A collection of the etiological theories, characteristics, and observations/phenomena of peptic ulcers in existing data

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**ABSTRACT**

In this article, we compiled 13 etiological theories, 15 characteristics, and 81 observations/phenomena of peptic ulcers, reported in reproducible, peer-reviewed studies from the literature, to reflect the historical evolution of studies on peptic ulcers and to provide a multidisciplinary view of this disease. This data was collected during the systematic review of topics on peptic ulcers including genetics, etiology, epidemiology, psychology, anatomy, neurology, bacteriology, pathology, and clinical statistics. The data curated herein was extracted via application of recently published basic theories and methodologies.

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**Specifications Table**

| Subject area               | Medicine |
|----------------------------|----------|
| More specific subject area | Gastroenterology |
| Type of data               | Tables |
| How data was acquired      | Systematic review of the existing data over the past 300 years |
| Data format                | Filtered and classified |
| Data source location       | Ottawa, Ontario, Canada |
| Experimental factors       | Not applicable |

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Value of the data

- Etiological theories proposing the correct cause of peptic ulcers should be able to explain all 15 characteristics and 81 observations/phenomena listed herein.
- Many etiological theories summarized herein were supported by valid laboratory results, clinical observations, and/or epidemiological surveys, and did make important discoveries.
- This article may prove useful in advancing the development of new experimental avenues by presenting data together that otherwise might be kept separate.
- Similar literature review can be repeated for any disease. Accordingly, the data obtained can be used to challenge etiological theories and provide new insights for any disease.

1. Data

Over the past 300 years, many etiological theories have been proposed to explain the pathogenesis of peptic ulcers (including gastric ulcer and duodenal ulcer), but none of these theories have ever been able to explain all the characteristics and observations/phenomena of this disease [1]. Currently, it is widely believed that there is a causal relationship between Helicobacter pylori (H. pylori) and peptic ulcers due to the revolutionary discovery of H. pylori in 1982 [2]. However, the role of H. pylori in peptic ulcers is controversial, and how the bacterial infection can lead to ulceration is presently unknown [3–6]. To address these challenges, we systematically reviewed all the topics on peptic ulcers over the past 300 years and applied novel basic theories and methodologies to analyze the existing data. We summarized our results into 6 manuscripts (prepared, unpublished) to explain the pathogenesis of peptic ulcers (Table 1). We also found that the pathogenesis of peptic ulcers included 15 characteristics (Table 2) and 81 observations/phenomena, which were grouped into four tables based on diseases and H. pylori (Tables 3–6).

2. Materials and methods

We developed a four-step strategy to collect the data presented herein. First, we reviewed all the topics on peptic ulcers, such as genetics, etiology, epidemiology, psychology, anatomy, neurology, bacteriology, pathology, and clinical statistics. To achieve this goal, we searched Medline, Embase, Web of Science, and Google Scholar for articles published over the past 300 years. Books published on peptic ulcers and on the pathogenesis of human disease were also included. Our search was completed without language restrictions. Second, we extracted data on study year, etiological theories, characteristics, observations, and phenomena of peptic ulcers. If an etiological theory in history had yet to be officially named, we named it based on its central idea. For instance, we designate the etiological theory based on H. pylori infection as “Theory of H. pylori”. Third, selected studies were summarized and unreproducible studies were excluded. If several studies had similar findings, we randomly selected one or two to avoid repetitive results. However, if a paper was identified to be the earliest study on a characteristic or phenomenon, this paper was selected because we determined the earliest paper provided the basis for the other similar studies that followed. Fourth, selected data was classified and curated into 6 tables.
### Table 1
Etiological theories in history.

| Etiological theory                  | Founder & year | Key points                                                                                           |
|-------------------------------------|----------------|------------------------------------------------------------------------------------------------------|
| 1 Circulation Theory [7]            | John Hunter, 1772 | Gastric acid is neutralized by the continuing circulation of alkaline blood through the tissue.       |
| 2 Ischemia Theory [8]               | Rudolf Virchow, 1853 | The presence or absence in the gastric mucosa of end arteries whose spasm or thrombosis might account for localized ulceration. |
| 3 Digestion Theory [9]              | Heinrich Irenaeus Quincke, 1882 | Peptic ulcer is caused by the proteolytic effects of pepsin and the corrosive effects of gastric acid. |
| 4 No Acid, No Ulcer [10]            | Dragutin (Carl) Schwartz, 1910 | Hypersecretion of gastric acid is the cause of peptic ulcer.                                          |
| 5 Nerve Theory [11]                 | Von Bergmann G., 1913 | The abnormality of neurotransmitters in the central nervous system is the cause of peptic ulcer.     |
| 6 Funktionell-mechanische Theorie [12]| Ludwig Aschoff, 1918 | Rubbing of food as it passes through the narrow pyloric portion of the stomach results in peptic ulcer. |
| 7 Inflammation Theory [13]          | Georg Ernst Konjetzny, 1923 | Chronic gastritis and duodenitis cause gastric and duodenal ulcers.                                  |
| 8 Psychosomatics Theory [14]        | Franz Gabriel Alexander, 1943 | Social, psychological, and behavioral factors are the cause of peptic ulcer.                        |
| 9 Stress Theory [15]                | Hans Selye, 1950 | Stress induced by personality traits, and social and natural events is the cause of peptic ulcer.   |
| 10 Balance Theory [16]              | Shay H and Sun C.H., 1963 | Peptic ulcer is the result of an imbalance of defensive and aggressive factors in the upper gastrointestinal tract. |
| 11 Pallium-viscus Theory (The Corticovisceral Theory) [17]| K.M. Bykov and I.T. Kurtsin, 1966 | A disturbance in the excitatory and inhibitory processes in the cerebral cortex is the cause of peptic ulcer. |
| 12 Double Restriction Mechanism [18] | Minoru Oi (大井実, Japanese), 1966 | Peptic ulcer is the coefficient results of anatomic factors and functional factors.                   |
| 13 Theory of H. Pylori [19]         | Barry J. Marshal and J. Robin Warren, 1988 | Peptic ulcer is an infectious disease caused by the infection of H. pylori.                          |

- We designate the etiological theory proposed by Rudolf Virchow as Ischemia Theory according to the mechanism described.
- We designate the etiological theory based on H. pylori infection as Theory of H. pylori.

### Table 2
Characteristics of peptic ulcers.

| Classification                              | Characteristics                                                                 | Year |
|---------------------------------------------|---------------------------------------------------------------------------------|------|
| General (3)                                 | 1) Genetic predisposition [20]                                                  | 1967 |
|                                              | 2) Etiology [21]                                                               | 1986 |
|                                              | 3) Epidemiology [22]                                                          | 1984 |
| Clinical symptoms (6)                       | 4) Predilection sites [23]                                                     | 2009 |
|                                              | 5) Morphology [24]                                                             | 2004 |
|                                              | 6) Bleeding [25]                                                               | 2010 |
|                                              | 7) Perforation [23]                                                            | 2009 |
|                                              | 8) Relapse [26]                                                                | 1998 |
|                                              | 9) Multiplicity [27]                                                           | 2002 |
| Local aggressive factors in the upper digestive tract (3) | 10) Gastric acid and pepsin [10]                                               | 1910 |
|                                              | 11) Helicobacter pylori [19]                                                   | 1988 |
|                                              | 12) NSAIDs and other medications [27]                                          | 2002 |
| Prognosis (3)                               | 13) Self-healing [28]                                                          | 1951 |
|                                              | 14) Effects of clinical treatments [29]                                        | 1995 |
|                                              | 15) Hospitalization rates, morbidity, and mortality [22]                       | 1984 |
Table 3
Duodenal ulcer-related observations/phenomena.

| Observations/phenomena                                                                                                                                                                                                 | Year  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| 1. No Acid, No Ulcer (true statement for duodenal ulcer) [10,24].                                                                                                                                                     | 1910  |
| 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 [24,30]. | 1978  |
| 3. Doll and Jones’ survey suggested a positive correlation between stressful occupations and duodenal ulcer, and a decreased incidence of ulcer among agricultural workers [31,32].  
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 [33]. | 1951  |
| 5. Rates of recurrence in patients whose initial ulcers healed during conventional anti-secretory therapy range from 60 to 100 percent per year [29].  
6. Duodenal ulcer had higher incidence in large cities compared to rural areas in Africa since the 1950s [34].                                                                 | 1952  |

Table 4
Gastric ulcer-related observations/phenomena.

| Observations/phenomena                                                                                                                                                                                                 | Year  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| 7. No Acid, No Ulcer (incorrect for gastric ulcers) [10,24].                                                                                                                                                          | 1910  |
| 8. In contrast to patients with duodenal ulcer, most patients with gastric ulcer are normo-secretors or hyposecretors. Decreased acid-peptic activity in these patients suggests impaired mucosal defence [10,35]. | 1996  |
| 9. Gastric ulcer is a sharply circumscribed loss of tissue involving the mucosa, submucosa, and muscular layer. Gastric ulcer has a characteristic “punch out” appearance with clean edges, as if it were cut by a knife [20,36]. | 1967  |
| 10. Gastric ulcers can be induced in only 8–30% of mouse models [37].  
11. Gastric ulceration begins in the mucosa and extends into the wall of the stomach [31].  
12. Bleeding and perforation of gastric ulcers [33,38].  
13. Self-healing and effects of clinical therapy [39,40].  
14. 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 [37,41,42].  
15. 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 [43].  
16. The predilection sites of gastric ulcers are the gastric antrum and lesser curvature [23].  
17. 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 [37,44]. | 1991  |
Table 5
Both gastric and duodenal ulcer-related observations/phenomena.

| Observations/phenomena                                                                 | Year   |
|--------------------------------------------------------------------------------------|--------|
| 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. Similar trends were found for duodenal ulcers, but followed approximately five years behind [45,46]. | 1962   |
| 19. Once an ulcer, always an ulcer [47].                                              | 1994   |
| 20. Seasonal occurrence of peptic ulcer diseases [48,49].                            | 1994   |
| 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 [31]. | 1952   |
| 22. Investigations of the effects of perceived stress on physiological parameters are scarce and the findings are often conflicting [50]. | 2005   |
| 23. There is no definitive study proving a causal relationship between psychological stress and the development of ulcer disease [51]. | 1986   |
| 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 [52]. | 1945   |
| 25. Peptic ulcer is a rare disease in childhood [53,54].                             | 1961   |
| 26. Although gastric ulcer and duodenal ulcer share something in common, they are believed to be different diseases [20,55]. | 1978   |
| 27. The final stage of ulceration is a corrosive rather than an infectious process [31,56]. | 1952   |
| 28. The gastric acid secretion of duodenal ulcer patients is much higher than normal controls, but only 7–8.5% of the duodenal ulcer patients suffer from gastric ulcer simultaneously [57,58]. | 1999   |
| 29. Severe emotional stress may contribute to ulcer perforation and bleeding in some patients [33]. | 2004   |
| 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]. | 1952   |
| 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 [59,60]. | 1960   |
| 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 [21]. | 1986   |
| 33. Peptic ulcer patients may have “ulcer personality”, such as immaturity, impulsivity, feelings of social isolation, and alienation [52]. | 1986   |
| 34. In a 2-year study of Pima Indians, Hesse did not find any peptic ulcer disease [61]. | 1959   |
| 35. In contrast to Pima Indians, 10% of Caucasians develop peptic ulcers [52,63]. | 1955   |
| 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 [64]. | 1962   |
| 37. The relationship between life event stresses, psychological factors and peptic ulcer diseases is not clearly established at the present time and warrants further study [52]. | 1986   |
| 38. Richard emphasized the different etiology of gastric and duodenal ulcers; persons with gastric and duodenal ulcers differ epidemiologically, behaviourally, and genetically [20,55]. | 1986   |
| 39. Gastric ulcer was more frequent than duodenal ulcer, 4 gastric:1 duodenal in 1900 versus 1 gastric:10 duodenal currently. More women than men had the disease (3F:1M), but now it has become reversed; as the ratio for gastric ulcer is now 1F:4M and 1F:10M for duodenal ulcer [20,65]. | 1991   |
| 40. Stress ulcers in the rat are primarily gastric rather than duodenal, the latter typically requiring additional artificial chemical potentiation (e.g., histamine) [37]. | 1991   |
| 41. Many ulcer patients and some physicians believe that symptomatic exacerbations of peptic ulcer disease occur during or shortly after stressful events [33,66,67]. | 1973   |
| 42. Mental disorders (or stress) are associated with increased rates of peptic ulcer diseases [68,69]. | 2009   |
| 43. The spontaneous remissions and relapses of peptic ulcers have never been explained [31]. | 1952   |
| 44. The pathophysiology of peptic ulcer has centred on an imbalance between aggressive and protective factors [70]. | 2004   |
| 45. No single theory in history could fully explain the pathogenesis of peptic ulcers [1]. | 1990   |
### Table 6
*H. pylori*-related observations/phenomena.

| Observations/phenomena                                                                 | Year |
|-------------------------------------------------------------------------------------|------|
| 46. African Enigma: the *H. pylori* infection rate is high (close to 100%) throughout Africa, but the prevalence of duodenal ulcer varied in different parts of the continent [34]. | 1995 |
| 47. Only the presence of duodenal ulcers, and not gastric ulcers, was associated with increasing *H. pylori* density. The association between gastric ulcers and *H. pylori* infection is less clear [71]. | 1992 |
| 48. Only 27% of symptomatic children with peptic ulcers were *H. pylori* positive [72]. | 2001 |
| 49. 48% of patients developed ulcers within six months of healing, but the re-infection rate after eradication was very low (< 2%) [5]. | 1994 |
| 50. In developing countries with uniformly high prevalence of *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 *H. pylori* strains [6]. | 1999 |
| 51. In the countries with low prevalence of *H. pylori*, 30–40% or more of duodenal ulcer patients are *H. pylori* negative, and the absence of *H. pylori* infection in early cases of duodenal ulcers was also reported [6,73]. | 1998 |
| 52. The role of *H. pylori* in peptic ulcers is controversial [3–6]. | 1999 |
| 53. *H. pylori* is the most important aetiological factor so far described for duodenal ulcer [19]. | 2000 |
| 54. How *H. pylori* infection can lead to ulceration is unknown [74]. | 2002 |
| 55. No *H. pylori*, No Ulcer; peptic ulcer is an infectious disease [75]. | 1989 |
| 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 [72,76–78]. | 1987 |
| 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 [34,79]. | 1994 |
| 58. 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 [70]. | 2001 |
| 59. A relatively isolated group of Australian aboriginals have virtually no *H. pylori* infection and hardly any peptic ulcer disease [34,80]. | 1995 |
| 60. 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 [73,81]. | 2004 |
| 61. 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 [82–84]. | 1998 |
| 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 [73,81]. | 1998 |
| 63. The prevalence of *H. pylori* in patients with bleeding ulcers may be 15–20% lower than in patients with non-bleeding ulcers [38,89,90,92]. | 1998 |
| 64. *H. pylori* infection in rats was successful and was accompanied by a mild 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 [85]. | 1986 |
| 65. More than 95% of patients with duodenal ulcers and more than 80% of patients with gastric ulcers are infected with *H. pylori* [29,86–88]. | 1991 |
| 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 [85,89–91]. | 1997 |
| 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 [29,34]. | 2003 |
| 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 [57]. | 1999 |
| 69. A negative interaction between *H. pylori* and NSAIDs on duodenal ulcers suggests that *H. pylori* reduces the development of ulcers in NSAIDs users [34]. | 1999 |
| 70. –20% of peptic ulcers in the Polish population are unrelated to *H. pylori* and NSAIDs use (idiopathic ulcers) [90]. | 1997 |
| 71. The prevalence of *H. pylori* in patients with bleeding ulcers may be 15–20% lower than in patients with non-bleeding ulcers [38,89,90,92]. | 1997 |
| 72. The eradication of *H. pylori* reduces the rate of re-bleeding in patients with ulcer disease [90,93,94]. | 1993 |
| 73. How *H. pylori* infection affects gastric acid secretion is still unclear [95]. | 1998 |
| 74. The incidence of peptic ulcer was higher in *H. pylori* infected patients than in the *H. pylori* negative group [96]. | 1999 |
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