Worldwide gastric cancer remains one of the most common cancers, killing upwards of one million people each year. While the molecular pathogenesis remains unclear, infection with the bacterium Helicobacter pylori is considered a "necessary but not sufficient" cause, not surprisingly as gastric cancer has long been known to be associated with atrophic gastritis. Eradication of H pylori is expected to virtually eliminate gastric cancer and H pylori associated peptic ulcer within approximately 40 years and thus reduce overall mortality. In the USA, the incidence of gastric cancer in the general population is low, reflecting the change in the pattern of gastritis from atrophic to non-atrophic and in the low and decreasing prevalence of H pylori infection in the middle and upper classes. However, the plan for eradication of this important pathogen must be considered within the context of the prevalence and outcome within specific populations.

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Cancer risk is negligible in those with a normal gastric mucosa and increases stepwise, with the increase in atrophic gastritis being highest in those with the most severe atrophy associated with spontaneous loss of H pylori infection.3,21 In this issue of Gut, Watabe and colleagues32 report on their findings of combining H pylori testing and pepsinogen testing to identify subgroups with different risks of developing gastric cancer (see page 764). Their results confirmed and extended prior observations showing that the highest incidence of gastric cancer was associated with the risk factors male, age greater than 60 years, severe atrophic gastritis (based on pepsinogen levels), and loss of H pylori antibody.42 The annual risk for their highest risk group was extremely high, being approximately 2000/100 000 per year, or 2% per year.

The actual incidence of gastric cancer in any population is dependent on a number of variables, including the proportion with H pylori infection, the proportion with atrophic (versus non-atrophic) gastritis, the severity of atrophy, and the rate with which atrophic gastritis develops. Factors which influence the development of atrophic gastritis and the rate in which it progresses include environmental factors such as diet (salt increases the risk, fresh fruits and vegetables reduce it), the virulence of the infecting strain, and host factors, especially polymorphisms in genes that enhance or reduce the inflammatory response to the infection.1 The relative importance of any one factor varies within populations and individuals. The lessons learned regarding the interactions between bacterial, host, and environmental factors by those studying periodontal disease are now being learned by those studying gastric cancer (reviewed by Dore and Graham33).

**EFFECT OF H PYLORI ERADICATION**

While no H pylori, no gastric inflammation, no atrophy, no gastric cancer is generally true, eradication of H pylori will not immediately result in elimination of gastric cancer. Because H pylori is the necessary cause of gastric cancer, eradication of H pylori will eventually lead to gastric cancer becoming a rare disease. The important question from treatment studies is what is the effect of H pylori eradication on progression to cancer among those at risk. Figure 1A shows the incidence of gastric cancer in Japan in 1986. In a theoretical experiment, consider the possible effects of eradication of H pylori infection in a subpopulation of 55 year old men. H pylori eradication is done at point “A” and patients and a suitable control group are followed for 10 years, to point “B”. During this interval, the incidence of cancer in the control group would be expected to approximately double (from 200/100 000/year to 400/100 000/year). The sample size calculation is then dependent on the effect of H pylori eradication in the treated group. Studies of H pylori eradication after mucosal resection of early gastric cancer14 15 suggest that H pylori eradication would reduce but not eliminate the risk of development of cancer compared with no eradication. Thus the study design might consider cancer risks ranging from 100 to 400/100 000 per year. If H pylori eradication reduced the incidence from 400 to 300 (50% reduction in the expected increase) the sample size to detect this difference would be 17 265 in each group with a 10 year follow up.

"Because H pylori is the necessary cause of gastric cancer, eradication of H pylori will eventually lead to gastric cancer becoming a rare disease."
Most current studies are small and have generally attempted to examine surrogate markers such as changes in intestinal metaplasia or atrophy. Both outcomes are extremely difficult to quantify using random or even targeted endoscopic biopsies such that likelihood of a meaningful result is extremely low.\textsuperscript{19} Small studies using surrogate markers are likely to achieve positive results because of pre and post therapy biases with regard to diagnosis of intestinal metaplasia or atrophy in the presence of \textit{H pylori} inflammation.\textsuperscript{49}

**PROPOSAL**

We propose that there are now sufficient data to consider strategies designed to both prevent gastric cancer and to reduce gastric cancer mortality. Screening programmes by themselves are akin to repairing the ceiling after each rain without also fixing the roof. We now know where the leak is as \textit{H pylori} infection is the necessary but not sufficient cause of gastric cancer. While gastric cancer incidence might be reduced by targeting cofactors, elimination of the reservoir of \textit{H pylori} infection is the only method to eliminate the disease.

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We propose a two pronged approach: eradication and targeted surveillance. Firstly, we propose nationwide or high risk population wide \textit{H pylori} eradication in countries and populations with a significant risk of gastric cancer (for example, Japan, Korea, China, etc). Eradication of \textit{H pylori} would eliminate gastric cancer in approximately 40 year as the number of new cases would fall each year as the proportion of the population with “no risk” increased. The fall in cases would likely be increased by \textit{H pylori} eradication, resulting in a truncation of the “natural” age related increase in incidence. \textit{H pylori} eradication would also be accompanied by a surveillance programme based on risk assessment using non-invasive markers designed to identify those at higher risk for development of gastric cancer. We propose that fig 1A, which shows the age related increasing risk of gastric cancer, actually represents a change in the proportion of the population in the higher risk category. Age is a poor discriminator of risk and we propose that it be replaced with a risk assessment. The population would then be divided into risk groups such as none, low, and high (fig 1B). All with \textit{H pylori} infection would receive eradication therapy and confirmation of cure. Those in the low risk group (defined as \textit{H pylori} infected but with normal pepsinogen levels) would undergo no further testing. Those in the high risk group would be enrolled in a screening programme to identify early cancers.

**RISK MODIFICATION PROGRAMMES**

There are a number of research questions arising from the proposal that require additional studies, including identification of risk factors and appropriate cut off for risk stratification. For example, the paper by Watabe et al suggests that a patient with an “atrophic” pattern of pepsinogens at age 60 years may have a different risk than a patient aged 50 years.\textsuperscript{42} Whether this possible age related risk factor would disappear when pepsinogen values were analysed by actual level (for example, pepsinogen I: pepsinogen II ratio of 1.1 v 2.9) or other analyses is a subject for research. Similarly, if one embarked on a follow up cancer screening programme for those in the high risk group (however defined), when could one stop? What is the pattern of change in risk after \textit{H pylori} eradication? What are the predictors of change? For example, \textit{H pylori} eradication in those with hypochlorhydria is expected to eliminate inflammation induced suppression of the remaining parietal cells. Therefore, even thought no new parietal cells may be produced, intragastric pH would be expected to fall, which will be reflected in a fall in gastrin 17 levels\textsuperscript{43}–\textsuperscript{46} as well as reduction in overgrowth by non-\textit{H pylori} in the stomach. Those with complete atrophy would not be expected to experience any change in pH or overgrowth such that comparisons might include those whose gastrin remains elevated compared with those in whom it returns to normal.

Other research questions include whether it may be possible to further reduce risks after \textit{H pylori} eradication. Possibilities include the effects of dietary modifications (for example, reducing the amount of salt and increasing intake of fresh fruits and vegetables), smoking cessation programmes, and possibly the use of drugs such as anti-inflammatory agents (that is, cyclooxygenase 2 inhibitors, rebamipide, or other drugs that have an effect on modifying gastric inflammation).

**COST EFFECTIVENESS OF SCREENING**

Assessment of cost effectiveness is dependent on determining actual costs, gains, and trade offs needed to achieve the goals.\textsuperscript{47}–\textsuperscript{49} As noted above, currently in Japan 5–6 million people are screened annually at a cost of at least $300 million US. The eligible population in Japan is 65 million over 40 years of age, of whom approximately half do not have \textit{H pylori} infections and are thus either not at risk or at very low risk. Studies are needed to define the effect of \textit{H pylori} eradication on subsequent cancer incidence and to identify the most cost effective strategy for post eradication cancer surveillance among high risk groups. Cost savings are obtained by limiting the population undergoing surveillance to those who might benefit, reducing the age specific increase in cancer incidence, more effective resource utilisation by identifying those at highest risk independent of age, and providing surveillance targeted specifically to them. It is important to remember that the costs of \textit{H pylori} screening and eradication for the population are a one time cost, as elimination of the reservoir eliminates transmission and therefore the diseases associated with the infection. In countries such as Japan where infection is uncommon in childhood, it is likely that screening could be targeted only to children within families where one or more parent had active \textit{H pylori} infection.

**SUMMARY**

Eradication of \textit{H pylori} is expected to virtually eliminate gastric cancer and \textit{H pylori} associated peptic ulcer within approximately 40 years (fig 1C) and thus reduce overall mortality and increase the number involved in productive endeavours. Elimination of a cause of death is always associated with an increase in the proportion of problems that the presence of the original disease prevented. Public health measures and the widespread use of vaccines led to an increased average lifespan and thus increased the problems and deaths from diabetes, heart disease, and cancer. No one suggests that we consider withholding vaccines and sanitation to prevent cancer deaths in the elderly. Prevention or lessening of corpus gastritis (the precursor lesion for gastric cancer) will reliably lead to increased acidity and worsening of the severity of gastro-oesophageal reflux disease among those who have abnormal barriers to the reflux of gastric contents into the oesophagus. In the early 1900s in the USA, the incidence of gastric cancer was similar to what it is today in Japan. In the USA today, the incidence of oesophageal adenocarcinoma among the high risk group of men aged 60–69 years is approximately 20 per 100 000/year, which is at least 30-fold less than the risk of gastric cancer among men.
of the same age in Japan today and among men in the USA when H pylori corpus gastritis was common.

“Eradication of H pylori is expected to virtually eliminate gastric cancer and H pylori associated peptic ulcer within approximately 40 years”

In the USA, the incidence of gastric cancer in the general population is low, reflecting the change in the pattern of gastritis from atrophic to non-atrophic and in the low and decreasing prevalence of H pylori infection in the middle and upper classes. None the less, H pylori, atrophic gastritis, and gastric cancer remain common in immigrants from countries where gastric cancer is still a problem (for example, lifetime risk among Korean Americans living in Los Angeles is 4.5%)29 suggesting that like syphilis, the plan for eradication of this important pathogen must be considered within the context of the prevalence and outcome within specific populations.

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Authors’ affiliations

D Y Graham, Department of Medicine, Michael E DeBokey Veterans Affairs Medical Center, Departments of Medicine and Molecular Virology and Microbiology, Baylor College of Medicine, Houston TX, USA

A Shiotani, Health Administration Center, Wakayama University, Wokaya, Japan

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D Y Graham and A Shiotani

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