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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

# History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer

David Y Graham

David Y Graham, Michael E DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX 77030, United States
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Correspondence to: David Y Graham, MD, Michael E DeBakey VA Medical Center, Baylor College of Medicine, 2002 Holcombe Blvd., Rm 3A-318B (111D), Houston, TX 77030, United States. dgraham@bcm.edu
Telephone: +1-713-7950232 Fax: +1-713-7901040
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## Abstract

*Helicobacter pylori* (*H. pylori*) infection underlies gastric ulcer disease, gastric cancer and duodenal ulcer disease. The disease expression reflects the pattern and extent of gastritis/gastric atrophy (*i.e.*, duodenal ulcer with non-atrophic and gastric ulcer and gastric cancer with atrophic gastritis). Gastric and duodenal ulcers and gastric cancer have been known for thousands of years. Ulcers are generally non-fatal and until the 20th century were difficult to diagnose. However, the presence and pattern of gastritis in past civilizations can be deduced based on the diseases present. It has been suggested that gastric ulcer and duodenal ulcer both arose or became more frequent in Europe in the 19th century. Here, we show that gastric cancer and gastric ulcer were present throughout the 17th to 19th centuries consistent with atrophic gastritis being the predominant pattern, as it proved to be when it could be examined directly in the late 19th century. The environment before the 20th century favored acquisition of *H. pylori* infection and atrophic gastritis (*e.g.*, poor sanitation and standards of living, seasonal diets poor in fresh fruits and vegetables, especially in winter, vitamin deficiencies, and frequent febrile infections in childhood). The latter part of the 19th century saw improvements in standards of living, sanitation, and diets with a corresponding decrease in rate of development of atrophic gastritis allowing duodenal ulcers to become more prominent. In the early 20th century physician's believed they could diagnose ulcers clinically and that the diagnosis required hospitalization for "surgical disease" or for "Sippy" diets. We show that while *H. pylori* remained common and virulent in Europe and the United States, environmental changes resulted in changes of the pattern of gastritis producing a change in the manifestations of *H. pylori* infections and subsequently to a rapid decline in transmission and a rapid decline in all *H. pylori*-related diseases.



**Key words:** *Helicobacter pylori*; Duodenal ulcer; Gastric ulcer; Gastric cancer; Medical history; Ulcer surgery; Epidemiology; Gastritis; Atrophic gastritis; Antiquity

**Core tip:** *Helicobacter pylori* (*H. pylori*)-related diseases reflect the pattern and extent of gastritis/atrophy (*i.e.*, duodenal ulcer signifies the presence of non-atrophic gastritis whereas gastric ulcer and gastric cancer signify atrophic gastritis). While, it has been suggested that gastric ulcer and duodenal ulcer both arose or became more frequent in Europe in the 19th century, the available data are more consistent with a change in the pattern of gastritis related to environmental conditions which previously had resulted primarily in atrophic gastritis. Duodenal ulcer then dominated clinically until the rapid decline in *H. pylori* transmission resulted in a rapid decline in all *H. pylori*-related diseases.

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## INTRODUCTION

It has been suggested that peptic ulcer disease, gastric and duodenal arose or became remarkably more prevalent in Western countries in the 19th century possibly because of a change in the epidemiology of *Helicobacter pylori* (*H. pylori*) infections[1]. That hypothesis was largely based in studies of hospital admissions and clinical presentations during that period (Figure 1). This review looks at the history of *H. pylori*-related diseases particularly gastric cancer, gastric ulcer, and duodenal ulcer over the last 2 millennia. We show that while *H. pylori* as been prevalent throughout human history the clinical manifestations changed recently in some Western countries. We also explain why duodenal ulcer disease appeared to appear suddenly in the late 19th century.

## HISTORICAL BACKGROUND

For centuries traditional learning focused on classic thinking and literature extending back to ancient Greece and scholars took great pride in their knowledge of works from preceding centuries. By the mid to late-20th century that tradition waned coincidence with an overwhelming outpouring of new information making it no longer possible even to stay abreast of current knowledge resulting in increasing specialization; observations from pre-20th century Medicine were largely ignored or forgotten. This process was aided and abetted by the introduction of electronic databases which made current literature increasingly available but failed to index the literature from before the mid-1960's.

The last half of the 19th century and the first half of the 20 century in European counties and the United States saw major changes in the clinical manifestations of *H. pylori* infection including changes in type and incidence of peptic ulcer disease and a fall in gastric cancer. These changes were not worldwide and were largely limited to what are now considered developed Western countries. As will be discussed later, similar changes are now occurring in many Asian countries as they change their status from developing to developed.

The period between 1800 and 1950 saw major changes in every aspect of life and any changes in the clinical manifestations of *H. pylori* and its related diseases must be considered within the context of what else was changing during the same interval. A survey of all the changes that occurred from 18th through the mid-20th centuries is not possible within the limitations of this essay, however I will attempt to provide an overview and point those interested to literature that will take them deeper if they desire.

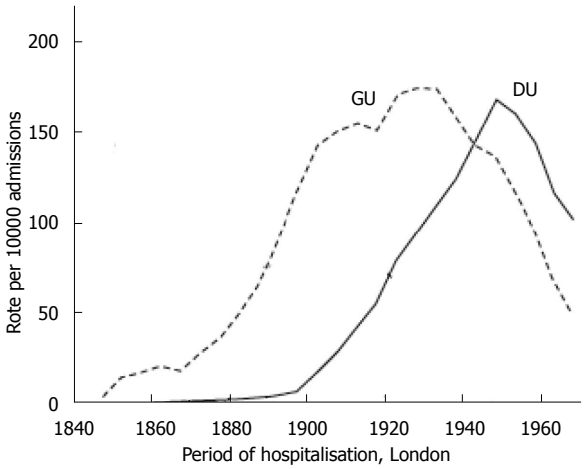


**Figure 1 Admissions for gastric ulcer and duodenal ulcer in 12 London hospitals associated with a medical school presented as mean rates per 10000 admissions in each of five year periods plotted as the moving average of three consecutive time periods.** Adapted from[1] with permission. GU: Gastric ulcer; DU: Duodenal ulcer.

While we might decry the fact that PubMed only indexed medical literature after the mid-1960's, recent advances in computer technology and the introduction of the "Web" has begun to compensate for that shortcoming as investigators have begun to have resources undreamed of by our forefathers. Who would have imagined that thousands of old medical books would have been scanned and indexed making their contents almost instantly available to anyone and anywhere. Portals such as Google books allow anyone to read and download much previously functionally lost material. For example, if one "goggles" "Moynihan Ulcer History" in Google books, one is presented with the chapter "History" in Moynihan's 1910 book, Duodenal Ulcer[2]. Here one can read "The earliest mention of duodenal ulcer in medical literature occurs in the London 'Medico-chirurgical Transactions' of 1817 (viii, 232). Mr. Travers there reports the following case: Case 1, Mr..., aged thirty-five, of a strumous habit..." and goes on to describe two cases, their history, physical, and autopsies. Moynihan quotes John Abercrombie who in the second edition of "Pathological and Practical Research on Diseases of the Stomach," (Edinburgh, 1830, pp. 103 *et seq.*) collected 5 cases from the literature. Moynihan cites Abercrombie as the first to describe the patients history with duodenal ulcer when he wrote "The leading peculiarity of disease the duodenum, so far as we are presently acquainted with it, seems to be that the food is taken with relish, and the first stage of digestion is not impeded; but the pain begins about the time when the food is passing out of the stomach or from two to four hours after a meal." and goes on to describe duodenal ulcer disease in the 19th century. A few clicks will bring us Abercrombie's paper where we can read the report of his cases of duodenal ulcer, gastric ulcer, and gastric cancer. This technology allows one to almost immediately to identify and read much of the basis for modern thought and without a trip

to the rare book room of a medical library.

## PEPTIC ULCER DISEASE IN ANTIQUITY

Peptic ulcer disease was well known in antiquity. It is not clear when the medical history of peptic ulcer was first written, possibly with the Egyptians, or with Hippocrates [born 460 BCE, or Diocles of Carystos (4th century BCE)][3]. One of the earliest descriptions is carved on a pillar of the temple of Aesculapius at Epidaurus (4th century BCE) where what might be considered the first surgery for a gastric ulcer was described by Goldstein "A man with an ulcer in his stomach. He incubated and saw a vision; the god seemed to order his followers to seize and hold him, that he might incise his stomach. So he fled, but they caught and tied him to the doorknocker. Then Asklepios opened his stomach, cut out the ulcer, sewed him up again, and loosed his bonds. He went away whole, but the chamber was covered with his blood"[3]. The first definite peptic ulcer in a human was described in the 20th century was from the autopsy of a mummy of a man from the Western Han dynasty who died in 167 BCE. The autopsy showed a clearly visible perforated prepyloric ulcer resulting in acute diffuse peritonitis complicated by disseminated coagulopathy[4]. So much for peptic ulcer as a modern disease!

Numerous authors in the 16th, 17th century, 18th and 19th centuries wrote on the topic and those interested in details are directed to excellent chapters on the history of peptic ulcer by Wilber[5] and Smith and Rivers[6] and two outstanding papers by Goldstein[3,7]. Besides these chapters and papers on the history of peptic ulcers, historically interested individuals should consider William Brinton's 1857 book on ulcer of the stomach[8] where he describe his extensive experiences with ulcer disease and gastric cancer. The historical era probably culminated about 1910 with Moynihan's books on duodenal ulcer[9,10]. However, the late 19th century which was a time of intense interest in the stomach and gastric physiology and there are many other important individuals and works not discussed here such as those by Ivan Pavlov, Walter Cannon, Theodor Billroth, and William Mayo.

## GASTRIC AND DUODENAL ULCERS AND GASTRIC CANCER ARE SURROGATES FOR THE PATTERN OF GASTRITIS

Endemic or common peptic ulcer is a complication of an *H. pylori* infection. A peptic ulcer occurs in areas exposed to acid and pepsin and is defined as a break in the mucosa lining the stomach or proximal intestine extending through the muscularis mucosae. Classic peptic ulcer disease is a chronic recurring disease that represented defective wound healing[11]. Peptic ulcer disease is typically a non-fatal disease that primarily presents with symptoms of epigastric pain typically relieved by food or alkali. Symptoms often exhibit periodicity meaning that they occur, wane, and recur over long periods. *H. pylori* is trophic for gastric type epithelium and thus *H. pylori* ulcers occur in the stomach and in the duodenum were *H. pylori* infects metaplastic gastric epithelium[12].

The site of a peptic ulcer is determined by the extent and distribution of gastritis. Normally, *H. pylori* cannot establish infections in the duodenum because the organism is inhibited by bile[12]. However, because low pH precipitates glycine conjugated bile acids, duodenal ulcers can occur if acid secretion is sufficient to chronically lower the pH in the duodenal bulb to allow the organism to infect and inflame the metaplastic or heterotopic gastric mucosa within the duodenal bulb[12]. Duodenal ulcer has a complicated pathophysiology that includes *H. pylori*-induced alterations in the regulation of acid secretion as well as alternations in duodenal bicarbonate secretion due to mucosal damage frequently compounded by smoking-induced inhibition of duodenal bicarbonate secretion.

The presence and maintenance of a duodenal ulcer requires that the stomach be able to secrete at least 12 moles of acid per hour and this requires a normal or near normal gastric corpus. Ulcers in the prepyloric area of the stomach are also associated with high acid secretion. The location of an ulcer in the gastric corpus is generally dictated by the location of the advancing atrophic border (see below)[13] (Figure 2). Figure 2 shows that duodenal ulcer (panel 1) is associated with normal or at most superficial gastritis. In contrast, as the site of gastric ulcers moves proximately in the stomach, the extent and severity of corpus gastritis/atrophy increases.

Although *H. pylori* can survive in an acid environment, it senses and moves away from acid so as to primarily reside on or near the mucosal surface where the pH is highest. The organism normally cannot survive in gastric pits of the gastric corpus, a region into which parietal cells secrete approximately 160 mmol/L HCl (pH < 1) for transport to the lumen of the stomach. *H. pylori* density and involvement of the gastric pits is initially greatest in the non-acid secreting portion of the stomach, (*i.e.*, the antrum) and thus gastritis tends to initially be most severe in the antrum and than to progress proximally into the acid secreting corpus. This progression occurs as an advancing front of a transitional zone of atrophic gastritis that borders the more normal corpus epithelium. The advancing front leaves an increasingly large lawn of atrophic mucosa where parietal cells are rare or absent which is variously called mucus, pyloric or spasmolytic polypeptide-expressing metaplasia[14]. Patchy areas of intestinal metaplasia probably arise from and occur within regions of pyloric metaplasia and their patchy nature was responsible for the erroneous belief that the atrophic process was multifocal when in fact it is typically more uniform (as a lawn) with multifocal areas of intestinal metaplasia.

Gastric ulcer tends to occur at the advancing atrophic front and therefore the site of an *H. pylori* gastric ulcer provides information regarding the extent and severity of gastritis, atrophy as well as acid secretion[13] (Figure 2). Just as duodenal ulcer disease equates with corpus-

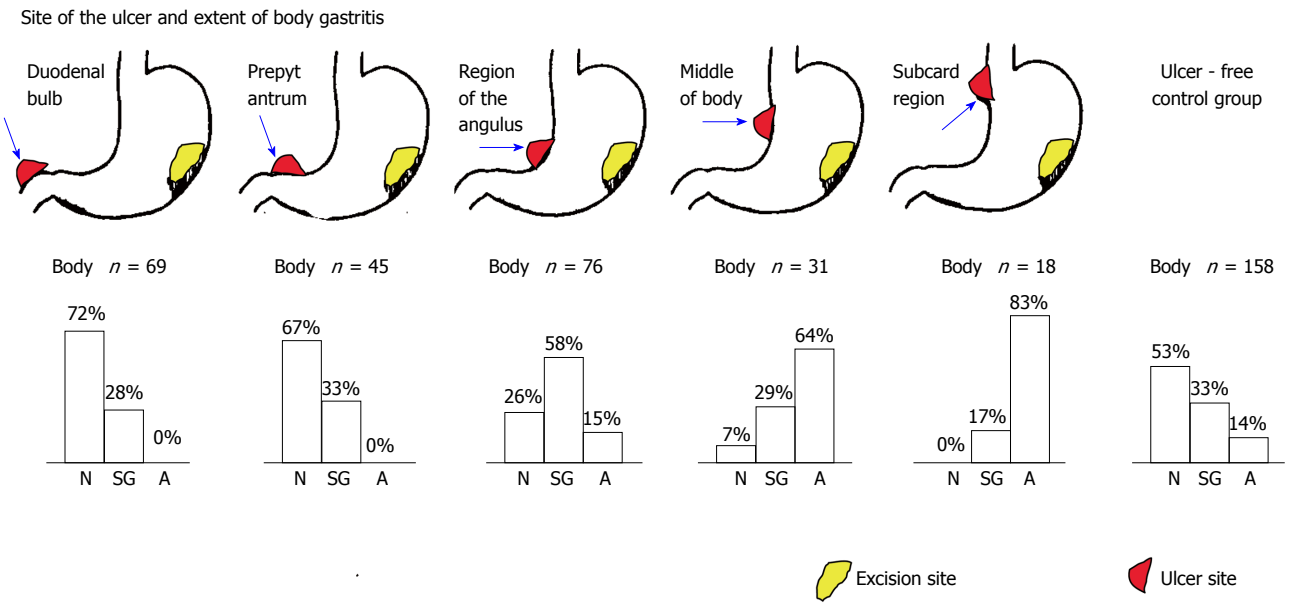


**Figure 2 Examples of the relation of the site of a peptic ulcer and its relation to the extent and severity of corpus gastritis/gastric atrophy.** The number of cases sampled for each ulcer site are shown. The control group consisted of 158 individuals without a peptic ulcer. Adapted from[13] with permission. N: Normal; SG: Superficial gastritis; A: Atrophy.

sparing or non-atrophic corpus gastritis with normal to high acid output, a gastric ulcer in the body of the stomach signifies the presence of corpus gastritis; the more proximal the ulcer the more extensive and severe the gastritis (Figure 2). Gastric cancers are also strongly associated with pangastritis. The incidence of gastric cancer increases with the extent and severity of the gastritis[15-17] such that gastric ulcer and gastric cancer form one axis (*e.g.*, atrophic pangastritis) whereas duodenal ulcer forms another (antral predominant or corpus sparing gastritis). As such while gastric ulcer and gastric cancer can evolve from those with duodenal ulcer but the opposite cannot occur.

Decades ago it was recognized that patients with duodenal ulcer rarely got gastric cancer and that observation has been repeated confirmed in the *H. pylori* era. However, because duodenal ulcer disease and gastric cancer represent different stages in the same process, the concept that patients with active duodenal ulcer disease are somehow "protected" against gastric cancer is largely an artifact reflecting the differences in the extent of *H. pylori* gastritis and acid secretion. Long ago it was suggested that the natural history of duodenal ulcer disease may be to "burn out" which reflected the fact that as the gastritis advanced into the corpus it would reduce gastric acid secretion below the level required to maintain active duodenal ulcer disease[15,18,19]. Thus, in regions where atrophic gastritis occurs early, such as Korea or Japan, there may only be brief window of time when the gastric corpus retains sufficient active parietal cells to allow duodenal ulcer to become manifest before burning out. This is also consistent with the fact that in areas where gastric cancer is common, scars of past duodenal ulcer disease are found in 1% to 7% of those with gastric cancer[20-28].

A change in the most common pattern of gastritis from the rapid onset of atrophic gastritis to a predominantly non-atrophic pattern would also result in a change the disease pattern from gastric ulcer and gastric cancer to predominantly duodenal ulcer. This is what we believed happened in the West and is responsible for the changes that have been observed. This paper will present the evidence and also speculations regarding how and why. It will be largely from the Eurocentric or Western-centric perspective since the available data and hypotheses are largely derived from data from those regions.

## ULCERS DISEASE IN THE 19th CENTURY

Although ulcers have long been known to medical science, ulcer disease only became a popular diagnosis in the late 19th century. This change in frequency of diagnosis can reflect a change in incidence or a change in diagnosis (*i.e.*, the symptoms of ulcer disease were previously attributed to some other process). Alternatively, the prevalence or virulence of *H. pylori* might have changed such that new disease patterns emerged. There are examples of populations where *H. pylori* is rare, such as ethnic Malays in whom peptic ulcer and gastric cancer were long recognized to be rare[29-32]. While, it is possible that *H. pylori* was either largely absent from Western countries or became widespread or more virulent in the 18th and 19th centuries[1,33], there is little to support those hypotheses and there are strong data against them (Table 1).

Using molecular techniques one can trace the migration of people by comparing their *H. pylori* strains and this approach has led to the recognition that *H. pylori* has traveled with mankind since at least the time that humans migrated out of Africa[34-36]. The initial studies of populations now living in the Americas found that their strains were of Western origin leading to the hypothesis that *H.*

**Table 1 Possibilities why duodenal ulcer seemed to appear in Europe at the end of the 19th century**

| |
|---|
| Change in prevalence of the infection (*e.g.*, acquisition of a new pathogen or increased prevalence of existing pathogen) |
| Change in the age of acquisition of the infection resulting in different clinical manifestations |
| Change in virulence of *Helicobacter pylori* (*H. pylori*) |
| Change in host-*H. pylori* interaction (*e.g.*, resulting in change in the intensity of inflammation) |
| Change in the host-bacterial-environmental interactions such that the host is better able, or less able to defend against the infection or the effects of the infection as reflected in the pattern and extent of gastritis/atrophy |

*pylori* might have been absent from the native American populations and were introduced as part of the post Columbus transmission of infectious agents[37]. However, subsequent studies showed that *H. pylori* strains in native Americans were derived from archaic North Western Asia strains[38]. It is now thought that the widespread presence of Western strains in the Americas reflects the fact that the original strains were replaced by Western strains. These data are consistent with *H. pylori* being widely present among Europeans during the 16th through the 19th century and has been confirmed studies of European strains among European populations.

If *H. pylori* prevalence did not change, did its virulence change? This possibility is not supported by the available data. Although the risk of a clinical disease outcome is approximately doubled when infected with a more virulent strain (*e.g.*, containing the cag pathogenicity island or cag PAI), all known *H. pylori* are associated with peptic ulcer and gastric cancer independent of whether they possess one or more putative virulence factors (*i.e.*, the differences are in degree of risk not in risk *per se*).

The incidence of gastric ulcer and gastric cancer is dependent in part on the presence of a reasonably sized population over 50 years age as well as the prevalence of atrophic gastritis. As noted above, gastric cancer was well known in the early 19th century[39] (*e.g.*, Brinton in the mid-19th century was able to find many cases)[8] and when records of gastric cancer were first being collected, Europeans led the world in incidence[40]. Since gastric atrophy generally requires decades to develop, the presence of gastric cancer despite the relatively short life expectancy reflects a high prevalence of *H. pylori* in birth cohorts in Europe extending back at least into the mid-17th century.

Area of in South and Central America have some of the highest gastric cancer/atrophic gastritis incidences in the world and the *H. pylori* strains currently infecting those populations are descendents of those strains brought to the Americas by European colonists. This also speaks against a relative absence or avirulence of *H. pylori* in European populations at that time. The ability of Europeans to export gastric cancer/atrophic gastritis to the Americas[41] does not support the suggestion that there was a sudden appearance of *H. pylori* or change in its virulence in the West during the periods when it has been speculated that peptic ulcers appeared as a new disease.

## GASTRIC CANCER AS A INDEX OF THE PREVALENCE OF ATROPHIC GASTRITIS IN THE 19th AND 20th CENTURIES

Gastric cancer was well known in the early 19th century (*e.g.*, in the 1830's both Cruveilhier and Rokitansky noted the coexistence of gastric cancer and gastric ulcer and William Brinton was able to pull together more than 200 cases)[39]. A turning point came in 1879 when von den Velden reported a link between achlorhydria and gastric cancer[17]. Because gastric cancer was then the most common type of cancer, his observation prompted an outpouring of research on gastritis, gastric acid secretion, and methods to diagnose gastric cancer other than autopsy (reviewed in reference[17]). The widespread interest in gastric cancer is reflected in the publications of Turck[42], Schlesinger and Kaufmann[43], Boas and Oppler[44] in 1895 when they all reported on the use of bacteriology of the stomach to diagnose gastric cancer which lead to a number of studies over the next two decades regarding the role of the Boas-Oppler bacillus (*Lactobacillus*) in the diagnosis of gastric cancer. Clearly, *Lactobacillus* was, and is, a common accompaniment of atrophic gastritis and it appears unlikely that changes in its consumption played a significant role in the change in the manifestations of *H. pylori*-related diseases[33].

Another major advance occurred during the late 19th and early 20th centuries, when Faber revolutionized gastric histopathology by the early post mortem administration of formalin directly into the abdominal cavity and into the stomach to allow gastric histology to be examined without the autolytic changes that had plagued earlier studies[45,46]. Development of atrophic gastritis and gastric atrophy at an early age was very common during the late 19th and early 20th century in both Northern Europe and in Northern United States) consistent with the high incidence of gastric cancer in both areas[17,45,46] (Figure 3). However, this was the same period that the incidence of duodenal ulcer was increasing and thus was a harbinger of the future as it signaled that the pattern of gastritis was changing from one of the early acquisition of atrophic gastritis to either a slower development of atrophy or to a predominantly non-atrophic gastritis which allowed the appearance of clinical duodenal acid disease[47]

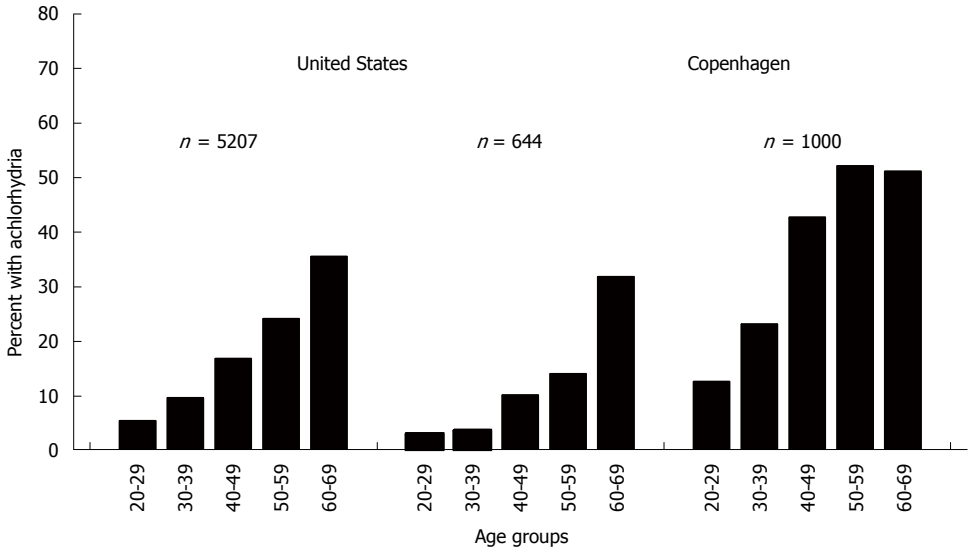


**Figure 3 Prevalence of atrophic gastritis/atrophy in the early twentieth century.** Example of studies in the United States and Europe showing the high prevalence of atrophic gastritis/atrophy as evidenced by the age-related prevalence of achlorhydria (from[17], with permission).

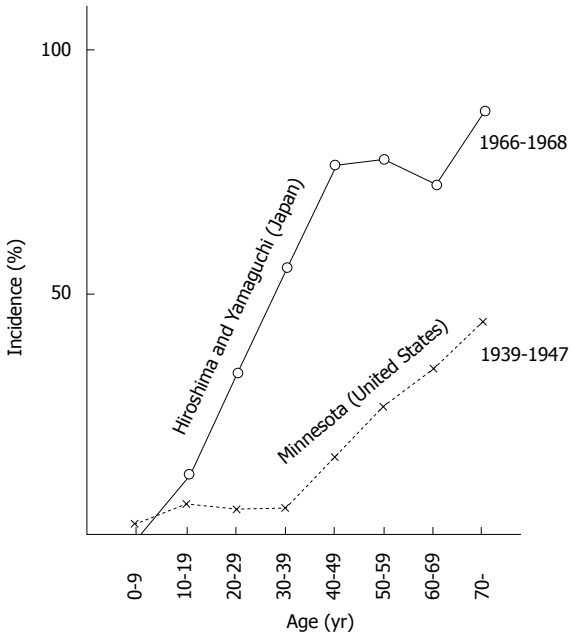


**Figure 4 Comparison of the prevalence of intestinal metaplasia on gastric antral biopsies in two areas of Japan and in one area in Minnesota, United States.** Adapted from[47] with permission.

(Figure 4). In Figure 4 the Japanese samples were taken in the late 1960's where as those in the United States were collected in the early 1940's. Japan remains a country with a high risk of gastric cancer. The United States saw a marked decline in gastric cancer incidence that became evident in the first half of the 20th century. The plot suggests that those born after 1910 (*e.g.*, more than 30 years old when the biopsies were taken, experienced a different environment than those born before that time. The rate of acquisition of intestinal metaplasia was also less among all those born in the United States (*e.g.*, the degree of atrophy among those of similar age was markedly less in those born in the United States. One suspects that if the samples had been taken in both groups earlier (*e.g.*, 1880, they would have been similar as the incidence of gastric cancer in the past was high in both countries.

## PEPTIC ULCER AS A NEW PROBLEM IN THE 19th CENTURY

Because peptic ulcer is typically a non-fatal disease it was difficult to diagnose reliably before the 20th century when surgery, radiology and endoscopy became available. Dyspepsia has been common throughout history but the cause(s) remained both unknown and generally unknowable. Until recently, autopsy was probably the only method allowing one a peek at which diseases had occurred during life. An autopsy can both identify what caused death as well as function as an form of medical archeology allowing the careful observer to obtain an inkling about what diseases might have occurred earlier in life. In their 1950 encyclopedic book summarizing peptic ulcer disease, Ivy, Grossman, and Bachrach included a 49 page chapter entitled "Postmortem incidence in relation to pathogenesis" where they analyzed the relevant autopsy data available from Europe during the 19th century[48]. Importantly, they used strict criteria for inclusion of an autopsy study and carefully considered factors that could potentially have biased the results. The studies the chose were required to have a sufficient number of cases (*e.g.*, $\geqslant$ 1000), the authors must have specifically examined for open ulcers and for ulcer scars, the data must have represented the population studied, the data were restricted to adults (or > 10 years old, as most deaths were in very young children), and finally, there must be a sufficient number age 50 or over (as gastric ulcer and gastric cancer are most common after age 50). They included 29 studies including 10 European studies performed between 1844

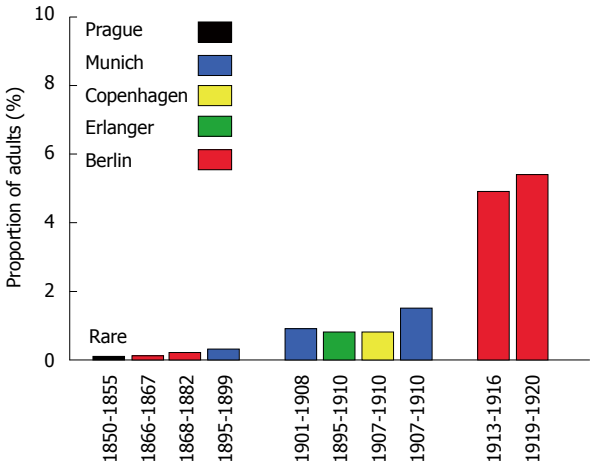


**Figure 5 Autopsy data from Europe showing the proportion of adults (*i.e.*, 10 or older) from large autopsy studies in which the presence of an ulcer or ulcer scar was specifically examined showing the increase in the incidence of duodenal ulcer in the latter part of the 19th and early 20th century.** Data from refererence[48].

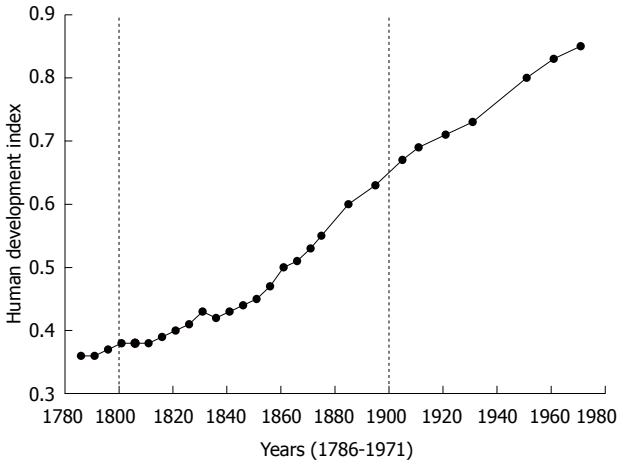


**Figure 6 Health, height, and welfare: Britain between 1700 and 1980 based on the human development index which is a composite statistic of life expectancy, education, and income indices used to rank human development.** A score below 0.5 signifies low development and 0.8 or greater, high development. Data from[59].

and 1899 which represented birth cohorts extending well back into the 18th century. On the basis of their analysis, they concluded that although the incidence of peptic ulcer was variable, there was no evidence of a change in incidence in gastric ulcer during the 19th century including the early 20th century. In contrast, the found clear evidence of an increase in duodenal ulcer in the last quarter of the 19th century that extended into the 20th century (Figure 5). Because duodenal ulcer and gastric ulcer represent entirely different patterns of gastritis, these data suggest that the incidence of *H. pylori* did not change, rather the pattern of gastritis changed or was changing.

## THE 19th CENTURY

The 19th century was a time of incredible change. It was the era of the industrial revolution and one with marked changes in transportation, diet, farming, food preservation, and type of work (*i.e.*, essentially every aspect of life). It was the time of Charles Dickens and Jane Austin; Dickens described the fate of the poor whereas Jane Austin dealt primarily with the upper classes. During this time that Reverend Robert Malthus provided his dire predictions of population growth and it effects on the future and when a number of individuals whose concerns for the poor had major future consequence (*e.g.*, Friedrich Engles, Karl Marx, and Henry Mayhew)[49]. The Napoleonic wars overlapped the beginning of the century and war within Europe remained endemic throughout the entire 19th century.

## LIFE IN 19th CENTURY EUROPE

The typical Englishman was a farm laborer. He was described by the English economic historian Gregory Clark as "his material living was not much better than that of the average Roman slave. His cottage consisted of a single dark room shared day and night with wife, children and livestock. His only source of heat was a smoky wood fire. He owned a single set of clothing. He traveled no further than his feet could carry him. His only recreations were sex and poaching. He received no medical attention. He was like illiterate. In good times, he ate only the coarsest foods - wheat and barley in the form of mush or bread. Clark estimated that the average British farm laborer consumed an average of only 1500 calories per day. Even potatoes were a luxury beyond his reach." (quoted from Nasar[49]). Prentice described life in the United Kingdom in 1844 as: "Full 1/3 of our population (in the United Kingdom) subsist almost entirely, or rather starve, upon potatoes alone, another 1/3 have, in addition to this edible, oaten or inferior wheaten bread with one or two meals of fat pork, or the refuse of shambles, per week; while a considerable majority of the remaining 1/3 seldom are able to procure an ample daily supply of good butcher's meat or obtain the luxury of poultry from year to year. On the Continent of Europe, population is still in worse condition"[50]. The average height fell in first quarter of 19th century and then began to improve. Infant mortality was high but declined after 1845 and life expectancy at birth rose after 1860 having been persistently below 50 overall and below 60 for males who survived the age of 5 for the first half of the century. Life expectancy for males who survived age 5 did not achieve 60 years until approximately 1910 (Figure 6). Figure 6 shows the human development index, a composite statistic of life expectancy, education, and income indices used to rank human development based on life expectancy at birth (an index of population health and longevity), knowledge and education (adult literacy rate), and the standard of living based on the gross national produce. Because of the short life expectancy both gastric ulcer and gastric cancer were less prevalent than in later years. In the last quarter of the century diets improved and homelessness,

begging declined and life expectancy increased.

"In 1842 the United Kingdom population was described as prolific, hungry and angry"[51]. The towns were described as "ill drained and ill built, of dirty brick and grimy stone, with large brutal factory buildings, were probably more like hell than should be the dwelling places of any children of God" and the people frequently out of work (*e.g.*, in 1841 in Paisley Scotland "between 10000 and 13000 persons, out of a population of about 60000 were dependent on relief"[51]. Such were the times during which Charles Dickens wrote his novel "Hard Times".

The 19th century was also the time of major advances. Water borne transportation was the only practical means of moving heavy or bulk cargo. Canal building began in Europe in the late 18th century and continued until supplanted by railroads. There were advances in transportation throughout the 19th century, first with canals, then railroads, and finally improved roads[52-54]. Improved transportation, farming land ownership, methods of farming and food preservation and development of synthetic fertilizers during this century markedly reduced the frequency of famine which however remained a regular occurrence well into the 20th century[50,52,55-59]. Entrepreneurship was developed which lead to new processes, inventions, management ideas, tools, training, *etc.* which led to improved productivity (*i.e.*, more output per worker). Work thus became "worth more" and workers became more difficult to replace and better paid and thus, workers experienced improved lifestyle, diet, housing, and sanitation[49,58]. It is hard for someone living today to imagine this time or even the world before world war Ⅱ.

## WHAT WAS RESPONSIBLE FOR A CHANGE IN THE PATTERN OF GASTRITIS IN THE 19th CENTURY?

Improvements in sanitation and standards of living resulted in a marked reduction in the incidence of deaths from infectious diseases, especially after 1850[60]. The improvements in transportation, farming, and income led to improved diets such that they were more varied and more likely to contain fruits and vegetables (*i.e.*, vitamin C)[61]. Improvements in life expectancy was evident both in a reduction in infant mortality and in overall survival such that the number of persons over age 50 increased. These improvement in standards of living, sanitation, and diet, especially the change in diets from seasonal to more varied and more fresh and less preserved foods are thought to be the critical elements in determining the rate of development of atrophic gastritis[62]. Changes in the pattern of gastritis were likely to first become evident in the upper classes as they were better able to take advantage of improvements[63]. However, over time any advantages would have extended to the entire society especially when food preservation changed from smoking and salting to refrigeration[64-68] and changes in farming and transportation became widespread. Although the incidence of gastric cancer typically declines following the introduction of refrigerators[64,65], refrigerators themselves cannot be a direct cause but rather are a surrogate for the change in food preservation and likely for the increased consumption of a fresher and more varied diet and less salt. The association of a reduction of gastric cancer incidence in relation to intake of fresh fruits and vegetables also suggests a role for phyto-nutrients in maintaining the health of the gastric corpus. Likely vitamin C plays an important role as ascorbic acid deficiency is associated with all forms of gastritis (*e.g.*, autoimmune, chemical, and infectious) whether due to insufficient intake, increased metabolic requirements, or destruction within the GI tract[61]. Importantly, gastritis-associated abnormalities in gastric ascorbic acid metabolism are reversed by *H. pylori* eradication[61] and diets rich in naturally occuring ascorbic acid are associated with protection of the gastric corpus from atrophy as well as a reduction in the incidence of gastric cancer possibly through the ability of ascorbic acid to reduce oxidative damage to the gastric mucosa by scavenging free radicals and attenuating the *H. pylori*-induced inflammatory cascade.

As noted above, *H. pylori* normally move away from acid environments which restricts their location to the antrum and to remain superficial in the acid producing corpus[62]. However, when acid secretion is decreased *H. pylori* can invade the gastric pits in the corpus which results in an extension of inflammation deeper into the mucosa. IL1β, a potent antisecretory agent, is stimulated by the inflamed mucosa and further suppresses acid secretion further enhancing the ability of *H. pylori* to permanently occupy a position near the replicative zone in the gastric pit of the corpus mucosa and likely accelerating both the rate of development and the severity of atrophic gastritis. This process has been clearly illustrated following highly selective (parietal call) vagotomy in patients with duodenal ulcer disease which is associated with a rapid expansion of gastritis into the corpus gastritis[15,69]. This process also occurs following institution of therapy with a proton pump inhibitor[70]. Probably the most important factors leading to early development of atrophic pangastritis in the past were the limited diets and the associated vitamin deficiencies which was exacerbated by frequent febrile illnesses which also inhibit acid secretion[62,71].

Finally, diphtheria can cause gastric damage and may even be a cause of gastric atrophy[46,62]. The role played by diphtheria and the effects of immunization against diphtheria in the prevention of early-onset atrophic gastritis remains unknown.

## MODERN EXAMPLES OF CHANGES IN THE PATTERN OF GASTRITIS

The changes that resulted in a change in the pattern of gastritis in the Western world in the late 19th and early 20th century are currently occurring in Japan, South Korea, and likely other Asian area where rapid development,

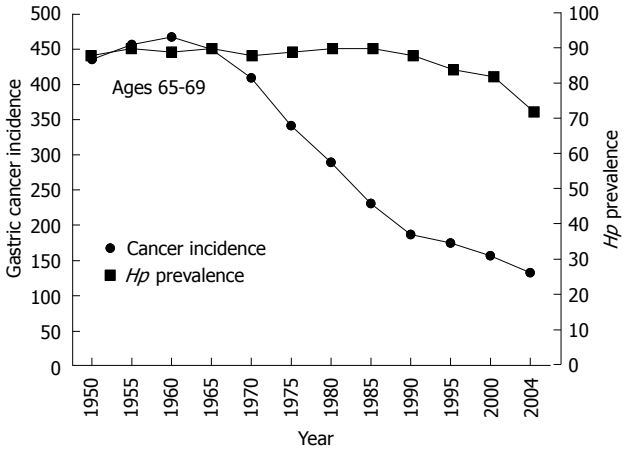


**Figure 7 Changes in the incidence of gastric cancer and *Helicobacter pylori* infection among Japanese men age 65-69 during the latter half of the 20th century (Constance Wang and David Y Graham, unpublished observations).** From reference[86], with permission. *Hp*: *Helicobacter pylori*.

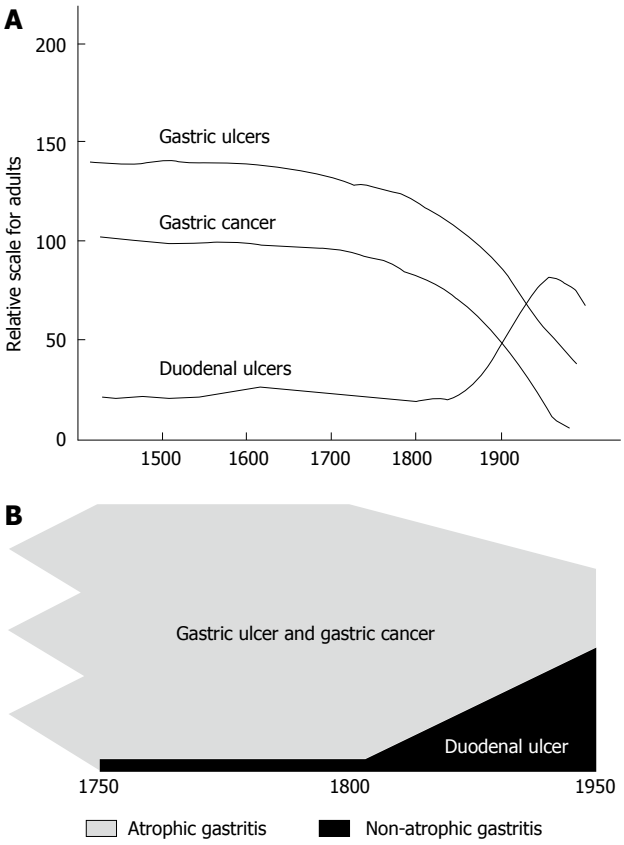


**Figure 8 In this 65 years old cohort the change in gastric incidence occurred without a change in the prevalence of *Helicobacter pylori*.** A: Model showing that gastric ulcer and gastric cancer were present and relatively common until the early 20th century when changes in the pattern of gastritis and also the prevalence of *Helicobacter pylori* (*H. pylori*) infection separately led to a reduction in incidence. In contrast, the change in the pattern of gastritis and new diagnostic modalities led to ascendance of duodenal ulcer until the rise was overtaken by the fall in *H. pylori* prevalence (the scale is arbitrary); B: The same results shown in relation to the underlying pathology, atrophic pangastritis which manifests clinically as gastric ulcer or cancer and non-atrophic gastritis which manifests as duodenal ulcer.

improved sanitation, diet and methods of food preservation have occurred. For example, in Japan the incidence of gastric cancer has rapidly fallen (*e.g.*, by approximately 60% between 1965 and 1995) and this has occurred in all age groups (Figure 7). As shown in Figure 8, in this 65 year old cohort the change in gastric incidence occurred without a change in the prevalence of *H. pylori*. During this short interval there was also no change in the virulence of the common *H. pylori* strain or in the host genetics showing the impact of improved standards of living, diet, and change in food preservation, *etc.* thus mirroring what had happened in the West a century before.

## BIRTH COHORTS

As noted above, the 19th and early 20th century were a time of tremendous change in standards of living, diet, and food preservation such that each birth cohort was born into a different world and thus experienced different risks of developing any particular pattern of gastritis. The use of birth cohort techniques to analyze the data allows one to estimate when the changes started to appear. This technique is particularly applicable to times of great change when almost any feature of the life that changed will exhibit a relation to birth cohorts. However, it cannot tell us the mechanisms. Overall, the current data support the concept that the pattern of gastritis is most related to changes in host, bacteria, and environmental interaction which is dominated by environmental changes likely diet.

## EFFECT OF THE SURGEONS

Until the late 19th century, the abdomen was considered off-limits to the surgeon. In 1879 Pean reported the first partial gastrectomy; the patient died[5]. In the Lancet of December 1, 1888, Mackensie reported two patients operated on for perforated ulcers: one was a 35 year old alcoholic who presented with indefinite epigastric pain, one week followed by sudden acute pain, vomiting and collapse[23,72]. He was operated on second day by Sidney Jones. He died. The second was a 31 year old who had an acute attack resembling intestinal obstruction with peritonitis. He was operated by John Croft on the third day and also died. Until this time, such patients were not brought to the attention of surgeons, or if they were, they were considered inoperable. However, Mackensie pointed out that these patients had conditions that were potentially surgical[23,72] and surgeons took up the challenge. In 1901 Moynihan was able to compile 51 cases operated in Europe on between 1888 and 1901 involving 40 different surgeons; 8 survived[73]. However duodenal ulcer and perforated ulcer was not a new problem having been recognized centuries before[2,3,6,22]. For example Moynihan noted that "In 1865 appeared Krauss 'Das perforirende Geschwur im Duodenum' [the perforating Ulcer in the duodenum] (Berlin, Aug. Hirschwald). In this pamphlet there are 80 case records, for the most part in full detail. Between 1863 and 1882 a series of Paris theses appeared,

in which a few additional cases were recorded, but nothing material was added to our knowledge"[2].

The late 19th and early 20th century was an era with a flurry of new surgical operations (*i.e.*, Billroth: 1891 performed the successful gastrectomy in 1891[5] and Codivilla operated for chronic duoden ulcer in 1893)[2]. Moynihan began operating on duodenal ulcer in 1899 and Moynihan in Leeds, and Mayo in the United States greatly popularized the surgical treatment of ulcer disease in the early 20th century.

In 1910 Moynihan published his classic book "Peptic Ulcer" (available as a free e-book on Google books) which was updated in 1912[9,10]. Details of the cases he operated on including history, physical examination, operative finding, and follow-up are given; he included 305 cases in the 1912 edition. The diagnosis of ulcer was based on symptoms and confirmed by operation[74]. Moynihan stated (on page 159) "I believe it to be true to say that the significance of the symptoms in these attacks has never yet been fully recognized by the physician. It has not been realized that these symptoms are due to a structural lesion, and consequently (after a diagnosis of "acid gastritis" or "neurosis") treatment has been perfunctual and brief. Up to the present time it is, with the exception of a single case I have mentioned, only after repeated attacks, sustained often over a period of years, that the surgical needs of the case have been recognized. If the first of the attacks be due to duodenal ulcer, then medical treatment of a sufficiently protracted and careful character should be tried. But when the attacks recur in the typical manner I have described, the lesion found is of such a nature that anything other than surgical treatment is not worth considering. It is safe, speedier, and more certain than any other mode of treatment"[9]. Moynihan reported that using history alone in a consecutive series he correctly (*i.e.*, confirmed surgically) diagnosed ulcer in 97 of 100 cases. His incorrect diagnoses included gall stones in 2 and gall stones and appendicitis in 1[75].

Within one generation, duodenal ulcer went from being largely unknown to being a surgical condition! However, the world was soon to change again for in 1915 Bertram W. Sippy published his "medical cure by an efficient removal of gastric juice corrosion" where he proposed diet therapy for both gastric and duodenal ulcers[76]. Sippy's therapy consisted of hourly small feedings to provide nutrition while not distending the stomach to cause it to secrete excessively alternating with antacids for 12 h per day. Importantly this was recommended to be done in hospital. Feedings started with milk and cream and gradually expanded into a diet. Diet therapy remained in vogue until the advent of $H_2$-receptor antagonists and during this time many doctors would prescribe the Sippy regimen or a variant of published "ulcer diets" along with antacid therapy. Because both surgical and medical therapy were hospital-based therapies, it should come as no surprise that the frequency of hospitalization for peptic ulcer increased rapidly in the first part of the 20th century (Figure 8).

The 1920's brought increasing use of contrast radiology. One of the early practitioners stated "we are told, with the most dogmatic assurance, that given a clinical history of recurrent pain, located in the epigastric region, occurring at certain intervals, varying from half an hour to three or four hours after means, relieved by food or baking soda, with variable periods of complete or partial remission, during which the patient suffers from little or no annoyance, that we have all that is essential to make a diagnosis of peptic ulcer. In fact, Moynihan goes so far as to maintain that any recurring hyperchlorhydria means ulcer"[77]. Ulcers were recognized radiologically by the presence of an ulcer niche, deformity, gastric hypermotility, or 6th hour retention with a differential for X-ray features of ulcer, gall stones, or chronic appendicitis. It would however take decades before the limitations of barium X-ray were fully recognized.

## COULD DUODENAL ULCER HAVE BEEN COMMON AND NOT BEEN RECOGNIZED?

It is difficult to believe that the epidemic of perforated ulcers reported by European surgeons in the late 19th century or the 305 ulcer cases operated on my Moynihan in the first decade of the 20th century represented an epidemic of a new disease rather than the result of the availability of new therapies (*i.e.*, surgery for the acute abdomen and for a easily recognizable chronic dyspeptic syndrome). The leaders at the time commented on the fact that physicians were now able to diagnose ulcer disease clinically. For example, Faber remarked "...it seemed as the scales fell from the eyes of the internists. The nervous secretion anomalies, the neurotic attacks of pain - the entire treasure house of nervous dyspepsia was broken into and plundered. Anatomical diagnosis had scored another triumph in medicine"[46].

Dyspepsia has been a common complaint throughout history and had long been recognized as particularly common in United States[78]. These physicians could distinguish episodic dyspepsia form heartburn, water-brash and pyrosis which were also widely recognized and prevalent. For example, in 1841 Thomas West published "A treatise on pyrosis idiopathica or water-brash as contrasted with certain forms of indigestion and of organic lesions of the abdominal organs, together with the remedies dietetic and medicinal"[79]. In his book he clearly described the clinical features of gastroesophageal reflux and its natural history. He noted that pyrosis was a chronic rather than an episodic condition that was best treated by alkali and contrasted the clinical condition with "episodic or spasmodic dyspepsia" which are more typical in peptic ulcer disease. Abercrombie, West and Brinton all had the ability to distinguish between different dyspeptic conditions and target the best available therapies despite the lack of knowledge of the causes of the symptoms. For example, these early workers preferred alkali for symptoms

of what we now call reflux esophagitis and bismuth for symptoms later to be described as characteristic of peptic ulcer.

John Eberle in his book "A treatise of the Materia Medica and Therapeutics" published in 1834 noted that bismuth had been introduced in 1697 by Jacobi and was popularized by Dr. Odier of Geneva, and De la Roche, of Paris[80]. Eberle stated"At present employment is chiefly confined to the cure of gastrodynia, pyrosis, and cardialgia. In these afflictions it seems to be pretty generally admitted to be a medicine of much value. Dr. Marcet, whose testimony deserves great respect, in a paper read in 1801 before the London Medical Society, says, "I have since had frequent opportunities, at Guy's Hospital of trying the oxide of bismuth in spasmodic conditions of the stomach, and those trials have fully confirmed the opinion which I formerly gave of the utility of this medicine." Dr. Samuel W Moore, of New York, in his excellent dissertation on the medical virtues of the white oxide of bismuth, relates three case of painful affections of the stomach, in which this remedy was employed with much success. I have employed it in several cases of spasmodic pain of the stomach, and in two the effects were decidedly beneficial; though in the others, which appeared to me perfect cases of gastrodynia, it had not the slightest effect whatsoever. Upon the whole, however, the evidence we have in favour of the powers of this remedy, in the diseases mentioned, entitles it to much attention from the profession[80]. Bismuth was widely used throughout the 19th century[81] and continued to be used successfully up to the discovery of *H. pylori* when finally its mechanism of action as an antimicrobial was identified[82,83].

## CONCLUSION

I believe that the available data overwhelming support the hypothesis that in what are now called Western countries, *H. pylori* was prevalent throughout history and its most common manifestation was to cause chronic atrophic gastritis at an early age. Life spans were short and thus while the late manifestations of *H. pylori* disease, gastric ulcer and gastric cancer were uncommon they were well known. Duodenal ulcer disease was likely largely limited to the young and would then typically "burn out" as the gastritis reduced acid secretion below the level required to support ulcer disease. Improvements in diet and standards of living resulted in a change in the pattern of gastritis such that non-atrophic gastritis became more common allowing duodenal ulcer to appear as a clinical problem and the ratio of gastric ulcers turned from positive to negative. Later, improvements in sanitation would lead to a decline in all *H. pylori* related diseases (Figure 8).

Throughout the 19th century duodenal ulcer remained particularly difficult to diagnose and as pointed out by Ivy *et al*[48] critical examination of the duodenum was infrequent even among those doing the most careful autopsies. There are many modern examples of duodenal ulcer being common but remaining underdiagnosed or more frequently misdiagnosed[84]. Examples include the so called debunked enigmas such as the "African enigma" which postulated that in Africa *H. pylori* was common but it rarely was associated peptic ulcer or gastric cancer[85,86]. There a examples prior to the *H. pylori* era as in Uganda where it was reported that peptic ulcer was rare. However, Roberts noted "the native of Uganda has sheltered gastric and duodenal ulcer from view under the cloak of *kifuba* (pain in the chest). Attention was drawn to this subject by the admission of a case of perforated duodenal ulcer in June 1931. Since then fourteen cases of *kifuba* have undergone surgical treatment for gastric and duodenal ulcer"[87].

Moynihan. despite his somewhat dogmatic statements. experienced a learning curve in diagnosing duodenal ulcer. For example, Collinson reviewed all of the cases Moynihan operated on and noted "In examining the case histories one is impressed by two facts: First, that in the earlier cases the clinical picture which we are now accustomed to associate with the presence of duodenal ulcer is only imperfectly indicated in the account of the patient' s symptoms, whilst in the majority of the later cases the patient's account of his symptoms given after careful enquiry is typical. The second point of interest is that in the early cases operation was in a large proportion of the cases undertaken for the more serious complications of duodenal ulceration rather than for the relief of symptoms due to the ulcer itself… The details of the cases mark the gradual increase of our knowledge of duodenal u1cer: in the earlier period symptoms were little understood, accurate information as to. the time of onset of pain was not sought, and it was only the grosser and more serious results of ulceration which brought the patient into the hands of the surgeon; as our knowledge of, and familiarity with, the condition have increased, so the cases have been seen earlier, their symptoms more carefully investigated, and operation advised and performed in most cases before the onset of dangerous complications"[74].

The main problem with knowing the incidence and prevalence of peptic especially duodenal ulcer is that correct diagnosis requires a reliable method for diagnosis and before the 20th century duodenal and gastric ulcers were likely lumped with the vast group of nervous diseases of the stomach mentioned by Moynihan and Faber. In the early 20th century Boas, in his textbook "Diseases of the Stomach" (translated from German in 1907), which included sections on "round ulcer of the stomach", devoted more than 90 pages to "Nervous diseases of the stomach"[88]. This section discusses numerous diseases of the stomach of nervous origin that were soon to largely disappear from medical textbooks. As peptic ulcer declined and it became clear that classic ulcer symptoms were not, or were no longer, diagnostic and even now we are required to use endoscopy to separate ulcer dyspepsia from uninvestigated dyspepsia (*i.e.*, organic from presumed functional diseases). It seems that some things never change.

Peptic ulcer is generally a non-fatal illness whose re-

ported prevalence depended largely on the physician's ability to diagnose it. Chronic duodenal ulcer was likely relatively uncommon in adults until the second half of the 19th century but may have been a common cause of symptoms in young people. Its rapid increase was a combination of an actual increase caused by a change in the rate of development of atrophy gastritis coupled with newly acquired abilities to diagnose it clinically and because both required that medical and surgical treatment include hospitalization. The 19th century was a remarkable period in history where standards of living, life expectancy, productivity, methods of production, transportation, increased more than in the prior two thousand years. At the same time common infectious diseases such as whooping cough, tuberculosis, measles, and diarrheal disease all underwent rapid declines in incidence and death rates and other diseases increased in prevalence even to the point of appearing to be new diseases (*e.g.*, paralytic polio, infectious hepatitis, and duodenal ulcer). These changes in disease reflected changes in standards of living and sanitation and in some instances represented a change in the clinical behavior of a disease (*e.g.*, polio or infectious hepatitis) related to a delay in the age of acquisition from infancy to later in life. This hypothesis was considered for *H. pylori* related diseases[89] but data from developing countries disproved it as in these countries the primary manifestation was duodenal ulcer despite the infection be acquired at a very early age[90].

Duodenal ulcer appeared to burst on the scene in the late 19th and early 20th century. However, duodenal ulcer, gastric ulcer, gastric cancer, and atrophic gastritis are all manifestations of the same root cause, *H. pylori* infection and more specifically to different host, bacterial and environmental interactions. The changes that occurred in the West 100 or so years ago and now occurring in Asian countries where gastric cancer is still endemic allowing us to study the past by examining the present. We have come a long way and followed many false paths. While it is useful to look back and see how wrong we were, hopefully, in the near future, all *H. pylori*-related diseases will become only of historic interest.

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