead>
<tbody>
<tr>
<td>General (3)</td>
<td>1) Genetic predisposition</td>
<td>Peptic ulcers are not an infectious disease caused by the H. pylori infection, but a psychosomatic disease triggered by psychological stress.</td>
<td>Article 1, Page 2, Right Column, Lines 30-48.</td>
</tr>
<tr>
<td></td>
<td>2) Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Epidemiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical symptoms (6)</td>
<td>4) Predilection sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5) Morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6) Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7) Perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8) Relapse</td>
<td>Clinical patients suffer relapses of peptic ulcers because neither anti-secretory nor anti-H. pylori therapy is an etiological treatment and thus, the hyperplasia and hypertrophy of gastrin and parietal cells and the impact of stress have not been eliminated.</td>
<td>Article 1, Page 8, Right Column, Lines 7-14.</td>
</tr>
<tr>
<td></td>
<td>9) Multiplicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local aggressive factors (3)</td>
<td>10) Gastric acid (in duodenal ulcer)</td>
<td>The hypersecretion of gastric acid is an intermediate process of duodenal ulceration, suggesting it is not a cause of duodenal ulcers, but an effect of stress triggered by personality traits or life events. Nevertheless, the hypersecretion of gastric acid is a determinant factor in the late phase of duodenal ulceration, governing many characteristics of this disease, especially the observations related to H. pylori and NSAIDs.</td>
<td>Article 1, Page 5, Right Column, Lines 15-35.</td>
</tr>
<tr>
<td></td>
<td>11) H. pylori (in duodenal ulcer)</td>
<td>H. pylori infection is not an etiological factor/a cause of duodenal ulcer, but plays a secondary role in only the late phase of duodenal ulceration, exacerbating clinical symptoms and increasing the clinical morbidity/mortality of the disease.</td>
<td>Article 1, Page 2, Right Column, Line 49-Page 3, Left Column, Line 17; Article 1, Page 7, Right Column, Lines 34-41.</td>
</tr>
<tr>
<td></td>
<td>12) NSAIDs (in duodenal ulcer)</td>
<td>NSAIDs usage is not an etiological factor/a cause of duodenal ulcer, but plays a secondary role in only the late phase of ulceration, exacerbating clinical symptoms and increasing the clinical morbidity/mortality of the disease.</td>
<td>Article 1, Page 2, Right Column, Line 49-Page 3, Left Column, Line 17; Article 1, Right Column, Page 7, Lines 34-41.</td>
</tr>
<tr>
<td>Prognosis (3)</td>
<td>13) Self-healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14) Effects of clinical treatments (Duodenal ulcer only)</td>
<td>The eradication of H. pylori would effectively cure the patients without recurrence in Cases G and I, but the eradication of H. pylori would not prevent the recurrence of ulcers in H. pylori-negative Cases D and F, or in the H. pylori-positive Cases J and R. Cases like Cases D, F, J and R explains a dramatic decrease of ulcer recurrences after H. pylori eradication.</td>
<td>Article 1, Page 8, Right Column, Lines 40-53.</td>
</tr>
<tr>
<td></td>
<td>15) Hospitalization rates, morbidity, and mortality (Duodenal ulcer only)</td>
<td>Neither H. pylori infection nor NSAIDs usage is an etiological factor. Both play a secondary role in only the late phase of duodenal ulceration, exacerbating clinical symptoms and increasing clinical morbidity and mortality rates.</td>
<td>Article 1, Page 7, Right Column, Lines 34-41.</td>
</tr>
</tbody>
</table>

Note: The blank will be filled in other articles of the series.
Table S3: Index of elucidated duodenal ulcer-related observations/phenomena

<table>
<thead>
<tr>
<th>Observations/phenomena</th>
<th>Explanation in the Article</th>
<th>Article, Page, Column &amp; Line #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No Acid, No Ulcer (True statement for duodenal ulcer)</td>
<td>The hypersecretion of gastric acid is the determinant factor in the late phase of duodenal ulceration, governing multiple characteristics of this disease, especially the observations related to H. pylori and NSAIDS.</td>
<td>Article 1, Page 5, Right Column, Lines 28-34.</td>
</tr>
<tr>
<td>2. The role of gastric acid in the pathogenesis of duodenal ulcer is further supported by the relief of pain observed after neutralization or buffering of gastric contents with alkali or food.</td>
<td>The late phase of duodenal ulcers is a corrosive process caused by local aggressive factors. Thus, neutralization or buffering of gastric contents with alkali or food results in the relief of pain in duodenal ulcer patients.</td>
<td>Article 1, Page 5, Right Column, Lines 15-34.</td>
</tr>
<tr>
<td>3. Doll and Jones’ survey suggested a positive correlation between stressful occupations and duodenal ulcer, a decreased incidence of ulcer among agricultural workers.</td>
<td>Psychosomatic factors such as hypochondriasis, a negative perception of life events, dependency, and lowered self-confidence, made ulcer patients more susceptible to stress than controls.</td>
<td>Article 1, Page 3, Right Column, Line 36-Page 4, Left Column, Line 9.</td>
</tr>
<tr>
<td>4. Studies suggest that severe anxiety caused acid hypersecretion which, in turn, contributed to ulceration and symptoms. The fact that acid hypersecretion and symptoms abated with alleviation of stress supports this hypothesis.</td>
<td>The hypersecretion of gastric acid is triggered by the perception of stress via vagus nerves, and the hyperplasia and hypertrophy of gastrin and parietal cells in the early phase significantly potentiated the individual’s response to life events.</td>
<td>Article 1, Page 5, Left Column, Lines 37-43.</td>
</tr>
<tr>
<td>5. Rates of recurrence in patients whose initial ulcers healed during conventional anti-secretory therapy range from 60 to 100 percent per year.</td>
<td>Neither anti-secretory nor anti-H. pylori therapy is an etiological treatment and thus, the hyperplasia and hypertrophy of gastrin and parietal cells and the impact of stress have not been eliminated. The pre-existing hyperplasia and hypertrophy and the perception of stress from time to time, resulting in ‘once an ulcer, always an ulcer’.</td>
<td>Article 1, Page 8, Right Column, Lines 7-14.</td>
</tr>
<tr>
<td>6. Duodenal ulcer had higher incidence in large cities compared to rural areas in Africa since the 1950’s.</td>
<td>Life in large cities is more competitive and stressful than in rural areas.</td>
<td>Article 1, Page 4, Left Column, Lines 9-12.</td>
</tr>
</tbody>
</table>

Table S4: Index of elucidated gastric ulcer-related observations/phenomena

<table>
<thead>
<tr>
<th>Observations/phenomena</th>
<th>Explanation in the Article</th>
<th>Article, Page, Column &amp; Line #</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. No Acid, No Ulcer (wrong statements for gastric ulcers).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. In contrast to patients with duodenal ulcer, most patients with gastric ulcer are normo-secretors or hypo-secretors. Decreased acid-peptic activity in these patients suggests impaired mucosal defence.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Gastric ulcer is a sharply circumscribed loss of tissue involving the mucosa, submucosa, and muscular layer and a characteristic “punch out” appearance with clean edges, as if it were cut by a knife.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Gastric ulcers can be induced only in 8-30% of mouse models.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Gastric ulceration begin in the mucosa and extend into the wall of the stomach.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Stress-related gastric lesions are ‘brain-driven’ events that may be more effectively managed through central manipulations than by altering local, gastric factors. For example, stimulation or lesions of the central nucleus of the amygdala produced or reduced gastric ulcers, respectively.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Development of gastric ulcers elicited by cold stress was significantly decreased by i.p. pre-treatment with EDTA or a-methyl tyrosine, which depleted neurotransmitters. Gastric ulcers were significantly increased by pre-treatment with CaCl2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. The predilection sites of gastric ulcers are gastric antrum and lesser curvature.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Vulnerability to gastric ulceration is modulated by psychologically meaningful experiences. Repeated stress of the same type generally, but not exclusively, provides some degree of protection against ulcer during the second or later exposures.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Although no observation/phenomenon of gastric ulcer was explained in this first article, for the integrity of all the 15 major characteristics and 81 observations/phenomena of peptic ulcers, it is still necessary to retain the observations/phenomena of gastric ulcer here. This table will be filled in the second article, which focuses exclusively on the topic of gastric ulcer.
Table S5: Index of 11 elucidated both gastric and duodenal ulcer-related observations/phenomena

<table>
<thead>
<tr>
<th>Observations/phenomena</th>
<th>Explanation in the Article</th>
<th>Article, Page, Column &amp; Line #</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. The pathogenesis of NSAID-induced peptic ulcers is complex and multi-factorial.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. 14% of patients taking NSAIDs chronically can be found to have lesions described as gastric ulcers and 10% have lesions described as duodenal ulcers.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 18. Birth-cohort Phenomenon: the mortality rate of gastric ulcers in England and Wales increased at the beginning of the 20th century, reached a peak and then began to fall in the early 1950s. They also found similar trends for duodenal ulcers but followed approximately five years behind. | Clinical patients suffer relapses of peptic ulcers because neither anti-secretory nor anti-
H. pylori therapy is an etiological treatment and thus, the hyperplasia and hypertrophy of gastrin and parietal cells and the impact of stress have not been eliminated. The pre-existing hyperplasia and hypertrophy and the perception of stress from time to time, resulting in ‘once an ulcer, always an ulcer’ | Article 1, Page 8, Right Column, Lines 7-14.                                                    |
| 19. Once an ulcer, always an ulcer.                                                    |                                                                                                                                                                                                                            |                                                                                                |
| 20. Seasonal occurrence of peptic ulcer diseases.                                      |                                                                                                                                                                                                                            |                                                                                                |
| 21. Patients free of ulcer distress for long periods of time were subjected to emotional trauma and feelings of insecurity during the symptom-free intervals. |                                                                                                                                                                                                                            |                                                                                                |
| 22. Investigations of the effects of perceived stress on physiological parameters are scarce and the findings are often conflicting. | Questionnaire-based epidemiological surveys may have discounted many chronic stressors during peptic ulcer research, and that the essential methodology to study psychosocial factors (the abstract essence of the human body) have not been established in modern medicine. | Article 1, Page 5, Left Column, Line 44; Page 5, Right Column, Line 13.                          |
| 23. There is no definitive study proving a causal relationship between psychological stress and the development of ulcer disease. | Without the CCR, there is no benchmark to identify the cause of ulcer disease. without the methodological concepts derived from the CCR, much invaluable historical data is deemed outdated and remains unanalyzed. | Article 1, Discussion, Page 9, Left Column, Lines 43-53; Article 1, Discussion, Page 9, Right Column, Lines 19-43. |
| 24. Feldman’s multidimensional case-controlled study found that ulcer patients exhibited significantly more emotional distress in the form of depression and anxiety. Hypochondriasis, a negative perception of their life events, dependency, and lowered self-confidence were the four variables that best discriminated ulcer patients from controls. | Peptic ulcers are a psychosomatic disease triggered by psychological stress. psychosomatic factors made individuals susceptible to psychological stress caused by current life events, leading to peptic ulceration. | Article 1, Page 2, Right Column, Lines 30-48.                                                  |
| 25. Peptic ulcers are a rare disease in childhood.                                      |                                                                                                                                                                                                                            |                                                                                                |
| 26. Although gastric ulcer and duodenal ulcer share something in common, they are believed to be different diseases. |                                                                                                                                                                                                                            |                                                                                                |
| 27. The final stage of ulceration is a corrosive rather than an infectious process.     | The late phase of duodenal ulcers is a corrosive process caused by local aggressive factors, including gastric acid and pepsin, *H. pylori*, mechanical abrasion, and chemical erosion from medications such as NSAIDs. | Article 1, Page 5, Right Column, Lines 15-34.                                                  |
| 28. The gastric acid secretion of duodenal ulcer patients is much higher than a normal person, but only 7–8.5% of the duodenal ulcer patients are suffering from gastric ulcer simultaneously. |                                                                                                                                                                                                                            |                                                                                                |
| 29. Severe emotional stress may contribute to ulcer perforation and bleeding in some patients. |                                                                                                                                                                                                                            |                                                                                                |
30. Many uncomplicated lesions heal in spite of the presence of acid gastric content, as shown by the "spontaneous" remissions of the disease and by the healed scars found at x-ray and at autopsy; however, the healing of peptic ulcer is much more rapid when the lesion is protected from the action of acid gastric juice.

31. Autopsy reports showed: 20%-29% of males and 11%-18% of females were found to have suffered from ulcers in the past or present.

32. It is believed that, not only should the prognosis and assessment of ulcer have mental assessment, but the treatment without mind adjustment is also incomplete.

33. Peptic ulcer patients may have "ulcer personality", such as immaturity, impulsivity, and feelings of social isolation and alienation.

34. In a 2-year study of Pima Indians, Hesse did not find any peptic ulcer disease.

35. In contrast to Pima Indians, 10% of Caucasians develop peptic ulcers.

36. To date, no consistent pattern of factors, in either host or organism, has been identified that successfully predicts which infected persons will subsequently have ulcer disease.

37. The relationship between life events stress, psychological factors and peptic ulcer diseases is not clearly established at the present time and warrants further study.

38. Richard emphasized the different aetiology of gastric and duodenal ulcers and persons with gastric and duodenal ulcers differ epidemiologically, behaviourally, and genetically.

39. Gastric ulcer was more frequent than duodenal ulcer, 4G:1D in 1900 versus 10D:1G currently. More women than men had the disease, but now it has become reversed; from 3F:1M to 4M:1F for gastric ulcer and 10M:1F for duodenal ulcer.

40. Stress ulcers in the rat are primarily gastric rather than duodenal, the latter typically requiring additional artificial chemical potentiation (e.g., histamine).

41. Many ulcer patients and some physicians believe that symptomatic exacerbations of peptic ulcer disease occur during or shortly after stressful events.

42. Mental disorders (or stress) are associated with increased rates of peptic ulcer diseases.
43. The spontaneous remissions and relapses of peptic ulcers have never been explained.

Clinical patients suffer the relapse of peptic ulcers, because neither anti-secretory nor anti-\textit{H. pylori} therapy is an etiological treatment and thus, the impact of stress caused by personality traits or negative life events has not been eliminated. Chronic stress-induced hyperplasia and hypertrophy of gastrin and parietal cells are the crux of duodenal ulcer issue, determining the spontaneous remissions and relapse of duodenal ulcer, but this psychopathological mechanism has never been elucidated in modern medicine. The etiology of peptic ulcer has never been identified, causing the problem.

44. The pathophysiology of peptic ulcer has centered on an imbalance between aggressive and protective factors.

Each of the single theory focused on only one area of the human body, and there is no holistic review of peptic ulcers before. Without the CCR, there is no benchmark to identify the true cause of disease. In addition, without the CCR, the methodologies for data analysis have never been established. Although each of the historical theory did make important discoveries and proved useful to understand peptic ulcers, they were overshadowed by the discovery of \textit{H. pylori}.

45. No single theory in history could fully explain the pathogenesis of peptic ulcers.

Table S6: Index of 25 elucidated \textit{H. pylori}-related observations/phenomena

<table>
<thead>
<tr>
<th>Observations/phenomena</th>
<th>Explanation in the Article</th>
<th>Article, Page, Column &amp; Line #</th>
</tr>
</thead>
<tbody>
<tr>
<td>46. African Enigma: The \textit{H. pylori} infection rate is high (close to 100%) throughout Africa, but the prevalence of duodenal ulcer varied in different parts of the continent.</td>
<td>Since each of the 3 local aggressive factors partially contributes to the corrosive intensity, and duodenal ulceration is caused by the total corrosive intensity, the higher the density of \textit{H. pylori}, the higher total corrosive intensity. As a result, the infection of \textit{H. pylori} exacerbates clinical symptoms and increases the clinical morbidity/mortality of the disease. Cases B to J explain why \textit{H. pylori} density is associated with the morbidity rate of duodenal ulcers. 'The association between gastric ulcers and \textit{H. pylori} infection is less clear' will be explained in A2, which focuses on the pathogenesis of gastric ulcer.</td>
<td>Article 1, Page 8, Right Column, Lines 7-14; Article 1, Discussion, Page 9, Left Column, Lines 15-26.</td>
</tr>
<tr>
<td>47. Only the presence of duodenal ulcers, and not gastric ulcers, was associated with increasing \textit{H. pylori} density. The association between gastric ulcers and \textit{H. pylori} infection is less clear.</td>
<td>For the 5th time, \textit{H. pylori} infection is not the cause of duodenal ulcers but plays a secondary role in only the late phase of ulceration and thus, \textit{H. pylori} strains such as CagA, VacA, and SecA cannot explain the higher prevalence of duodenal ulcers.</td>
<td>Article 1, Page 3, Left Column, Lines 20-29; Article 1, Discussion, Page 9, Left Column, Lines 43-53; Article 1, Discussion, Page 9, Right Column, Lines 19-43.</td>
</tr>
<tr>
<td>48. Only 27% of symptomatic children with peptic ulcers were \textit{H. pylori} positive.</td>
<td>H. pylori infection is not the cause of duodenal ulcers but plays a secondary role in only the late phase of ulceration and thus, \textit{H. pylori} strains such as CagA, VacA, and SecA cannot explain the higher prevalence of duodenal ulcers.</td>
<td>Article 1, Page 8, Left Column, Lines 2-16.</td>
</tr>
<tr>
<td>49. 48% of patients developed ulcers within six months of healing, but the re-infection rate after eradication was very low (&lt;2%).</td>
<td>H. pylori infection is not the cause of duodenal ulcers but plays a secondary role in only the late phase of ulceration and thus, \textit{H. pylori} strains such as CagA, VacA, and SecA cannot explain the higher prevalence of duodenal ulcers.</td>
<td>Article 1, Page 8, Left Column, Lines 2-16; Article 1, Page 8, Right Column, Lines 19-27.</td>
</tr>
<tr>
<td>50. In developing countries with uniformly high prevalence of \textit{H. pylori} infection, there are marked regional differences in the prevalence of duodenal ulcers, which could not be explained by the more toxic CagA and VacA \textit{H. pylori} strains.</td>
<td>H. pylori infection is not the cause of duodenal ulcers but plays a secondary role in only the late phase of ulceration and thus, \textit{H. pylori} strains such as CagA, VacA, and SecA cannot explain the higher prevalence of duodenal ulcers.</td>
<td>Article 1, Page 8, Left Column, Lines 2-16; Article 1, Page 8, Right Column, Lines 19-27.</td>
</tr>
<tr>
<td>51. In the countries with low prevalence of \textit{H. pylori}, 30%-40% or more of duodenal ulcer patients are \textit{H. pylori}-negative, and the absence of \textit{H. pylori} infection in early cases of duodenal ulcers was also reported.</td>
<td>H. pylori infection is not the cause of duodenal ulcers but plays a secondary role in only the late phase of ulceration and thus, \textit{H. pylori} strains such as CagA, VacA, and SecA cannot explain the higher prevalence of duodenal ulcers.</td>
<td>Article 1, Page 8, Left Column, Lines 2-16; Article 1, Page 8, Right Column, Lines 19-27.</td>
</tr>
</tbody>
</table>
52. The role of *H. pylori* in peptic ulcers is controversial.

Without the CCR, there is no benchmark to identify the cause of disease, and the methodologies essential for data analysis have never been established, resulting in many unsolved mysteries and massive challenges. No longer controversial after the application of the CCR.

53. ‘*H. pylori* is the most important aetiologic factor so far described for duodenal ulcer’.

This is a wrong statement. The hyper-secretion of gastric acid is a determinant factor in the late phase of duodenal ulceration; Administering cysteamine or propionitrile, which effectively stimulates the hypersecretion of gastric acid in rats, can induce acute and chronic duodenal ulcers in normal rats, whereas the inoculation of *H. pylori* alone cannot, suggesting it is not *H. pylori* but gastric acid that plays a primary/decisive role in the pathogenesis of duodenal ulcers.

54. How *H. pylori* infection can lead to ulceration is unknown.

This statement is based on a wrong assumption. Without the hypersecretion of gastric acid, the corrosive intensity caused by either *H. pylori* or NSAIDs could not reach the threshold of ulceration. *H. pylori* alone cannot lead to ulceration and thus, the etiology based on *H. pylori* infection would never be able to explain peptic ulcerations.

55. No *H. pylori*, No Ulcer; peptic ulcer is an infectious disease.

These are wrong statements. Neither *H. pylori* infection nor NSAIDs usage is essential for ulceration. Therefore, duodenal ulcers may occur in the absence of *H. pylori* and/or NSAIDs, leading to idiopathic (*H. pylori*-negative and non-NSAIDs user) ulcer patients.

56. In spite of a high prevalence of *H. pylori* infection worldwide, the incidence of duodenal ulcer disease in both adults and children is low in comparison.

Case B is applicable to most *H. pylori* infected individuals, but only those also impacted by the hyper-secretions of gastric acid due to psychological stress (Case G) will have the chance to become ulcer patients.

57. Kato and colleagues’ retrospective analysis found that *H. pylori* prevalence in gastric ulcer did not reach 50%; they concluded while *H. pylori* infection appears to be a risk factor in gastric ulcer, other causes are responsible for most cases. Only 56-96% of gastric ulcer patients are *H. pylori*-positive, so other factors must be involved.

58. Despite the fall in prevalence of *H. pylori* infection, the attributable risk of *H. pylori* infection in peptic ulcer disease has not changed.

59. There was a significantly higher incidence of idiopathic duodenal ulcers in the younger generation.

60. There are basically three different types of peptic ulcer: *H. pylori*-related peptic ulcer; NSAID-related peptic ulcer; and non-*H. pylori*, non-NSAID ulcer.

This classification is because the cause of peptic ulcers has never been identified in modern medicine. This classification overlooks the primary/decisive factor in the occurrence of duodenal ulcers, the hypersecretion of gastric acid.

61. A relatively isolated group of Australian aboriginals have virtually no *H. pylori* infection and hardly any peptic ulcer disease.

Cases D and F were caused simply by the hypersecretion of gastric acid due to psychological stress, which explain 20%-40% of patients with idiopathic ulcers (*H. pylori*-negative and non-NSAIDs user) and the eradication of *H. pylori* cannot prevent the relapse of these cases.

62. Up to 20% of patients with ulcers suffer a relapse of ulcer disease despite successful eradication of their infections, suggesting that *H. pylori* was not the cause of their original ulcers.

63. Difference in virulence of *H. pylori* strains (cag- and cag+) has been considered as a putative explanation as to why only a minority of infected population develop peptic ulcers.

*H. pylori* infection is not the cause of duodenal ulcers but plays a secondary role in only the late phase of ulceration and thus, *H. pylori* strains such as CagA, VacA, and SecA, cannot explain the higher prevalence of duodenal ulcers.
64. *H. pylori* infection in rats was successful and was accompanied by amild to moderate mucosal inflammation. After *H. pylori* inoculation, an ulcer was induced in the oxyntic mucosa of both infected and uninfected rats by exposing the serosal side to acetic acid.

For those individuals with severe hyperplasia and hypertrophy of gastrin and parietal cells, the hypersecretion of gastric acid alone is sufficient to induce duodenal ulcerations. In that case, neither *H. pylori* infection nor NSAIDs usage is essential for ulceration. Therefore, duodenal ulcers may occur in the absence of *H. pylori* and/or NSAIDs, leading to idiopathic (*H. pylori*-negative and non-NSAIDs user) ulcer patients. Administering cysteamine or propionitrile, which effectively stimulates the hypersecretion of gastric acid in rats, can induce acute and chronic duodenal ulcers in normal rats, whereas the inoculation of *H. pylori* alone cannot, further indicating that gastric acid plays a more important role than *H. pylori* in duodenal ulcerations.

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<th>Article 1, Page 5, Right Column, Lines 36-52</th>
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65. More than 95 percent of patients with duodenal ulcers and more than 80 percent of patients with gastric ulcers are infected with *H. pylori*.

66. The corresponding ulcer areas in the *H. pylori*-infected rats were significantly larger in the infected than in the uninfected rats, and ulcer healing was delayed in the infected rats. Eliminating *H. pylori* accelerates the healing of ulcer.

67. Eradication of *H. pylori* in gastric ulcer patients has also been shown to be associated with a significant reduction in ulcer relapse rate, compared with those who remain infected.

68. Clinical data reported that the recurrence rate is as high as 74-80% in *H. pylori* positive group of duodenal ulcer patients who have healed, but the negative group is only 0-28%. The discrimination was remarkable.

The eradication of *H. pylori* would effectively cure the patients without recurrence in Cases G and I, which are representative of most clinical patients. However, the eradication of *H. pylori* would not prevent the recurrence of ulcers in *H. pylori*-negative Cases D and F, or in the *H. pylori*-positive Cases J and R, where the damage caused by the bacterium was not a determinant factor in ulceration. It is more common to identify cases similar to Cases G and I in clinical patients, whereas cases like Cases D, F, J and R occur less frequently, which explains the dramatic decrease of ulcer recurrences after *H. pylori* eradication.

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69. A negative interaction between *H. pylori* and NSAIDs on duodenal ulcers suggests that *H. pylori* reduces the development of ulcers in NSAIDs users.

*H. pylori* upregulates the expression of COX-2 and subsequently results in the biosynthesis of gastroprotective prostaglandins, which in turn offsets the corrosive intensity of NSAIDs and thus is conducive to the healing of NSAIDs-induced ulcers, causing ‘*H. pylori* reduces the development of ulcers in NSAIDs users’.

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70. ~20% of peptic ulcers in the Polish population are unrelated to *H. pylori* and NSAIDs use (idiopathic ulcers).

For individuals with severe hyperplasia and hypertrophy of gastrin and parietal cells, the hypersecretion of gastric acid alone is sufficient to induce duodenal ulcerations. In that case, neither *H. pylori* infection nor NSAIDs usage is essential for ulceration. Therefore, duodenal ulcers may occur in the absence of *H. pylori* and/or NSAIDs, leading to idiopathic (*H. pylori*-negative and non-NSAIDs user) ulcer patients.

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71. The prevalence of *H. pylori* in patients with bleeding ulcers may be 15~20% lower than in patients with non-bleeding ulcers.

Bleeding indicates patients are more likely to be seriously impacted by psychological stress with severe hyperplasia and hypertrophy of parietal and gastrin cells as Cases F and H. *H. pylori* infection is not essential for ulceration. In contrast, non-bleeding ulcer suggests the patients are more likely to be slightly impacted by stress with mild hyperplasia and hypertrophy, and *H. pylori* infection is essential to increase the total corrosive intensity for the induction of ulcers as Case G. As a result, clinical bleeding ulcer patients are more likely to be Case F without *H. pylori* and non-bleeding patients are more likely to be Case G with H.
72. The eradication of H. pylori reduces the rate of re-bleeding in patients with ulcer disease.

73. How H. pylori infection affects gastric acid secretion is still unclear.

74. The incidence of peptic ulcers was higher in H. pylori-infected patients than in the H. pylori-negative group.

75. Duodenal acid load determines whether H. pylori can cause duodenal ulcer.

76. The increase in H. pylori density is related to the presence of duodenal ulcer disease.

77. H. pylori-negative duodenal ulcers were associated with a poorer prognosis mainly because of a higher rate of ulcer and symptom relapse.

78. When H. pylori persisted, 61% of duodenal ulcers healed and 84% relapsed. When H. pylori was cleared, 92% of ulcers healed and only 21% relapsed during the 12 months follow-up period.

79. Jyotheeswaran and colleagues from greater Rochester, New York, reported a 48% prevalence of H. pylori-negative duodenal ulcers in white patients and 15% in non-white patients, with an overall negative prevalence of 39%. Parsonnet’s meta-analysis indicates the overall prevalence of H. pylori-negative duodenal ulcers is 40%.
A statement originated from wrong etiology. ‘A causal role for H. pylori in stress ulcer’ indicates that without stress, H. pylori alone can not induce ulcer. Administering cysteamine or propionitrile, which effectively stimulates the hypersecretion of gastric acid in rats, can induce acute and chronic duodenal ulcers in normal rats, whereas the inoculation of H. pylori alone cannot, further indicating it is not H. pylori but gastric acid that plays a primary/decisive role in the pathogenesis of duodenal ulcer.

Case B in Figure 2 is applicable to most H. pylori infected individuals, but only those also impacted by the hypersecretions of gastric acid due to psychological stress (Case G) will have the chance to become ulcer patients. *That explained the wrong statement “a causal role for H. pylori in stress ulcer formation”*

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<th>80. A review by van der Voort and colleagues suggests that existing data are consistent with a causal role for <em>H. pylori</em> in stress ulcer formation.</th>
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<th>81. Barry Marshall drank a concoction made from cultured H. pylori and came down with gastritis that could be cured with antibiotics.</th>
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