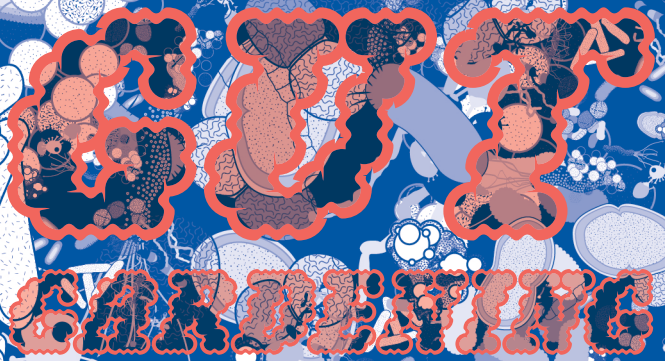
ISSN 2372-6504

GUT GARDENING

FOOD PHREAKING

ISSUE 03

FOOD PHREAKING



ISSUE 03

PREFACE

FOOD PHREAKING: issue 03

Food Phreaking is a publication of experiments, exploits, and explorations of the human food system. It aims to connect farmers, foodies, hackers, artists, and scientists. Food Phreaking is where food, technology, and open culture meet.

This issue explores some of the bacteria that populate the human gut and body. We asked a handful of the world's leading experts to write a few words about their favorite microorganism, and we asked other contributors to reflect on their current relationship to the largely invisible and undiscovered world of the human microbiome.

Food Phreaking Issue 03 assembles these short texts, which collectively provide a snapshot of a field in transition. How will this research into the mysteries of our internal ecosystems change the relationship between our brains, guts, and diets? We think this issue will become more valuable each year in reminding us of the hype, hope, and ignorance we had back in 2016. Enjoy!

CONTENTS

INTRO

In this issue of Food Phreaking we turn our attention to the microorganisms that inhabit our bodies and our bellies, collectively known as the human microbiome. What does the human microbiome have to do with Food Phreaking? Food Phreaking is the journal of experiments, exploits and explorations of the human food system. Research into the human gut microbiome has the potential to restructure the human food system; fundamentally changing the way we grow, breed, prepare and consume food. We may all become Gut Gardeners.

There are over seven billion human guts on the planet, and trillions of microorganisms living in each one. Each human gut is a crucial, but mostly invisible, node in the global food system, and we are only just starting to learn how to explore and experiment with them. For this publication we got to know the bacteria in our guts through small talk—the basic questions: What is your name? What do you do? It's as if we'd just met a close family member whose existence was previously unknown.

Barely a decade after Joshua Lederberg, a Nobel Prize-winning biologist, first used the term "microbiome" to refer to the trillions of micro-organisms that reside in and on our bodies, it seems that gut bacteria hold the key to happiness, health, and—at least for the companies who raced to cash in on the resulting probiotic gold rush—wealth. Over the last few years the hype about the human microbiome has exploded in both the scientific and popular press. Early adopters began video blogging Do-It-Yourself (DIY) fecal transplant techniques that had not yet been approved for medical use, while Silicon Valley start-ups promised a future of Cola-flavored genitalia.

We at the Center for Genomic Gastronomy are not immune to this flurry of ideas and hype. To find out more, members of our research team have spent some of their time during the last two years as Artists in Residence at the Rowett Institute of Nutrition and Health, home to one of the largest gut bacteria libraries in the world. While there, we had the privilege of talking to research scientists about their fields of expertise. Dr Wendy Russell and Dr Sylvia Duncan co-edited this publication and helped us track down leading microbiologists to write about their favorite bacteria.

As we began to ask more and more questions about the human microbiome, we were surprised

to hear that scientists in the field also had many unanswered questions—it is a new frontier. It turns out that the human body is as mysterious and unexplored as outer space or the depths of the ocean. What does the microbiome actually contain? What microorganisms are present and what are their relationships to each other and to us? Do they come in peace? Who is in control here? For this issue of Food Phreaking we invited scientific experts and artists to trace the knowns and unknowns of our tiny intestinal microcosms.

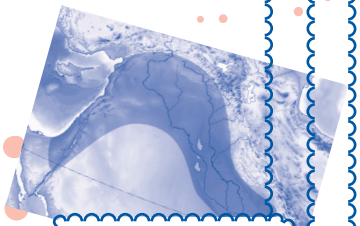
500–1000 species of bacteria live in our guts. But even the 15 species featured in this publication, which are 15 of the most famous human microbiome bacteria in the world, remain shrouded in mystery. On pages 22–52 you can read what the world leading microbiologists DO know about their favorite species of bacteria. There is so much still to be discovered, not just about each individual species, but about how they all interact with each other and with the food we feed them. To read more about these known unknowns, see Dr Wendy Russell's essay on page 54 about Microbial Dark Matter.

And why should we care? Studies are showing that our guts can have a massive impact on our overall well being. Sometimes an imbalance in bacterial communities in the human gut can result in serious pain or even life threatening illnesses, such as *Clostridium difficile*, named after a bacterium of the same name (page 36). For a personal account of what it is like living with Crohn's Disease, another disease that is linked to the gut microbiome, turn to artist Kathy High's essay on page 69.

Since we can potentially modify our microbiome by what we eat (or by administering fecal transplants), the human microbiome is an area that is well suited for self-experimentation and manipulation by the individual. As you will see in our timeline on page 8, humans have a long history of experimenting with and altering our gut microbiomes. We can envision one possible future where hobbyists and experts study and experiment with the human microbiome in a collaborative and transparent way—a future where each of the organisms catalogued here become household names and ideas and research about how we can safely manipulate and manage them is readily shared. In other futures, microbiome research becomes proprietary, overly-commercialized or closed off to amateurs. But one thing is for sure: as we learn more and more about the gut microbiome, we will see a rising trend of what Nicola Twilley calls, 'enterogastronomy' - eating with the gut in mind.

GETTING TO KNOW OUR GUTS

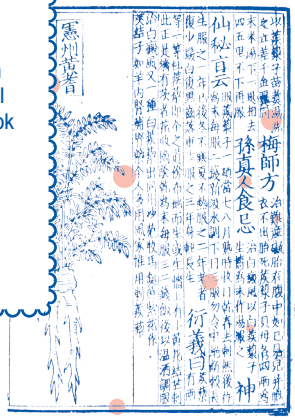
A TIMELINE



6000 BC
Earliest recorded use of fermentation in the Fertile Crescent.

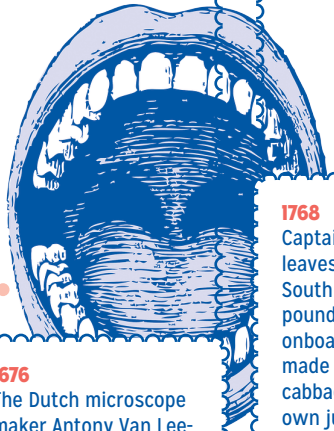
300 AD
In the first Chinese handbook of emergency medicine, alchemist Ge Hong documents the use of orally administered feces to cure food poisoning and severe diarrhea.

1500s
Li Shizhen, an herbologist, acupuncturist, medical doctor, and scientist from the Ming Dynasty era, well known for his scientific book Compendium of Materia Medica (Bencao Gangmu), writes recipe for "Yellow (Dragon) Soup" and other fecal-solution remedies and prescriptions.



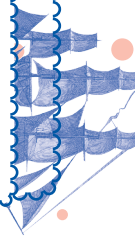
Mid 1500s
Suleiman the Magnificent of Turkey sends a physician to France to prescribe yogurt as a cure for King Francis I's diarrhea.

Late 1500s
The Microscope is invented, finally revealing parts of the microbiological world.

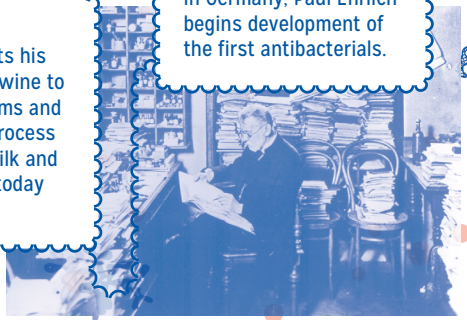


1676
The Dutch microscope maker Antony Van Leeuwenhoek (who came to the trade through a desire to closely inspect fabrics as a draper) writes to the Royal Society in London informing them of his first observations of single-celled organisms, which he scraped from a human mouth.

1768
Captain James Cooke leaves England for the South Pacific with 7,860 pounds of sauerkraut onboard. Sauerkraut is made from thinly sliced cabbage preserved in its own juices. Once fermented, the cabbage can last for over a year. The fermentation process creates vitamin C as a by product of the bacteria digesting the cabbage. Vitamin C prevents and cures scurvy, which at the time was a common disease, killing approximately two million sailors between 1500 and 1800.



1865
Louis Pasteur patents his process for heating wine to kill off microorganisms and fight disease. This process was also used for milk and beer, and is known today as “pasteurization.”



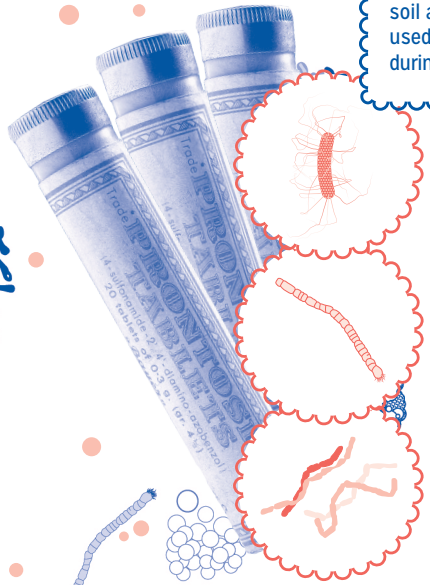
Late 1880s
In Germany, Paul Ehrlich begins development of the first antibacterials.

1907
Elie Metchnikoff hypothesizes that yogurt and other fermented dairy products could add beneficial bacteria to the guts of elderly people, which would aid digestion and maintain bowel health as well as prolonging life. The world of Western medicine had little interest in Metchnikoff’s studies and they went largely unnoticed.

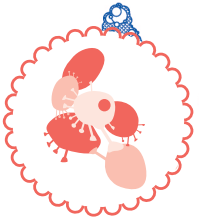
1928
Alexander Fleming discovers Penicillin.

1932
Prontosil, created by Gerhard Domagk at Bayer Laboratories in Germany, becomes the first commercially available antibiotic. In 1939, Domagk receives a Nobel Prize for Medicine.

1939
Tyrothricin, the first naturally made antibiotic, is discovered by the French-American microbiologist Rene Dubos. It was obtained from a bacterium found in soil and was subsequently used to treat patients during World War II.



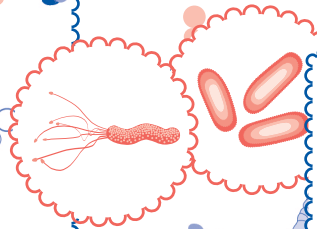
1940
Abraham and Chain observe that a bacterial enzyme can destroy penicillin, an early demonstration of antibiotic resistance.



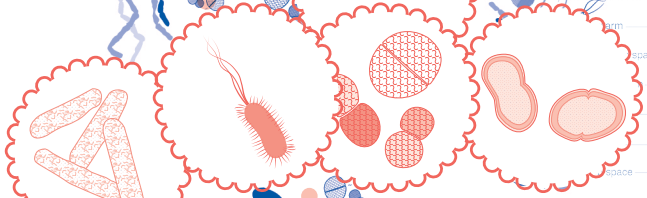
1940s
German soldiers in Africa use the traditional Bedouin method of curing dysentery by consuming fresh camel feces.

1958
The first contemporary report of a Fecal Microbiota Transplant (FMT) is done by Ben Eiseman and a team of surgeons from Colorado, USA.

Though FMT had been used regularly in veterinary practices since the 17th century, this example was the first modern use on a human. It was used to treat inflammation of the large intestine by reducing the presence of *Clostridium difficile colitis* (*C. diff*, for short). *C. diff* is a spore-forming bacterium that can cause inflammation in the gut if it outgrows other gut bacteria. *C. diff* can harm those who suffer from it and can even cause death. The four patients in this experiment were successfully cured.



1985
Carl Woese is credited with initiating the use of 16S rRNA sequencing. This marked the beginning of identifying bacteria by their genomes, which in time became quicker and more cost effective.



1998
A Swedish study shows that the consumption of togwa, a traditional East African fermented gruel made from sorghum or maize, prevents the colonization of diarrhoea-causing pathogens in children.

2008
Recognizing a lack of understanding around the human microbiome, the United States National Institutes of Health (NIH) launches a new initiative called the Human Microbiome Project (HMP). Using DNA sequencing, the project aims to identify all the microorganisms found in and on a healthy or diseased human body.

2011
Rob Knight, a leading microbiome researcher, famously swabs his newborn baby with its mother's vaginal fluid after an emergency c-section, giving the infant the microbial community it would have received through a vaginal birth.

2013
AOBiome launches a line of cosmetic and therapeutic skin microbiome products. The products use beneficial ammonia-oxidizing bacteria (AOB) to alter the skin microbiome and combat acne, eczema, bad skin odor, and more.

2013
In the US and Canada, FMT becomes classified as an Investigational New Drug, preventing doctors and clinics from using it as a treatment for anything other than cases of *C. diff* that have resisted several courses of antibiotics. Those suffering from gut illnesses turn to YouTube as a provider of DIY fecal transplant instructionals.

2014
In an attempt to diversify his own microbiota, Jeff Leach, an anthropologist researching the human microbiome, gives himself a DIY fecal transplant in Tanzania using a turkey baster and a fecal donation from a Hadza tribe member.

2016
The biopharmaceutical startup Synlogic secures $29.4 million in venture capital for the development of synthetic biotics. The aim is to program probiotic bacteria using synthetic DNA or RNA, an engineering approach designed to target infections or boost the immune system via an individual's microbiome.

2016
The White House announces the National Microbiome Initiative (NMI), a nation-wide effort "to foster the integrated study of microbiomes across different ecosystems." Over one hundred external institutions pledged their support and $121 million is raised to fund the first year of the initiative.

2020
A Silicone Valley startup called UProbiotica is brought to court after a series of deaths related to cosmetic microbiome hacking.

2028
Faecal microbiota transfer tourism takes off, and wealthy individuals venture to distant continents in search of exotic poop.

2036
Instead of plastic surgery, aging celebrities become obsessed with "beautifying their insides," publishing weekly readouts of their gut microbiomes.

2049
Biotech devices allow humans to monitor and manage their microbiomes as tiny internal ecosystems.

PHYLUM	GENUS	SPECIES	
Actinobacteria		*Eggerthella lenta*	P.24
		Collinsella aerofaciens	P.27
	Bifidobacteria		P.30
Bacteroidetes	*Prevotella*		P.33
		Bacteriodes dorei	P.34
Firmicutes		*Blautia wexleri*	P.35
		Clostridium difficile	P.36
		Faecalibacterium prausnitzii	P.37
		Ruminococcus bromii	P.40
	Veillonella		P.43
	Anaeroglobus		P.46
		Lactobacillus rhamnosus	P.47
		Staphylococcus aureus	P.50
Proteobacteria		*Helicobacter pylori*	P.51
Verrucomicrobia		*Akkermansia muciniphila*	P.52

Eggerthella lenta

Discovered by Arnold Eggerth in 1935 and famous for metabolizing the cardiac drug digoxin, it is still not well understood and can be both positive and negative for human health.

I am the counter-culture of the human gut microbiome. While most of my friends are scavenging around for sugar, I choose to take the road less traveled. I am on the ultimate low carb diet. My favorite snack is arginine, found in all sorts of proteins. If I can't get enough arginine, I start to get creative, searching for more exotic small molecules.

I'm most famous for metabolizing the cardiac drug digoxin and interfering with its ability to prevent heart failure and irregular heartbeat, but that's just scratching the surface. I can also transform bile acids, which help digest fat. If I'm in a good mood, I can be helpful, boosting the anti-cancer effects of veggies and seeds. But I also have a nasty streak. Sometimes I invade the bloodstream, wreaking havoc.

Some people think I might even cause type 2 diabetes. But despite all my wonderful and unique traits, scientists have largely ignored me. Arnold Eggerth found me way back in 1935, but he thought I was a Bacteroides! That's like mistaking a tiger for a tree! Since then, I've been renamed twice, but I'm still waiting for my time in the spotlight.

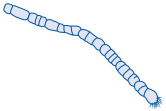
When the human microbiome project started, I thought the time had come, but everyone is still focused on boring old Bacteroidetes and Firmicutes. Sure, they're more abundant, but it's not the size of

your colony that matters, it's what you do with it. Hopefully this book will get the word out and 2016 will be the start of the Eggerthella revolution. Viva Actinobacteria!

Peter Turnbaugh is an Assistant Professor of Microbiology & Immunology, University of California, San Francisco. He studies how microbes that live in the human gut shape the food we eat and the drugs we take.

Collinsella aerofaciens

First isolated by Arnold Eggerth in 1935, this bacterium belongs to our core microbiota, but when and how it affects human health requires further investigation.



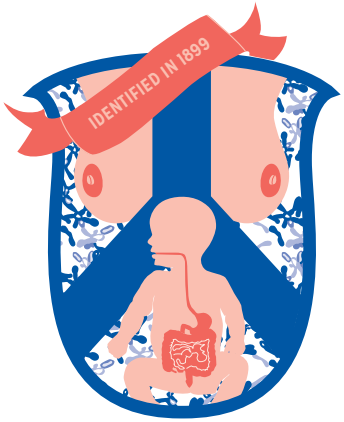
Collinsella aerofaciens is a gut bacterium that does not grow with oxygen. Although it can tolerate some oxygen, it grows under anaerobic conditions. It was first isolated from human stool in 1935 by Arnold Eggerth in Brooklyn, New York, USA, and named *Bacteroides aerofaciens*, which literally means anaerobic non-spore-forming rod that makes gas. However, Eggerth was already convinced that it was different from other Bacteroides. Its name was later changed to *Eubacterium aerofaciens*, which it kept until 1999, when molecular analysis revealed that it belonged to the actinobacteria phylum. It was at that point renamed *Collinsella aerofaciens*.

A benign bacterium, it colonizes our gut early in life. Babies born vaginally are usually colonized faster than those born via caesarian section. The gut microbiota of a one-month-old baby can be up to 30 percent *Collinsella aerofaciens*, especially if he or she is formula-fed. The bacterium grows on simple sugars, such as glucose and lactose, and may utilize fatty acids. It produces hydrogen gas, ethanol, formic acid and lactic acid. *Collinsella aerofaciens* is present in most humans and makes up around 5 percent of all bacteria in the gut, although its presence can vary from 0.2 to over 10 percent.

Collinsella aerofaciens is thought to influence many aspects of our health. It may play a negative role in situations where the environment changes negatively due to, for instance, an unhealthy diet. It may also be beneficial to humans, since it acidifies our guts early in life, protecting us from harmful pathogens. It may produce beneficial substances and could stimulate the immune system of the host. There is even a patent application for the use of this bacterium to prevent bloating in irritable bowel syndrome patients.

It is also associated with different diseases, such as obesity, high cholesterol, triglycerides and type 2 diabetes, but the bacterium's most remarkable association has to do with rheumatoid arthritis. In studies with mice, it was observed that *Collinsella aerofaciens* increased gut permeability, exacerbating rheumatoid arthritis. When and how this bacterium is beneficial or not requires further investigation, but we know it has an important function in the gut ecosystem.

Hermie J.M. Harmsen is an associate professor of Medical Microbiology, University of Groningen, University Medical Center Groningen. He studies beneficial gut bacteria and their role in health and disease, aiming to develop it into the next generation of probiotics for therapeutic and health promoting products.



Bifidobacteria

Discovered by Henry Tissier in 1899 and used as one of the first probiotics, they are particularly abundant in infants and are believed to benefit human health in many ways.

Bifidobacteria were discovered by the French paediatrician Henry Tissier in 1899, when he was working at the Pasteur Institute in Paris.

From the stool of healthy, breast-fed infants, he isolated large quantities of y- or bifid-shaped bacteria. Tissier observed that these microbes were abundant in healthy infants, yet appeared to be absent in infants suffering from diarrhoea. He proposed the oral administration of bifidobacteria as a therapeutic approach, performing one of the first probiotic applications.

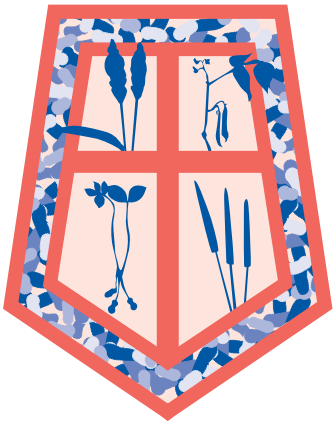
Bifidobacteria are easily isolated from human fecal samples and are particularly abundant in the guts of infants, where they are thought to play an important role in the development of a baby's immune system and in establishing a healthy gut microbiota. Once a baby has been weaned off breast milk, bifidobacteria populations decrease, yet they remain important for digesting carbohydrates from food and those produced by the human body itself.

Certain bifidobacteria have also been associated with many other beneficial roles in human health, such as reducing cholesterol levels, preventing constipation, reducing allergies, alleviating acute gastro-enteritis, reducing lactose intolerance and alleviating inflammatory bowel disease symptoms.

Despite all these proclaimed health-promoting activities, we actually know embarrassingly little about the mechanisms that cause such beneficial effects. Extensive scientific efforts are needed in order to understand the biology of bifidobacteria, especially their positive interactions with a human host. Such knowledge will not only allow us to fully understand how bifidobacteria endow their good fortune on humans, but it will also lead to more targeted and improved therapies that fully exploit their health-promoting potential.

Douwe van Sinderen is in the School of Microbiology & APC Microbiome Institute, University College Cork, Ireland. He studies bifidobacterial biology through functional genomics.

Marco Ventura is in the Laboratory of Probiogenomics, Department of Life Sciences, University of Parma, and he investigates genomics and ecology of bifidobacteria.



Prevotella

This genus of bacteria is commonly found in the guts of humans with non-western diets or diets high in complex carbohydrates, especially fibre. It is the indicator for the Type 2 enterotype classification.

Bacteroides dorei

Named after the French microbiologist Joel Doré, this species is implicated in inflammatory disorders of the gut. It is also associated with type 1 diabetes mellitus, though it's unclear whether the bacterium is a cause or an effect.

Blautia wexleri

Important for nutrient assimilation, named in honour of the microbiologist Hannah M. Wexler, strains of this genus may be shared among culturally and geographically distinct human populations.

Clostridium difficile

Fecal transplants can treat infections of this tough, opportunistic and difficult to expel bacteria that can hog space in the human colon and cause inflammation, diarrhea, or death.

Faecalibacterium prausnitzii

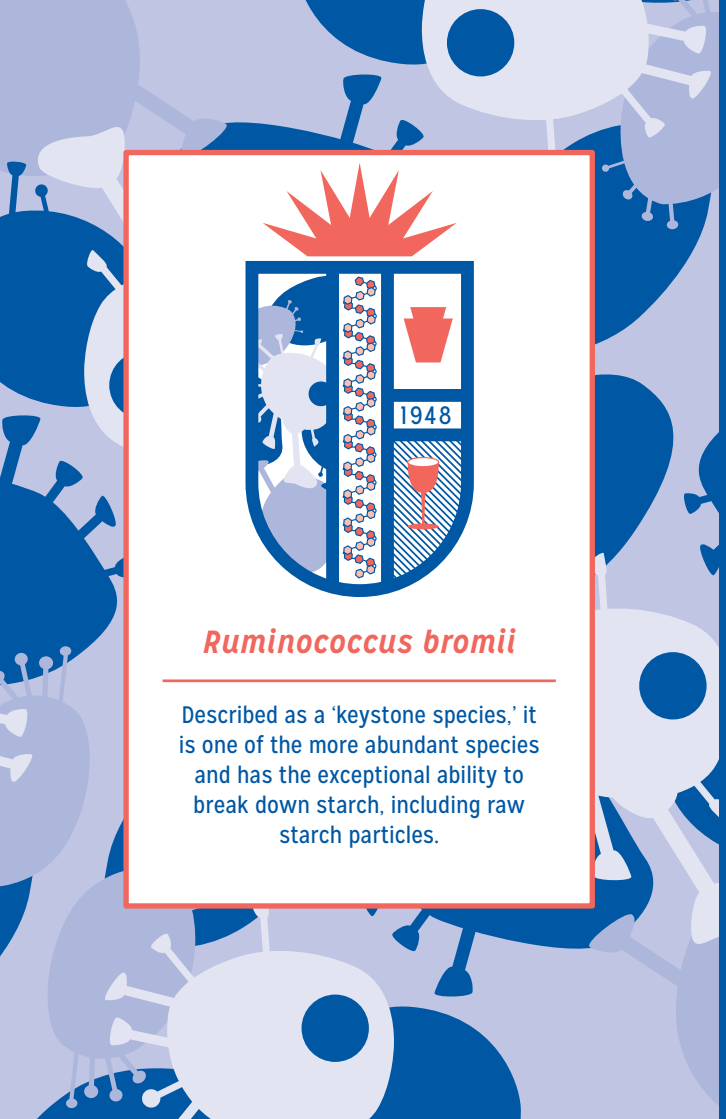
Described by Duncan et al. in 2002 it is the most abundant species in the gut microbiota and thought to contribute to a stable immune system in the intestine.

Faecalibacterium prausnitzii is the single most abundant species in the healthy human large intestine. It makes up about 8% of the total microbiota in most healthy adults. However, it reportedly has less of a presence in the intestines of people who are suffering from inflammatory bowel disease and the elderly.

The genus Faecalibacterium was first described by Duncan et al. in 2002, when the Rowett Institute of Nutrition and Health Microbiology group held the largest collection of this gut bacterium. The species name prausnitzii comes from the name of the German physician and bacteriologist Carl Prausnitz who first isolated this organism. *F. prausnitzii* is an anaerobe that belongs to the Ruminococcaceae family within the Firmicutes phylum.

F. prausnitzii ferments derivatives of dietary residues that reach the large intestine. An important characteristic of this bacterium is its ability to ferment carbohydrates to form butyrate. Bacteria can take different pathways to form this important fermentation product, and *F. prausnitzii* employs the butyryl CoA: acetate CoA transferase route. In addition to forming butyrate which is a major energy source for the epithelial cells that line the colon, *F. prausnitzii* also stimulates potent anti-inflammatory activity, partly through its ability to secrete high amounts of interleukin-10. It is likely that this abundant bacterium contributes to immune homeostasis in the intestine through its anti-inflammatory properties. There is currently active research in identifying the bacterial products responsible for this benefit. Furthermore, there is interest in developing *F. prausnitzii* as one of the new generation of probiotics promoting both intestinal and general health.

Sylvia H. Duncan is a Research Fellow at the Rowett Institute for Nutrition and Health, University of Aberdeen. She is investigating the impact of different dietary fibres on modulating the composition of the gut microbiota to promote health and identifying inter-individual responses to dietary change.



Ruminococcus bromii

Described as a 'keystone species,' it is one of the more abundant species and has the exceptional ability to break down starch, including raw starch particles.

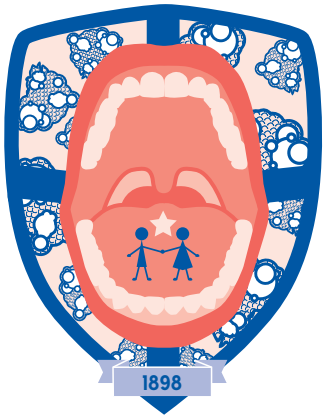
Ruminococcus bromii is one of the six most abundant bacterial species to be found in the gut microbiota of most healthy adults, but very few cultured isolates exist, probably because the species requires multiple vitamins in order to grow. The isolates that we do have are remarkably specialized, since they can use only starch and its breakdown products, or fructose, as energy sources. Their ability to break down starch, including raw starch particles, is exceptional when compared to other human gut bacteria. This ability may be explained by the recent finding that their starch-degrading enzymes are organized into a unique complex called an 'amylosome' that is present on the cell surface (Ze X et al. MBio, 2015). As a result, this species increases rapidly in numbers when people consume dietary starches that are resistant to digestion in the upper gut.

All starchy foods contain some resistant starch (RS), which can account for less than 1-10 percent of the total starch content. Relatively high RS levels (5-10 percent) are found in bananas (raw), beans and pulses (cooked), uncooked oats, some breakfast cereals, and some types of bread (e.g. rye bread, sourdough). Much depends on the cooking method employed. For example, raw potato starch is highly resistant, which is why we cook it. However, if it

is cooled and stored the percent of RS goes up. Although RS consumption is widely considered to have health benefits, we do not yet know the full consequences of increases in the *R. bromii* population.

The bacterium produces acetate, formate, and ethanol when grown in pure culture (indeed the species name 'bromii' refers to the god of alcohol!), but their production is likely to be altered by interactions with other members of the microbial community. There is evidence that people who lack *R. bromii* in their microbiota fail to ferment RS fully, hence this organism is called a 'keystone species.'

Harry J Flint is a Professor at the Rowett Institute of Nutrition and Health, University of Aberdeen. He is investigating microbial fermentation of dietary carbohydrates in the gut of humans and farm animals with the goal of improving nutrition and health.



Veillonella

Commonly found in the oral cavity, gut, and vagina of humans, Veillonella cannot metabolise carbohydrates, so they use lactate produced by other bacteria as a carbon source.

Veillonella are famous for what they do not do. They cannot metabolise carbohydrates but need lactate (or similar) as a carbon source. This is a bit like preferring vinegar to sugar. Lactate is not common in the environment. To survive, Veillonella cooperate with bacteria that produce lactate through the fermentation of carbohydrates. Veillonella are not considered to be harmful and have rarely been associated with human disease.

Veillonella were first recognised and described in 1898. This assignation was later changed in 1933 and seven species of Veillonella were identified. While being classified as Gram negative by staining, they are phylogenetically closer to Gram positive species. Veillonella have several secrets and idiosyncratic characteristics.

Cooperation is key to the survival of Veillonella. In the oral cavity (which is, after all, the top of the gastrointestinal tract), it is found in dental plaque. A second problem Veillonella face is that they are unable to adhere to surfaces. This means that in order to survive in niche areas, such as the oral cavity, they need another organism with which they can co-aggregate to form biofilms and, eventually, plaque. The other organism must be able to adhere to surfaces and provide lactate. In the oral cavity, the most efficient and useful, dual purpose organism is Streptococcus mutans. Biofilms generally contain multiple species and exhibit symbiotic cooperativity between the organisms.

The ability of Veillonella to metabolise lactate might have a positive outcome for humans. They reduce acidity by removing lactate, which may slow down the formation of caries (tooth decay caused by bacteria). It has been found that there are fewer species of Veillonella in oral cavity sites of children with caries than those of caries-free individuals. However, the situation is complex, and some studies have shown Veillonella to be a predominant species in the subgingival biofilm of periodontal pockets, and so might be associated with periodontitis–an inflammatory process of the soft gum tissue.

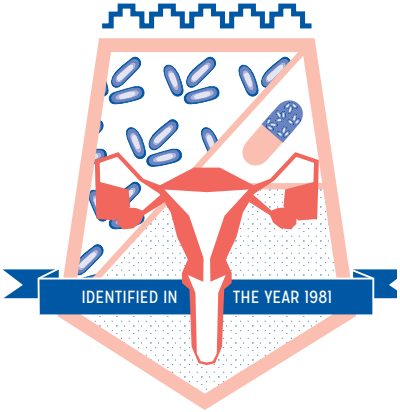
When it is with its mates in plaque, Veillonella seems to be a good guy, when it is on its own in periodontal pockets, it seems like it is a delinquent.

Friends are good.

Bryan Hanley is a natural product chemist who has worked in research institutes and in industry in the UK, Ireland and the US. He was Director of Scientific Discovery at the Wm. Wrigley Global Innovation Center in Chicago where he was responsible for the internal and external research programmes on oral health and on the psychology of chewing.

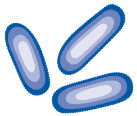
Anaeroglobus

Discovered when isolated from fluid collected after an operation. It is genetically distinct from other known bacteria and may represent a novel lineage within the family Veillonellaceae.



Lactobacillus rhamnosus

Isolated in 1981, it was tested for preventing urinary tract infection in women. It is now used to create a probiotic yogurt that is thought to benefit the immune system.



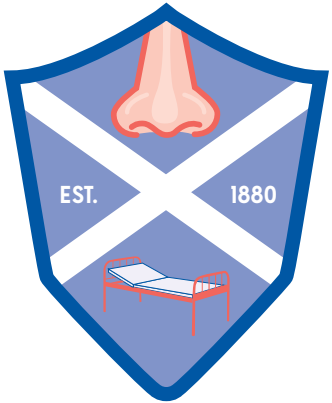
Lactobacillus rhamnosus GR-1 has lived an interesting life. Initially isolated in 1981 from the distal urethra of a healthy woman from Kingston Ontario and identified as *Lactobacillus casei*, it was given the designation GR-1, as my post-doctoral fellow Roger Cook and I needed to differentiate strains. Little did we know that by 2016, it would have made such an impact on the health of so many people. Its anti-urogenital pathogen activities, demonstrated in vitro, made us select it for clinical studies with a view to preventing urinary tract infection (UTI) in women. The idea came from Dr. Andrew Bruce, a urologist who observed that lactobacilli are dominant in the healthy vagina, while *E. coli* are dominant in women with UTI. He believed that lactobacilli could be administered to the vagina to displace the pathogens and reduce shedding into the bladder.

While other lactobacilli were commercialized with little knowledge of their properties, we chose to study the GR-1 strain to understand its capabilities and safety. In addition to showing that it could survive and multiply in the vagina, we found that it could up regulate host defenses and modulate gut immunity. As regulatory agencies viewed vaginal instillation as a drug therapy, and product development would be extremely expensive, we decided to test oral administration. This followed pilot studies showing GR-1 could be delivered in yogurt form and potentially confer benefits to immunity in patients with inflammatory bowel disease, HIV/AIDS, arthritis, and allergies.

The strain was dried and applied in a capsule, along with *Lactobacillus reuteri* RC-14, and shown not only to reach the vagina via the rectum, but to improve efficacy of UTI and bacterial vaginosis therapy and prevent recurrences. It also does not generate drug resistance the way antibiotics do. The strains are sold in over 30 countries, and it has helped many women to restore and maintain their urogenital health.

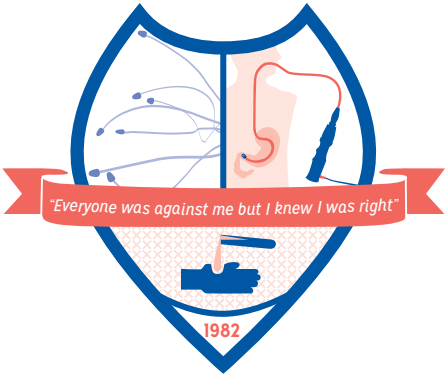
The GR-1 strain has another legacy under a Western Heads East project to create probiotic yogurt produced by local people in Africa. Soon there will be other partners, including Heifer International. In Wisconsin, *Lactococcus lactis* has been named the State Microbe. Maybe one day, the GR-1 strain will eclipse that honour! At least it is impacting the world one person at a time.

Gregor Reid is a Scientist at Lawson Health Research Institute and Professor at Western University. He is currently focused on providing African communities with access to affordable probiotic food, that counters environmental toxins and pathogens.



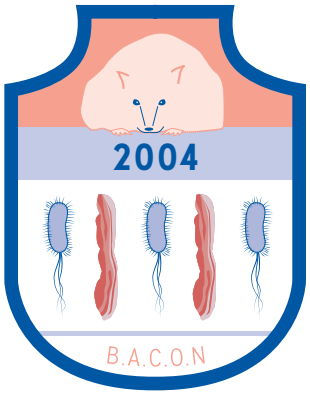
Staphylococcus aureus

Infamous for causing skin and respiratory tract infections. The toxins it creates, called superantigens, have recently been identified as a possible cause of type 2 diabetes.



Helicobacter pylori

Under investigation in relation to stomach cancer, though the evidence is insufficient to convict. 50% of humans harbor it: should it be eliminated or is it important & necessary? The jury is still out.



Akkermansia muciniphila

Its presence is believed to thicken the gut wall, helping to combat obesity. Researchers are working to understand its relationship to metabolism, diabetes, and inflammation.

MICROBIAL DARK MATTER

THE UNCULTURED MAJORITY

Wendy Russell *is a chemist specializing in molecular nutrition at the Rowett Institute of Nutrition and Health, University of Aberdeen. She is researching the complex interplay of food and health and in particular the function of the gut microbiota in the prevention of diet-related disease.*

Despite the best of efforts of our finest microbiologists, many of the microbial species that inhabit our bodies remain unclassified or poorly understood.

These are not just a few species living in the shadows of our knowledge. It could be as much as 99.9 percent of the human microbiota, although it is obviously difficult to accurately estimate the unknown.

So how do we know, what we don't know?
The so-called 'Great Plate Count Anomaly' has consistently demonstrated that we can see things under the microscope that can't be grown under laboratory conditions. We have been aware of this constraint for at least a century and a half, but the science only moved forward with the advent of culture-independent techniques in the 1980s. Using these sequencing technologies, we can identify the genome of uncultivated bacteria.

Why should we care, if we can sequence?
All you need is a high quality draft genome and

a comprehensive description of the sequence and you have your newly named species 'in the bag'. Genome-enabled technologies and single cell genomics are facilitating the identification of many of the species that have eluded us for so long. However, being 'in the bag' does not mean that it is 'in the Petri dish'. Without culturing the species in the laboratory, we really have no understanding of the function of the organism. This limits the expansion of scientific knowledge, particularly our understanding of chronic disease and the critical search for effective anti-microbials.

So how do we achieve the impossible? Despite being unculturable, certain bacteria are exceptionally social and need the company of other bacteria to divide and conquer. Forcing bacteria to grow in isolation, even with the perfect nutrient balance and environmental conditions, might still be a problem. Microfluid chips, which contain thousands of wells, might be useful in allowing a large number of experimental conditions to be evaluated in parallel, increasing the chances of success. Another approach might be to allow the organism of interest to thrive within its natural environment, harvesting when in abundance.

These techniques are valuable, but seem like a hit-or-miss approach at best. What is needed is new thinking, new technologies and most likely new mathematics: bioinformatics, which can link genome-identified species to their functions. We need a systematic approach that is more comprehensive and better able to account for the complex interactions of the microbial ecosystem. With serious investment we might begin to understand the function of the trillions of bacteria that live within us. Then we can pay more attention to the archaea, the viruses, and possibly the not-yet-discovered life forms. In order to move this dark matter into the light, we will need to learn to ask new questions in new ways.

MINING THE GUT

Nicola Twilley *is a co-host of the award-winning Gastropod podcast, author of the blog Edible Geography, and a contributing writer at The New Yorker. She is deeply obsessed with refrigeration, and is currently writing a book on the topic. She is also co-authoring a nonfiction exploration of quarantine with Geoff Manaugh for Farrar, Straus & Giroux.*

As soon as the *American Gut Project* launched on the crowd-funding platform Indiegogo in February 2013, I signed up to get my microbiome sequenced. Yet when the kit—basically an oversized Q-tip—finally arrived later that summer, I hesitated.

It wasn't the fecal sampling that put me off, although there is, apparently, a right and a wrong way to do that (many of the first specimens the American Gut team received were overloaded, leading them to put out an email advising participants that, when it comes to shit, less is definitely more). Instead, I was suffering from a sort of microbial performance anxiety. I wanted to make sure that I sampled on a day when my gut microbes were at their best. After all, I wouldn't sit for a portrait without putting on make-up, or go for a job interview without ironing my shirt—why would I immortalize my microbes after a week that had been shamefully short on vegetables?

The weeks became months, and then years: I had been traveling, or drinking, or both; I hadn't eaten any yogurt or whole grains in at least a month; I had somehow consumed my bodyweight in ice cream (for work!). All the while, I followed microbiome research closely. Barely a week went by without some new study, most of which contained cause for alarm. I began to worry that the multiple courses of antibiotics I'd taken for childhood ear infections had doomed me to obesity, depression, and Alzheimer's. I started making my own kimchi. I even worried that my germ-phobic husband's hand-sanitizer habit might be negatively affecting my own gut microbe community. Barely a decade after Joshua Lederberg, a Nobel Prize-winning biologist, first used the term "microbiome" to refer to the trillions of microoganisms that reside in and on our bodies, it seemed that gut bacteria held the key to happiness, health, and—at least for the companies who raced to cash in on the resulting probiotic gold rush—wealth.

I was not alone in feeling that the microbial stakes were terrifyingly high. Microbiologist Martin Blaser, author of *Missing Microbes: How the Overuse of Antibiotics Is Fueling Our Modern Plagues*, issued a stern warning that humanity's gut bacteria was in the middle of an extinction crisis, and essential species risked being lost forever. Bioinformatician Robert Beiko called for the creation of a "microbial commons," through which the global human microbiome could be managed for the collective good, and reckless mismanagement prohibited as a crime against public health. Not to be outdone, the U.S. Department of Defense's advanced research agency, DARPA, launched Operation Intestinal Fortitude, a research effort designed to perpetuate American military dominance through warfighter gut enhancement.

Then, in 2014, the Human Microbiome Project published its final report. At the end of a five-year, $115 million initiative by the U.S. National Institutes of Health to pin down the microbial membership of healthy versus unhealthy guts, the findings showed… that there was no such thing. Sequencing the stool samples of 242 healthy adults had revealed 242 unique microbial communities. There was no baseline, let alone an ideal to which I should aspire.

What this meant was that it simply wasn't possible to declare Bifidobacteria and Prevotella good, for instance, and Firmicutes bad. The presence or absence of individual species seemed to matter much less than the way the community functioned as a whole. In other words, a Bacteroides-rich microbial community and one dominated by Rumincoccus perform the same basic activities: fermenting the carbohydrates and proteins that arrive undigested in the large intestine to extract energy while excreting gases and other chemicals.

It's just that the way they do it will be different—and those different metabolic pathways end up affecting the amount of energy the microbes extract and share with their hosts, as well as the particular chemicals produced in the process—vitamins, peptides, and lipases that may well regulate functions elsewhere in the body.

It now seems our gut microbiome is not a single organ, like a heart, that can function well or badly. Instead it is a series of negotiations and trade-offs, in which distinctions between good and bad have become increasingly difficult to extract from the white noise generated by up to a thousand different microbial species, all interacting with each other and their human host in ways that we mostly don't yet understand.

Every American Gut Project result sheet helpfully provides Michael Pollan's sequence, as a sort of reference gut against which to compare your own sample. His colon is, apparently, rich in Prevotella, a bacteria often associated with traditional rather than Western diets. "I was very proud of my Prevotella," Pollan said. But, in the years that followed this initial sample, he explained, "I learned some other things"—for example, that AIDS patients have very high levels of Prevotella, "and that, you know, it didn't necessarily correlate with health." Pollan's confidence in his gut's superiority had begun to erode, just as my own fears of microbial inadequacy had waned.

I finally took my monster Q-tip into the bathroom a couple of months ago. I haven't received my results yet (the American Gut Project has been overwhelmed by its own popularity and is, to use an unfortunate expression, somewhat backed up), but now I'm curious rather than anxious. After all, it will likely be a long time before my results can be interpreted with any confidence—and even longer before I can reliably manipulate my microbiome with probiotics, medicines, or even personalized enterogastronomy.

In 2003, the sequencing of the human genome was greeted with promises of precision medicine and genetically engineered überbabies; the reality has proved much more complex, but no less interesting. As the initial hype around the human microbiome fades, it seems that getting to know our microbiota will be even trickier than we initially hoped—and much more fascinating, besides.

INTERNAL POSTNATURAL HABITAT: DOMESTICATION AND ENGINEERING

The Center for PostNatural History *is dedicated to the advancement of knowledge relating to the complex interplay between culture, nature, and biotechnology. Their mission is to acquire, interpret, and provide access to a collection of living, preserved, and documented organisms of postnatural origin. Essay by Richard Pell and Lauren B. Allen, CPNH.*

People have intentionally manipulated the living world to suit their own needs and desires for a long while. It's one of the things that makes us human. We breed, prune, and fertilize the living world to meet these desires.

Nearly all the food we eat comes from plants or animals that have been domesticated over time. They've been radically altered in both form and function. At the Center for PostNatural History, we refer to the organisms that are produced in the intentionally managed habitats of farms and laboratories as 'postnatural'. Unlike the 'natural' organisms that populate the collections of Natural History Museums, postnatural organisms bear the hallmarks of the culture that shaped them.

The biological fact that our sensory organs are on the outside of our bodies biases us to thinking of the world as something that exists outside of us, and that our 'habitat' is something that we live inside. We often overlook the habitats that exist inside our

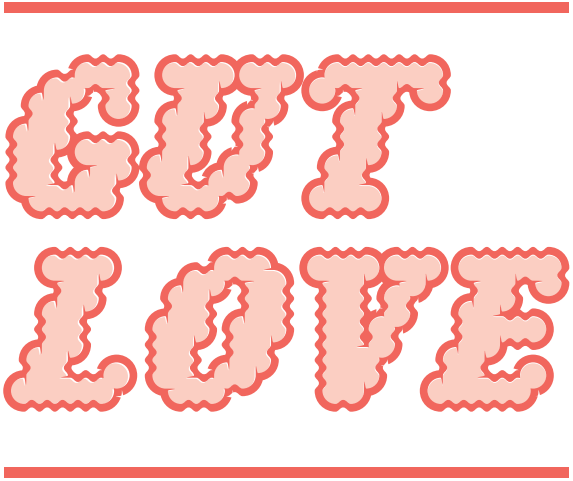
own bodies. There is actually a specific biological moment (called gastrulation) in the development of every animal in which they go from only having an outside, like a ball, to having an inside, like a tube or a donut. It's one of the things that makes us animals. We eat other things, digest them, and excrete the parts we don't need. Nobody escapes this paradigm. According to biologist Lewis Wolpert, "It is not birth, marriage, or death, but gastrulation which is truly the most important time in your life."

Gastrulation is the moment in which each of us becomes a permanent habitat for an entire ecosystem that lives within us. It is genuine co-dependency, and ultimately, co-evolution. It shouldn't be a surprise that the human influence over the external living world, particularly the things we eat, should have an impact on the internal world of the human digestive tract. One need not look further than the final gauntlet of the grocery store check-out lines to see magazine racks crowded with publications promising vital analysis on the effects, and corrective measures, for coping with our rapidly shifting dietary regimes.

Making matters more complicated is a continuous stream of newly developed compounds entering the human digestive system originating from pharmaceuticals, personal care products, industrial food production, and heavy industry. Some of these compounds and their combinations have consequences for the bacteria that inhabit our guts. Culprits that have been popularly implicated in disturbing the bacterial balance include: heartburn medication, anti-diabetic drugs, antibiotics, proton pump inhibitors, psychiatric medication, mouthwash, aspirin, antacids, painkillers, laxatives, chlorinated drinking water, pesticides, herbicides, genetically modified foods, plastic bottles, and artificial sweeteners, just to name a few.

The emerging awareness and uncertainty surrounding our gut universes, coupled with advancement in experimental procedures, has created a new frontier for intentional human influence of the microbial world. Fecal transplants offer the possibility of re-colonizing a battle-torn intestinal tract with a microbial population that is more at peace with itself. Fecal cryostorage is already a reality and ancient fecal bio-resurrection is a real possibility. Fecal transplants are also being suggested as a means to reverse the conditions that promote obesity. Even the intestinal parasites that have plagued humankind as long as we've been human are being offered their old jobs back, as useful symbionts that help to restore balance. Beyond simply restoring the normal balance, some over-the-counter probiotic products promise increased muscle production and even improved brain functioning.

We at the Center for PostNatural History are merely interpreters of this new frontier. We recognize that the human gut system has all the hallmarks of a postnatural habitat. As such, the inhabitants of this inner habitat reflect the human desires and anxieties that influence them, just as domesticated plants and animals do in the habitats outside of our bodies. We just haven't decided where to place the interpretive plaque yet.



Kathy High *is an interdisciplinary artist working in the areas of technology, science, speculative fiction and art. She produces videos and installations posing queer and feminist inquiries into areas of medicine/bio-science, and animal/interspecies collaborations.*

I am extremely interested in shit.

As a long-time patient with Crohn's disease, I have a complicated relationship to shit. I deal with it everyday—and often. I quickly flush it away. But it always surprises me how easily I can get rid of it. Dominique Laporte in his *History of Shit* talks about the shift in 16th century France when shit needed to be hidden—taken out of the streets—taken away by the State, made shameful. The Hygiene Edict of 1539 in France demanded that cesspools be built in every house: "Hold on to your shit," declared the Monarch. "Dispose of it only in the dark of night. Remove your pigs from sight beyond the city's walls, or I will seize your person and your goods, engulf your home in my capricious purse, and lock your body in my jail."

The idea that the medical establishment might now turn to our shit (those piles of diverse bacteria from our distal bowel), our human microbiota systems, and the ecology of our bodies to research new ways to treat illness is a revolutionary concept. A paradigm shift. But we know so very little about these bacteria with whom we co-habit. How do all these bacteria work together in our bodies? How does their collective effort affect us—in our gut, on our skin, in our reproductive organs and more?

All these beautiful and evil bacteria pulling together, breaking from the idea that bacteria are just pathogens, and stopping the incessant sanitization of our lives. Now maybe I can begin to embrace my own shit.

Welcome fecal microbiota transplantation (FMT). Here all kinds of taboos are foregone. No longer is our waste matter, our fecal matter, unwanted. It could be precious, curative, magical. What do we take on if we take in someone else's shit, their microbiota? What part of them do we inherit from such a transplant? Who is our new self with new shit inside us? Can we even become immortal?

The future poo gift economy will include the creation of personal stool banks—storing one's own healthy poo for reuse when needed, encouraging do-it-yourself methods of FMT treatment. The search for the perfect stool will result in biopiracy and stool thievery from far away communities where there are no McDonald's, and the life and food and shit are simple and pure. Stool will become our new perfume products, used in new dating services, and new restaurants will serve poo derived foods. I predict shit will become the next big gift exchange.

"The transformation of waste is perhaps the oldest pre-occupation of man."
– Patti Smith, *25th Floor/High On Rebellion*

Dear David Bowie,

I have a bargain for you…I am writing you with a strange request…I am a life-long fan…

I have been following your career since I was little. I was born in 1954, so not that much younger than you…but enough so that I feel like a younger sister….

I want to [make an] exchange for a throw-away item. Your poo.

I want to conduct a fecal transplantation with your stool—implanting your poop/gut biome into my colon.

This goes against all the "rules"—it should be someone close to me, someone under 60, pre-tested, etc., but I know we will be compatible.

And basically if I could become you….well, say no more….

I eagerly await your response.

Your fan,

Kathy

Written in 2015 prior to Bowie's death

GLOSSARY

Aerobic
requiring air

Anaerobic
living without air

Bacteria
single-celled organisms that can be rod, spherical or spiral in shape. They have symbiotic and parasitic relationships with animals and plants, and are found in soil, water, and seemingly inhospitable places like radioactive waste. Different species of bacteria are involved in important processes like nitrogen fixing, infectection and diseases, fermentation, decay, rotting, and the production of chemicals.

Bacteroides
the most common genus of bacteria found in the gut of mammals. Bacteroides are one of the three human enterotypes. Larger amounts of bacteroides are found in humans with diets that are high in protein and animal fats.

Butyrate
a short-chain fatty acid that functions as food for the cells that line the colon. Butyrate is created by beneficial bacteria as they consume and/or ferment dietary fiber from plants.

Carbohydrates
molecules made from carbon, hydrogen and oxygen that bacteria use for energy.

Caries
tooth, bone or plant decay caused by bacteria.

Cultured isolate
a pure culture of bacteria grown in a laboratory.

DNA Sequencing
encompasses all of the techniques and technologies for determining the exact order of nucleotides (basic structural units) in a molecule of DNA. DNA sequencing is commonly used in identification or classification on a genetic level.

Entero-
of or relating to the intestine

Enterotype classification
a classification system that breaks humans into three groups based on bacterial populations in the gut. Humans with high levels of Bacteroides are classified as type 1 and generally have high diets high in protein. Type 2 have high amounts of Prevotella and diets high in carbohydrates and dietary fiber. Ruminococcus is found in high quantities in the gut of type 3.

Faecal microbiota transfer
a procedure known as FMT whereby a stool sample is collected from a tested donor and placed in a patient by the oral route, colonoscopy or enema.

Fermentation
energy-yielding metabolism of complex substrates to simpler products, including short chain fatty acids, under anaerobic conditions.

Gram Negative / Gram Positive
a method for classifying bacteria based on a dye test. Gram Positive bacteria retain the stain because of a thick cell wall. Gram Negative do not retain the stain due to their thin cell wall. They are also more resistant to antibodies.

Immune Homeostasis
balance in the immune system. Immune homeostasis is often regulated by an individual's gut bacteria, which can fight off disease and maintain a healthy balance for the host.

Lactate
a metabolite that is formed as a byproduct during the fermentation process (as bacteria convert glucose into cellular energy).

Metabolism
includes all chemical processes that sustain the life of a living organism and its cells. Metabolism includes both the breakdown of matter (the extraction of energy) and the build up of matter (consumption of energy.)

Microbiome
an entire environment including the microorganisms that are present, their genomes and the prevailing environmental conditions.

Microbiota
the collective community of microorganisms present in a given environment.

Phylogenetic
the study of evolutionary history and relationships between organisms or groups of organisms.

Phylum
a taxonomic rank below kingdom and above class. There are currently 29 bacterial phyla, which form the major lineages of bacteria.

Prebiotics
non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria.

Prevotella
a common genus of bacteria found in the gut of mammals. Prevotella are one of the three human enterotypes. Humans who consume larger amounts of dietary fiber and carbohydrates typically have higher amounts of Prevotella in their guts.

Probiotics
live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.

Ruminococcus
a genus of bacteria that is commonly found in the human gut. Enterotype 3 is characterized by high amounts of this Ruminococcus.

Subunit ribosomal RNA
essential for protein synthesis in all living organisms

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ISSN 2372-6504
Produced and published by
The Center for Genomic Gastronomy
October, 2016

Editors
Wendy Russell, Sylvia Duncan, Zack Denfeld, Emma Conley
and Cathrine Kramer

Design & Illustration
Cathrine Kramer and Emma Conley

Print
Printed by Hato, 2016

Support & Thank You
The work and printing of this publication was financially supported by **The Leverhulme Trust** artist in residence grant.

This support is gratefully acknowledged.

Thank you to all the contributors and the Rowett Institute for Nutrition and Health.
Special thanks to Chris Fremantle, who first introduced us to Wendy, for his continued support.

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