Past Questions and Current Understanding About Gastric Cancer

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What have we learned about gastric cancer in the 75 years since the first issue of *Gastroenterology*? The earliest, to our knowledge, comprehensive review in *Gastroenterology* on this topic was by Russell Boles,[1] a gastroenterologist from the University of Pennsylvania. He posed 7 questions that he identified as the most important unanswered issues facing the field.[1]

1. The environmental, genetic, and injurious factors that give rise to gastric cancer are uncertain.
2. In certain countries, like Japan, gastric cancer is for some reason far more frequent than in the United States and in Northern and Western Europe.
3. Certain histologic and physiologic changes, like atrophic gastritis and pernicious anemia, increase the risk for progression, yet "little can be offered in explaining their relationship." Interestingly, Boles pointed out that Sir Arthur Hurst preceded Boles by 30 years in discussing the importance of understanding "certain conditions that were regarded as precursors of the disease." Unfortunately, Boles noted, "Conceptions in these respects have changed little since Hurst's time."
4. Boles was excited about new work that showed that achlorhydria, decreased pepsin secretion, and pernicious anemia (ie, chronically decreased gastric intrinsic factor secretion) all correlated positively with cancer (see, for example, the October, 1955 issue of *Gastroenterology*[2] as well as another important paper from Sara Jordan et al in October, 1952[3]).
5. Boles commented on the uncertain relationship of gastric peptic ulcers to cancer. It was not clear if ulcers that harbored cancers were simply cancers that caused ulcers or if benign ulcers increased the risk for progression to cancer.
6. Boles analyzed total funding from the US Public Health Service (largely via the newly established National Cancer Institute) for gastric cancer research relative to funding for other cancers and as a function of deaths caused by cancer. He found that not much more than 2% of total cancer funding in the decade preceding his article went to gastric cancer research, yet cancer of the stomach accounted for nearly 12% of cancer deaths. Thus, he said, "One of the purposes of this paper . . . was to focus on the relative indifference being shown in the field of gastric cancer research." He claimed that, "One can only speculate on the reasons for this."
7. Boles also cited his *Gastroenterology* paper from 1955 (March issue[4]) showing data noting the beginning of a trend that would continue for much of the twentieth century, which is that rates of gastric cancer in the United States were suddenly (within the span of a decade) beginning to dramatically decrease, in particular among white men.

Here, we discuss the progress made since 1958 on these 7 issues, focusing on key articles in *Gastroenterology* that highlight where the field has evolved over the past 60 years. We commence with the areas where the field, arguably, has not progressed substantially.

Inadequate Funding for Gastric Cancer Research

Relative to morbidity/mortality and to nearly every other cancer, gastric cancer remains strikingly neglected in terms of research investment. As of 2013, 1 study showed that gastric cancer was last or nearly last in funding in the United States, which has been normalized in several ways.[5] A subsequent study showed that stomach cancer funding was last among all cancer types examined in both the UK and the United States, normalized to years of life lost.[6] And it was among the least funded in a follow-up study on UK funding.[7] Gastric cancer continues to be a significant health burden, estimated to be the cause of 10,800 deaths in the United States this year (National Cancer Institute). Thus, to paraphrase Boles, we still can only speculate about why gastric cancer research is poorly funded.

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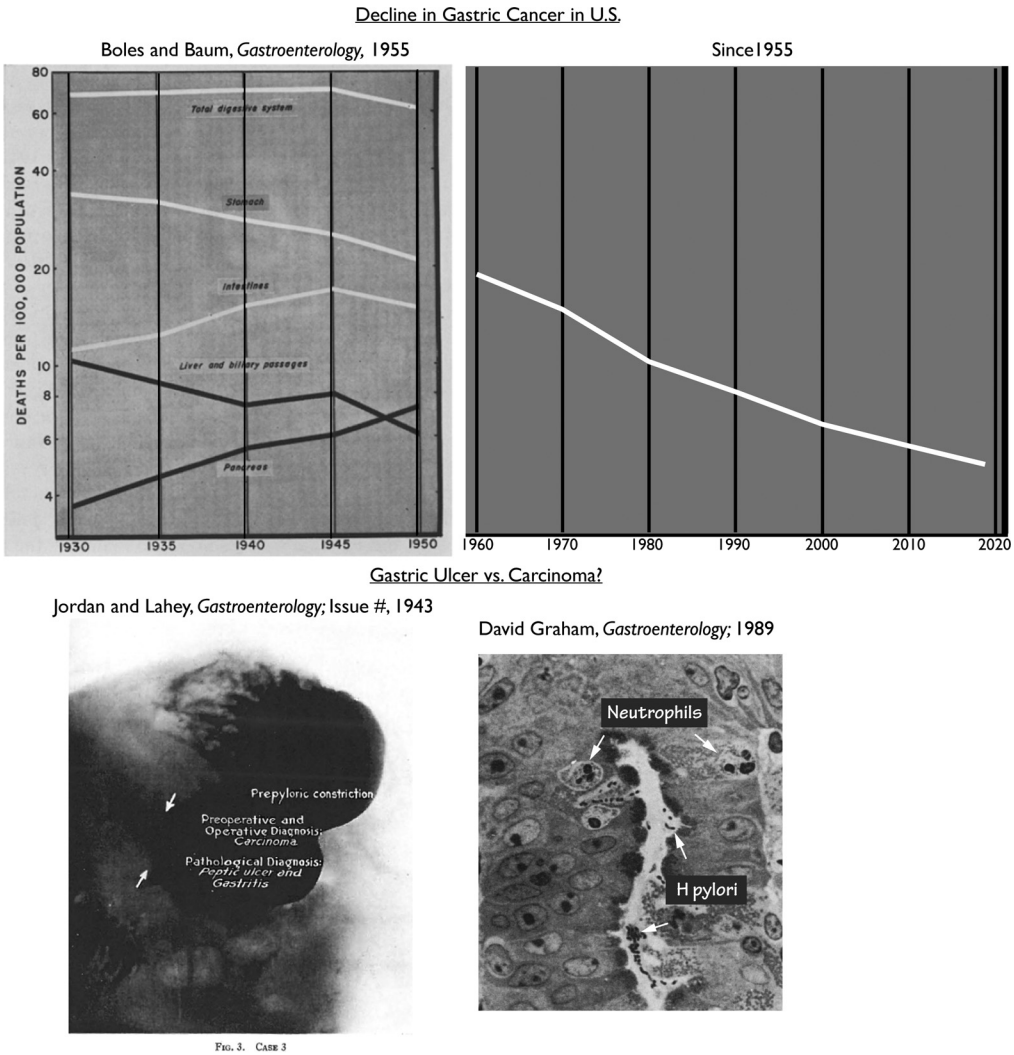

Figure 1. Gastric cancer then and now. In some cases, we have learned a lot since 1958 when Boles wrote a review in *Gastroenterology* on gastric cancers. *Top*, Boles had identified a surprising decline in deaths owing to gastric cancer in his 1955 article[4] on the subject in *Gastroenterology* (graphed are white male deaths). That trend continued through the end of the twentieth century and then has since leveled off (note log axis). Data in the graph on the right estimated from multiple sources but primarily based on the American Cancer Society online tool (available at: https://cancerstatisticscenter.cancer.org). The reasons for the decline are not entirely clear but are discussed in the text. *Bottom*, Gastroenterologists have struggled with distinguishing benign gastric ulcers from cancer since the eighteenth century and the relationship between the two had been unclear until the role of *H pylori* in ulcers and cancer was discovered. Depicted is a roentgenogram with contrast (Figure 3 from the first article in the first issue of *Gastroenterology*)[37] from a 58-year-old man who had black stools and 6 weeks of epigastric distress relieved somewhat by food; there was no weight loss. Achlorhydria and slight anemia with a constricted antrum led to concern about gastric cancer and exploratory laparotomy with pathology showing a punched out, 1-cm ulcer and an ultimate diagnosis of chronic peptic ulcer. At right, a portion of a photomicrograph from one of the early *Gastroenterology* papers discussing pathology caused by *H pylori*,[38] the bacteria that were, at the time, being revealed to be the primary cause of both peptic ulcers and gastric cancer.

Basis for Differences in Gastric Cancer Incidence

With regard to issue 7, the decrease in gastric cancer in white American men, which Boles was among the first to recognize by the mid-twentieth century,[4] persisted to nearly the end of the century (Figure 1). Since 1992, in people <65 years of age, the decreasing incidence has essentially stopped[8] and might even be reversing if not increasing again in recent years among younger (<50 years of age) males.[8] Other than the fact that human colonization by one of the key etiologic agents, *Helicobacter pylori* (discussed elsewhere in this review), has also decreased over the last century and a half, the reasons for the decrease in rates of gastric cancer are still not apparent. Similarly, with regard to Boles's issue 2, the rates of gastric cancer and death from gastric cancer are still much higher in Japan, perhaps owing in part to higher rates of infection with *H pylori* or at least with more oncogenic strains thereof, along with poorly understood environmental factors (discussed elsewhere in this article and reviewed in reference[9]).