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—*Philadelphia Inquirer*

10% Human

HOW YOUR BODY'S MICROBES HOLD THE KEY TO HEALTH AND HAPPINESS

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HARPER

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DEDICATION

For Ben and his microbes.
My favourite superorganism.

EPIGRAPH

At the heart of science is an essential balance between two seemingly contradictory attitudes – an openness to new ideas, no matter how bizarre or counterintuitive they may be, and the most ruthless sceptical scrutiny of all ideas, old and new. This is how deep truths are winnowed from deep nonsense.

CARL SAGAN

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PROLOGUE

Being Cured

As I walked back through the forest that night in the summer of 2005, with twenty bats in cotton ba hanging around my neck and all manner of insect life dashing for the light of my head torch, I realis my ankles were itching. I had my repellent-soaked trousers tucked into my leech socks, with anoth pair underneath for good measure. The humidity and drenching sweat, the muddy trails, my fear tigers, and the mosquitoes were enough to contend with as I made my rounds, collecting bats out traps in the darkness of the rainforest. But something had got through the barrier of fabric a chemicals protecting my skin. Something itchy.

At twenty-two, I spent what turned out to be a life-changing three months living in the heart Krau Wildlife Reserve in peninsular Malaysia. During my biology degree, I had become fascinated b bats, and when the opportunity came up to work as a field assistant to a British bat scientist, I sign up immediately. Encounters with leaf monkeys, gibbons and an extraordinary diversity of bats ma the challenges of sleeping in a hammock and washing in a river populated by monitor lizards see worthwhile. But, as I was to discover, the trials of life in a tropical forest can live on far beyond th experience itself.

Back at base camp, in a clearing next to the river, I peeled back the layers to reveal the source my discomfort: not leeches, but ticks. Perhaps fifty or so, some embedded in my skin, others crawli up my legs. I brushed the loose ones off, and turned back to the bats, measuring and recordi scientific data about them as quickly as I could. Later, with the bats released, and the forest pitc black and buzzing with cicadas, I zipped myself into my cocoon-like hammock, and, with a pair tweezers, under the light of my head torch, I removed every last tick.

A few months later, at home in London, the tropical infection introduced to me by the ticks too hold. My body seized up and my toe bone swelled. Weird symptoms came and went, as did variou blood tests and hospital specialists. My life would be put on hold for weeks or months at a time bouts of pain, fatigue and confusion gripped me without warning, then released me again as if nothi had happened. By the time I was diagnosed many years later, the infection was entrenched, and I w given a course of antibiotics long and intense enough to cure a herd of cattle. At last, I was going to b myself again.

But, unexpectedly, the story did not end there. I was cured, but not just of the tick-borne infectio Instead, it seemed I had been cured as if I were a piece of meat. The antibiotics had worked the magic, but I began to suffer new symptoms, as varied as before. My skin was raw, my digestiv system was choosy, and I was prone to picking up every infection going. I had a suspicion that th antibiotics I had taken had not only eradicated the bacteria that plagued me, but also those th belonged in me. I felt like I had become inhospitable to microbes, and I learnt just how much I need the 100 trillion friendly little creatures who had, until recently, called my body their home.

You are just 10 per cent human.

For every one of the cells that make up the vessel that you call your body, there are nine impost

cells hitching a ride. You are not just flesh and blood, muscle and bone, brain and skin, but als bacteria and fungi. You are more 'them' than you are 'you'. Your gut alone hosts 100 trillion of them like a coral reef growing on the rugged seabed that is your intestine. Around 4,000 different speci carve out their own little niches, nestled among folds that give your 1.5-metres-long colon the surfa area of a double bed. Over your lifetime, you will play host to bugs the equivalent weight of fi African elephants. Your skin is crawling with them. There are more on your fingertip than there ar people in Britain.

Disgusting, isn't it? We are surely too sophisticated, too hygienic, too *evolved* to be colonised this way. Shouldn't we have shunned microbes, like we did fur and tails, when we left the forest Doesn't modern medicine have the tools to help us evict them so that we can live cleaner, mo healthy, independent lives? Since the body's microbial habitat was first discovered we have tolerate it, as it seemed to do us no harm. But unlike the coral reefs, or the rainforests, we have not thought protect it, let alone to cherish it.

As an evolutionary biologist, I am trained to look for the advantage, the *meaning*, in the anatom and behaviour of an organism. Usually, characteristics and interactions that are truly detrimental a either fought against, or lost in evolutionary time. That set me thinking: our 100 trillion microb could not call us home if they brought nothing to the party. Our immune systems fight off germs ar cure us of infections, so why would they tolerate being invaded in this way? Having subjected my ov invaders, both good and bad, to months of chemical warfare, I wanted to know more about th collateral damage I had caused.

As it turned out, I was asking this question at exactly the right time. After decades of slow-pace scientific attempts at learning more about the body's microbes by culturing them on Petri dishe technology had finally caught up with our curiosity. Most of the microbes living inside us die whe they are exposed to oxygen, because they are adapted to an oxygen-free existence deep in our gut Growing them outside the body is difficult, and experimenting with them is even harder.

But, in the wake of the seminal Human Genome Project, in which every human gene was decode scientists are now capable of sequencing massive quantities of DNA extremely quickly and cheapl Even our dead microbes, expelled from the body in the stool, could now be identified because the DNA remained intact. We had thought our microbes didn't matter, but science is beginning to reveal different story. A story in which our lives are intertwined with those of our hitchhikers, where ou microbes run our bodies, and becoming a healthy human is impossible without them.

My own health troubles were the tip of the iceberg. I learnt of the emerging scientific eviden that disruptions to the body's microbes were behind gastrointestinal disorders, allergies, autoimmun diseases, and even obesity. And it wasn't just physical health that could be affected, but mental healt as well, from anxiety and depression to obsessive–compulsive disorder (OCD) and autism. Many the illnesses we accept as part of life were not, it seemed, down to flaws in our genes, or our bodi letting us down, but were instead newly emerging conditions brought on by our failure to cherish th long-held extension to our own human cells: our microbes.

Through my research, I hoped not only to discover what damage the antibiotics I had taken had don to my microbial colony, but how it had made me unwell, and what I could do to restore the balance microbes I had harboured before the night of the tick bites, eight years earlier. To learn more, I signe up to take the ultimate step in self-discovery: DNA sequencing. But rather than sequence my ow genes, I would have the genes of my personal colony of microbes – my microbiome – sequenced. B knowing which species and strains of bacteria I contained, I would have a starting point for sel

improvement. Using the latest understanding of what *should* be living in me, I might be able to judg
just how much damage I had done, and attempt to make amends. I used a citizen-science programm
the American Gut Project, based at the laboratory of Professor Rob Knight at the University
Colorado, Boulder. Available to anyone around the world for a donation, the AGP sequences sample
of microbes from the human body to learn more about the species we harbour and their impact on o
health. By sending a stool sample containing the microbes from my own gut, I received a snapshot
the ecosystem that called my body home.

After years of antibiotics, I was relieved to find I had *any* bacteria living in me at all. It w
pleasing to see that the groups I harboured were at least broadly similar to those in other America
Gut Project participants, and not the microbial equivalent of mutant creatures eking out a living on
toxic wasteland. But, perhaps predictably, the diversity of my bacteria seemed to have taken a beatin
At the highest level of the taxonomic hierarchy, the diversity was relatively low, looking a b
bipartisan compared with the guts of other people. Over 97 per cent of my bacteria belonged to t
two major bacterial groups, compared with around 90 per cent making up these two groups in t
average participant. Perhaps the antibiotics I had taken had killed off some of the less abunda
species, leaving me with only the hardy survivors. I was intrigued to know whether this loss might
related to any of my more recent health troubles.

But, just as comparing a tropical rainforest and an oak woodland by looking at the proportion
trees to shrubs, or birds to mammals, reveals little about how both ecosystems function, compari
my bacteria at such a broad scale may not tell me all that much about the health of my inn
community. At the other end of the taxonomic hierarchy were the genera and species that I containe
What could the identities of the bacteria that had either clung on throughout my treatment, or returne
since it ended, reveal about my current state of health? Or perhaps more pertinently, what did th
absence of species that might have fallen victim to the chemical warfare I had unleashed on ther
mean for me now?

As I embarked on learning more about *us* – myself and my microbes – I resolved to put what
learnt into practice. I wanted to get back on their good side, and I knew I needed to make changes
my life to restore a colony that would work in harmony with my human cells. If my most rece
symptoms were stemming from the collateral damage I had inadvertently inflicted upon m
microbiota, perhaps I could reverse it and rid myself of the allergies, the skin problems and the nea
constant infections? My concern wasn't just for myself, but for the children I hoped to have in th
coming years. As I would pass on not only my genes, but also my microbes, I wanted to be sure I ha
something worth giving.

I resolved to put my microbes first, altering my diet to better suit their needs. I planned to have
second sample sequenced after my lifestyle changes had had a chance to take effect, in the hope th
my efforts might be evident from the change in the diversity and balance of the species I play host t
Most of all, I hoped that my investment in them would pay dividends, by unlocking the door to bett
health and happiness.

INTRODUCTION

The Other 90%

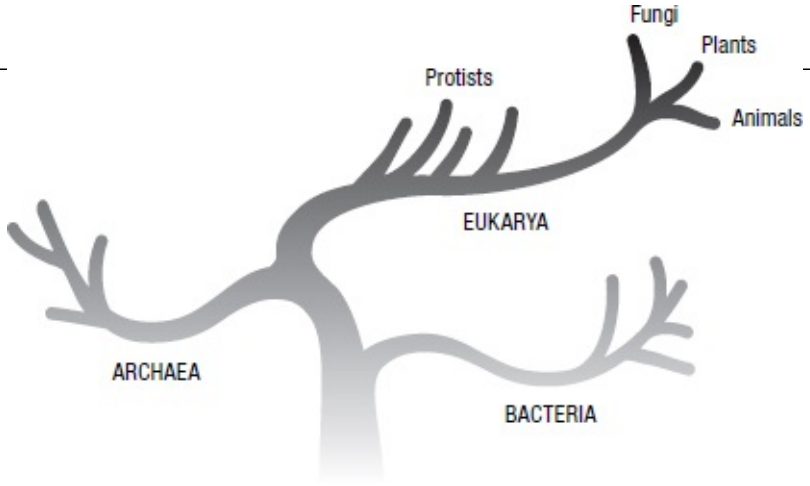
In May 2000, just weeks before the announcement of the first draft of the human genome, a noteboo began circulating among the scientists sitting at the bar in Cold Spring Harbor Laboratory in Ne York State. Excitement was building about the next phase of the Human Genome Project, in which th DNA sequence would be split into its functional parts – genes. The notebook contained a sweepstak the guesses of the best-informed group of people on the planet concerning one intriguing questio How many genes does it take to build a human?

Senior research scientist Lee Rowen, who was leading a group working on decoding chromosom 14 and 15, sipped her beer as she pondered the question. Genes make proteins, the building blocks life, and the sheer complexity of humans made it seem probable that the number would be hig Higher than the mouse, surely, which was known to have 23,000 genes. Probably also higher than th wheat plant, with 26,000 genes. And, no doubt, far higher than 'The Worm', a favourite laborator species of developmental biologists, with its 20,500 genes.

Despite guesses averaging over 55,000 genes, and topping 150,000, Rowen's understanding of th field meant she was inclined to go low. She placed a bet of 41,440 that year, and followed it up a yea later with a second bet of just 25,947 genes. In 2003, with the true gene number only just emergi from the nearly finished sequence, Rowen was awarded the prize. Her entry was the lowest of all 16 bets, and the latest gene count had just dropped even lower than any scientist had ever predicted.

With just shy of 21,000 genes, the human genome is hardly bigger than that of The Worm (*elegans*). It is half the size of the rice plant, and even the humble water flea outstrips it, with 31,00 genes. None of these species can talk, create, or think intelligent thoughts. You might think, as th scientists entering the Genesweep pool did, that humans would have a great many more genes tha grasses and worms and fleas. After all, genes make proteins, and proteins make bodies. Surely a boo as complex and sophisticated as a human's would need more proteins, and therefore more genes, tha a worm's?

But these 21,000 genes are not the only genes that run your body. We do not live alone. Each of u is a superorganism; a collective of species, living side-by-side and cooperatively running the body th sustains us all. Our own cells, though far larger in volume and weight, are outnumbered ten to one b the cells of the microbes that live in and on us. These 100 trillion microbes – known as the microbio – are mostly bacteria: microscopic beings made of just a single cell each. Alongside the bacteria a other microbes – viruses, fungi and archaea. Viruses are so small and simple that they challenge ou ideas of what even constitutes 'life'. They depend entirely on the cells of other creatures to replica themselves. The fungi that live on us are often yeasts; more complex than bacteria, but still smal single-celled organisms. The archaea are a group that appear to be similar to bacteria, but they are different evolutionarily as bacteria are from plants or animals. Together, the microbes living on th human body contain 4.4 *million* genes – this is the microbiome: the collective genomes of th microbiota. These genes collaborate in running our bodies alongside our 21,000 human genes. By th count, you are just half a per cent human.



A simplified tree of life, showing the three domains and four kingdoms of Domain Eukarya.

We now know that the human genome generates its complexity not only in the number of genes contains, but also through the many combinations of proteins these genes are able to make. We, ar other animals, are able to extract more functions from our genomes than they appear to encode at fir glance. But the genes of our microbes add even more complexity to the mix, providing services to th human body that are more quickly evolved and more easily provided by these simple organisms.

Until recently, studying these microbes relied on being able to culture them on Petri dishes fille with broths of blood, bone marrow, or sugars, suspended in jelly. It's a difficult task: most of th species living in the human gut die on exposure to oxygen – they simply haven't evolved to tolerate What's more, growing microbes on these plates means guessing what nutrients, temperature and gase they might need to survive, and failing to figure this out means failing to learn more about a specie Culturing microbes is the equivalent of checking who's turned up for class by running down a regist – if you don't call someone's name, you won't know if they are there. Today's technology – the DN sequencing made so fast and cheap by the efforts of those working on the Human Genome Project – more like requesting ID at the door; even those that you weren't expecting can be accounted for.

As the Human Genome Project came to a close, expectations were high. It was seen as the key our humanity, God's greatest work, and a sacred library holding the secrets of disease. When the fir draft was completed in June 2000, under budget at $2.7 billion and several years early, the U President, Bill Clinton, declared:

> Today, we are learning the language in which God created life. We are gaining ever more awe for the complexity, the beauty, the wonder of God's most divine and sacred gift. With this profound new knowledge, humankind is on the verge of gaining immense new power to heal. Genome science will have a real impact on all our lives – and even more, on the lives of our children. It will revolutionise the diagnosis, prevention and treatment of most, if not all, human diseases.

But in the years that followed, science journalists the world over began expressing the disappointment in the contribution that knowledge of our complete DNA sequence had made medicine. Although decoding our own instruction book is an irrefutable achievement that has made difference to treatments for several important illnesses, it has not revealed as much as we expecte about the causes of many common diseases. Searching for genetic differences in common to peop with a particular disease did not throw up straightforward links for as many conditions as had bee expected. Often, conditions were weakly linked to tens or hundreds of gene variants, but rarely was

the case that possessing a given gene variant would lead directly to a given disease.

What we failed to appreciate at the turn of the century was that those 21,000 genes of ours are n the full story. The DNA-sequencing technology invented during the Human Genome Project enable another major genome-sequencing programme, but one that received far less media attention: t Human Microbiome Project. Rather than looking at the genome of our own species, the HMP was s up to use the genomes of the microbes that live on the human body – the microbiome – to identi which species are present.

No longer would a reliance on Petri dishes and an over-abundance of oxygen hold back researc into our cohabiters. With a budget of $170 million and a five-year programme of DNA sequencing, t HMP was to read thousands of times as much DNA as the HGP, from microbes living in eightee different habitats on the human body. It was to be a far more comprehensive survey of the genes th make a person, both human and microbial. At the conclusion of the Human Microbiome Project's fir phase of research in 2012, not one world leader made a triumphant statement, and only a handful newspapers featured the story. But the HMP would go on to reveal more about what it means to b human today than our own genome ever has.

Since life began, species have exploited one another, and microbes have proved themselves to b particularly efficient at making a living in the oddest of places. At their microscopic size, the body another organism, particularly a macro-scale backboned creature like a human, represents not just single niche, but an entire world of habitats, ecosystems and opportunities. As variable and dynam as our spinning planet, the human body has a chemical climate that waxes and wanes with hormon tides, and complex landscapes that shift with advancing age. For microbes, this is Eden.

We have been co-evolving side-by-side with microbes since long before we were humans. Befo our ancestors were mammals even. Each animal body, from the tiniest fruit fly to the largest whale, yet another world for microbes. Despite the negative billing many of them get as disease-causi germs, playing host to a population of these miniature life-forms can be extremely rewarding.

The Hawaiian bobtail squid – as big-eyed and colourful as any Pixar character – has diminished major threat to its life by inviting just one species of bioluminescent bacterium to live in a speci cavity in its underbelly. Here, in this light organ, the bacteria, known as *Aliivibrio fischeri*, conve food into light, so that viewed from below, the squid glows. This obscures its silhouette against th moonlit ocean surface, camouflaging it from predators approaching from beneath. The squid owes th protection to its bacterial inhabitants, and they owe the squid for their home.

While housing a microbial light source might seem a particularly inventive way to increase one life chances, squid are far from the only animal species who owe their lives to their body's microbe Strategies for living are many and varied, and cooperation with microbes has been a driving force the evolutionary game since living beings with more than one cell first evolved, 1.2 billion years ago

The more cells an organism is made of, the more microbes can live on it. Indeed, large anima such as cattle are well known for their bacterial hospitality. Cows eat grass, yet using their own gen they can extract very little nutrition from this fibrous diet. They would need specialist proteins, call enzymes, that can break down the tough molecules making the cell walls of the grass. Evolving t genes that make these enzymes could take millennia, as it relies on random mutations in the DN code that can only happen with each passing generation of cows.

A quicker way to acquire the ability to get at the nutrients locked away in grass is to outsource t task to the specialists: microbes. The four chambers of the cow's stomach house populations of plan fibre-busting microbes numbering in their trillions, and the cud – a ball of solid plant fibre – trave

back and forth between the mechanical grinding of the cow's mouth and chemical breakdown by th enzymes produced by microbes living in the gut. Acquiring the genes to do this is quick and easy fo microbes, as their generation times, and therefore opportunities for mutations and evolution, are ofte less than a day.

If bobtail squid and cows can both benefit from teaming up with microbes, is it possible that w humans do as well? We may not eat grass and have a four-chambered stomach, but we do have ou own specialisations. Our stomachs are small and simple, there just to mix the food up, throw in som enzymes for digestion, and add a bit of acid to kill unwelcome bugs. But travel on, through the sma intestine, where food is broken down by yet more enzymes and absorbed into the blood through th carpet of finger-like projections that give it the surface area of a tennis court, and you reach a cul-d sac, more of a tennis ball than a tennis court, that marks the beginning of the large intestine. Th pouch-like patch, at the lower right corner of your torso, is called the caecum, and it is the heart of th human body's microbial community.

Dangling from the caecum is an organ that has a reputation for being there simply to cause pa and infection: the appendix. Its full title – the vermiform appendix – refers to its worm-lik appearance, but it could equally be compared to a maggot or a snake. Appendices vary in length fro a diminutive 2 cm to a distinctly stringy 25 cm, and, rarely, a person may even have two of them, o not one at all. If popular opinion is to be believed, we would be better off without one at all, since f over one hundred years they have been said to have no function whatsoever. In fact, the man wh finally put the anatomy of animals into an elegant evolutionary framework is apparently responsib for this persistent myth. Charles Darwin, in *The Descent of Man*, a follow-up to *On the Origin Species*, included the appendix in a discussion of 'rudimentary' organs. Having compared it with th larger appendices of many other animals, Darwin felt that the appendix was a vestige, steadi withering away as humans changed their diets.

With little to indicate otherwise, the vestigial status of the appendix was barely questioned for th next 100 years, and the perception of its uselessness is only enhanced by its tendency to cause nuisance. So pointless has the medical establishment assumed it to be, that by the 1950s, removing became one of the most common surgical procedures carried out in the developed world. A appendectomy was even often tacked on as a bonus during other abdominal surgery. At one point, man stood a one in eight chance of having his appendix removed during his lifetime, and for a woma the odds were one in four. About 5–10 per cent of people get appendicitis at some stage in their lif usually in the decades before they have children. Untreated, nearly half of these people would die.

This presents a conundrum. If appendicitis were a naturally occurring disease, frequently causin death at a young age, the appendix would be quickly eliminated by natural selection. Those wi appendices large enough to become infected would die, most often before reproducing, and wou therefore fail to pass on their appendix-forming genes. Over time, fewer and fewer people would hav an appendix, and eventually it would be lost. Natural selection would have preferred those witho one.

Darwin's assumption that it was a relic of our pasts might have carried some weight, were it n for the often fatal consequences of possessing one. There are two explanations, therefore, for th persistence of the appendix, and they are not mutually exclusive. The first is that appendicitis is modern phenomenon, brought on by some environmental change. Thus, even a pointless organ cou have persisted in the past simply by keeping out of trouble. The other is that the appendix, far fro being a malign vestige of our evolutionary past, actually has health benefits that outweigh its da side, making its presence worthwhile despite the risk of appendicitis. That is, natural selection prefe

those of us who possess one. The question is, why?

The answer lies in its contents. The appendix, which averages about 8 cm in length and centimetre across, forms a tube, protected from the flow of mostly digested food passing its entranc But rather than being a withered strand of flesh, it is packed full of specialised immune cells ar molecules. They are not inert, but rather an integral part of the immune system, protecting, cultivatir and communicating with a collective of microbes. Inside, these microbes form a 'biofilm' – a layer individuals that support one another and exclude bacteria that might cause harm. The appendix, f from being functionless, appears to be a safe-house that the human body has provided for its microbi inhabitants.

Like a nest egg stashed away for a rainy day, this microbial stockpile comes in handy at times strife. After an episode of food poisoning or a gastrointestinal infection, the gut can be repopulate with its normal inhabitants, which have been lurking in the appendix. It might seem like an excessiv bodily insurance policy, but it is only in recent decades that gut infections such as dysentery, cholei and giardiasis have been all but eliminated in the Western world. Public sanitation measure including sewerage systems and water-treatment plants, have prevented such illnesses in develope countries, but globally, one in five of all childhood deaths are still caused by infectious diarrhoea. Fe those who do not succumb, possession of an appendix likely hastens their recovery. It is only in context of relatively good health that we have come to believe that the appendix has no functio Indeed, the negative consequences of undergoing an appendectomy have been masked by the moder sanitised lifestyle.

As it turns out, appendicitis *is* a modern phenomenon. In Darwin's day, it was extremely rar causing very few deaths, so we can perhaps forgive him for thinking the appendix was merely one evolution's leftovers, neither harming nor helping us. Appendicitis became common in the la nineteenth century, with cases in one British hospital shooting up from a stable rate of three or fo people per year prior to 1890, to 113 cases per year by 1918; a rise mirrored throughout th industrialised world. Diagnosis had never been a problem – the cramping pain followed by a quic autopsy if the patient didn't make it revealed the cause of death even before appendicitis became common as it is now.

Many explanations were put forward to explain it, from increased meat, butter and sug consumption, to blocked sinuses and rotting teeth. At that time, consensus opinion alighted on reduction in fibre in our diets as the ultimate cause, but hypotheses still abound, including one th blames the rise on improved water sanitation and the hygienic conditions it brings – the ve development that appeared to render the appendix almost impotent. Whatever the ultimate cause, b the Second World War our collective memory had been purged of the rise in appendicitis case leaving us with the impression that it is an expected, though unwelcome, feature of normal life.

In fact, even in the modern, developed world, keeping hold of the appendix at least until adultho can prove to be beneficial, protecting us from recurring gastrointestinal infections, immun dysfunction, blood cancer, some autoimmune diseases and even heart attacks. Somehow, its role as sanctuary of microbial life brings these benefits.

That the appendix is far from pointless tells us something bigger: our microbes matter to o bodies. It seems they are not just hitching a ride, but providing a service important enough that o guts have evolved an asylum just to keep them safe. The question is, who is there, and what exactly d they do for us?

Although we have known for several decades that our bodies' microbes offer us a few perks, lik synthesising some essential vitamins, and breaking down tough plant fibres, the degree of interactio

between our cells and theirs wasn't realised until relatively recently. In the late 1990s, using the too of molecular biology, microbiologists took a great leap into discovering more about our strang relationship with our microbiotas.

New DNA-sequencing technology can tell us which microbes are present, and allows us to pla them within the tree of life. With each step down this hierarchy, from domain to kingdom the phylum through class, order and family, and on to genus, species and strain, individuals are more ar more closely related to one another. Working from the bottom up, we humans (genus *Homo* ar species *sapiens*) are great apes (family Hominidae), which sit alongside monkeys and others with the primates (order Primates). All of us primates belong with our fellow furry milk-drinkers, as member of the mammals (class Mammalia), who then fit within a group containing animals with spinal cord (phylum Chordata), and finally, amongst *all* animals, spinal cord or otherwise (think our squid, for example), in kingdom Animalia, and domain Eukarya. Bacteria and other microb (except the category-defying viruses) find their place on the other great branches of the tree of lif belonging not to kingdom Animalia, but to their own unique kingdoms in separate domains.

Sequencing allows different species to be identified and placed within the hierarchy of the tree life. One particularly useful segment of DNA, the 16S rRNA gene, acts as a kind of barcode f bacteria, providing a quick ID without the need to sequence an entire bacterial genome. The mo similar the codes of the 16S rRNA genes, the more closely related the species, and the more twigs ar branches of the tree of life they share.

DNA sequencing, though, is not the only tool at our disposal when it comes to answering questio about our microbes, especially regarding what they do. For these mysteries, we often turn to mice. particular, 'germ-free' mice. The first generations of these laboratory staples were born by Caesarea section and kept in isolation chambers, preventing them from ever becoming colonised with microbe either beneficial or harmful ones. From then on, most germ-free mice are simply born in isolation germ-free mothers, sustaining a sterile line of rodents untouched by microbes. Even their food ar bedding is irradiated and packed in sterile containers to prevent any contamination of the mic Transferring mice between their bubble-like cages is quite an operation, involving vacuums ar antimicrobial chemicals.

By comparing germ-free mice with 'conventional' mice, which have their full complement microbes, researchers are able to test the exact effects of having a microbiota. They can even coloni germ-free mice with a single species of bacterium, or a small set of species, to see precisely how ea strain contributes to the biology of a mouse. From studying these 'gnotobiotic' ('known life') mic we get an inkling of what microbes do in us as well. Of course, they are not the same as humans, ar sometimes results of experiments in mice are wildly different from results in humans, but they are fantastically useful research tool and very often provide crucial leads. Without rodent models, medic science would progress at a millionth of the speed.

It was by using germ-free mice that the commander-in-chief of microbiome science, Profess Jeffrey Gordon from the University of Washington in St Louis, Missouri, discovered a remarkab indication of just how fundamental the microbiota are to the running of a healthy body. He compare the guts of germ-free mice with those of conventional mice, and he learnt that under the direction bacteria the mouse cells lining the gut wall were releasing a molecule that 'fed' the microbe encouraging them to take up residence. The presence of a microbiota not only changes the chemist of the gut, but also its morphology. The finger-like projections grow longer at the insistence microbes, making the surface area large enough to capture the energy it needs from food. It's bee estimated that rats would need about 30 per cent more to eat if it weren't for their microbes.

It is not only microbes that are benefiting from sharing our bodies, but us too. Our relationsh with them is not just one of tolerance, but encouragement. This realisation, combined with th technical power of DNA sequencing and germ-free mouse studies, began a revolution in science. Th Human Microbiome Project, run by the United States' National Institutes for Health, alongside man other studies in laboratories around the world, has revealed that we utterly depend on our microbes f health and happiness.

The human body, both inside and out, forms a landscape of habitats as diverse as any on Earth. Just a our planet's ecosystems are populated by different species of plants and animals, so the habitats of th human body host different communities of microbes. We are, like all animals, an elaborate tube. Foo goes in at one end of the tube and comes out the other. We see our skin as covering our 'outside' surface, but the inner surface of our tube is also 'outside' – exposed to the environment in a simila way. Whilst the layers of our skin protect us from the elements, invading microbes and harmf substances, the cells of the digestive tract that runs right through us must also keep us safe. Our tru 'inside' is not this digestive tract, but the tissues and organs, muscles and bones that are packed awa between the inside and the outside of our tubular selves.

The surface of a human being, then, is not just their skin, but the twists and turns, furrows an folds of their inner tube as well. Even the lungs, the vagina and the urinary tract count as being on th outside – as part of the surface – when you view the body in this way. No matter if it's inner or oute *all* of this surface is potential real estate for microbes. Sites vary in their value, with dense city-lik communities building up in resource-rich prime locations like the intestines, while sparser collection of species occupy more 'rural' or hostile locations such as the lungs and the stomach. The Huma Microbiome Project set out to characterise these communities, by sampling microbes from eighte sites across the inner and outer surfaces of the human body, in each of hundreds of volunteers.

Over the first five years of the HMP, molecular microbiologists oversaw a biotechnological ech of the golden age of species discovery; one that saw formaldehyde-infused collecting cabinets stuffe with the haul of birds and mammals discovered and named by explorer–biologists in the eighteen and nineteenth centuries. The human body is, as it turns out, a treasure trove of strains and speci new to science, many of them present on only one or two of the volunteers participating in the stud Far from each person harbouring a replicate set of microbes, very few strains of bacteria are commo to everyone. Each of us contains communities of microbes as unique as our fingerprints.

Though the finer details of our inhabitants are specific to each of us, we all play host to simil microbes at the highest hierarchical levels. The bacteria living in your gut, for example, are mo similar to the bacteria in the gut of the person sitting next to you, than they are to the bacteria on yo knuckles. What's more, despite our distinctive communities, the functions they perform are usuall indistinguishable. What bacterium A does for you, bacterium B might do for your best friend.

From the arid, cool plains of the skin on the forearms to the warm, humid forests of the groin an the acidic, low-oxygen environment of the stomach, each part of the body offers a home to tho microbes that can evolve to exploit it. Even within a habitat, distinct niches host different collection of species. The skin, all two square metres of it, contains as many ecosystems as the landscapes of th Americas, but in miniature. The occupants of the sebum-rich skin of the face and back are as differe from those of the dry, exposed elbows as the tropical forests of Panama are from the rocks of th Grand Canyon. Where the face and back are dominated by species belonging to the genu *Propionibacterium*, which feed off the fats released by the densely packed pores in these areas, th elbows and forearms host a far more diverse community. Moist areas, including the navel, th

underarms and the groin, are home to *Corynebacterium* and *Staphylococcus* species, which love th high humidity, and feed off the nitrogen in the sweat.

This microbial second skin provides a double layer of protection to the body's true interio reinforcing the sanctity of the barrier formed by the skin cells. Invading bacteria with malicio intentions struggle to get a foothold in these closely guarded bodily border towns, and face a onslaught of chemical weapons when they try. Perhaps even more vulnerable to invasion are the so tissues of the mouth, which must resist colonisation by a flood of intruders smuggled on food an floating in the air.

From the mouths of their volunteers, researchers working on the Human Microbiome Project too not just one sample, but nine, each from a slightly different location. These nine sites turned out have discernibly different communities, within mere centimetres of one another, made up of aroun 800 species of bacteria dominated by *Streptococcus* species and a handful of other group *Streptococcus* gets bad press, on account of the many species that cause diseases, from 'strep throa to the flesh-eating infection necrotising fasciitis. But many other species in this genus behav themselves impeccably, crowding out nasty challengers in this vulnerable entrance to the body. C course these tiny distances between sampling locations within the mouth may seem insignificant to u but to microbes they are like vast plains and mountain ranges with climates as different as northe Scotland and the south of France.

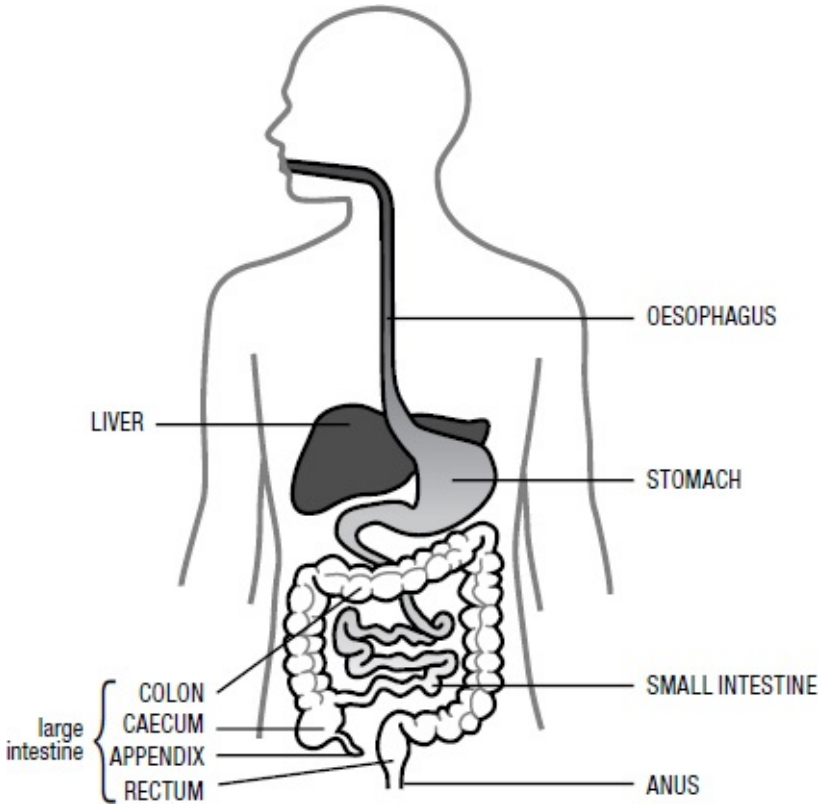
Imagine, then, the climatic leap from the mouth to the nostrils. The viscous pool of saliva on rugged bedrock replaced by a hairy forest of mucus and dust. The nostrils, as you might expect fro their gatekeeper status at the entrance to the lungs, harbour a great range of bacterial group numbering around 900 species, including large colonies of *Propionibacterium, Corynebacteriu Staphylococcus* and *Moraxella*.

Heading down the throat towards the stomach sees the enormous diversity of species found in th mouth drop dramatically. The highly acidic stomach kills many of the microbes that enter with foo and just one species is known for certain to reside there permanently in some people – *Helicobact pylori*, whose presence may be both a blessing and a curse. From this point on, the journey through th digestive tract reveals an ever-greater density – and diversity – of microbes. The stomach opens in the small intestine, where food is rapidly digested by our very own enzymes and absorbed into th bloodstream. There are still microbes here though; around ten thousand individuals in every millilit of gut contents at the start of this 7-m-long tube, rising to an incredible ten million per millilitre at th end, where the small intestine meets the large intestine's starting point.

Just outside the safe-house created by the appendix is a teeming metropolis of microbes, in th heart of the microbial landscape of the human body – the tennis-ball-like caecum, to which th appendix is attached. This is the epicentre of microbial life, where trillions of individual microbes at least 4,000 species make the most of the partially digested food that has passed through round on of the nutrient-extraction process in the small intestine. The tough bits – plant fibres – are left over f the microbes to tackle in round two.

The colon, which forms most of the length of the large intestine, running up the right-hand side your torso, across your body under your rib cage, and back down the left-hand side, provides hom for microbes, numbering one trillion (1,000,000,000,000) individuals per millilitre by now, in th folds and pits of its walls. Here, they pick up the scraps of our food and convert them into energ leaving their waste products to be absorbed into the cells of the colon's walls. Without the gut microbes, these colonic cells would wither and die – whilst most of the body's cells are fed by sug transported in the blood, the colonic cells' main energy source is the waste products of the microbiot

The colon's moist, warm, swamp-like environment, in parts completely devoid of oxygen, provid not only a source of incoming food for its inhabitants, but a nutrient-rich mucus layer, which ca sustain the microbes in times of famine.



The human gut.

Because HMP researchers would have to cut open their volunteers to sample the different habita of the gut, a far more practical way of collecting information about the gut's inhabitants was sequence the DNA of microbes found in the stool. On its passage through the gut, the food we eat mostly digested and absorbed, both by us and our microbes, leaving only a small amount to come o the other end. Stool, far from being the remains of our food, is mostly bacteria, some dead, son alive. Around 75 per cent of the wet weight of faeces is bacteria; plant fibre makes up about 17 p cent.

At any one time, your gut contains about 1.5 kg of bacteria – that's about the same weight as th liver – and the lifespans of individuals are a matter of just days or weeks. The 4,000 species bacteria found in the stool tell us more about the human body than all the other sites put togethe These bacteria become a signature of our health and dietary status, not only as a species, but as society, and personally. By far the most common group of bacteria in the stool are the *Bacteroide* but because our gut bacteria eat what we eat, bacterial communities in the gut vary from person person.

The gut microbes aren't just scavengers, though, taking advantage of our leftovers. We hav exploited them too, especially when it comes to outsourcing functions that would take us time evolve for ourselves. After all, why bother having a gene for a protein that makes Vitamin B12, whic is essential for our brain function, when *Klebsiella* will do it for you? And who needs genes to shap the intestine's walls, when *Bacteroides* have them? It's much cheaper and easier than evolving the afresh. But, as we will discover, the role of the microbes living in the gut goes far beyond synthesisin a few vitamins.

The Human Microbiome Project began by looking only at the microbiotas of healthy people. Wi
this benchmark set down, the HMP went on to ask how they differ in poor health, whether our mode
illnesses could be a consequence of those differences, and if so, what was causing the damage? Cou
skin conditions like acne, psoriasis and dermatitis signal disruption to the skin's normal balance
microbes? Might inflammatory bowel disease, cancers of the digestive tract and even obesity be du
to shifts in the communities of microbes living in the gut? And, most extraordinarily, could condition
that were apparently far removed from microbial epicentres, such as allergies, autoimmune diseas
and even mental health conditions, be brought on by a damaged microbiota?

Lee Rowen's educated guess in the sweepstake at Cold Spring Harbor hinted at a much deep
discovery. We are not alone, and our microbial passengers have played a far greater role in ou
humanity than we ever expected. As Professor Jeffrey Gordon puts it:

> This perception of the microbial side of ourselves is giving us a new view of our individuality. A new sense of our connection to the microbial world. A sense of the legacy of our personal interactions with our family and environment early in life. It's causing us to pause and consider that there might be another dimension to our human evolution.

We have come to depend on our microbes, and without them, we would be a mere fraction of ou
true selves. So what does it mean to be just 10 per cent human?

ONE

Twenty-First-Century Sickness

In September 1978, Janet Parker became the last person on Earth to die of smallpox. Just 70 mil from the place where Edward Jenner had first vaccinated a young boy against the disease with cowpo pus from a milkmaid, 180 years earlier, Parker's body played host to the virus in its final outing human flesh. Her job as a medical photographer at the University of Birmingham in the UK would n have put her in direct jeopardy were it not for the proximity of her dark room to the laborato beneath. As she sat ordering photographic equipment over the telephone one afternoon that Augus smallpox viruses travelled up the air ducts from the Medical School's 'pox' room on the floor belov and brought on her fatal infection.

The World Health Organisation (WHO) had spent a decade vaccinating against smallpox arour the world, and that summer they were on the brink of announcing its complete eradication. It had be nearly a year since the final naturally occurring case of the disease had been recorded. A your hospital cook had recovered from a mild form of the virus in its final stronghold of Somalia. Such victory over disease was unprecedented. Vaccination had backed smallpox into a corner, ultimatel leaving it with no vulnerable humans to infect, and nowhere to go.

But the virus did have one tiny pocket to retreat to – the Petri dishes filled with human cells th researchers used to grow and study the disease. The Medical School of Birmingham University w one such viral sanctuary, where one Professor Henry Bedson and his team were hoping to develop th means to quickly identify any pox viruses that might emerge from animal populations now th smallpox was gone from humans. It was a noble aim, and they had the blessing of the WHO, despi inspectors' concerns about the pox room's safety protocols. With just a few months left befor Birmingham's lab was due to close anyway, the inspectors' worries did not justify an early closure, o an expensive refit of the facilities.

Janet Parker's illness, at first dismissed as a mild bug, caught the attention of infectious disea doctors a fortnight after it had begun. By now she was covered in pustules, and the possible diagnos turned to smallpox. Parker was moved into isolation, and samples of fluid were extracted for analysi In an irony not lost on Professor Bedson, his team's expertise in identifying pox viruses was calle upon for verification of the diagnosis. Bedson's fears were confirmed, and Parker was moved to specialist isolation hospital nearby. Two weeks later on 6 September, with Parker still critically ill i hospital, Professor Bedson was found dead at his home by his wife, having slit his own throat. On 1 September 1978, Janet Parker died of her disease.

Janet Parker's fate was that of many hundreds of millions before her. She had been infected by strain of smallpox known as 'Abid', named after a three-year-old Pakistani boy who had succumbed the disease eight years previously, shortly after the WHO's intensive smallpox eradication campaig had got under way in Pakistan. Smallpox had become a significant killer across most of the world b the sixteenth century, in large part due to the tendency of Europeans to explore and colonise oth regions of the world. In the eighteenth century, as human populations grew and became increasing mobile, smallpox spread to become one of the major causes of death around the world, killing as mar

as 400,000 Europeans each year, including roughly one in ten infants. With the uptake of variolation a crude and risky predecessor of vaccination, involving intentional infection of the healthy with th smallpox fluids of sufferers – the death toll was reduced in the latter half of the eighteenth centur Jenner's discovery of vaccination using cowpox in 1796 brought further relief. By the 1950s, smallpo had been all but eliminated from industrialised countries, but there were still 50 million cas annually worldwide resulting in over 2 million deaths each year.

Though smallpox had released its grip on countries in the industrialised world, the tyrannical reig of many other microbes continued in the opening decade of the twentieth century. Infectious diseas was by far the dominant form of illness, its spread aided by our human habits of socialising an exploring. The exponentially rising human population, and with that, ever-greater populatio densities, only eased the person-to-person leap that microbes needed to make in order to continue the life cycle. In the United States, the top three causes of death in 1900 were not heart disease, cancer an stroke, as they are today, but infectious diseases, caused by microbes passed between people. Betwee them, pneumonia, tuberculosis and infectious diarrhoea ended the lives of one-third of people.

Once regarded as 'the captain of the men of death', pneumonia begins as a cough. It creeps dow into the lungs, stifling breathing and bringing on a fever. More a description of symptoms than disease with a sole cause, pneumonia owes its existence to the full spectrum of microbes, from tin viruses, through bacteria and fungi, to protozoan ('earliest-animal') parasites. Infectious diarrhoe too, can be blamed on each variety of microbe. Its incarnations include the 'blue death' – cholera which is caused by a bacterium; the 'bloody flux' – dysentery – which is usually thanks to parasit amoebae; and 'beaver fever' – giardiasis, again from a parasite. The third great killer, tuberculosi affects the lungs like pneumonia, but its source is more specific: an infection by a small selection bacteria belonging to the genus *Mycobacterium.*

A whole host of other infectious diseases have also left their mark, both literally and figurativel on our species: polio, typhoid, measles, syphilis, diphtheria, scarlet fever, whooping cough an various forms of flu, among many others. Polio, caused by a virus that can infect the central nervou system and destroy nerves controlling movements, paralysed hundreds of thousands of children eac year in industrialised countries at the beginning of the twentieth century. Syphilis – the sexuall transmitted bacterial disease – is said to have affected 15 per cent of the population of Europe at som point in their lifetime. Measles killed around a million people a year. Diphtheria – who remembe this heart-breaker? – used to kill 15,000 children each year in the United States alone. The flu kille between five and ten times as many people in the two years following the First World War than wer killed fighting in the war itself.

Not surprisingly these scourges had a major influence on human life expectancy. Back then, i 1900, the average life expectancy across the whole planet was just thirty-one years. Living in developed country improved the outlook, but only to just shy of fifty years. For most of ou evolutionary history, we humans have managed to live to only twenty or thirty years old, though th *average* life expectancy would have been much lower. In one single century, and in no small pa because of developments in one single decade – the antibiotic revolution of the 1940s – our averag time on Earth was doubled. In 2005, the average human could expect to live to sixty-six, with those the richest countries reaching, again on average, the grand old age of eighty.

These figures are highly influenced by the chances of surviving infancy. In 1900, when up to thre in ten children died before the age of five, average life expectancy was dramatically lower. If, at th turn of the next century, rates of infant mortality had remained at the level they were in 1900, ov half a million children would have died before their first birthday in the United States each yea

Instead, around 28,000 did. Getting the vast majority of children through their first five yea unscathed allows most of them to go on and live to 'old age' and brings the average life expectancy u accordingly.

Though the effects are far from fully felt in much of the developing world, we have, as a specie gone a long way towards conquering our oldest and greatest enemy: the pathogen. Pathogens disease-causing microbes – thrive in the unsanitary conditions created by humans living en mass The more of us we cram onto our planet, the easier it becomes for pathogens to make a living. E migrating, we give them access to yet more humans, and in turn, more opportunity to breed, muta and evolve. Many of the infectious diseases we have contended with in the last few centuri originated in the period after early humans had left Africa and set up home across the rest of th world. Pathogens' world domination mirrored our own; few species have as loyal a pathogen following as us.

For many of us living in more developed countries, the reign of infectious diseases is confined the past. Just about all that remain of thousands of years of mortal combat with microbes a memories of the sharp prick of our childhood immunisations followed by the 'reward' of a polio vaccine-infused sugar lump, and perhaps more clearly, the melodramatic queues outside the dinn hall as we waited with our school friends for a teenage booster shot. For many children and teenage growing up now, the burden of history is even lighter, as not only the diseases themselves, but once routine vaccinations, such as the dreaded 'BCG' for tuberculosis, are no longer necessary.

Medical innovations and public health measures – largely those of the late nineteenth and ear twentieth centuries – have made a profound difference to life as a human. Four developments particular have taken us from a two-generation society to a four-, or even five-generation society just one, long, lifetime. The first and earliest of these, courtesy of Edward Jenner and a cow name Blossom, is, of course, vaccination. Jenner knew that milkmaids were protected from developin smallpox by virtue of having been infected by the much milder cowpox. He thought it possible that th pus from a milkmaid's pustules might, if injected into another person, transfer that protection. H first guinea pig was an eight-year-old boy named James Phipps – the son of Jenner's gardener. Havin inoculated Phipps, Jenner went on to attempt to infect the brave lad, twice injecting pus from a tru smallpox infection. The young boy was utterly immune.

Beginning with smallpox in 1796, and progressing to rabies,typhoid, cholera and plague in th nineteenth century, and dozens of other infectious diseases since 1900, vaccination has not on protected millions from suffering and death, but has even led to countrywide elimination or comple global eradication of some pathogens. Thanks to vaccination, we no longer have to rely solely on o immune systems' experiences of full-blown disease to defend us against pathogens. Instead acquiring natural defences against diseases, we have circumvented this process using our intellect provide the immune system with forewarning of what it might encounter.

Without vaccination, the invasion of a new pathogen prompts sickness and possibly death. Th immune system, as well as tackling the invading microbe, produces molecules called antibodies. If th person survives, these antibodies form a specialist team of spies that patrol the body looking o specifically for that microbe. They linger long after the disease has been conquered, primed to let th immune system know the moment there is a reinvasion of the same pathogen. The next time it encountered, the immune system is ready, and the disease can be prevented from taking hold.

Vaccination mimics this natural process, teaching the immune system to recognise a particula pathogen. Instead of suffering the disease to achieve immunity, now we suffer only the injection, oral administration, of a killed, weakened or partial version of the pathogen. We are spared illness bu

our immune systems still respond to the introduction of the vaccine, and produce antibodies that he the body to resist disease if the same pathogen invades for real.

Society-wide vaccination programmes are designed to bring about ‘herd immunity’ by vaccinatin a large enough proportion of the population that contagious diseases cannot continue their sprea They have meant that many infectious diseases are almost completely eliminated in develope countries, and one, smallpox, has been totally eradicated. Smallpox eradication, as well as droppin the incidence of the disease from 50 million cases a year worldwide to absolutely none in little mo than a decade, has saved governments billions in both the direct cost of vaccination and medical car and the indirect societal costs of illness. The United States, which contributed a disproportionate large amount of money to the global eradication effort, recoups its investment every twenty-six da in unspent costs. Governmental vaccination schemes for a dozen or so other infectious diseases hav dramatically reduced the number of cases, reducing suffering and saving lives and money.

Today, most countries in the developed world run vaccination programmes against ten or s infectious diseases, and half a dozen are marked for regionwide elimination or global eradication b the World Health Organisation. These programmes have had a dramatic effect on the incidence o these diseases. Before the worldwide eradication programme for polio began in 1988, the viru affected 350,000 people a year. In 2012, the disease was confined to just 223 cases in only thre countries. In just twenty-five years, around half a million deaths have been prevented and 10 millio children who would have been paralysed are free to walk and run. Likewise for measles and rubella: a single decade, vaccination of these once-common diseases has prevented 10 million deat worldwide. In the United States, as in most of the developed world, the incidence of nine maj childhood diseases has been reduced by 99 per cent by vaccination. In developed countries, for eve 1,000 babies born alive in 1950, around forty would die before their first birthday. By 2005, that figu had been reduced by an order of magnitude, to about four. Vaccination is so successful that only th oldest members of Western society can remember the horrendous fear and pain of these deadl diseases. Now, we are free.

After the development of the earliest vaccines came a second major health innovation: hygien medical practice. Hospital hygiene is something we are still under pressure to improve today, but i comparison with the standards of the late nineteenth century, modern hospitals are temples o cleanliness. Imagine, instead, wards crammed full with the sick and dying, wounds left open an rotting, and doctors’ coats covered in the blood and gore of years of surgeries. There was little point i cleaning – infections were thought to be the result of ‘bad air’, or *miasma*, not germs. This toxic mi was thought to rise from decomposing matter or filthy water – an intangible force beyond the contr of doctors and nurses. Microbes had been discovered 150 years previously, but the connection had n been made between them and disease. It was believed that miasma could not be transferred b physical contact, so infections were spread by the very people charged with curing them. Hospita were a new invention, born of a drive towards public health care and a desire to bring ‘moder medicine to the masses. Despite the good intentions, they were filthy incubators for disease, and tho attending them risked their lives for the treatment they needed.

Women suffered most as a result of the proliferation of hospitals, as the risks of labour and givin birth, rather than falling, actually rose. By the 1840s, up to 32 per cent of women giving birth hospital would subsequently die. Doctors – all male at that time – blamed their deaths on anythin from emotional trauma to uncleanliness of the bowel. The true cause of this horrifyingly high dea rate would at last be unravelled by a young Hungarian obstetrician by the name of Ignaz Semmelweis

At the hospital where Semmelweis worked, the Vienna General, women in labour were admitte

on alternate days into two different clinics. One was run by doctors, and the other by midwives. Eve second day, as Semmelweis walked to work, he'd see women giving birth on the street outside th hospital doors. On those days, it was the turn of the clinic run by doctors to admit labouring wome But the women knew the odds for their survival would not be good if they could not hold on until th following day. Childbed fever – the cause of most of the deaths – lurked in the doctors' clinic. So the waited, cold and in pain, in the hope that their baby would delay its entrance to the world until aft midnight had struck.

Getting admitted to the midwife-run clinic was, relatively speaking, a far safer propositio Between 2 and 8 per cent of new mothers would die of childbed fever in the care of midwives – f fewer than succumbed in the doctors' clinic.

Despite his junior status, Semmelweis began to look for differences between the two clinics th might explain the death rates. He thought overcrowding and the climate of the ward might be blame, but found no evidence of any difference. Then, in 1847, a close friend and fellow doctor, Jako Kolletschka, died after being accidentally cut by a student's scalpel during an autopsy. The cause death: childbed fever.

After Kolletschka's death, Semmelweis had a realisation. It was the doctors who were spreadi death among the women in their ward. Midwives, on the other hand, were not to blame. And he kne why. Whilst their patients laboured, the doctors would pass the time in the morgue, teaching medic students using human cadavers. Somehow, he thought, they were carrying death from the autops room to the maternity ward. The midwives never touched a corpse, and the patients dying on the ward were probably those whose post-natal bleeding meant a visit from the doctor.

Semmelweis had no clear idea of the form that death was taking on its passage from the morgue the maternity ward, but he had an idea of how to stop it. To rid themselves of the stench of rottin flesh, doctors often washed with a solution of chlorinated lime. Semmelweis reasoned that if it cou remove the smell, perhaps it could remove the vector of death as well. He instituted a policy th doctors must wash their hands in chlorinated lime between conducting autopsies and examining the patients. Within a month, the death rate in his clinic had dropped to match that of the midwive clinic.

Despite the dramatic results Semmelweis achieved in Vienna and later in two hospitals Hungary, he was ridiculed and ignored by his contemporaries. The stiffness and stench of a surgeon scrubs were said to be a mark of his experience and expertise. 'Doctors are gentlemen, an gentlemen's hands are clean,' said one leading obstetrician at the time, all the while infecting an killing dozens of women each month. The mere notion that doctors could be responsible for bringi death, not life, to their patients caused huge offence, and Semmelweis was cast out of th establishment. Women continued to risk their lives giving birth for decades, as they paid the price the doctors' arrogance.

Twenty years later, the great Frenchman Louis Pasteur developed the germ theory of diseas which attributed infection and illness to microbes, not miasma. In 1884, Pasteur's theory was prove by the elegant experiments of the German Nobel prize-winning doctor Robert Koch. By this tim Semmelweis was long dead. He had become obsessed by childbed fever, and had gone mad with rag and desperation. He railed against the establishment, pushing his theories and accusing h contemporaries of being irresponsible murderers. He was lured by a colleague to an insane asylu under the pretence of a visit, then forced to drink castor oil and beaten by the guards. Two weeks late he died of a fever, probably from his infected wounds.

Nonetheless, germ theory was the breakthrough that gave Semmelweis's observations and polici

a truly scientific explanation. Steadily, antiseptic hand-washing was adopted by surgeons acro Europe. Hygienic practices became common after the work of the British surgeon Joseph Lister. In th 1860s, Lister read of Pasteur's work on microbes and food, and decided to experiment with chemic solutions on wounds to reduce the risk of gangrene and septicaemia. He used carbolic acid, which w known to stop wood from rotting, to wash his instruments, soak dressings and even to clean woun during surgery. Just as Semmelweis had achieved a drop in the death rate, so too did Lister. Where 4 per cent of those he operated on had died before, Lister's pioneering use of carbolic acid slash mortality by two-thirds, to around 15 per cent.

Closely following Semmelweis's and Lister's work on hygienic medical practice was a thi public health innovation – a development that prevented millions from becoming ill in the first plac As in many developing countries today, water-borne diseases were a major health hazard in the We before the twentieth century. The sinister forces of miasma were still at work, polluting rivers, wel and pumps. In August 1854, the residents of London's Soho district began to fall ill. They develope diarrhoea, but not as you or I might know it. This was white, watery stuff, and there was no end of Each person could produce up to 20 litres per day, all of which was dumped in the cesspits benea Soho's cramped houses. The disease was cholera, and it killed people in their hundreds.

Dr John Snow, a British doctor, was sceptical of the miasma theory, and had spent some yea looking for an alternative explanation. From previous epidemics, he had begun to suspect that chole was water-borne. The latest outbreak in Soho gave him the opportunity to test his theory. H interviewed Soho residents and mapped cholera cases and deaths, looking for a common source. Sno realised that the victims had all drunk from the same water pump on Broad Street (now Broadwi Street) at the heart of the outbreak. Even deaths further afield could be traced back to the Broad Stre pump, as cholera was carried and passed on by those infected there. There was one anomaly: a grou of monks in a Soho monastery who got their water from the same pump were completely unaffecte It was not their faith that had afforded them protection, though, but their habit of drinking the pump water only after they had turned it into beer.

Snow had looked for patterns – connections between those who had become ill, reasons why othe had escaped, links explaining the appearance of the disease outside its Broad Street epicentre. H rational study used logic and evidence to unravel the outbreak and trace its source, eliminating re herrings and accounting for anomalies. His work led to the disabling of the Broad Street pump and th subsequent discovery that a nearby cesspit had overflowed and was contaminating the water supply. was the first-ever epidemiological study – that is, it used the distribution and patterns of a disease understand its source. John Snow went on to use chlorine to disinfect the water supplying the Broa Street pump, and his chlorination methods were quickly put to use elsewhere. As the nineteen century came to a close, water sanitation had become widespread.

As the twentieth century unfolded, all three public health innovations became more and mo sophisticated. By the end of the Second World War, a further five diseases could be prevented throug vaccination, taking the total to ten. Medical hygiene techniques were adopted internationally, an chlorination became a standard process in water-treatment plants. The fourth and final innovation put an end to the reign of microbes in the developed world began with one world war and conclude with the second. It was the result of the hard work, and good fortune, of a handful of men. The first these, the Scottish biologist Sir Alexander Fleming, is famously credited with 'accidentally discovering penicillin in his laboratory at St Mary's Hospital in London. In fact, Fleming had bee hunting for antibacterial compounds for years.

During the First World War he had treated wounded soldiers on the Western Front in France, onl