

SLAYING THE TRAVELER'S DEMON

Battling the Military's Most Ancient Foe by Nurturing Gut Bacteria

Abstract

It isn't just bullets or rockets that soldiers, sailors, Marines and airmen must contend with when they deploy. Often, it's their own guts that wind up taking them out of service. As any medic knows, the afflictions that are responsible for huge amounts of unexpected downtime target the GI tract. But over the last few years, an expeditionary unit of researchers at the Natick Soldier Systems Center, have been working to prevent the GI illnesses that can cripple a fighting force. They have gone deep into a world that few care to think about: the trillions of bacteria, collectively called the human gut microbiome, that call our intestines home.

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Slaying the 'Traveler's Demon

Battling the Military's Most Ancient Foe by Nurturing Gut Bacteria

To the U.S. Army leaders of Logistics Support Area-Anaconda in Balad, Iraq, the local sheikh's lunch invite was an opportunity they knew they couldn't pass up. It was May 2003. The U.S. invasion of Iraq codenamed Operation Iraqi Freedom was only months old. Maj. David Accetta, a public affairs officer at Anaconda, joined the facility's commanding general, command sergeant major and seven other staff for the meeting. They wanted a better understanding of the area's political and socioeconomic landscape, and how best to work with Iraqis to reestablish their government after it fell.

These were trained Army officers, so they knew that eating and drinking local offerings could be playing with gastrointestinal (GI) fire. But this influential local leader was their key in. So they stood with him and his consort around a table to break bread together.

A large platter of goat, vegetables and rice was served. No silverware was offered. Instead, the local custom was for everyone to grasp the food they wanted from the communal platter with their right hand, place it in their left hand and eat from there. "We weren't sure what to expect and we didn't want to insult our host, so we ate," says Accetta, who is now a retired lieutenant colonel.

His concerns eased when he saw bottled water being served—a source of hydration that is filtered and sanitized of pathogens at a bottling plant.

"I thought we might be ok because of that and since all the food was cooked. But then I watched the server take one of the empty water bottles, bring it back to the kitchen and refill it straight from the faucet," he says. "I knew we were going to be sick."

It doesn't take a microbiology degree for anyone who's been to a developing part of the world to know that his conjecture was more than a hunch. More than 60 percent of travelers to developing countries will come down with a condition called traveler's diarrhea every year, according to a study in the *Clinical Infectious Diseases* journal. That's up to 20 million people annually who succumb to three or more unformed bowel movements and associated symptoms of vomiting, fever and cramps from GI-attacking pathogens endemic to developing countries.

"The next day, we were all off our feet," says Accetta, who currently works as public affairs chief for the U.S. Army Natick Soldier Research, Development & Engineering Center (NSRDEC) in Natick, Massachusetts. All told, 10 people were laid up for as much as a few days in the aftermath of that lunch.

"The general's driver was so sick, he couldn't get off his cot, even to go to the bathroom. He made a mess on himself he was so sick," Accetta says.

Anaconda's top leadership wasn't fit to get off the toilet, let alone run one of the U.S. military's biggest operations in Iraq.

At that delicate point of the invasion, more than 10,000 service members and contractors were taking their orders from the general commanding Anaconda's operations. The facility supplied materiel, food, and other critical goods warfighters needed, all moving based on the general's changing threat assessments and orders.

“Having him and the rest of the senior leadership of the Army’s logistics effort out of commission is not something that you want to happen,” Accetta says.

Confronting a Common Enemy with Longtime Friends

The experience endured by Accetta and his team is far from abnormal. A trip to the developing world for military service or even a short vacation often involves an unwanted encounter—getting sick from bacteria or other pathogens in food or water.

It isn’t just bullets or rockets that soldiers, sailors, Marines and airmen must contend with when they deploy. Often, it’s their own guts that wind up taking them out of service. As any medic knows, the afflictions that are responsible for huge amounts of unexpected downtime target the GI tract. Everyone gets exposed to illness-causing bacteria, viruses or other microbes through the food they eat or water they drink at some point. And the infection that follows can be debilitating.

Traveler’s diarrhea. GI distress. The runs. Different names for the same thing, which can seriously affect the readiness of a fighting force no matter what you call it.

Diarrhea accounted for a staggering 18 percent of all hospital admissions at one U.S. Army medical facility from October 2013 to June 2014 during Operation Iraqi Freedom, according to a study recounted in a review article published in *The American Journal of Tropical Medicine and Hygiene*.²

The article’s authors also pointed to an analysis of 5,000 medical records from a British field hospital during the first year of military operations in Southern Iraq. That study found that gastroenteritis, the inflammation of the stomach and GI tract resulting from infectious diarrhea, accounted for 31 percent of admissions, the leading reason people reported to hospital.

“Infectious diarrhea has been among the most common maladies of military deployments throughout time,” according to the study. There are “remarkable similarities in the prevalence” of this type of infection between current conflicts and World War II, despite the false perception that militaries have become better at preventing outbreaks.

But over the last few years, an expeditionary unit of researchers at the Natick Soldier Systems Center, has been working to prevent the GI illnesses that can cripple a fighting force. They have gone deep into a world that few care to think about: the trillions of bacteria, collectively called the human gut microbiome, that call our intestines home. The center’s team, composed of scientists working in the NSRDEC and the U.S. Army Research Institute of Environmental Medicine (USARIEM), is one of a few organizing around the Department of Defense looking to reduce the impact of infectious diarrhea.

Many institutions around the world are pulling back the veil on the intricate relationships between our microbes and our health. The work at Natick is looking to apply this newfound knowledge to improve the health and performance of warfighters who operate under unique conditions that can cause injury to the gut ecosystem’s delicate balance.

Their goal is to maintain or augment soldiers’ gut microbes in times of high stress, little sleep and

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4703254/>

extreme exercise, factors that are now thought to harm each person's natural balance of flora. And in several years their work could lead to a prophylactic, food-based intervention that strengthens the body's own microbiome so that it can better fend off disruptions caused by foreign invaders.

Microbes Married To Us

About 40 minutes' drive west of Boston, on a spit of land that juts into a lake surrounding it on three sides, a campus of about a dozen buildings sits quietly amid tree-lined streets and broad parking lots. Inside, the dispersed labs and offices of the Natick human microbiome study group hold biologists, chemists, engineers and nutritionists trying to understand the complex relationship between human health and an average of around 1,000 species of bacteria, fungi and viruses that live in our intestines. It's no small task they've set for themselves: There are about 10 times as many microbial cells in and on the body as there are in human cells. And 90 percent of the estimated 39 trillion bacteria inside humans live within our large intestines. Each of these interacts with one other and our bodies in myriad ways.

These foreign organisms are critical for human health and well being. Certainly, if they find their way into the wrong place, they can cause potentially deadly infections. But when safely ensconced inside the tubular passageway of our intestines, they're busy helping us survive. There they create an intricate ecosystem that breaks down foods into useful nutrients our bodies alone could not digest. They also fend off invading microbes that can cause infection.

"We have co-evolved with these organisms," says J. Philip Karl, a USARIEM nutrition scientist who leads part of Natick's microbiome effort. "Our bodies have developed ways to work with them. We provide a place to live and ask them to do things for us like fighting off bad bacteria and producing metabolites that are useful to us."

But this relationship is complex and delicate. Human guts don't like change and have evolved to move only relatively short distances over a lifetime. They're not built for modern global travel, military or civilian. The human body doesn't come equipped to recognize and fight off microbes that are different depending on where in the world it is. That's why a cup of water, innocuous to a local, can lead to debilitating gastrointestinal distress to a visitor.

Many have had the experience of Marine 1st Lt. Mark Bodrog. He describes in his book, *Second Platoon: Call Sign Hades*, how the platoon he led in Afghanistan in 2010 discovered too late that pathogens in the food and water were making them sick⁴.

"Within the first week of occupying [Patrol Base] Brannon, just about every one of my Marines and Navy Corpsmen, including myself, had some type of gastrointestinal parasite or virus that became known as 'the demon,'" he wrote. "It was awful! Constant diarrhea, dehydration, delusions, and vomiting were the common symptoms...When one became stricken with the demon, he was out of commission for 24 to 96 hours and lost at least 15 pounds of body weight."

Mounting evidence shows that healthy gut ecosystems lead to better health outcomes in people with them⁵. Along with helping feed and protect humans from foreign microbes, they work together with the

³ <https://www.scientificamerican.com/article/do-probiotics-really-work/>

⁴ <http://news.rutgers.edu/news/rutgers-graduate-student-pens-memoir-marine-service-afghanistan/20131211>

⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4528021/>

human immune system and help maintain humans' intestinal lining. Meanwhile, studies have linked intestinal flora dominated by certain species with inflammation, obesity and diabetes⁶.

“Our bodies are covered with trillions of microorganisms and we know they matter to our health,” says Karl, who heads volunteer studies meant to uncover how things like high altitude and exercise impact gut health and military performance. “It’s a bidirectional relationship between humans and microbes, and the environment plays a role, too. How does all of this impact warfighter performance?”

Answering this question requires work on numerous fronts. Karl’s research in the USARIEM uses volunteers to uncover associations between the state and composition of a person’s microbiome and their performance and health. Does sleep deprivation, for instance, cause real changes to the makeup of gut microbes? If so, how does that affect their ability to work and fight?

Extreme physical exertion, sleep deprivation and insufficient food intake by test subjects caused as much stress to gut microbes as it did to them physically, according to a recent study⁷ by Karl and his colleagues. The team monitored 73 Norwegian army soldiers as they pushed through an intense cross-country skiing training exercise.

By examining blood, urine and stool samples from the soldiers, they found that gut microbial composition changed over the course of the four-day event. Those changes coincided with an increase in something called intestinal permeability, allowing more intestinal contents to flow into and out of tissue. This situation, also called “gut leakiness,” ups the chances of infection, inflammation and diarrhea.

The study merely demonstrates correlation between stress and microbiome impact, Karl says. The next step is to put volunteers through a sleep deprivation experiment to see how that stress impacts intestinal permeability, and hopefully expand understanding about interactions between human hosts and the microbes they harbor. But it’s just the beginning. Ultimately, the goal is to establish how microbiome species impact human health and create real interventions that will help people.

It’s a challenge Karl is up for.

His passion is trying to decipher the complicated ways our bodies interact with the organisms living within us. It’s a calling that took root during his years pursuing a doctorate in biochemical and molecular nutrition at Tufts University. The Department of Defense saw his potential and the promise of his cutting-edge work, so he was awarded a prestigious Science, Mathematics and Research for Transformation (SMART) Scholarship. The program paid for his degree and guaranteed work after graduation. “I just found it so fascinating,” he says. “It’s so complex and difficult. I am amazed at how these tiny organisms can have such a huge impact on our health.”

“The Ice Cream Sandwich Experiment”

The NSRDEC’s researchers are laboring to translate studies like Karl’s into food-based products that can counter the negative effects of travel, exertion and other stresses. It’s work they’ve been

⁷ <http://ajpgi.physiology.org/content/312/6/G559>

⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4912704/>

chasing for several years. One member of the team, NSRDEC nutritional biochemist Ken Racicot, recalls one such effort.

Racicot leads the NSRDEC's performance nutrition team, which develops foods and feeding strategies to boost the physical and cognitive capabilities of service members. Over the years he's been studying Army personnel, he's found that many favor junk foods that offer fewer nutrients and components like soluble fiber that gut organisms prefer to eat. "If you advertise that something is good for them, they'll often prejudge it and won't choose it," he says.

He's been working on food technology at NSRDEC for 17 years and considers his effort part of a personal mission. Though he never served in the military, his brother Richard was a proud Marine. Now, his research to help keep warfighters healthy and from experiencing GI problems is in honor of Richard and, he says, his way to contribute.

"I do it for him—that's my motivation every day," Racicot says. "It's what I can do. It's my part I can play."

A former chef, he says that food and nutrition are fascinating for him, and understanding how these play into performance is the challenge of his life. So in 2007, he and his colleagues tried integrating beneficial gut microbes, often generally labeled probiotics on supermarket and pharmacy shelves, into the kinds of foods personnel do like to eat.

His team sprinkled bacteria commonly found in the gut, like species in the genus *Lactobacillus*, into ice cream. Giant steel vats sit next to mixers and other kitchen and packaging equipment in the first-floor food production room of the Combat Feeding Directorate's nondescript Building 36. On any day, the smell of different types of cooking food wafts through the cavernous area. Using some of this equipment, they turned the probiotic ice cream into freeze-dried ice cream sandwiches. They also mixed a batch of power bars with the probiotics in them.

They took a small development batch of a couple hundred of the dried desserts and subjected them to shelf life tests, eventually finding that the live cultured organisms rapidly degraded after about a year. That's not good enough for something like the famous Meal, Ready to Eat, or MRE, which is designed to be shelf-stable and nutritious for up to three years.

Further testing showed that the microbes that did survive the freeze-drying and shelving process were weakened to the point that they could not survive inside the highly competitive world of the human gut ecosystem. The microbes inside the power bars showed only marginally better resilience. "That helped us conclude that probiotics aren't going to work in rations, at least not as the technology now stands," Racicot says.

His team is now focusing on prebiotics, ingredients like certain types of plant fiber that are indigestible to us but that our gut microbes like to eat and thrive on. They already know that different foods cause the microbiome to change and adapt. Eat a diet free of plant-based foods for a day and this will temporarily alter the community. That's their starting point. They think with more experimentation they'll be able to make foods tailored to support gut bacteria stressed with high altitudes, lack of sleep or even cold weather.

"Our approach now is to optimize the food we feed the soldier to better feed their microbes," he says.

Broader Interest Drives Research, But Major Challenges Ahead

Racicot's group is a small one inside the NSRDEC's Combat Feeding Directorate, which develops rations like the MRE and equipment to provide warfighters with the food they need to complete their missions. His lab now focuses on something called host response—how the human interacts with the bacteria inside. Much of its work involves growing intestinal cells, which rub against gut microbes, and determining how the combination responds to the stresses of military deployment.

They keep these cells happy for a while, then “kick them with stressors,” Racicot says.

Their experiments are meant to mimic temporary malnutrition and weight and muscle loss associated with combat deployments. They are now coalescing with other research in the field, which points to physical changes in the intestinal lining during severe stress. One working hypothesis is that “your microbe shifts to start eating you—the mucosal layer of your intestines, which lets all kinds of things in,” he says. “We’re just not sure yet.”

While earlier work wasn't organized under a unifying program, that structure is now just starting to come together. Racicot and Karl, along with NSRDEC colleagues Jason Soares and Steve Arcidiacono, are central figures in launching the Tri-Service Microbiome Consortium, a group composed of researchers across the departments of Defense and Veterans Affairs.

The military's push into this area coincides with rapidly increasing civilian interest and understanding of gut bacteria's role in health. The National Institutes of Health is leading a multimillion-dollar effort by many institutions and researchers to learn how the microbiome affects human health and disease. Mainstream media have drawn public attention to the story and increased awareness about the concept of “good bacteria.” Cultured milk-based products like yogurts and ice creams tout live, active gut bacteria cultures on their packaging. Every hip coffee house has at least one flavor of the fermented drink called kombucha, which is teeming with living microbes.

But unlike the simple connections that advertisers and the media draw between eating a yogurt every morning and good gut health, the reality is, of course, much more complex. With few direct links decoding how exactly the microbiome can impact the host's performance and mental and physical health, there is still a long way to go.

“We really don't know if [human gut microbiome imbalance is] a problem,” says Capt. Mark Riddle, a doctor who is an expert on infectious GI diseases and the Uniformed Services University of the Health Sciences chairman of the Department of Preventive Medicine and Biostatistics. “People's microbiomes are very different and the scientific field does not yet know what's ‘normal’ and what's not normal.”

And, like Racicot's ice cream sandwich experiment, experiments have revealed very little evidence that eating the same bacteria that live in human guts does anything to improve the health of already healthy people.

8 <https://www.facebook.com/notes/us-army-medical-research-materiel-command-usamrme/tri-service-microbiome-consortium-holds-inaugural-workshop/10155442768419612/>

9 <https://www.scientificamerican.com/article/do-probiotics-really-work/>

Still, plenty of clues between these direct connections warrant further study, says Riddle, who is not involved in the microbiome research happening at Natick. Among them—that infections, stress, antibiotics, diet and other factors cause changes to our microbiome. These clues could lead to interventions that help decrease GI-related downtime in deployed personnel.

Now is the time for more research, Riddle says, because “we don’t really have a clear understanding yet of how these changes in microbiome could affect the individual...If mental fitness and cognition (e.g. memory, anxiety, concentration, mood) can be affected by changes in the gut, this should be better understood.”

The Colon on a Bench

That’s one reason why Soares and Arcidiacono are testing how different ingredients affect actual gut microbes in their labs. They’re trying to isolate direct causal relationships between human bacteria and us—feed oats, for example, to a sample of gut microbes and watch how their composition changes. What parts of the oat get broken down by the organisms and what type of metabolic products does that breakdown create? And perhaps the most important question—what changes do those metabolic products cause to human systems?

Outside the locked doors of a row of laboratories on the third floor, overhead air conditioning whirs loudly above exposed water and gas pipes that crisscross the ceiling. Shoes squeak on the hallway’s gray-white linoleum tiles as lab technicians and researchers come and go. The walls are covered with electron microscopy images of common food pathogens—*listeria*, *vibrio*, *salmonella*—the agents of danger hidden in improperly kept rations.

No odor emanates from Soares and Arcidiacono’s lab. A nod to the possible is almost immediately obvious: two plush “Smiling Poop” emoji dolls sitting above a fume hood in the main room, like clocks on a fireplace mantle, a gift from Arcidiacono’s wife.

“Our wives are poop-work deniers in mixed company, but they’re also poop-work enablers,” Arcidiacono says, jokingly. He and Soares analyze the fecal samples generated during Karl’s human studies to characterize the microbial communities living inside the volunteers. They’ve also become accustomed to the noxious smells generated by gut bacteria—compounds like skatole, indole and methyl and hydrogen sulfides. There’s no shortage of poop jokes in their lab.

A door next to the hood leads into another part of the lab, where two clear plastic benchtop tents maintain oxygen-free environments to preserve the samples by simulating the intestines inhabited by gut bacteria. In the next room, light streams in from large windows, illuminating various steel vessels that sit on the floor, valves and tubes protruding at odd angles.

Against the far wall, the team has built a marvel: a gigantic large intestine.

This labyrinthine contraption, which took three years to build, might be the only one of its kind throughout Defense Department labs, and it is the team’s pride and joy. Other researchers, like those from the University of Rhode Island who are collaborating on the current pomegranate and maple syrup study, come calling to have it digest their foods of interest to see what comes out the other side. The uniqueness of the machine isn’t lost on one of Soares’s colleagues, chemical engineer Laurel Doherty,

who was instrumental in producing it and now has visions of expanding its capabilities. “We’ve created a model of the colon, but that’s only one part of the human microbiome,” she says. “I want to take everything we’ve learned over the last three years to also model the microbiome of the small intestine.”

Most biomedical researchers looking to create facsimiles of human organs for drug testing and research generally strive for miniaturization. Current microfluidic devices called organs-on-a-chip can mimic the activity of a heart, a kidney or even a whole physiological system. 3-D bioprinting is leading to bespoke production of tiny organs or synthetic tissue samples for research.

Soares, Arcidiacono and their team have gone the other direction, expanding the large intestine that is home to most of the bacteria living in the body into a unit several feet wide and a couple feet high.

The system of glass labware, pumps, controllers and tubes spans half the length of the wall. It’s lovingly manipulated by Doherty. She positions multi-port caps onto the last of eight bioreactor flasks. Probes and liquids pass through the ports into a brown liquid within that’s designed to mimic the nutrients, temperature and anaerobic environment of the colon.

The team prepares to inject bacteria isolated from volunteer fecal samples into the portals. The microbiome live in a “ferment,” growing and dividing until they’re ready to be tested, Soares says. In this trial, Doherty and Soares will introduce three different ingredients—maple syrup, pomegranate, and ellagic acid, which is a purified component of pomegranate that can be useful against diabetes—to see how each is broken down by the artificial colon over time. “This is all about understanding these gut bacteria and how they react to stress,” Soares says.

Soares’s interest in what stresses the bacteria is an idea that keeps coming up with these researchers. They think that the extreme stresses experienced by deployed military personnel—days of sleep deprivation, intense physical exercise, the psychological burden of combat, and just switching to a diet of packaged rations—eventually impacts our microbes.

A Long Road To A Gut-Healthy Ice Cream Sandwich

The team says their work could take a decade or two to translate into products that help warfighters maintain a strong and healthy gut microbiota that makes them more resistant to GI infections like those that cause traveler’s diarrhea.

The space between now and then will be filled with designing new lab and field experiments to make sense of what’s going on inside the gut. Inevitably, it will also be filled with freezers full of volunteer feces to test and massive amounts of data generated from it all.

“If we’re merely preventing a decrement—traveler’s diarrhea or muscle loss due to malnutrition during multiday expeditionary-type work because people don’t eat enough—that’s a win,” Racicot says. “But that’s just maintaining the individual and the microbiome.”

Looking beyond the prevention of GI infections, Racicot says he envisions soldiers banking samples of their own fecal microbiome, as sort of a vaccine to ingest or perhaps insert as a suppository before going into situations that will impact their bodies. These could help shield and support their guts while enduring the rigors of sleeplessness, stress, fatigue and living on rations.

Karl, meanwhile, says he is captivated by the remote possibility of a specialty pill cocktail consisting of modified gut microbes that give soldiers the ability to live off the land—eating and digesting bark and grass for energy when necessary in survival situations. And Arcidiacono says he thinks it’s possible to genetically engineer gut organisms to live within the ecosystem and detect the intrusion of new pathogenic microbes, producing special metabolites to fight them off.

There are lots of ways to enhance the warfighter, Racicot says. “How can gut bacteria improve performance so they can drink the water and eat local food? If you’re on a march for 10 days, how can we improve the microbiome to decrease how much food you need to get by?” These are questions nobody else is asking outside of the DoD.”

Theater-wide strengthened gut microbiomes could alter the most fundamental aspects of putting a force in the field—decreasing dangerously exposed and fragile supply lines needed to transport food and potable water.

Solutions might prevent a bunch of misery for the deployed infantry soldier slogging down a sun-bleached trail all the way up to the general directing combat or logistics operations for tens of thousands of warfighters. Whether the microbiome-strengthening answers come from Natick or one of the other department labs could keep service members and their leadership from being laid out and cot-bound when they’re needed most.

Down the road, Natick’s microbiome research could help broader society, and contribute to the next generation of self-sufficient, optimized warfighter. All microbiome researchers need is time, funding, good luck and more samples of poop.

If they can crack the microbiome’s code, they might be able to engineer a prophylactic that Anaconda’s Accetta could only dream about when he was woken up in the middle of the night by a severe stomach flu. With cramps and diarrhea already starting, he stumbled out into the dark to find the camp’s nearest wooden outhouse with a metal drum underneath.

“It wasn’t like home where you could just go out to the pharmacy,” he says. “This was not a pleasant place to have this kind of GI distress.”

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