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James L. A. Webb, Jr
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Introduction

The Guts of the Matter is a study of our oldest ecological problem: the transmission of infectious intestinal pathogens from human waste.[1] Over deep time, fecal pathogens have killed innumerable infants and young children and been a principal constraint on human population growth. Over the past several generations, we have gained increasing control over the transmission of infectious intestinal disease. These advances have contributed to an ongoing population explosion that is dramatically transforming global ecological systems.

I was drawn to this project by an apparently simple question: why were diarrheal diseases still killing so many children in the twenty-first century? In the course of research, the project deepened in time and broadened in scope. It grew into a global history ranging from the early hominin era to the present, exploring human waste disposal, infectious intestinal disease, and the uneven impacts of modern sanitation. It came to grapple with environmental perspectives on some foundational disease processes that have shaped the human past.

[1] I have defined the term *infectious intestinal disease* to mean the negative health consequences caused by the viral, bacterial, protozoal, and helminthic biological agents that are passed by a fecal route, ingested via an oral route, and then reinfect the intestines and, sometimes, reach other internal organs. I have expanded the reach of the term to encompass hookworm, which is passed by a fecal route and then is contracted by dermal exposure with feces-contaminated soils, from which hookworm larvae penetrate the skin and migrate to reinfect the intestines, because the epidemiology of hookworm is in many other respects similar to that of roundworm and whipworm, the other major soil-transmitted intestinal helminths, and co-infections are common.

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In the course of writing the book, many friends and colleagues expressed some discomfort when they learned of its topic. The quasi-unmentionable nature of human waste underscores the fact that in the developed world, we carry out our excretory functions in private in special rooms devoted to this purpose, and many of us have little idea of what happens after we flush the toilet. Several times a day, we sit astride (or stand in front of) a section of the largest and most expensive environmental infrastructure in the world – the vast underground systems of sewers and wastewater treatment plants that are a defining feature of the developed world. Fully one-half of humanity squats today without these appurtenances, suffers the indignities of infectious intestinal disease, and mourns the diarrheal deaths of their infants and young children.

The Guts of the Matter is organized into eight chapters. Chapter 1, "Pathogens and Parasites," introduces the major helminthic, protozoal, viral, and bacterial intestinal disease agents, and it provides estimates of their current prevalence and contribution to the burden of human disease. The chapter discusses the biological and social determinants of infectious intestinal disease transmission, and it makes the point that, although a range of hygienic practices can have a significant influence on transmission, owing to a range of ecological and cultural variables, few universal rules apply. It discusses some recent findings from the microbiome project that provide new ways of thinking about infectious intestinal disease, and it makes the case that a deeper understanding of the historical epidemiology of infectious intestinal diseases can potentially improve the public health outcomes from contemporary interventions.

Chapter 2, "Early Change," explores what is known about environments in which intestinal disease transmission emerged. It marshals research in the biological sciences to discuss the settings in which early communities were able to transmit some intestinal pathogens and parasites, long before the agricultural revolution. It suggests that the construct of the "first epidemiological transition" needs to be revised. It explores the patterns of vulnerability to infectious intestinal disease associated with hunting, gathering, and fishing in an early era and those associated with early farming practices, settlements, and pastoral nomadism. It provides an historical overview of the evolution of zones of infectious intestinal disease; the various Eurasian attitudes toward human waste; regional patterns in the use or nonuse of human excreta in early agriculture; and early urban sanitation.

Chapter 3, "Diffusion and Amplification," discusses the long era in which pathogens and parasites were extended to new regions. As human

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communities became more complex, networks of trade expanded and became denser, allowing for the rapid, long-distance transmission of intestinal pathogens. Over the first millennium and a half of the Common Era, the disease pool of Eurasia and northern Africa became increasingly integrated. In the late fifteenth century, some Old World intestinal pathogens crossed the Atlantic and became established in the Americas. By the early nineteenth century, the integration had become global. Rapid urbanization in the industrializing North Atlantic states created a crisis of urban fecal pollution. In response, the first public health reform movements emerged. Beginning in the first half of the nineteenth century, cholera pandemics spread along global trade routes and infected all the inhabited continents. This provoked the first efforts at the international control of disease.

Chapter 4, "Innovations," discusses the environmental challenges in a rapidly urbanizing London, the capital of the largest empire of the modern period. It explores the early innovations in dealing with excreta disposal, including the creation of an underground sewer system and efforts to use the highly dilute sewer effluvia as fertilizer. The direct health benefits of modern sewerage alone were modest. Many smaller and less wealthy cities and towns opted for other methods of human waste disposal, including the tub-and-pail system. Much infectious intestinal disease was the result of pathogen-laden flies alighting on food and the contamination of the urban milk supply. The major reductions in mortality and morbidity from intestinal pathogens came about as a result of the filtration and chemical treatment of drinking water with chlorine or ozonation.

Chapter 5, "Adoptions and Adaptations," explores the evidence for the adoption of modern sewerage and water purification systems beyond the early centers in northern Europe and North America. The principal constraints to adoption of modern sanitation were fiscal, although ecological, political, and cultural forces also played large roles. The overall result was that the sanitation revolution beyond the North Atlantic was adopted piecemeal and that the benefits were generally concentrated in the core urban areas inhabited by those with political and economic power. Into the mid-twentieth century, the flush toilet and the disposal of human waste via water carriage made little impact on the overall problem of excreta disposal, and even the provision of piped water was generally limited to the cities and large towns in which Europeans, local elites of European ancestry, and/or non-European elites had an authoritative presence.

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Chapter 6, "The Struggle against Hookworm Disease," examines the early campaigns of the Rockefeller Foundation to reduce transmission of the widespread helminthic infection. Launched in the southern United States and then extended southward in the western hemisphere and into the eastern hemisphere, the anti-hookworm campaigns became the very first global health initiative. Although the campaigns utilized chemical therapies to reduce the intestinal worm load, their primary focus was on changing defecation habits to encourage better sanitation. The campaigns failed to meet their goals, underscoring the limitations of mass drug treatment and the difficulties of changing entrenched defecation practices and the use of human waste as fertilizer.

Chapter 7, "An Era of Optimism," analyzes the new culture of sanitation practices that helped to define modernity. In the late nineteenth and early twentieth centuries, those living in the developed world became accustomed to wearing shoes, using toilet paper, bathing regularly with soap, and utilizing refrigeration systems to extend the life of foods. In the mid-twentieth century, populations in the Global North benefited from population-wide vaccination programs against poliomyelitis, whose prevalence seemed to have increased as a result of the implementation of better sanitation systems. Based on the "hygiene hypothesis," many specialists believed that poliomyelitis was rare in regions without modern sanitation. This was not the case. Regrettably, polio vaccination did not begin in the developing world until the 1970s. Oral rehydration therapy, a major breakthrough in the treatment of diarrheal disease, saved millions of lives.

Chapter 8, "Global Health and Infectious Intestinal Disease," explores the major challenges to and advances in the control of infectious intestinal diseases since 1970s, when new sets of actors took up the crusade against diarrheal diseases. Physicians and activists organized in response to a spike in infant deaths in the Global South linked to bottle-feeding. Nongovernmental agencies and national politicians encouraged behavioral change to end open defecation. Biomedical scientists developed additional vaccines against poliovirus and rotavirus. Epidemiologists threw new light on the global prevalence of diarrheal diseases and regional disparities in childhood survival rates. The new focus on biomedical interventions and programs of community- or national-level behavioral change constituted a new era in the control of infectious intestinal disease.

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1

Pathogens and Parasites

It is a shitty world out there. Many hundreds of millions of people will fall ill this year from infectious intestinal pathogens passed in human feces. Just how many hundreds of thousands will die can only be reckoned roughly. Consider cholera. The World Health Organization estimates that most cholera outbreaks are not detected by public health agencies and that the officially reported cases of cholera probably represent 5 to 10 percent of the actual number of cases worldwide. Their experts guess at 2.8 million cases of cholera every year and an estimated 91,000 deaths, of which approximately half occur in children under the age of five years.[1] Typhoid fever probably afflicts annually more than 20 million, of which about a quarter of a million die.[2] Shigella infections take the lives of more than 200,00.[3] Each year, children suffer around 1.7 billion bouts of diarrheal disease from mostly undetermined causes.[4] From these bouts,

[1] Mohammed Ali, Anna Lena Lopez, Young Ae You, Young Eun Kim, Binod Sah, Brian Maskery, and John Clemens, "The Global Burden of Cholera," *Bulletin of the World Health Organization*, vol. 90 (2012), 209, 214.

[2] www.who.int/immunization/diseases/typhoid/en/.

[3] Ibrahim A. Khalil, Christopher Troeger, Brigette F. Blacker, Puja C. Rao, Alexandria Brown, Deborah E. Atherly, Thomas G. Brewer et al. "Morbidity and Mortality due to Shigella and Enterotoxigenic Escherichia coli Diarrhoea: the Global Burden of Disease Study 1990–2016," *Lancet Infectious Diseases*, vol. 18, no. 11 (2018), 1229–40.

[4] The burden of novel pathogenic agents that have yet to be discovered is high. Case studies of diarrheal illness in young children from low-income countries have determined that in fewer than 50 percent of the cases could researchers find any known pathogenic agents. Mihai Pop, Alan W. Walker, Joseph Paulson, Brianna Lindsay, Martin Antonio, M. Anowar Hossain, Joseph Oundo et al., "Diarrhea in Young Children from Low-Income Countries Leads to Large-Scale Alterations in Intestinal

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more than a half a million children under five years of age die.[5] The number of deaths is appallingly high, yet it represents a major decline from just a generation ago, when the annual diarrheal death toll was estimated at more than 3 million.[6]

The pathogens that cause these illnesses and deaths are passed in human waste. When microscopically tiny particles of fecal matter contaminate hands, serving vessels, bowls, plates, tableware, liquids, or foods, the pathogenic agents – whether viruses, bacteria, or protozoa – travel to our intestines through the digestive tract. There, they disrupt the functioning of our guts, the incredibly complex universe known as the human microbiome. Another set of infections is caused by parasitic intestinal worms. In small numbers, some worms seem to contribute to the well-functioning of our immune systems, but in larger numbers, the same worms cause illness and, in rare cases, death. We can also become sick from contact with the fecal matter of wild or domesticated animals, but these infections are a relatively minor part of the story. Human beings transmit to each other the major infections that wreak illness and death. We are our own worst enemies.

INTESTINAL VIRUSES, PROTOZOA, AND BACTERIA

Five intestinal viruses are particularly dangerous to human health: poliovirus, hepatitis A, hepatitis E, rotavirus, and norovirus. They are passed virtually exclusively by human beings to other human beings, and their range has been global. Immunization campaigns against poliovirus, which can cause muscular paralysis and, in rare cases, death, have been highly successful and have reduced the number of new poliovirus infections to twenty-two in 2017. Hepatitis A and hepatitis E attack the liver and remain global menaces. There are effective vaccines against both, but

Microbiota Composition," *Genome Biology*, vol. 15, no. 6 (2014), R76. http://genomebiology.com/2014/15/6/R76.

For estimates of the impacts of the known intestinal pathogens, see Christopher Troeger, Mohammad Forouzanfar, Puja C. Rao, Ibrahim Khalil, Alexandria Brown, Robert C. Reiner Jr, Nancy Fullman et al., "Estimates of Global, Regional, and National Morbidity, Mortality, and Aetiologies of Diarrhoeal Diseases: A Systematic Analysis for the Global Burden of Disease Study 2015," *Lancet Infectious Diseases*, vol. 17, no. 9 (2017), 909–48.

[5] www.who.int/mediacentre/factsheets/fs330/en/.

[6] C. Bern, J. Martines, I. de Zoysa, and R. I. Glass, "The Magnitude of the Global Problem of Diarrhoeal Disease: A Ten-Year Update," *Bulletin of the World Health Organization*, vol. 70, no. 6 (1992), 705–14.

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the public health systems are too weak in many countries to allow for population-level coverage. There are thought to be about 114 million infections of hepatitis A and 20 million infections of hepatitis E every year, although most cases are asymptomatic. More than 1 percent of those annually infected with hepatitis A (about 1.4 million people) and more than 15 percent of those afflicted with hepatitis E (about 3.3 million people) experience the characteristic symptoms of dark urine, jaundice, and extreme weakness. Those who recover from hepatitis A are immune to reinfection. There are multiple genotypes of hepatitis E, however, and the extent to which survivors enjoy any degree of protective immunity has not been determined. A high percentage of the population in the Global North is potentially susceptible because of the low levels of endemic transmission. In the Global South, virtually all adolescents and adults have been exposed to hepatitis A, and new cases are found almost exclusively among the young.[7] Hepatitis E affects a broader spectrum of the population and is a particular threat to adults with compromised immune systems.[8]

By contrast, until the first decade of the twenty-first century, rotavirus infections were nearly universal. Before the rollout of a vaccine in 2006, rotavirus infected virtually all children in the United States before their fifth birthday. Rotavirus continues to infect unvaccinated children around the world and kills 200,000 each year. Rotavirus transmission is principally via fomites, that is, surfaces on which we inadvertently deposit invisibly small viral particles from fecal matter, which are then inadvertently picked up by others. In the developed world, children's toys, doorknobs, and shared tableware are the usual culprits.[9] Norovirus is also a very bad actor, and because there is no vaccine, its prevalence is roughly equivalent to rotavirus earlier in the century. It is responsible for about 20 percent of all cases of diarrhea and vomiting in the United States. Indeed, norovirus is the leading cause of severe gastroenteritis worldwide.

[7] K. H. Jacobsen and S. T. Wiersma, "Hepatitis A Seroprevalence by Age and World Region, 1990 and 2005," *Vaccine*, vol. 28, no. 41 (2010), 6653–7. doi:10.1016/j.vaccine.2010.08.037.

[8] Lisa J. Krain, Kenrad E. Nelson, and Alain B. Labrique, "Host Immune Status and Response to Hepatitis E Virus Infection," *Clinical Microbiology Reviews*, vol. 27, no. 1 (2014), 139–65.

[9] Jacqueline E. Tate, Anthony H. Burton, Cynthia Boschi-Pinto, Umesh D. Parashar, World Health Organization–Coordinated Global Rotavirus Surveillance Network, Mary Agocs, Fatima Serhan et al., "Global, Regional, and National Estimates of Rotavirus Mortality in Children < 5 Years of Age, 2000–2013," *Clinical Infectious Diseases*, vol. 62, suppl. 2 (2016), S96–105.

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It spreads when we ingest food and water contaminated with microscopically small specs of fecal matter.[10]

There are two major protozoa that infect the human intestinal tract: *Giardia lamblia* and *Entamoeba histolytica*.[11] These infections are infrequent in the developed world. They are introduced to humans via contamination from the feces and urine of other animals, such as dogs, cats, birds, sheep, deer, beaver, and cattle.[12] Hikers in remote areas who drink from streams and rivers are particularly at risk. Both protozoal intestinal infections produce diarrhea (and in the case of *Giardia lamblia*, sometimes severe constipation), but they are generally cleared within a matter of days or, at most, weeks. In the rural areas of the less developed world, these protozoal intestinal infections are common. The rural water supplies are frequently contaminated because human beings get their water from the same sources as do domesticated and wild animals. In many regions, the chains of infection are nearly continuous. Giardiasis is the most common cause of parasitic diarrhea in the world, although it does not kill. Amoebiasis from *Entamoeba histolytica* (also known as amoebic dysentery), however, is also widely distributed and causes about 50 million cases of diarrhea per year and kills about 100,000 people. It can be particularly destructive to the intestinal walls and open the gates to other infectious diseases.

Bacterial intestinal infections have been among the deadliest scourges of humankind. Two infections have killed large numbers of adults: typhoid fever (*Salmonella typhi* and *Salmonella paratyphi*) and cholera (*Vibrio cholerae*). Typhoid fever could exact a toll on the order of a 10–30 percent case fatality rate. It typically involved the passage of the bacteria from the intestine into the blood, producing sepsis. Cholera was even deadlier, with a case fatality rate that could reach 50 percent. Untreated cholera typically killed via severe diarrhea, which led to fatal dehydration.[13] A large number of additional pathogens could kill infants

[10] Sharia M. Ahmed, Aron J. Hall, Anne E. Robinson, Linda Verhoef, Prasanna Premkumar, Umesh D. Parashar, Marion Koopmans, and Benjamin A. Lopman, "Global Prevalence of Norovirus in Cases of Gastroenteritis: A Systematic Review and Meta-analysis," *Lancet Infectious Diseases*, vol. 14, no. 8 (2014), 725–30.

[11] Protozoa are similar to bacteria in that they are single celled, but they behave more like animals in that they typically have a sexual stage to their reproduction, whereas bacteria reproduce asexually.

[12] In the system of classification proposed by Thomas Cavalier-Smith, *G. lamblia* would be considered a member of the Archaea kingdom, rather than the Protozoa.

[13] The poor were particularly susceptible to infection by cholera and typhoid because many suffered from undernutrition, which is accompanied by low gastric acid activity in the

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and young children whose immune systems were not fully developed. Even common, run-of-the-mill *E. coli* infections could pull into the grave infants and small children who were already weakened by malnutrition and/or other infections. They robbed the body of fluids and nutrients, causing severe diarrhea, dehydration, and, ultimately, death.

Today, typhoid fever, cholera, and amoebic dysentery are rare in communities that disinfect their water supplies with chlorine or ozone and maintain the physical integrity of the water delivery systems, from the reservoir to the tap. Even with this broad public health success, occasionally some bacterial pathogens, such as variants of *Escherichia coli, S. enterica,* and *Campylobacter,* enter the food supply and cause outbreaks of diarrheal disease and vomiting. But these are generally small-scale events that are easily contained, unless the local water supply system has become contaminated. For those who fall ill, the results are highly unpleasant but only temporarily debilitating, except in the case of the elderly and those with compromised immune systems, who are at greater risk for more serious consequences. The relative infrequency of bacterial infections is a positive reflection of our safe water treatment systems and our relatively high nutritional status. If bacterial pathogens are introduced only occasionally and the host's immune system is competent, the host is able to clear the infection and, generally, to kill or expel the pathogen. In the developed world, the risk of death from a bacterial pathogen is very low.

INTESTINAL WORMS

The final group of unwelcome visitors to the human intestinal tract comprises intestinal worms known as helminths. Some of the worms attach themselves to the linings of the human intestines and draw their nourishment by sucking blood from their hosts. Most live from nutrients available in the intestinal tract. Some helminths, such as tapeworms and pinworms, are of minor public health significance. They spread via infinitesimally small eggs passed in human feces. The tapeworm eggs are ingested by cattle (*Taenia saginata*) or pigs (*T. solium* and *T. asiatica*),

stomach. This is one of the first lines of biological defense against *V. cholerae*, and normal gastric acid activity reduces the chances of the bacteria surviving its journey through the stomach to the small intestine. On the role of poverty and undernutrition in explaining the higher historical vulnerability of people of African descent in the Caribbean to cholera, see Kenneth F. Kiple, "Cholera and Race in the Caribbean," *Journal of Latin American Studies*, vol. 17, no. 1 (1985), 157–77.

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where they develop into larvae, known as cysticerci, in the musculature of the animals and then are transferred to human beings who eat undercooked beef or pork, in which the taenia larvae survive. Once ingested, the cysticerci develop into adult tapeworms in the human intestine.[14] The pinworms (*Enterobius vermicularis* and *E. gregorii*) do not have a nonhuman host. They release tiny eggs that are deposited in tiny folds in the human anus, which becomes irritated and demands to be scratched. Sufferers from pinworm can then inadvertently transfer the eggs from hand to mouth, and once ingested, the cycle continues. It is also possible to transmit pinworm eggs via fomites – clothing, utensils, furniture, or other surfaces on which pathogens and parasites can survive – and a small proportion of the tiny eggs may become airborne and make their way to a human mouth and be inadvertently swallowed. They are remarkably common even in the developed world. An estimated 20 percent of the people in the United States will acquire a pinworm infection at some point in life.[15]

Far and away, however, the biggest intestinal worm challenges in global health are from a category known as soil-transmitted helminths (S-THs). A major difference is that the tiny eggs of the soil-transmitted helminths, after being passed through human feces, must mature in the soil. The three major S-THs are roundworms, whipworms, and hookworms. They are far and away most common of all the intestinal worms, and today they have a global distribution centered on the tropics and subtropics. The roundworms live from nutrients in the intestines. The hookworms and whipworms attach themselves to the human intestinal walls, where they grow to maturity, feeding upon human blood.

Researchers agree that roundworms, whipworms, and hookworms produce a large, global burden of disease. The difficulties in estimating the extent of the disease burdens are very considerable, because the data are not comprehensive or fully reliable. What seems clear, however, is that the likely total number of global deaths caused by complications from soil-transmitted helminths would be relatively small in comparison to the mortality caused by bacterial, protozoal, and viral infections.[16]

[14] It is also possible for human beings inadvertently to ingest *Taenia* eggs and host the development of the larvae in human tissues, such as the lung, liver, or brain.

[15] Edy Stermer, Igor Sukhotnic, and Ron Shaoul, "Pruritus Ani: An Approach to an Itching Condition," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 48, no. 5 (2009), 513–16.

[16] Simon Brooker, "Estimating the Global Distribution and Disease Burden of Intestinal Nematode Infections: Adding Up the Numbers – A Review," *International Journal of Parasitology*, vol. 40, no. 10 (2010), 1137–44.

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