

# Part 1

## **Gastrointestinal Diseases and Disorders: The Public Health Perspective**



# 1

# The Importance of GI Epidemiology

*G. Richard Locke III and Nicholas J. Talley*

## Key points

- Gastrointestinal (GI) epidemiology is underestimated as a scientific discipline.
- GI epidemiologic insights have greatly improved the lives of patients.
- The current disease specificity of GI epidemiologic research may not provide the best milieu for advancement of the field.
- Great opportunity exists for a person interested in GI epidemiology.

## Introduction

If one does a literature search and types in “epidemiology” over 76 000 references are cited; yet if one types in “GI epidemiology” the reference list is blank. Maybe the abbreviation is the problem. A search for “gastrointestinal epidemiology” yields just one paper that was published 10 years ago [1]. The combination of “gastrointestinal diseases” and “epidemiology” produces 200 citations. Yet, the combination of “cardiovascular diseases” and “epidemiology” produces 979 papers; and the combination of “neoplasm” and “epidemiology” provides 2413. The key word “epidemiology” has almost 6000 citations.

This exercise does not make GI epidemiology appear very important. However, the editors of this text strongly disagree. GI epidemiology is very important, but is underappreciated. Great work is being done in GI epidemiology, but is not recognized as GI epidemiology. By putting current work together in this book we hope to improve the understanding and recognition of this field.

Readers of this text will likely come from one of two backgrounds: (i) people who are trained and/or work in epidemiology and wish to learn more about gastroenterology, or (ii) people who are trained and/or work in gastroenterology and wish to learn more about epidemiology. GI epidemiology is of interest to both these groups of people but for different reasons. This chapter will highlight the importance of GI epidemiology from each perspective.

## Why is GI epidemiology important to an epidemiologist?

The importance of GI epidemiology to the epidemiologist is nicely illustrated by the early work of Dr John Snow. The 150th anniversary of his work tracing a cholera epidemic was recently celebrated and an entire book has been written about this insightful use of epidemiologic methods to help save lives [2]. In 1851, people living in central London were suffering and dying from the acute onset of a fatal disease characterized by stomach cramps, vomiting and diarrhea. Snow examined the distribution of these cases and determined the source to be the water coming from the Broad Street pump. The handle was removed from the pump and the deaths stopped. Some consider this event to be the birth of the science of epidemiology.

Although this might be viewed as an example of infectious disease epidemiology, Snow did not know the organism. He studied the pattern of a gastrointestinal illness that was later shown to be cholera. Since that time, epidemiologists have worked diligently on eradicating infectious diseases and improving the health of the public. Infectious disease epidemiology is a well-established field and mysterious epidemics continue to fascinate both epidemiologists and the general public. Often these involve digestive diseases. For example, the recent problems of Norwalk virus outbreaks on ocean cruise liners and *E. coli* from fast food vendors have certainly kept this in the public mind. Countless times epidemiologic methods have been used to help reduce the outbreak of a disease.

Unfortunately, infectious disease epidemiologists do not focus much on digestive diseases that do not seem to have an infectious basis. This can limit opportunities. The great case in point is the story of *Helicobacter pylori* (HP) [3,4]. A later chapter in this book will review this topic in more detail, but a brief summary is in order. For decades, peptic ulcer disease was thought to be a disease of gastric acid production. Gastric cancer was thought to be caused by diet. The incidence of gastric cancer started to decline and no one understood why. Later, peptic ulcers became less of a problem and this was ascribed to the development of acid-blocking medication. Then two people, a pathologist and a gastroenterology fellow, postulated that an unknown organism seen on silver staining of gastric biopsy material was associated with peptic ulcers. The organism was quite difficult to culture and many had assumed it was just a commensal. The conventional wisdom could not accept that ulcers were an infectious disease. Barry Marshall first cultured the bacteria and in a later experiment then ingested the organism, developed gastritis and then eradicated the organism to partially fulfill Koch's postulates. Eradication of *H. pylori* healed and helped prevent ulcers. In 2005, Barry Marshall and Robin Warren received the Nobel Prize in Medicine and Physiology for their work discovering HP. One can argue that this Nobel Prize was awarded for work in GI epidemiology.

Before 1900, HP was endemic around the world. Over the past 100 years, the prevalence of HP has declined in developed countries and with that decline came the decline in gastric cancer and peptic ulcers. Epidemiologists have contributed greatly to our understanding of HP and have helped to prevent further digestive disease. One question to ask, however, is why did it take so long? Why wasn't HP discovered in 1930? The answer was there, right before our eyes. Perhaps the wrong eyes were looking at the problem. Traditional epidemiologists did not study ulcers. Gastroenterologists were not looking to epidemiologists for help as they thought they understood the problem well. Might the answer have come sooner if GI epidemiology was a more mature discipline? One can only wonder.

Epidemiologists have been interested in cancer for a long time. The epidemiology of colon and pancreatic cancer has been well studied. Still, numerous opportunities exist for an epidemiologist to contribute to the understanding of digestive disease. Unfortunately, gastroenterology is increasingly becoming a divided field. First hepatology established itself as distinct discipline. Subsequently the endoscopists, pancreatologists, esophagologists, neurogastroenterologists and experts in inflammatory bowel

disease (IBD) followed suit. Each of these groups has focused its efforts on additional years of training, separate meetings and separate societies, and even certification. While this has greatly enhanced these fields, it has also made it harder to think of GI epidemiology as a single discipline. People consider themselves as IBD or *H. pylori* experts rather than GI epidemiologists even if they are doing population research. This helps explain the challenge of searching the literature as highlighted at the start of this chapter. People don't think of GI epidemiology like cardiovascular epidemiology; they think about the epidemiology of the individual diseases.

Yet diseases happen to an individual, not just an organ. Exposures can affect the entire GI tract. Diet and ingested organisms may impact the gut based on location, but the entire GI tract is exposed to cigarette smoking, alcohol ingestion and bloodstream infections. Why should one person study the impact of cigarettes on the pancreas and another assess the impact on the stomach? Epidemiologists are needed to think in a horizontal fashion and link digestive diseases together. Such people can understand all the nuances of measuring exposures and translate these skills from one disease to another.

The opportunities for an epidemiologist interested in gastroenterology are further enhanced by the availability of data. As medical science has progressed and data systems developed (e.g., death certificates, mandatory reporting of specific infections) the possible uses of epidemiologic techniques have grown. However, the key development has been the introduction of computers and subsequent improvements in speed and memory. With modern computers, the epidemiologist can conduct and analyze studies with many thousands of participants and even millions of data points.

With such studies has come the development of enormous databases. For example the United States Public Health Service has organized several large studies and made the data available for public use. The National Health Interview Study (NHIS), which began in 1957, has over 100 000 subjects. The National Health and Nutrition Examination Surveys (NHANES) have been in continuation since 1971. Similarly, the National Ambulatory Medical Care Survey (NAMCS) and the Surveillance, Epidemiology and End Results (SEER) program have existed for decades. Because these studies have included hundreds of thousands of patients they provide the statistical power that epidemiologists need. These studies have not specifically focused on digestive diseases but yet have included data on symptoms, diagnoses, incidence rates and even measures of liver function and ultrasound assessments for

gallstones. What have been missing have been individuals with an understanding of these data sets who are interested in GI topics.

Similarly, several large cohort studies such as the Nurses' Health Study have collected data on digestive problems. The primary aim of these studies has not been in digestive disease but they serve as a great resource for individuals interested in GI and epidemiology.

What about the more modern epidemics? Epidemiologists have long been interested in nutrition, and recently their attention has focused on obesity. The growing waistlines of Americans represent perhaps the most important epidemic of our time. Traditionally, obesity has been viewed as a risk factor for digestive diseases such as gastroesophageal reflux and non-alcoholic liver disease, but now obesity is viewed as a disease itself. Digestion certainly plays a role in obesity and may offer clues for how to stop this epidemic. GI epidemiologists have the opportunity to make a major impact in this field.

So why is GI epidemiology important to an epidemiologist? The reasons are clear. There has been a long history of outstanding work that has earned the highest awards that medicine has to offer. The opportunities for study are almost endless as the available data sources have been underutilized for the multiple digestive diseases that exist. The sky is the limit for a young person interested in this field.

### Why is GI epidemiology important to a gastroenterologist?

Although GI epidemiology has been in existence for over 100 years it has not been an area of focus. Years ago, gastroenterologists were mostly physiologists. More recently the field has shifted toward endoscopy. In the 1990s considerable attention was given to outcomes research. This field was defined by the American Gastroenterological Association as being a combination of epidemiology, health services research, clinical investigation and clinical trials. Now the focus is on quality. In the past, quality improvement has not been considered research. Organizations have kept this work confidential under the cover of peer review. However, in the modern environment quality metrics are being collected by insurers and placed on the internet. Although quality improvement has a skill set that was largely developed in industry; the skills of an epidemiologist can be very helpful in advancing this field. Gastroenterologists in both private practice and in academic medical centers need to understand the tools of epidemiology and out-

comes research to improve the performance of their practice and the lives of their patients.

Gastroenterologists may not appreciate the story of the Broad Street pump [2], but they certainly appreciate the story of HP [3,4]. Although this topic was covered earlier from the perspective of the epidemiologist, the perspective of the gastroenterologist is slightly different. People in training today may find it hard to appreciate the impact that HP has had on our field. In 1930, gastric cancer was the most common cancer in America. The pathway of gastric carcinogenesis was well described. People were concerned about diet, especially the absence of fruits and vegetables and the presence of smoked or grilled meat and salted fish. However, then the incidence of gastric cancer started to decline and no one understood why. However, along came the "discovery" of HP and our understanding all changed. The cohort effect of birth year is now evidence-based and well understood (people born today are much less likely to acquire the infection than 50 years ago) and in retrospect, this all makes sense [5].

On a similar note, in the early 1980s gastroenterologists thought they knew a lot about peptic ulcers. Acid production was one of the best-studied elements of GI physiology. "No acid no ulcer" was the rule of the day. Again along came HP and everything changed. Now it is hard to imagine a world where people routinely need vagotomies or antrectomies. The Nobel Prize winners, Drs Barry Marshall and Robin Warren, were not themselves epidemiologists but used epidemiologic techniques to establish the importance of HP.

The importance of epidemiology to the gastroenterologist is not limited to HP. Perhaps the second greatest discovery of the past 20 years in GI was that of the viral agent hepatitis C [6,7]. Here again, epidemiology played a key role. People recognized the entity of non-A non-B hepatitis, but what was the cause? The lettering system even left room for this elusive agent. Although the agent was discovered using molecular techniques, the discovery was driven by what was known about the epidemiology of hepatitis.

These examples from the past just illustrate the importance of epidemiology to the gastroenterologist. What about future challenges and opportunities? Where can epidemiology help? We are making progress against colon cancer based on our understanding that adenomatous polyps are the precursors for this condition. In the 21st century we have to hope that the incidence of colon cancer declines just like gastric cancer in the last century. We recognize the importance of Barrett's esophagus in the development of esophageal cancer. The incidence of

adenocarcinomas of the esophagus is increasing at an alarming rate. When will this modern epidemic peak? We need some type of screening test of Barrett's. Will it be a capsule? Will it be a blood test? But would such screening reduce mortality? Only time and research will tell.

Why is GI epidemiology important to the gastroenterologist? For many, the issue is simply furthering their understanding of the specific condition that interests them. Experts in any disease need to know the prevalence, incidence, impact, cost and prognosis of every important condition. New diseases will almost certainly be discovered (like HP) and knowledge of their epidemiology will be crucial to understanding how to maximize health.

We also have to be very careful not to let conventional wisdom "blind" us to solutions to today's challenges. Could colon polyps be due to an infection? Might esophageal cancer be the result of the decreasing prevalence of HP? What are the environmental causes of obesity or irritable bowel syndrome? Gastroenterologists with an interest in epidemiology are needed to keep asking these types of questions even when it seems the "answers" are known.

### Challenges in GI epidemiology

Surely opportunities abound in GI epidemiology. We now have the ability to visualize the GI tract in its entirety. We have blood tests for viruses, HP and celiac disease. We have enormous databases and powerful computers. What is there to stop us?

Of course the first answer is we need people. In order for us to make progress in GI epidemiology we need people interested in the field. At present GI epidemiology is practiced in two ways. People with expertise in a specific disease include epidemiology as a component of what they do, or epidemiologists who have developed or have access to large databases ask questions related to GI diseases. Just a few people are truly GI epidemiologists. Fortunately or unfortunately, GI embraces many diseases and thus the field is spread thinly. We hope that by reading this book you have or may develop an interest in this field, and that this book will help nourish that interest so you decide to commit yourself to this field. Without a cadre of skilled investigators, the field will go nowhere and public health will not be best served.

The next issue is money. Fortunately the National Institutes of Health (NIH) and similar agencies around the globe have been very supportive of GI epidemiology. Training opportunities and initial grant support are plentiful. Of course the challenge is doing good work and obtaining long-term funding. These challenges and opportunities are discussed in detail in later chapters.

Perhaps the harder step is developing new techniques. Population-based research needs simple tests. We need a blood test for Barrett's esophagus; and we need simple blood or stool tests for inflammatory bowel disease, irritable bowel syndrome and colon cancer.

None of these challenges is insurmountable. The opportunities far outweigh the challenges in this field.

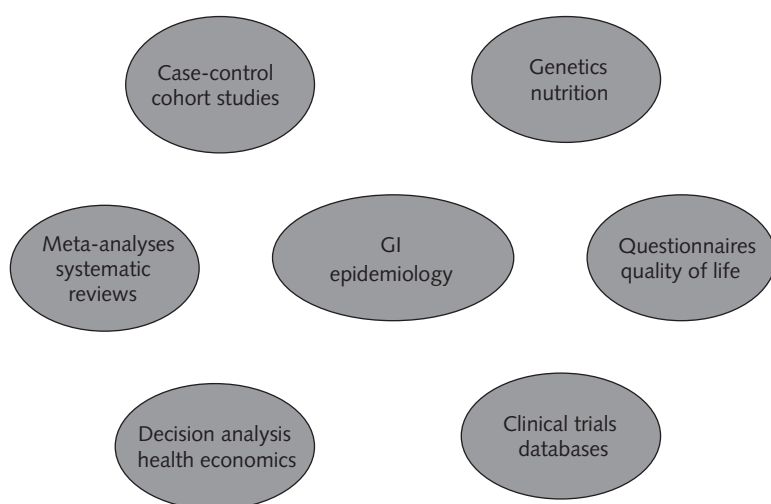


Fig. 1.1 The GI epidemiologist toolkit.

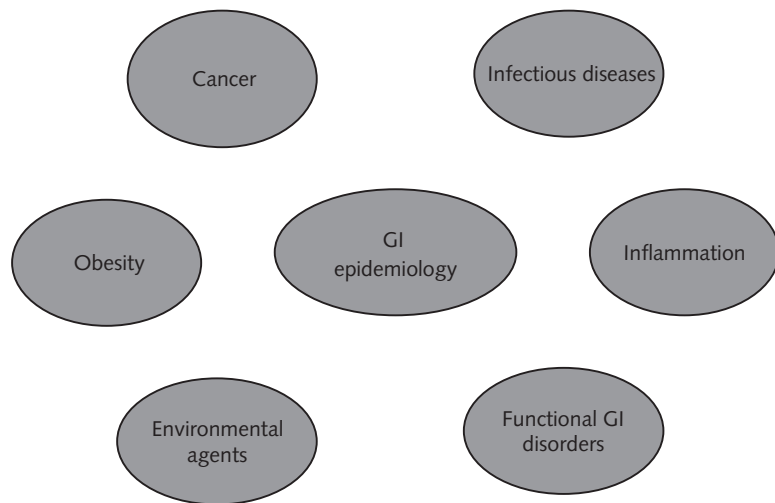


Fig. 1.2 The world of GI epidemiology.

## Conclusions

This book embraces a broad definition of GI epidemiology. First the stage is set with a review of the burden of GI diseases. Then the tool box of the modern GI epidemiologist (Fig. 1.1) is reviewed in a series of chapters on traditional epidemiologic methods, patient-reported outcomes, meta-analyses, systematic reviews, decision analysis, health economics and even clinical trials. The specific areas of genetic, nutritional and infectious disease epidemiology are highlighted. The resources available to get a person started are discussed. The disease-specific chapters cover the world of the GI epidemiologist (Fig. 1.2). The diseases of the entire alimentary tract are reviewed from esophagus to anal canal as well as the liver and pancreas. Taken together this book represents an attempt at defining our field – GI epidemiology.

So why is GI epidemiology important? GI conditions are common and sometimes lethal. Many significantly impact on quality of life. GI conditions are expensive. The study of GI epidemiology is needed to understand how common, how deadly, how significant, and how expensive. But perhaps more importantly, GI epidemiology has

the potential to change significantly the way we understand disease and practice medicine. Changing the way we practice to benefit the people we see... what could be more important than that?

## References

1. Jorgensen T *et al.* Epidemiology in gastroenterology. *Scand J Gastroenterol* 1996;**216**(Suppl.):199.
2. Johnson S. *The Ghost Map. The Story of London's Most Terrifying Epidemic and How it Changed Science, Cities, and the Modern World.* London: Riverhead Books, 2006.
3. Marshall BJ. The Lasker Awards: celebrating scientific discovery. *JAMA* 2005;**294**:1420.
4. Talley NJ, Richter J. Nobel Prize in Medicine awarded to a gastroenterologist in 2005. *Am J Gastroenterol* 2006;**101**:211.
5. Sonnenberg A. Causes underlying the birth-cohort phenomenon of peptic ulcer: analysis of mortality data 1911–2000, England and Wales. *Int J Epidemiol* 2006;**35**:1090.
6. Sherlock S. Landmark perspective: landmarks in viral hepatitis. *JAMA* 1984;**252**:402.
7. Purcell RH. The discovery of the hepatitis viruses. *Gastroenterology* 1993;**104**:955.