HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Gastroenterology. 2018 October ; 155(4): 939–944. doi:10.1053/j.gastro.2018.06.044.

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, 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 US and in Northern and Western Europe.
3. Certain histological and physiological changes, like atrophic gastritis and pernicious anemia, increase 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, e.g., October, 1955 issue of *Gastroenterology*[2] as well as another important paper from Sara Jordan and coworkers in October, 1952[3]).

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5. Boles commented on the uncertain relationship of gastric peptic ulcers to cancer. It wasn't 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 U.S. 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 death. 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: "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 20th 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 will 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 is still strikingly neglected in terms of research investment. As of 2013, one study showed that gastric cancer was last or nearly last in funding in the U.S., normalized in several ways[5]. A subsequent study showed that stomach cancer funding was last among all cancer types examined in both the U.K. and U.S., normalized to years of life lost[6]. And it was among the least funded in a follow-up study on U.K. funding[7]. Gastric cancer continues to be a significant health burden, estimated to be the cause of 10,800 deaths in the U.S. this year (NCI). Thus, to paraphrase Boles, we still can only speculate about why gastric cancer research is poorly funded.

Basis for Differences in Gastric Cancer Incidence

With regard to issue #7, the decline in gastric cancer in white American men, which Boles was among the first to recognize by the mid-20th century[4], persisted to nearly the end of the century. Since 1992, in people younger than 65, the decreasing incidence has essentially stopped[8] and might even be reversing if not rising again in recent years among younger (<50) males[8]. Other than the fact that human colonization by one of the key etiological agents, *Helicobacter pylori* (see below), has also declined 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, rates of gastric cancer and death from gastric cancer are still much higher in Japan, perhaps due 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 below and reviewed in ref.[9]). Notably, rates in Japan have also been decreasing, as have rates in other countries with traditionally higher incidence[9].

Etiology of Gastric Cancer: *H. pylori*, and Genetic and Environmental Factors

With regard to Boles's issue #1 ("environmental, genetic, and injurious factors,"), there has been a considerable increase in our understanding of "injurious factors" to the stomach (discussed below), and regarding the environmental and genetic factors, the field has made important progress as well. The game-changing environmental agent *H. pylori,* first discovered by Marshall and Warren in 2005 (see *Gastroenterology*, December, 2005[10], was shown to be almost required for nearly 90% of global gastric cancer[11]. *H. pylori* has been estimated to be the single most common cancer-causing infectious agent in the world, responsible for over one-third of cancers caused by infections[11]. Statistics like those, as well as studies showing the decrease in gastric cancer caused by population eradication efforts (see, e.g., May, 2016 *Gastroenterology*[12]), lends support to the Japanese effort to eradicate *H. pylori* in the population at large (see, e.g., the Japanese approach discussed in *Gastroenterology* from January, 2018[13]). However, the vast majority of people colonized by *H. pylori* do not get gastric cancer. A recent meta-analysis in the August, 2017 *Gastroenterology* showed that almost 4 and a half billion people are infected worldwide[14], yet far less than 1% will develop gastric cancer. What is different about cases where gastric cancer occurs? In part, it may be the strain of *H. pylori*, with those expressing the oncogenic toxin CagA much more tumorigenic than CagA- strains. There are even variants of CagA in East Asian strains that may further increase risk[15] (see also *Gastroenterology*, July, 2008[16]). A recent article (February, 2018) in *Gastroenterology* highlighted how the rapidly mutating *H. pylori* genetic and epigenetic landscape might complicate population-based studies of how different strains might increase cancer risk[17].

Host genetic and epigenetic variation may also affect whether *H pylori* causes gastric cancer. Multiple articles published over the past two decades in *Gastroenterology* chart our growing understanding of the influence of host genetics on disease progression; for example, in reverse chronological order just from the past decade: 1) *FOXD3* was shown to be epigenetically dysregulated in gastric carcinogenesis (January, 2013)[18], 2) variants in the autophagy pathway-associated gene *ATG16L1* were shown to increase risk to *H. pylori* infection (May, 2012)[19], 3) *TFF2* methylation was shown to increase in *H. pylori* infection and gastric tumorigenesis (December, 2010)[20], 4) the RNA/DNA editing enzyme activation-induced cytidine deaminase (AID) shows aberrant expression in *H. pylori* infected patients, which may cause mutation of the tumor suppressor *CDKN2b-CDKN2a* locus (December, 2010)[21], 5) methylation of O6-methylguanine DNA methyltransferase (*MGMT*) is increased in patients infected with CagA+ *H. pylori*, suggesting disrupted DNA repair (May, 2010)[22], 6) polymorphism in the *TLR4* gene increases risk of gastric cancer (March, 2007)[23]. One of the first host polymorphisms to be described that increases risk for gastric cancer precursor lesions was in the gene *IL1B*, reported in the July, 2002 issue[24], an article cited over 270 times.

In addition to numerous gene polymorphisms that increase risk -- especially in the context of *H. pylori* infection – discussed above, the field has progressed tremendously in the understanding of the genetic determinants for diffuse gastric cancers of the signet ring variety, which are rarer and less associated with *H pylori* infection. Mutations in the *CDH1* (E-cadherin) gene have been shown to be responsible for a large fraction of hereditary diffuse gastric cancer cases[25–28]. The association between *CHD1* mutations and breast and gastric cancer was studied in a large cohort and published in the December, 2001 *Gastroenterology*[29].

Other environmental factors interact with *H. pylori* to help promote gastric cancer. For example, lower host cholesterol levels can block *H. pylori* pathogenesis (reviewed in[9]), with an article currently in press in *Gastroenterology* indicating that the bacteria may scavenge cholesterol to help mute the inflammatory response[30]. Iron deficiency seems to accelerate gastric carcinogenesis via interaction with *H. pylori* (reviewed in[9] and see especially ref[31]); a relationship between *H. pylori* and iron was noted as early as the August, 1998 issue of *Gastroenterology*[32]. Other environmental factors that may influence risk for gastric cancer include the level of salt (high salt increases risk) and fresh fruits and vegetables (high and diverse intake decrease risk). Thus, many environmental factors, most centered around *H. pylori* infection, have been discovered to increase gastric cancer risk since the Boles review in 1958, and much of the key work has been published in *Gastroenterology*.

Advances in understanding mechanisms of *H. pylori* function as a carcinogen along with other environmental and host factors has emerged from research on rodent models, such as a seminal article in January, 2000 on how mice with genetically-induced hypergastrinemia model gastric tumorigenesis[33] (a paper cited over 425 times) with a follow up in June, 2003 (cited over 141 times), and the introduction of a Mongolian gerbil model in the September, 1998 issue[34] (cited over 844 times), that helped fulfill Koch's postulates as to the bacterium as a carcinogen[35].

Relationship of Gastric Ulcers with Gastric Cancer

Progress has been made on Boles's question #5 regarding the relationship between gastric ulcers and gastric cancer. Whether gastric cancers tended to arise in ulcers, or whether gastric cancers developed first and then frequently ulcerated has been an issue that has perplexed gastroenterologists since the time of Ménétrier[36], who himself cited references up to a half century earlier than when he wrote on this topic in 1900. In fact, the issue of ulcers and cancer was in part the subject of Sara Jordan's and Frank Lahey's article on pages 1–12 of the first issue of *Gastroenterology* in 1943[37], the anniversary of which we are commemorating with this series of reviews! Our understanding since the era of Boles and his predecessors has increased substantially as we now know that *H. pylori* is also the cause of nearly all duodenal and the majority of gastric peptic ulcers. An early article on this link appeared in the February, 1989 *Gastroenterology*[38] (cited over 650 times), which described how *Helicobacter* (then called *Campylobacter*) *pylori* gastritis in the antrum led to chronic increase in acid production, which was the underlying cause of peptic ulcers. In a Reply to the 1989 article (November, 1990), a link was also noted between *H. pylori* and atrophic

gastritis[39], which, as we discuss below, is a lesion that indicates increased risk for gastric cancer.

Atrophic gastritis occurs when, in some patients, *H. pylori* spreads proximally from its original and more common antral niche into the body and fundus of the stomach. The associated inflammatory reaction correlates with loss of parietal cells and decreased acid production. Thus, the consensus in the field is that peptic ulcers and gastric cancer are related in having *H. pylori* as an important etiological agent but largely reflect two different courses (or stages) of disease caused by the bacterium: one characterized by increased acid production and ulceration, and the other by decreased acid production and potential progression to cancer. Some authors, including the one who penned the 1989 article, argued that ulcers (especially those in the body/fundus) may also be earlier manifestations with cancer being a later manifestation of the disease[40]. In either case, the consensus is that the vast majority of ulcers in which cancer is found are due to the growth of the cancer in an ulcerated morphology and not due to cancer arising within an earlier, active, benign peptic ulcer. Thus, while a diagnostic challenge for the endoscopist as to whether an ulcer is benign and peptic or an ulcerated malignant cancer, the etiology of the two entities has been reasonably well established since the Boles review.

Cellular Remodeling, Gastric Metaplasia and Cancer Progression

Finally, now that we, as a field, have resolved how *H. pylori* plays a dual role in ulcers, and that benign peptic ulcers are not usually direct precursor lesions for gastric cancer, we can turn to Boles's issues #3 (the role of precursor lesions like atrophic gastritis in tumorigenesis) and #4 (the link between achlorhydria and progression to cancer). We can also touch on the final aspect of issue #1 (injurious agents and cancer). The idea that gastric atrophy, involving loss of the normal mature cells of the body/fundus, was a precursor state for gastric cancer had already been postulated by Ménétrier, who noted by 1900 that cancers seem to arise in regions where the rich cellular architecture of gastric glands had atrophied to relatively simple glands filled with mucus-stuffed cells[36]. The pathologist George Adami in the same year had also remarked how, as glandular tissue aged, cancers seemed to arise after they'd atrophied[41]. Both had speculated that infectious agents or other irritants caused these changes. As discussed, we now know that *H. pylori* is the infectious agent at the root of most gastric cancer. In recent years, we have learned, with many of the most important papers published in *Gastroenterology* (e.g., April 2008[42] cited over 269 times), that, when *H. pylori* spreads beyond the antrum to cause gastritis of the whole stomach ("pangastritis"), it slowly causes the pattern of inflammation and cellular changes known as chronic atrophic gastritis[40, 43]. The cells that are atrophied are mature digestive-enzyme-secreting chief and acid-secreting parietal cells (see, e.g., February, 2011 issue[44]). Just as Ménétrier described, the metaplastic cells that replace the atrophied parietal and chief cells are stuffed with mucins (like MUC6), and with other proteins (like TFF2), whose expression is normally in a much more limited cohort of progenitor cells in the isthmus or neck of the gland (see, e.g., *Gastroenterology*[45, 46]. Thus, atrophic gastritis is invariably associated with metaplasia, which has been called pyloric or pseudopyloric (because the pattern of mucinous cells from top to bottom of the gastric unit resembles the antrum/pyloric region) or Spasmolytic Polypeptide Expressing Metaplasia (SPEM), as TFF2's erstwhile name was Spasmolytic

Polypeptide[47]. Additionally, it is the view of the authors that this pattern of metaplasia may resemble the juvenile or embryonic stomach most of all, and may represent a conserved repair process when deep glandular cells like parietal cells are injured[48].

The link between SPEM/atrophy and risk for gastric cancer is well established, and, thus, the reason why achlorhydria indicates increased risk for gastric cancer is straightforward: the less acid, the less parietal cell mass, the more atrophy. Interestingly, another metaplasia has drawn a great deal more attention during the second half of the 20th Century: intestinal metaplasia. A relatively early mention of the potential role for "intestinalization" of the stomach as a gastric cancer precursor was in the March, 1964 Issue[49]. Given that eventual gastric cancers that arise have, to varying degrees from region to region and from person to person, intestinal morphological characteristics, has suggested that tumors arise from intestinal metaplasia. It seems clear that SPEM or pseudopyloric metaplasia arises first, and some have argued that intestinal metaplasia may arise from SPEM, making SPEM the root lesion, even if intestinal metaplasia or certain types of intestinal metaplasia may be the more proximate route to gastric cancer (see, e.g., June, 2010 issue[50]).

Current Questions

Why SPEM increases the risk for cancer is open to debate; however, the plasticity that must occur for the stomach to retool the types of cells that are produced may carry inherent risk[43]. Some have proposed that the change in cell fate may occur in the actively proliferating isthmal progenitor cells (e.g., June, 2017 issue[51]). In contrast, others have made the case in multiple issues of *Gastroenterology*[52–55] that it seems more likely that mature chief cells scale down their secretory architecture through a conserved set of cellular and molecular events (recently dubbed "paligenosis"[56]) to become proliferative SPEM cells.

Currently, the field is in an active state of debate about the mechanisms that determine which cells fuel metaplasia (see, e.g., the summary on the Freston metaplasia meeting in the July, 2017 issue[57]). Time will tell whether a stem-cell based or mature-cell based plasticity event (or both) is the one that occurs in human patients. In multiple other organs, mature secretory cells, like chief cells, can undergo cellular reprogramming (paligenosis) to become proliferative[56]. There would be risks associated with a long-lived cell, such as a chief cell, that could warehouse mutations for months or years, recalled into a state wherein oncogenes and epigenetic changes favoring the progenitor or embryonic state could be unmasked. This would especially be true over cycles of recruitment as progenitor cells (via paligenosis) and redifferentiation[43, 56] where mutations can accumulate over time.

More research – in our underfunded field! -- will eventually help reveal how atrophic gastritis and metaplasias contribute to gastric cancer, with many more exciting studies sure to come. The bulk of the most important work will likely continue to be published in *Gastroenterology*. Certainly, one can hope that we will be much farther into understanding the key questions on gastric cancer posed by Boles well before we reach the second diamond or sesquicentennial anniversary of the journal!

Acknowledgments

Funding: JCM is supported by grants NIDDK R01s (DK094989, DK105129, DK110406), Alvin J. Siteman Cancer Center/Barnes Jewish Hospital Foundation Cancer Frontier Fund, NIH NCI P30 CA091842, The Barnard Trust, and DeNardo Education & Research Foundation grants to J.C.M., L.C.S. has research support through NIH P01-DK062041, NIH 5R01-DK096972, NCI P50-CA130810 and the AGA Research Foundation.

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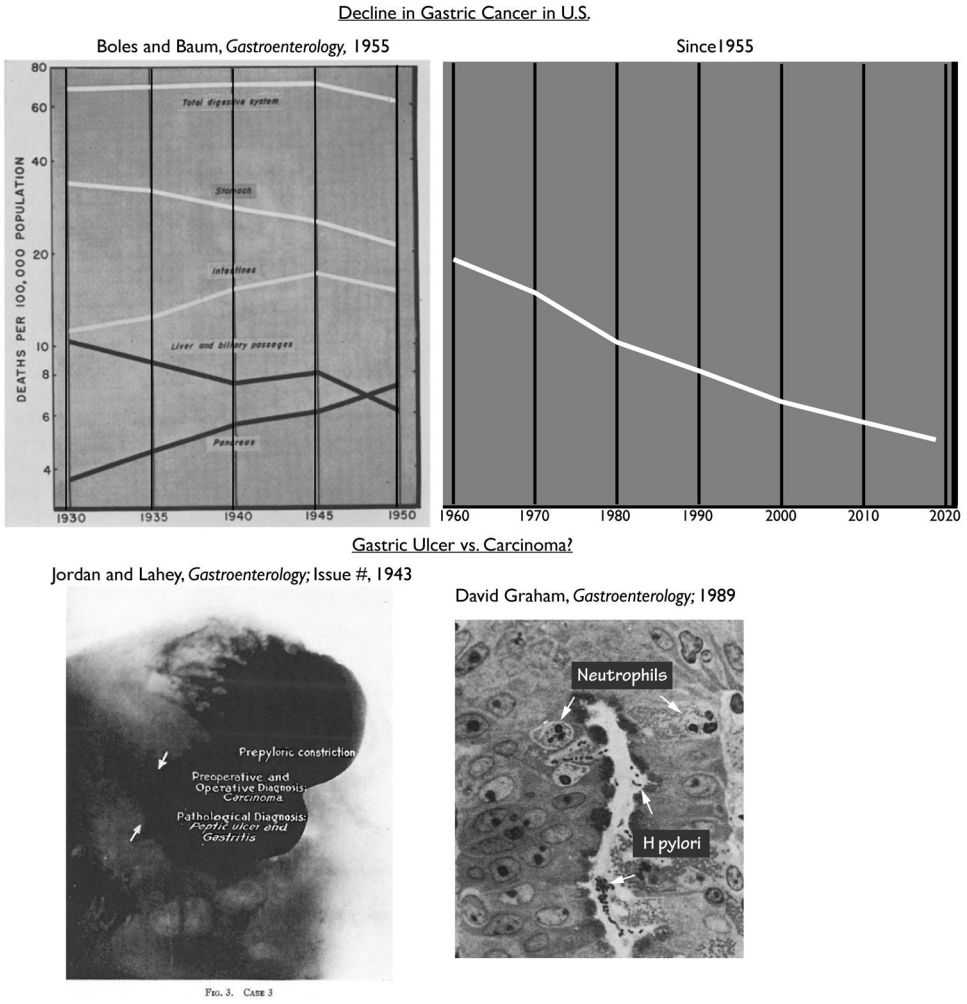

Figure. Gastric Cancer Then and Now

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 due 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 20th Century and then has since leveled off (note log axis). Data in graph on right estimated from multiple sources but primarily based on the American Cancer Society online tool (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 18th 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 (Fig. 3 from the first article in the first issue of *Gastroenterology*) from a 58 year-old male who had black stools and 6 weeks of epigastric distress relieved somewhat by food; there was no weight loss. Achlorhydria and slight anemia with constricted antrum led to concern about gastric cancer and exploratory laparotomy with pathology showing a punched-out 1 cm ulcer and 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*, the bacteria that were, at the time, being revealed to be the primary cause of both peptic ulcers and gastric cancer.