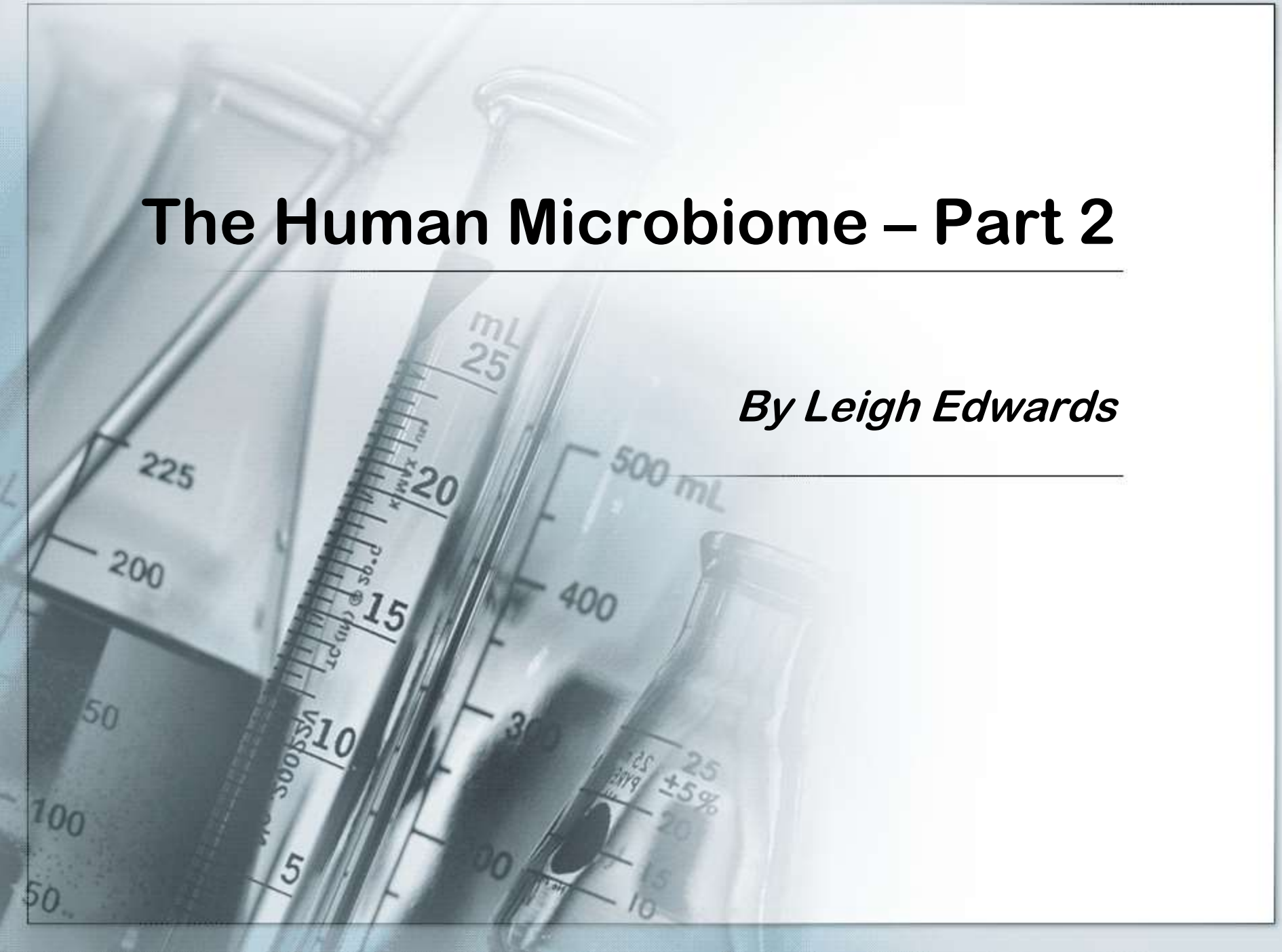
The Human Microbiome – Part 2



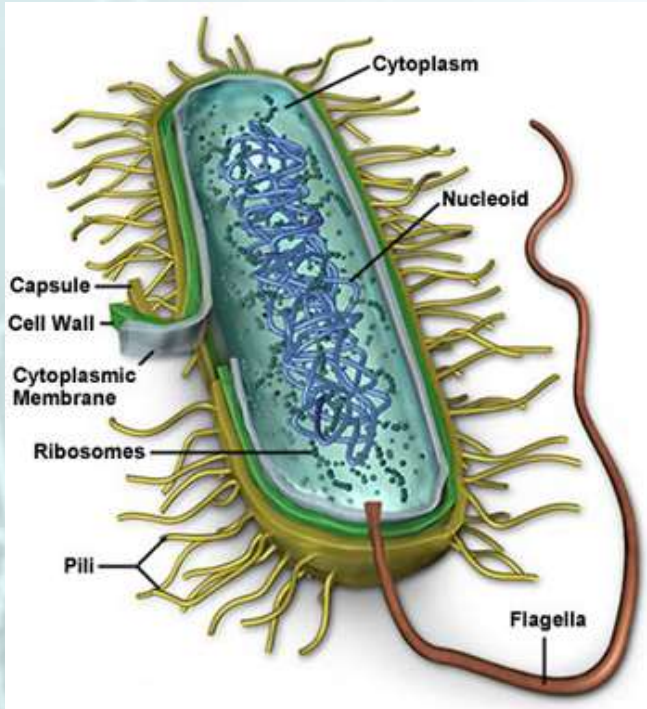
By Leigh Edwards

Life on Earth

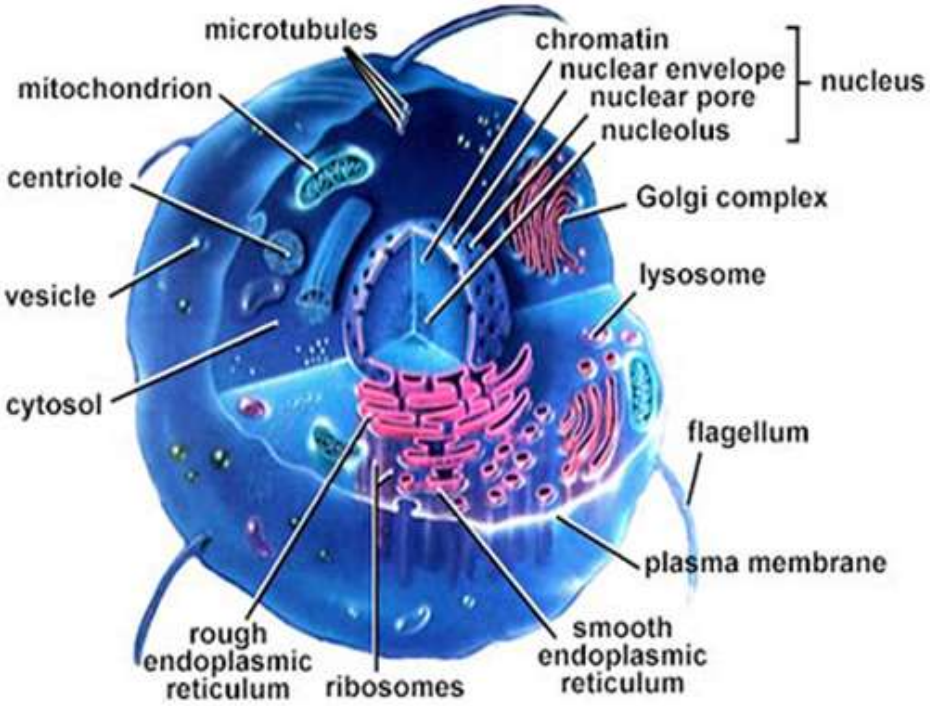
- Earth formed around 4.5 Bya
- The first appearance of life around 3.86 billion years ago (Bya)
- First life was single cells e.g. bacteria - evidence of stromatolites in Greenland rock formations
- Life remained as simple single cells for Billions of years

Divisions of Life - Cells

- Prokaryotes are tiny compared to eukaryotes
- Viruses are tiny compared to prokaryotes
- Viruses 25 – 250 nm, prokaryotes 100 – 5000 nm, eukaryotes 10,000 – 100,000 nm



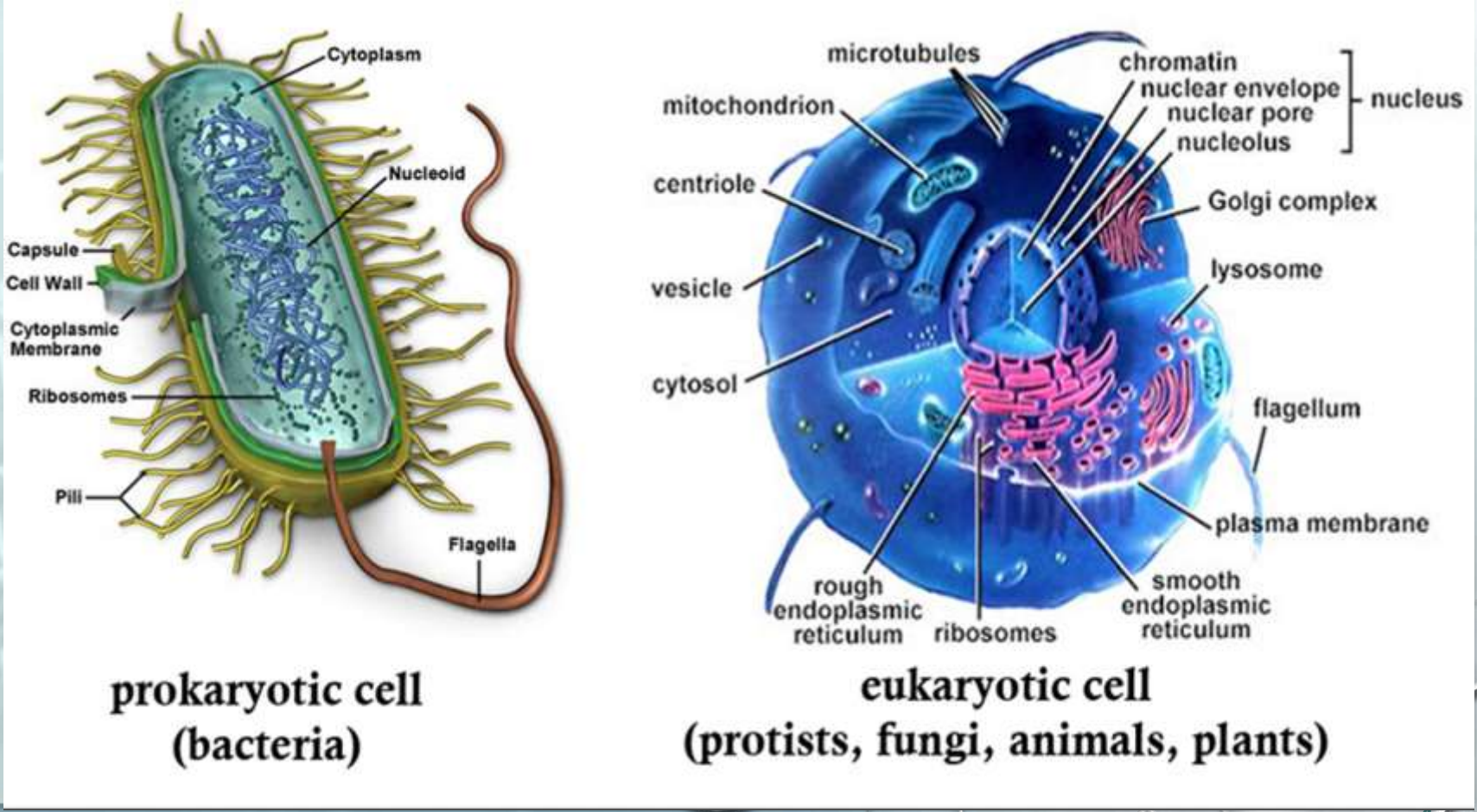
prokaryotic cell
(bacteria)



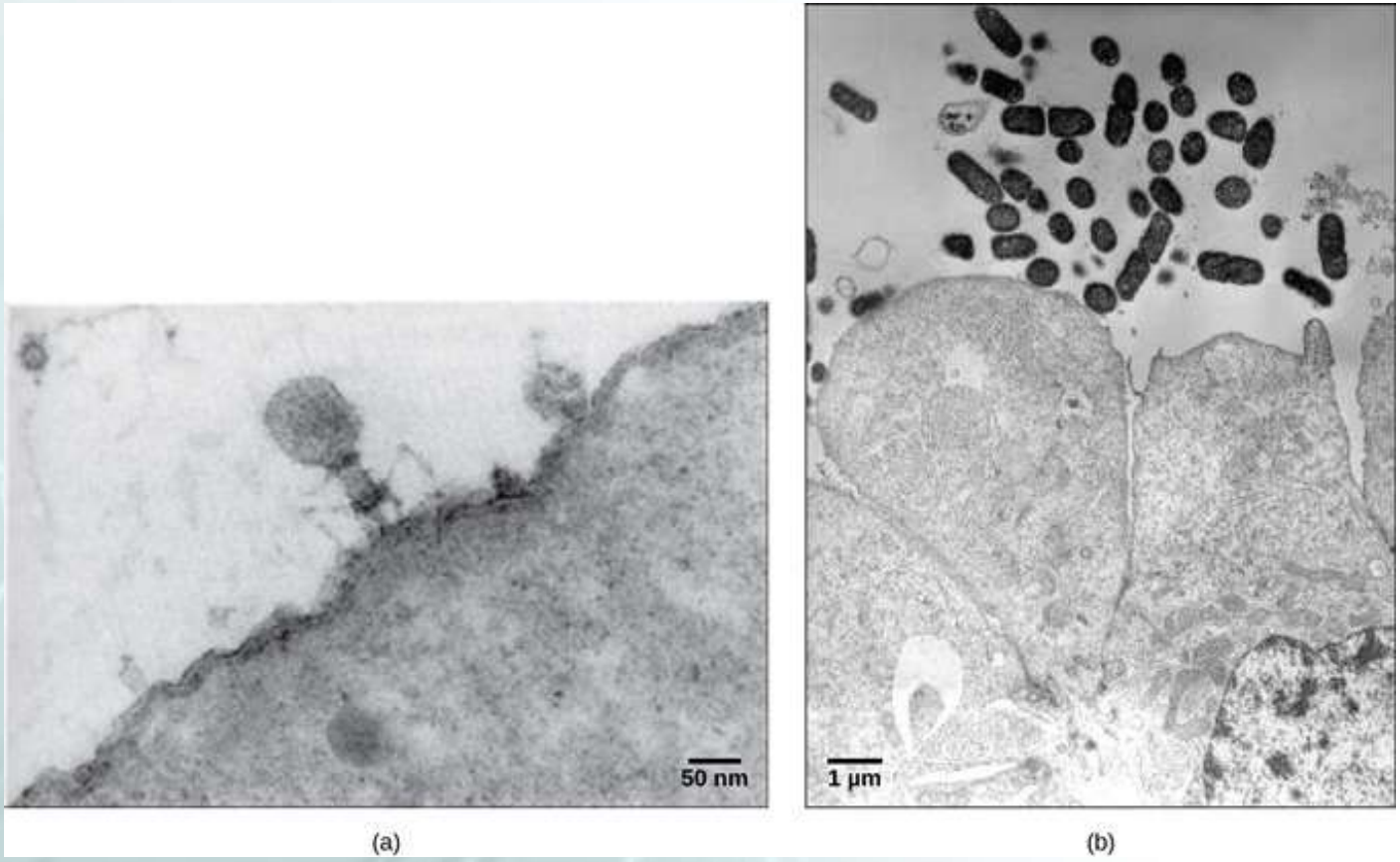
eukaryotic cell
(protists, fungi, animals, plants)

Divisions of Life - Cells

- Eukaryotic cells – animals, plants, fungi and protists
  - Protists are single-celled organisms, such as a protozoan or simple alga



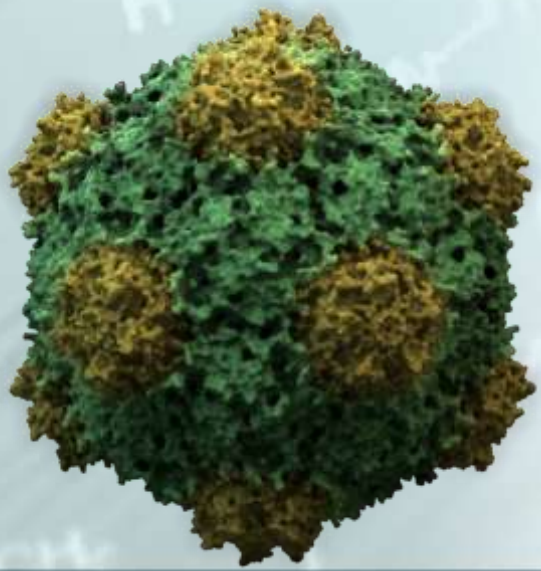
Divisions of Life - Cells

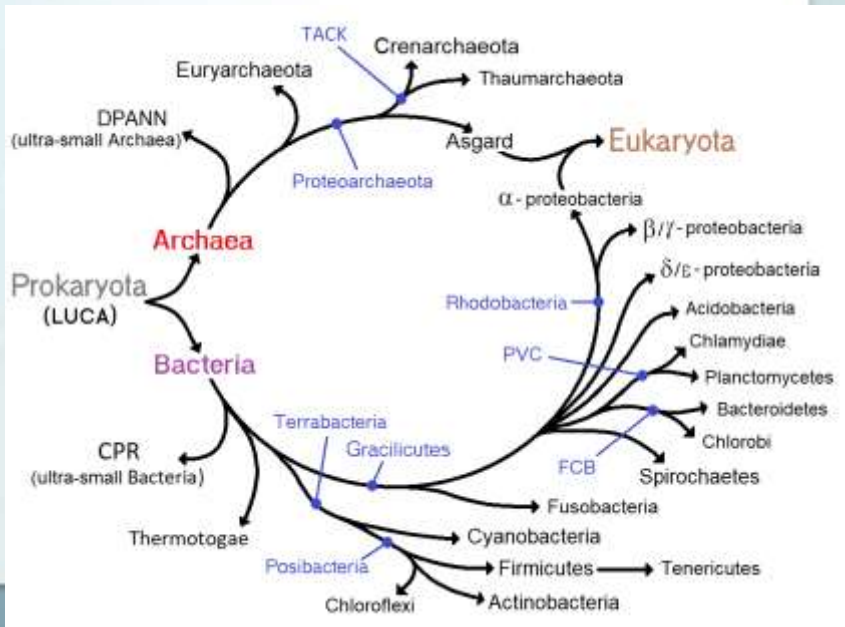


- Examples of transmission electron micrographs of viruses: In these transmission electron micrographs, (a) a virus is dwarfed by the bacterial cell it infects, while (b) these E. coli cells are dwarfed by cultured colon cells.

Divisions of Life

- For every person and child on the planet there estimated to be 50 tonnes of bacteria alive and well
- Estimated to be 10^{31} viruses in our biosphere and a significant number are in the oceans and in the ocean sediments
- In 1 ml of seawater there are around 1 million viruses
- Viruses are by far the most abundant biological entity on Earth

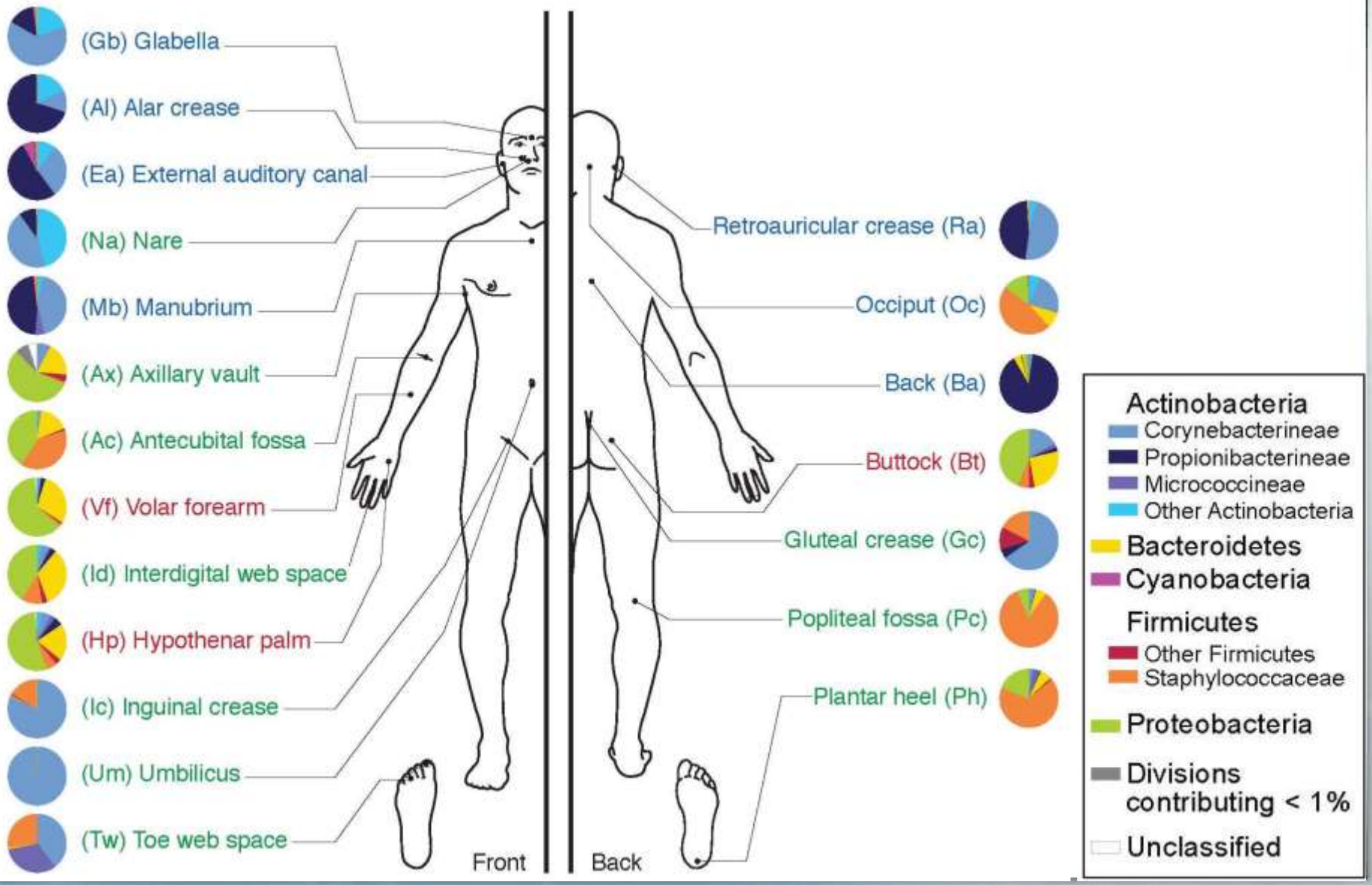




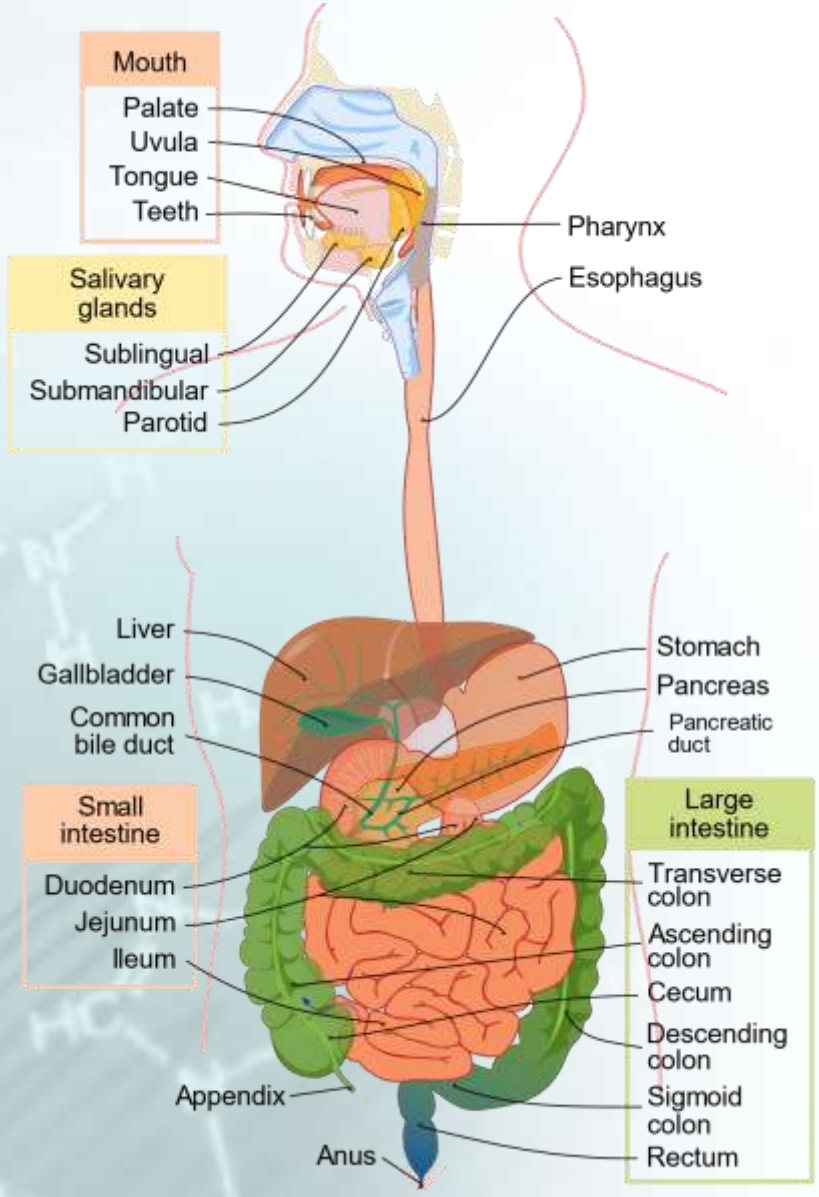
What are Microbiomes?

- Our bodies harbour a huge array of micro-organisms
  - Bacteria are the biggest players, we also host single celled organisms known as archaea
  - As well as fungi, viruses and other microbes – including special viruses that attack bacteria called bacteriophages – yeasts are (eukaryotic) fungi
  - Viruses are tiny protein capsules (capsids) containing DNA or RNA – they need cells to reproduce
- Together these organisms are dubbed the human microbiota
- Your body's microbiome is all the genes your microbiota contains
- Colloquially the two terms are often used interchangeably

What are Microbiomes?



What are Microbiomes?



What are Microbiomes?

- Animals and plants are no longer seen as autonomous entities but rather as biomolecular networks
  - Composed of the host plus its associated microbes
  - As such, they forge a collective genome

- Human microbiome project – genetic analysis

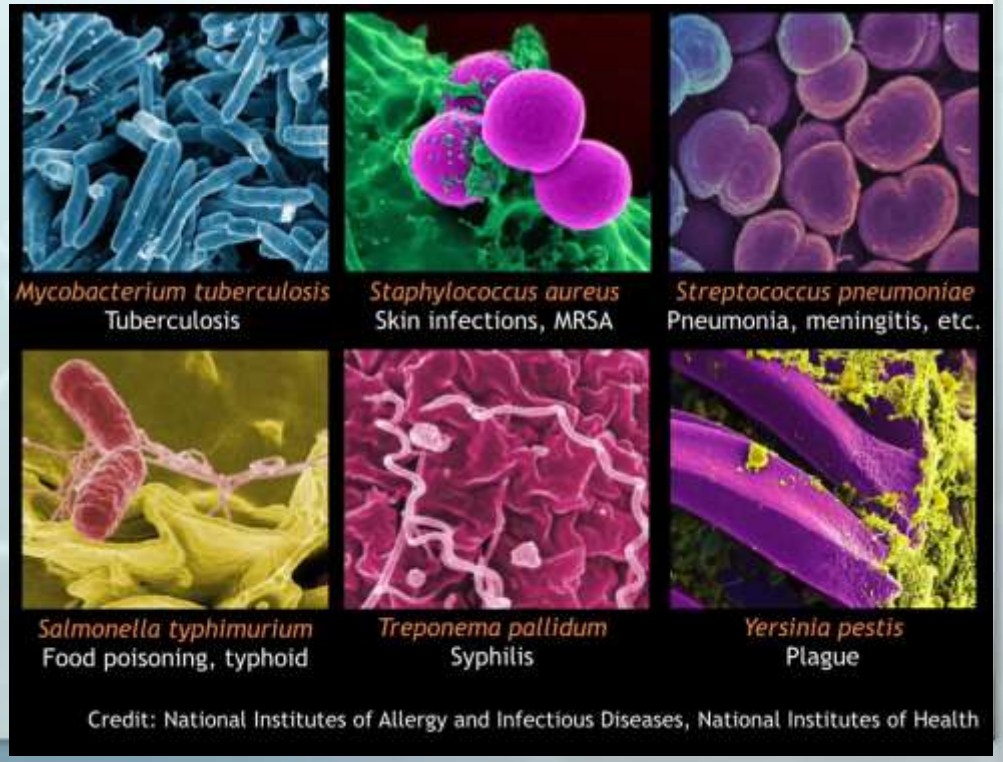
- I'm going to focus on the microbes in our guts to best illustrate our co-dependencies
  - In one gram of faeces there are 100M bacteria, 100M viruses, skin cells, yeasts and other fungi – so it is not just the bacteria!

What are Microbiomes?

- Symbiosis – where two organisms live together, usually to their mutual benefit
  - E.g. a symbiotic pair are cows and the bacteria that live in their guts gain 70% of their energy via their microbes – Humans 10%
- Commensal - a class of relationships between two organisms where one organism benefits without affecting the other's parts
  - Clostridium difficile (C-diff) is typically a normal commensal member of our gut microbiome, but after a course of antibiotics can opportunistically cause life-threatening infection
  - The balance has been destroyed & then C-diff grows like a weed
  - Bacterial toxins then cause leaky junctions in the cells lining the gut leading to a horribly infectious & severe diarrhoea
  - Dangerous in the elderly where it kills 1 out of 11 sufferers
- Pathogenic microbes – those causing disease
  - Or just got into the wrong place
- Parasitic organisms – mostly negative for the host, but not always!

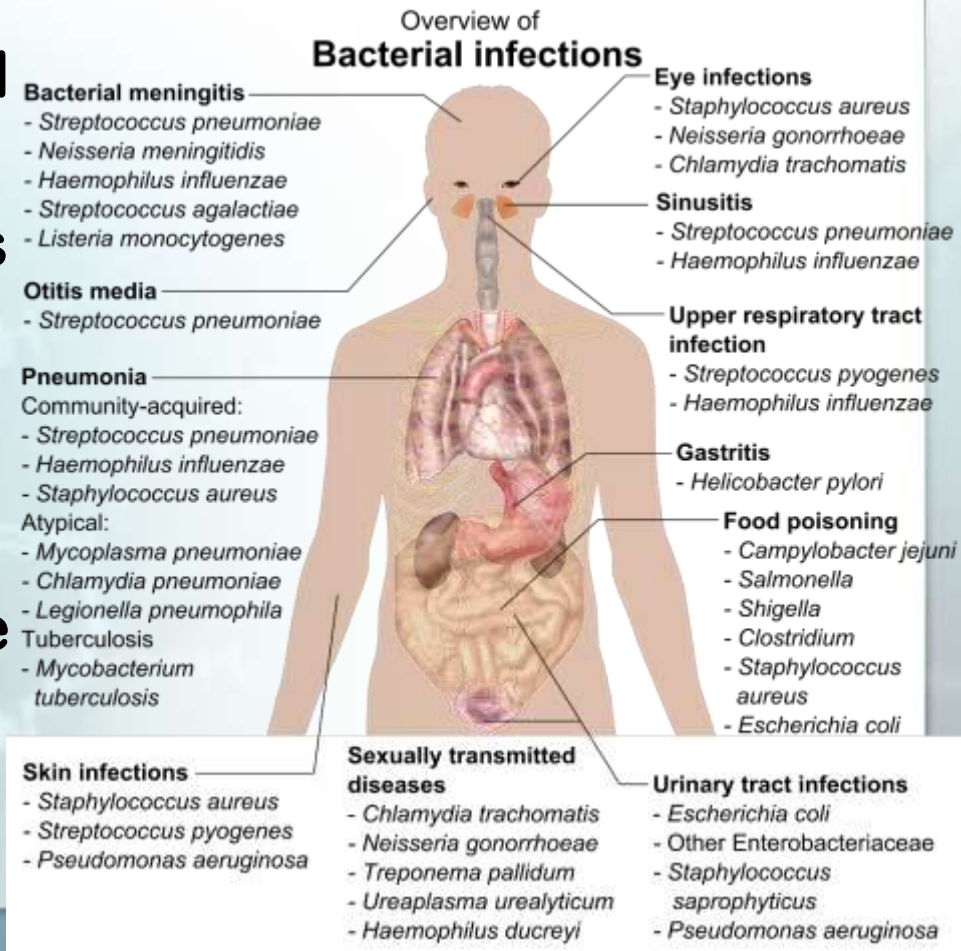
Microbes and Disease

- The view we have today of microbes is as agents of disease and of dirt and filth
- It became clear that many of the most infamous plagues of humanity were in fact caused by bacteria
- Everything from tuberculosis, plague, cholera, leprosy, gonorrhea, syphilis - all of these terrible diseases are the work of microbes



Microbes and Disease

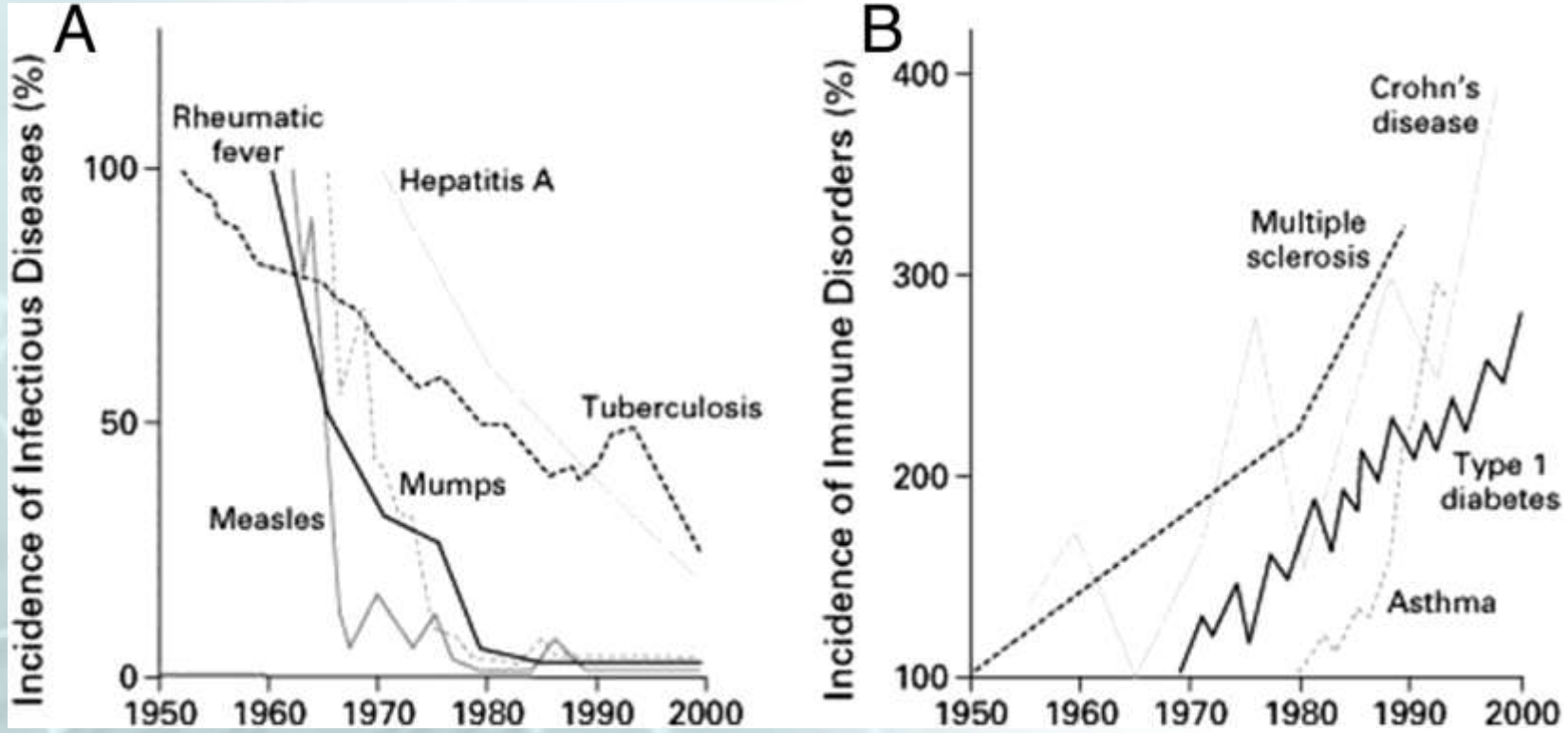
- So they were forever billed as things kill us, things that we need to destroy
- Headlines like this abound in the papers
- Every time someone takes a swab of a random surface, a beard, a desk or a microphone or a piece of clothing, and finds bacteria in there, the implication is always we've done a poor job of cleaning



Microbes and Disease

- This reputation is deeply unfair because only a small minority of microbes are actually responsible for disease
- Maybe a hundred harmful kinds or so, the vast majority are actually benign or beneficial to us
- Humans aerosolise around 37 million microbes per hour
- They are in fact the Lords of the planet, they run the show
- We are just a footnote in their world and they've been here for the longest time

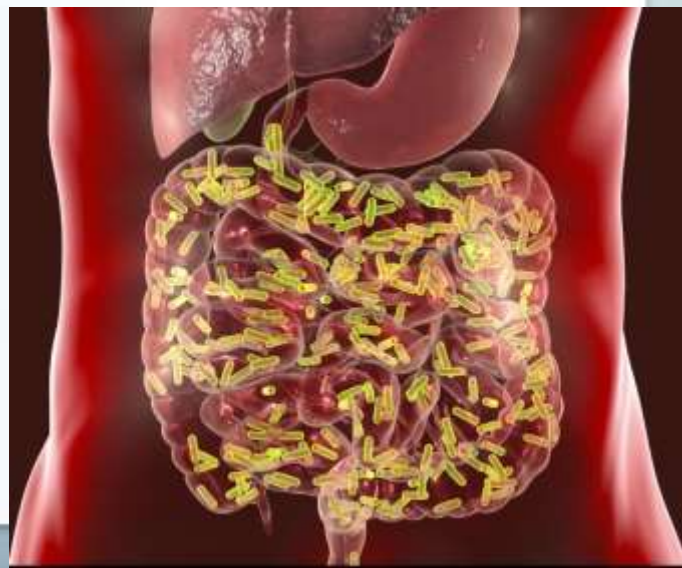
The inverse relationship between
(A) infectious disease incidence and
(B) the rates of immune disorders suggested that a reduction in infections might be causing the human immune system to malfunction



Megan Scudellari PNAS 2017;114:7:1433-1436

Gut Microbes and Wellbeing

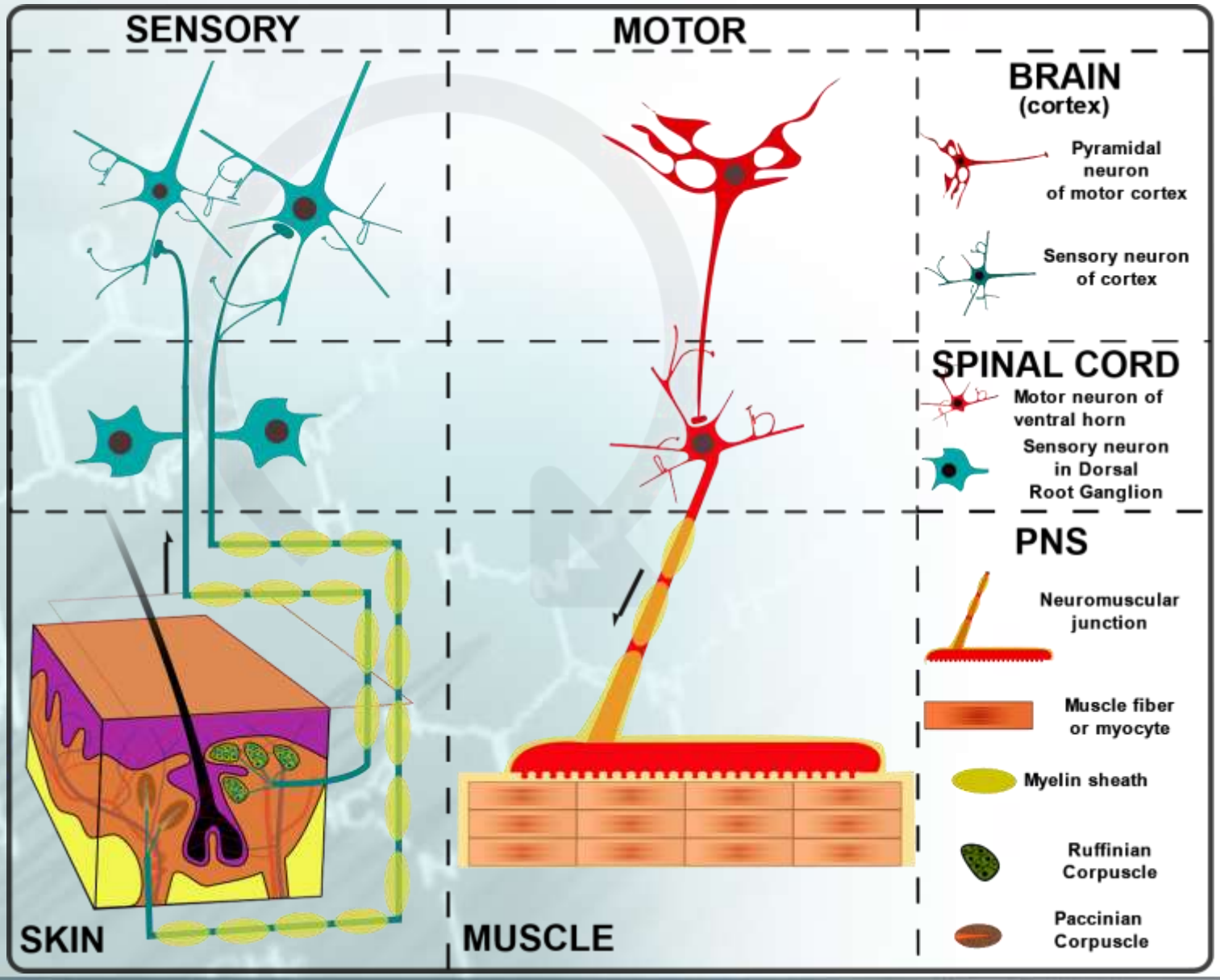
- The relationship between the makeup of a person's gut microbiome and:
  - Their immune systems function
  - Nutritional health
  - Body form and obesity
  - Disease incidence such as MS, Crones disease, IBS, Parkinson's Disease and Dementia
  - All are under detailed study by Scientists, globally



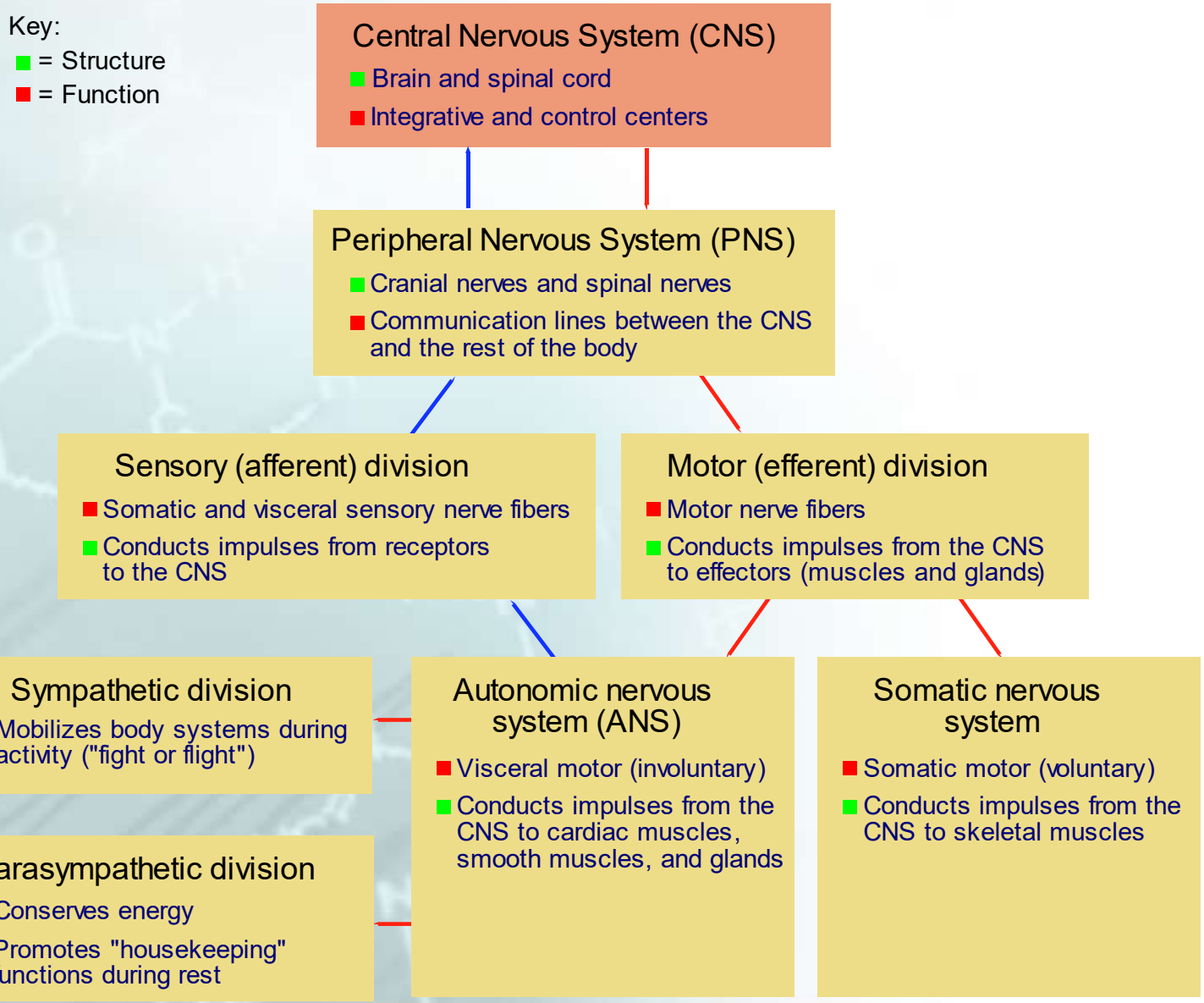
Gut Microbes and Wellbeing

- Your immune system is key to your health because most of it (70%)is located in your digestive system!
- The surface of your skin may be a $2m^2$
- The surface area of your digestive system particularly the small intestine is 30 to 40 m^2 if you unfolded it all
  - It's got huge surface area due to folds and fingers called villi (in the small and large intestines)
  - A huge surface area to maximize the absorption of the nutrients from the foods
- Our greatest surface area of exposure to the outside world it's actually not our skin, it is actually our intestines
- So whenever you eat food your body / immune system has to decide if it's food or something to be attacked

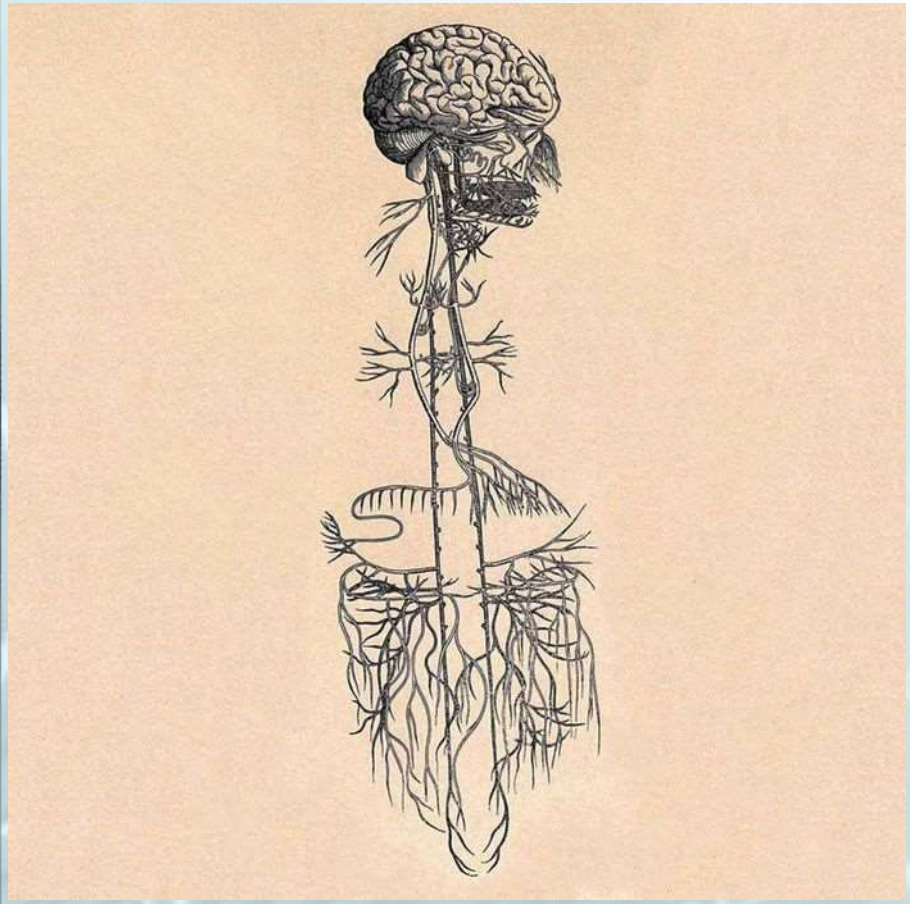
Nervous System

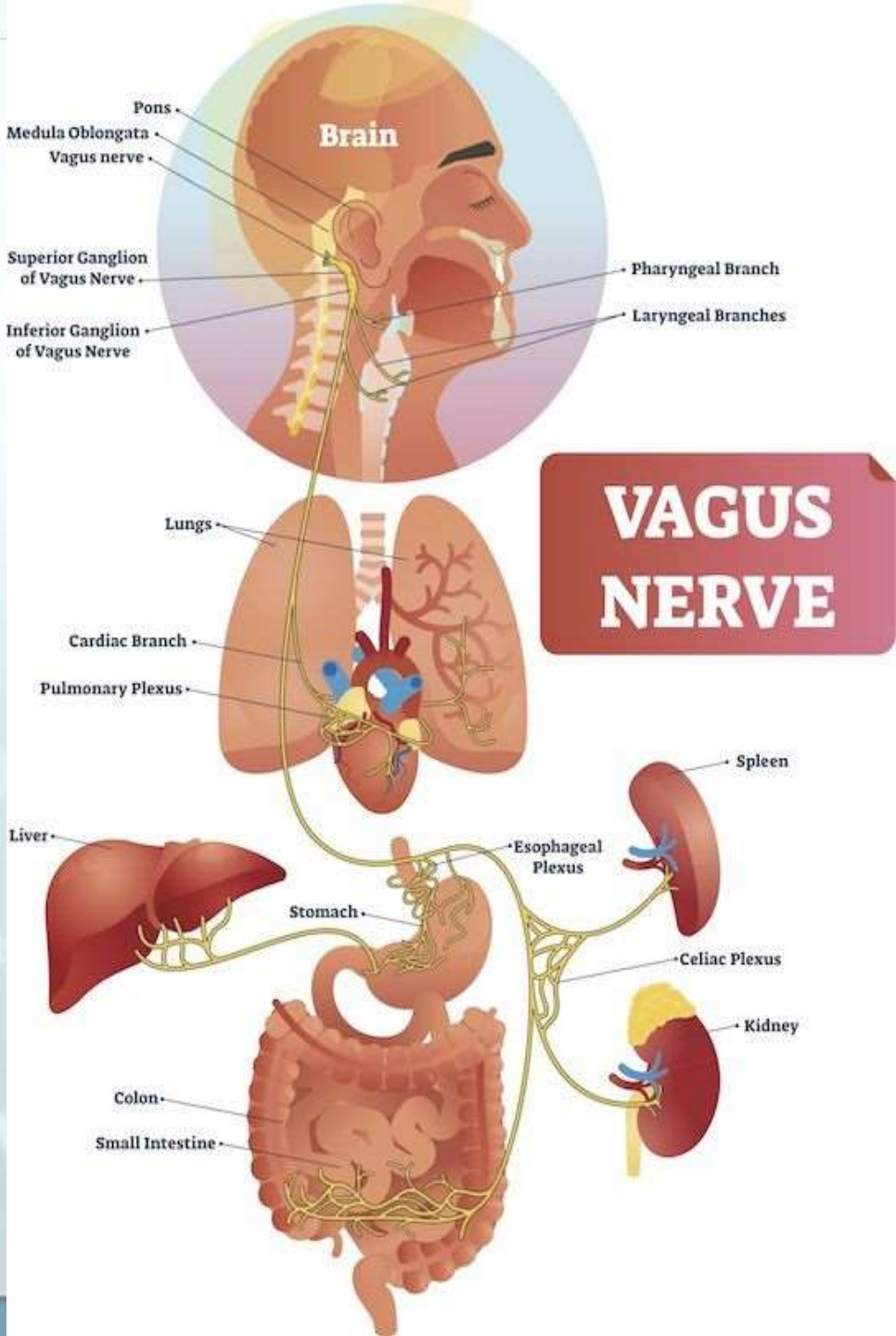


Nervous System



Microbiomes Vagus Nerve





Microbiomes - Vagus Nerve

- Provides the primary control for the nervous system's parasympathetic division: the rest-and-digest counterpoint to the sympathetic nervous system's fight-or-flight response
  - When the body is not under stress, the Vagus nerve sends commands that slow heart and breathing rates and increase digestion
  - In times of stress, control shifts to the sympathetic system, which produces the opposite effect

- The Vagus nerve also carries sensory signals from internal organs back to the brain, enabling the brain to keep track of the organs' actions

- About 10% to 20% of the Vagus nerve cells connect with the digestive system to send commands from the brain to control muscles that move food through the gut

- The movement of those muscles is then controlled by a separate nervous system embedded within the walls of the digestive system

Microbiomes - Vagus Nerve

- The remaining 80% to 90% of the neurons carry sensory information from the stomach and intestines to the brain
  - This communication line between the brain and the gastrointestinal tract is called the gut-brain axis
  - It keeps the brain informed about the status of muscle contraction
  - The speed food is passing through the gut
  - Plus feelings of hunger or satiety
- A 2017 study published in the Journal of Internal Medicine found that the Vagus nerve is so closely entwined with the digestive system that stimulation of the nerve can improve Irritable Bowel Syndrome (IBS)
- In recent decades, many researchers have found that this brain-gut axis has another counterpart — the bacteria that live inside the intestines
- This microbiome communicates with the brain through the Vagus nerve, affecting not just food intake but also mood and inflammation response
- Much of the existing research involves experiments with mice and rats rather than humans
  - Nonetheless, the results are striking and show that changes in the microbiome may cause changes in the brain

Microbiomes – Effects

- Gut brain axis - a two-way line of communication via nerves that run from the gut to the brain
  - The immune system can send signals between the two and bacteria in our gut produce chemicals like dopamine and serotonin
  - Gut bacteria communicate with Enterochromaffin (EC) cells, the gut-derived serotonin is a pathway by which microbes can impact our metabolism
- The Enteric Nervous System (ENS) is one of the main divisions of the Autonomic Nervous System (ANS)
- Consists of a mesh-like system of neurons that governs the function of the gastrointestinal tract
- It is capable of acting independently of the sympathetic and parasympathetic nervous systems, although it may be influenced by them
- The ENS is also called the second brain – hundreds of millions of neurons

Microbiomes – Effects

- Peptic ulcers are painful affecting approximately 50 million Americans each year

- Physicians long thought that stress and spicy food caused people to develop these sores — that seemed to make sense, given that ulcer patients often complain about burning pain after eating spicy food

- So for almost 100 years, doctors prescribed rest and a bland diet

Microbiomes – Effects

- Vagotomy (cutting of the Vagus nerve) is a now-obsolete therapy that was performed for peptic ulcer disease
- Reduced the secretion of stomach acid
- Now being researched as a less invasive alternative weight-loss procedure to gastric bypass surgery
- The procedure curbs the feeling of hunger and is sometimes performed in conjunction with putting bands on patients' stomachs, resulting in an average of 43% of excess weight lost at six months with diet and exercise

Microbiomes – Effects

- One serious side effect of a vagotomy is a vitamin B12 deficiency later in life – perhaps after about 10 years – that is similar to pernicious anemia
- The vagus normally stimulates the stomach's parietal cells to secrete acid and intrinsic factor
- Intrinsic factor is needed to absorb vitamin B12 from food
- Vagotomy reduces this secretion and ultimately leads to the deficiency, which, if left untreated, causes nerve damage, tiredness, dementia, paranoia, and ultimately death

Microbiomes – Effects

- Researchers from Aarhus University and Aarhus University Hospital have demonstrated that vagotomy prevents (halves the risk of) the development of Parkinson's disease

- Suggesting that Parkinson's disease begins in the gastrointestinal tract and spreads via the Vagus nerve to the brain

- Giving further evidence to the theory that dysregulated environmental stimuli, such as that received by the Vagus nerve from the gut, may have a negative effect on the dopamine reward system of the substantia nigra, thereby causing Parkinson's disease

Microbiomes – Effects

- In 1982, Australian researchers Barry Marshall and Robin Warren discovered that the real culprit behind peptic ulcers
- The cause is the bacterium Helicobacter pylori, which burrows into the stomach's mucosal lining
- Doctors have come up with a better treatment for ulcers: antibiotics
- The discovery of Helicobacter pylori earned Marshall & Warren the Nobel Prize in Physiology or Medicine in 2005

Microbiomes – Effects

- Sometimes called the forgotten organ
- Can affect our appetite (food preferences) & weight
- Helps regulate our blood pressure
- Initially similar to mother's, but it stabilises by the time we are about 2 - 3 years old - becomes adult like
- Individual genetics matter
- Our microbiome changes / cycles over 24 hours
- Our microbiome changes throughout our life
- But our environment, our long-term diet, stress and the drugs we take, such as antibiotics, continue to play key roles in shaping our microbiome
- As we age our microbiomes tends to become much less diverse & less stable

Microbiomes – Effects

- Laboratory mice raised in sterile conditions
- Never encountered bacteria before so has no gut bacteria
- As a result of that it has many physiological problems
- Their bones don't develop properly nor do it's blood vessels
- Various parts of its body are imperfectly formed because they have never encountered any microbial signals
- It’s a testament to how microbes shape and sculpt our bodies
- They help to influence the development of our organs and that includes the immune system
  - It promotes many kinds of immune cells
  - Calibrates the immune system striking a right balance between inflammatory responses that will help us deal with infection
- Such sterile mice can then be exposed to particular microbes, or groups of microbes, to explore their impact

Microbiomes – Effects

- Stops us from overreacting to imagined and harmless threats
  - Things like dust and pollen and other allergens in the world around us
- Microbes allow us to calibrate our responses, that we can strike a balance between reacting and overreacting
- In return the immune system selects for those microbes that live with us, rather than indiscriminately killing them
- It gets to decide which species get to live with us & where
- The immune system cares for the helpful species, decides who gets to live there & their population sizes
  - It can also chuck out invaders

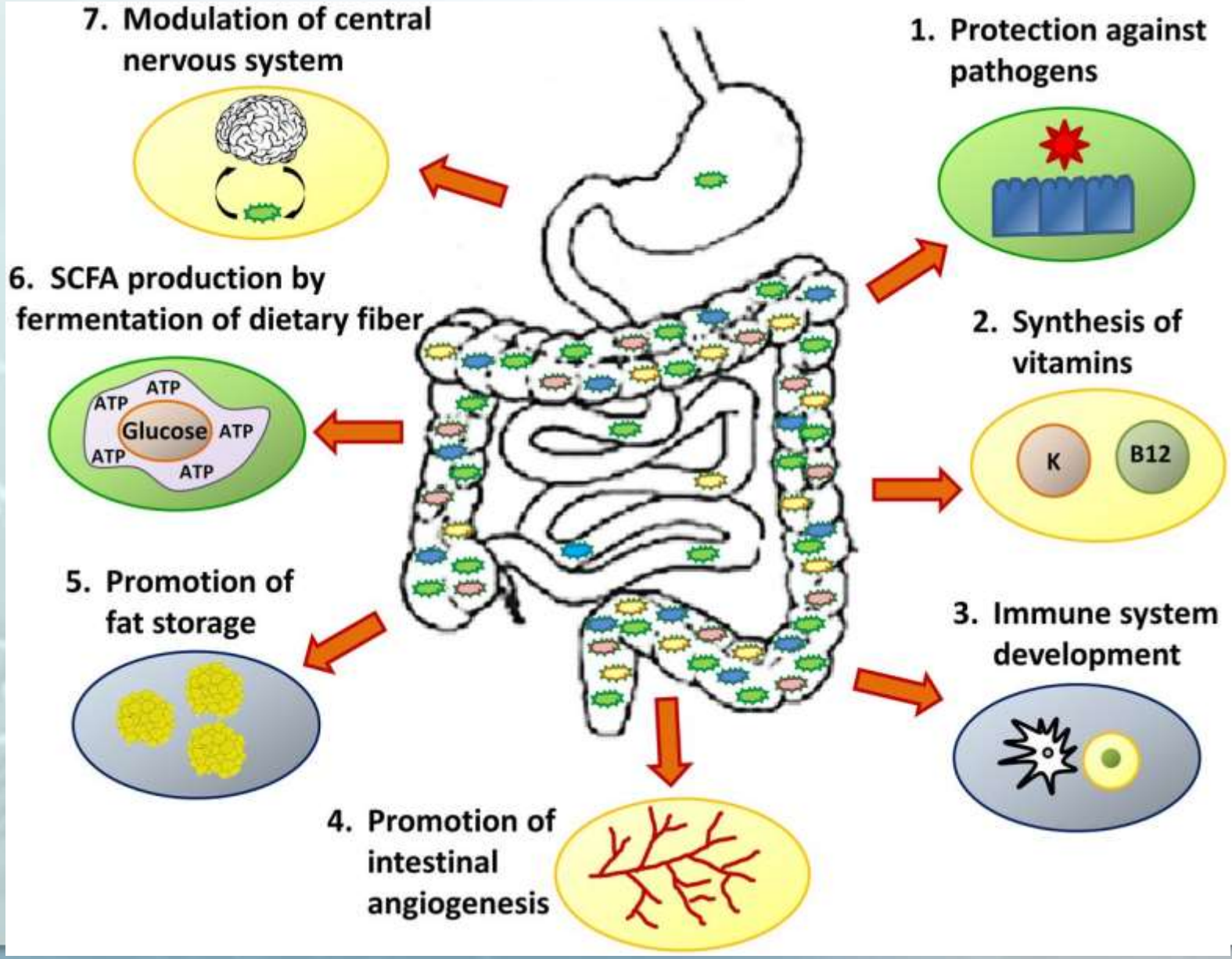
Microbiomes – Effects

- The particular collection of microbes we carry are specific to each of us – different from person to person
- Geographic location is a major determinant of microbiome variation
- Personal genetics, diet, health and current microbiome
  - A virtuous circle
- Most of the compositional variance is still unexplained

Microbiomes – Effects

- Differences between people helps to explain why people respond differently to the same foods
  - Whether tomatoes are good or bad for you, whether rice is good for you or worse for you than ice cream and so on is explained by your microbiome – glycemic index is personal!
- How patients respond differently to the same drugs
  - E.g. Digoxin (10%), Paracetamol, Statins (improved microbiome)
  - In particular variable responses to cancer therapy (toxicity and efficacy)
- COVID-19 gut issues – related to microbiome differences?
- It's about having the right community of bacteria that are working together producing the right chemicals for your body
- All the systems in the body have all co-evolved, with our microbes
- We are very much human-focused and we feel that human cells and genes have primacy, but the microbes were there first – by a long way!

Microbiomes – Effects

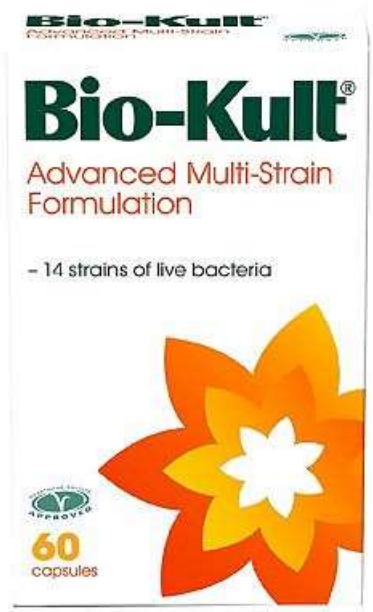


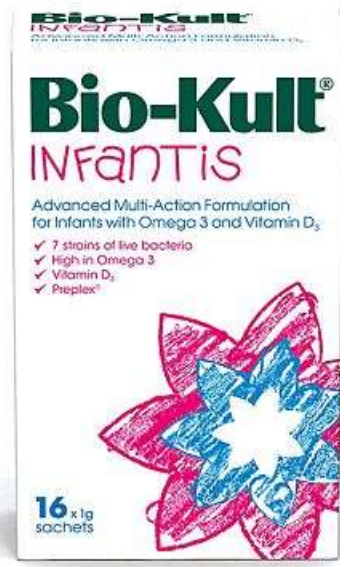
Microbiomes – Affects

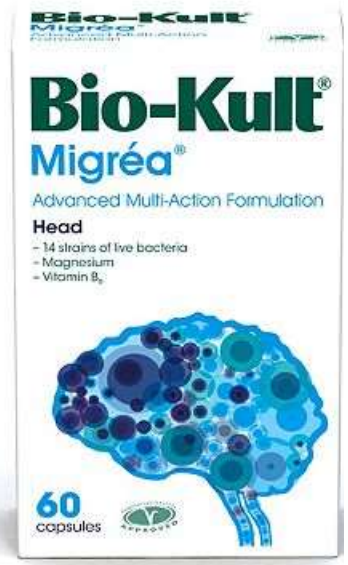
- We can shape our own microbiomes
- What we eat strongly influence the makeup of microbes that share our bodies, as does exercise – athletes more varied!
- A diet with plenty of variety, especially of fruit & vegetables & other sources of fibre – produce SCFA's (and stop mucus destruction)
  - Decreased from 150 to 15g per day over last 10,000 years
- Prebiotics (feed) and probiotics (add) – the jury is still out on probiotics benefiting healthy individuals
  - But if you're taking antibiotics, or have IBS etc., there is some evidence that supplementary probiotics are good
- Effects of Intermittent Fasting is now being studied
- Keto diet changes the microbiome

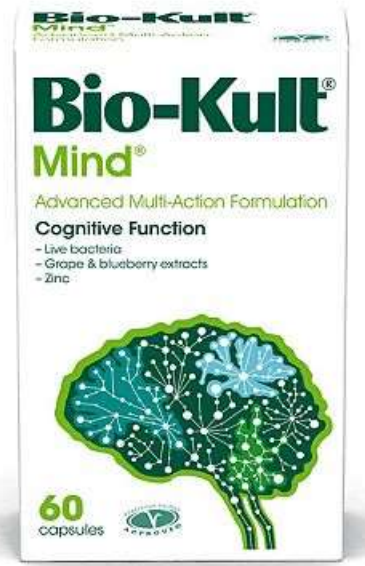
Microbiomes – Affects

- Probiotics – consuming beneficial bacteria
- Most products or supplements only add one or two species and your gut has / needs hundreds, if not thousands
- New products are becoming available with many kinds e.g.









- With up to 14 species of – stomach acid resistant - beneficial microbes
- But it works on first-come-first-served basis, the microbes that are there already dictate who gets to come into the party has now been shown very clearly

Foods and Genes

- It's not just our own genes that are affected by the substances in our foods but also the microbial genes as well
- In some respects the microbial genes are acting as amplifiers of the messages received via our diet
- Using germ-free mice versus control animals John Cryan et al July 2017 UCC showed that many aspects of brain health are dependent on gut having microbes
  - For example they've shown recently that myelination is regulated by microbes in the gut – myelin is a key insulation in nerve cell communication
- Polyphenols are really important dietary substances found in dark chocolate, red wine, onions, grape juice and green tea etc.
  - Have been shown to have really good anti-aging properties and affect learning and memory as well
  - It's recently been shown that a lot of polyphenols actually don't get don't get absorbed but get acted upon by microbes in the lower gut
  - Polyphenols affect the composition of these microbes – so you are what your microbes are eating

Foods and Genes

- Avoid over refined foods such as white flour rice & pasta, avoid fried foods
- Fats and particularly the type of fats are very important to health
  - Omega 6 vs Omega 3 fatty acids – particularly for brain development and health
- Vitamins and minerals are important
- So if Omega 3s, polyphenols, vitamins and minerals are important - could we devise a diet that would be rich in these and beneficial effects on our health?
- Well we don't have to go too far – just to the Mediterranean Diet
- The Mediterranean Diet has long been known to have beneficial effects
  - In cardiovascular health and reduced heart disease
    - Microbes can affect cholesterol levels & fatty arteries (atherosclerotic plaques) – possible future therapies via cyclic peptides
  - To lower the incidence of stroke, diabetes, obesity
  - Increased lifespan – or at least health-span
  - Even improved mental health and mood
  - It is a really rich source of polyphenols, Omega 3s, vitamins and minerals

Microbes and Diet

- Research has shown that following a Mediterranean diet can improve your gut diversity & reduce inflammation, which may put you in a better position to fight viral pathogens like Coronavirus
- This involves high diversity & eating plenty of fruit, vegetables, nuts, seeds, whole grains, legumes & pulses; healthy fats (Omega 3) like high-quality extra virgin olive oil; & lean meat or fish - for those who wish
- At the same time, keep your gut bugs healthy by limiting alcohol intake, salt, sweets & sugary drinks & artificial sweeteners
- You can also try to naturally support your microbiome by including probiotic-rich foods like live dairy, curds, yoghurt, kefir (fermented milk) or kombucha (fermented tea – but without sweeteners & additives), Sourdough bread
- Or take a tip from the Koreans and tuck into some kimchi - a tasty mix of fermented vegetables like cabbage, chili & garlic or sauerkraut etc., but only the live versions!
  - May 2020 unprecedented evidence that fermented foods are a possible source of lactic acid bacteria for the gut microbiome

Microbiomes – Affects

- Fad weight loss diets are dangerous!
- So are some food additives
  - e.g. CMC – Carboxy Methyl Cellulose E466/469
  - and P80 Potassium Sorbate – E433
  - Both said to alter the permeability of the gut wall & allow invaders to get in
- Also some artificial sweeteners (e.g. saccharin) – implicated in changes in gut microbiome and the proper handling of glucose & obesity
- TiO_2 nano particles from a food additive known as E171

Microbiomes – Disorders

- There is no such thing as a good microbe or a bad microbe!
- Gut microbes are not our buddies!
- If they cross the lining of the gut and enter our bloodstream they can cause inflammation and sepsis
- In the wrong place microbes can cause terrible illnesses for the matter of just a millimetre, our allies can quickly turn into our enemies
- An entire community can shift from a healthy state into a sickly one - it's called dysbiosis
- Using the sterile mice (and other organisms) experiments suggest that gut microbes, out of balance may cause and/or, be a symptom of, conditions such as:
  - IBD (Ulcerative Colitis / Crohn's), Diabetes (I & II), Rheumatoid Arthritis, & other Autoimmune Diseases, Obesity, Malnutrition, Parkinson's disease, and Colorectal Cancer (a type of E-coli and its toxin colibactin)
- Studying other gastrointestinal cancers – liver, pancreas etc
  - Via toxicity due to leaky gut caused by bacterial & fungal species

Microbiomes – Disorders

- Parkinson's disease - that the gut might be involved in emerged more than 200 years ago
- In 1817, the English surgeon James Parkinson reported that some patients with a condition he termed "shaking palsy" experienced constipation
  - In one of the six cases he described, treating the gastrointestinal complaints appeared to alleviate the movement-related problems associated with the disease
  - Physicians have noted that constipation is one of the most common symptoms of Parkinson's
  - Appearing in around half the individuals diagnosed with the condition
  - Often preceding the onset of movement-related impairments
  - Yet for many decades, the research into the disease has focused on the brain - concentrating on the loss of neurons producing dopamine
    - A molecule involved in many functions including movement

Microbiomes – Disorders

- More recently, researchers also focused on the aggregation of alpha-synuclein, a protein that twists into an aberrant shape in Parkinson's patients
- A shift came in 2003, when Heiko Braak, a neuroanatomist at the University of Ulm in Germany, and his colleagues proposed that Parkinson's may actually originate in the gut rather than the brain
  - This theory was grounded in the observation that in post-mortem samples of Parkinson's patients, Lewy bodies, clumps of alpha-synuclein, appeared in both the brain and the gastrointestinal nervous system that controls the functioning of the gut
  - Braak and his colleagues also suggested that the pathological changes in patients typically developed in predictable stages that starts in the gut and ends in the brain
  - The researchers speculated that this process was linked to a "yet unidentified pathogen" that travels through the Vagus nerve—a bundle of fibers connecting major bodily organs to the brainstem, which joins the spinal cord to the brain

Microbiomes – Disorders

- Some studies propose that aggregates of alpha synuclein move from the intestines to the brain through the Vagus nerve
- Others suggest that molecules such as bacterial breakdown products stimulate activity along this channel, or that that the gut influences the brain through other mechanisms, such as inflammation
- These findings add to the growing consensus that "even if the pathology of Parkinson's is very much driven by brain abnormalities, it doesn't mean that the process starts in the brain," says Michael Schlossmacher, a physician-scientist at the Ottawa Hospital Research Institute
- Researchers from the Universities of Edinburgh and Dundee have identified a probiotic – called Bacillus subtilis that could not only protect against the build-up of this protein associated with Parkinson's, but can also clear some of the already formed protein clumps
- These new findings could pave the way for future studies that gauge how supplements such as probiotics impact Parkinson's

Microbiomes – Disorders

- Recent epidemiological examinations of vagotomy patients show that they have a 50% lower risk of developing Parkinson's
- Researchers have also demonstrated that alpha-synuclein fibers, injected into the gastrointestinal tracts of rodents, can traverse through the Vagus into the brain
- Last year, Michael Zasloff, a professor at Georgetown University, and his colleagues reported that the protein appeared in the guts of otherwise healthy children after norovirus infections, and that, at least in a lab dish, alpha-synuclein could attract and activate immune cells, so it may accumulate as a protective reaction?
- Some proteins made by bacteria may form small, tough fibers, whose shape could cause nearby proteins to misfold and aggregate in a manner akin to the prions responsible for mad cow disease, explains Robert Friedland, a neurologist at the University of Louisville
- The microbiome is now under intense scrutiny by Parkinson's researchers

Microbiomes – Disorders

- Reports have noted that individuals with the disease harbour a unique composition of gut microbes
- Scientists have also found that transplanting fecal microbes from patients into rodents predisposed to develop Parkinson's can worsen motor symptoms of the disease and increase alpha-synuclein aggregation in the brain
- Yet another idea holds that that intestinal inflammation, possibly from gut microbes, could give rise to Parkinson's disease
- Evidence supporting this idea comes from a large epidemiological study investigating the overlap between Inflammatory Bowel Diseases (IBD) and Parkinson's
- The analysis revealed that the prevalence of Parkinson's was 28 percent higher in individuals with the IBD than in those in the control group, supporting prior findings from the same researchers that the two disorders share genetic links
- In addition, people who received drugs used to reduce inflammation—Tumor Necrosis Factor (TNF) inhibitors—the incidence of the neurodegenerative disease dropped 78 percent

Microbiomes – Disorders

- This study further validates the theory that gut inflammation could drive Parkinson's pathogenesis, says Madelyn Houser, a graduate student in neuroscientist Malú Tansey's lab at Emory University
- The anti-TNF finding in particular, she adds, suggests that the "overlap between the two diseases might be primarily mediated by inflammation."
- While many lines of evidence support the gut origins of Parkinson's, the question of how early the gastrointestinal changes occur remains
- Other scientists have suggested that it is still possible that the disease begins elsewhere in the body
- In fact, Braak and his colleagues also found Lewy bodies in the olfactory bulb, which led them to propose the nose as another potential place of initiation
- "I think there's likely multiple sites of origin for Parkinson's disease," says Viviane Labrie, a neuroscientist at the Van Andel Research Institute in Michigan. "For some individuals, it might be the gut, for others it might be the olfactory system"

Microbiomes – Disorders

- Parkinson's disease stinks, figuratively, but according to new research (March 2019), it literally stinks too
- Thanks to the help of one of these "super-smellers," a team of scientists has identified subtle volatile compounds produced by Parkinson's sufferers

- Joy Milne (left) and researcher Perdita Barran. (Credit: The University of Manchester)

Microbiomes – Disorders

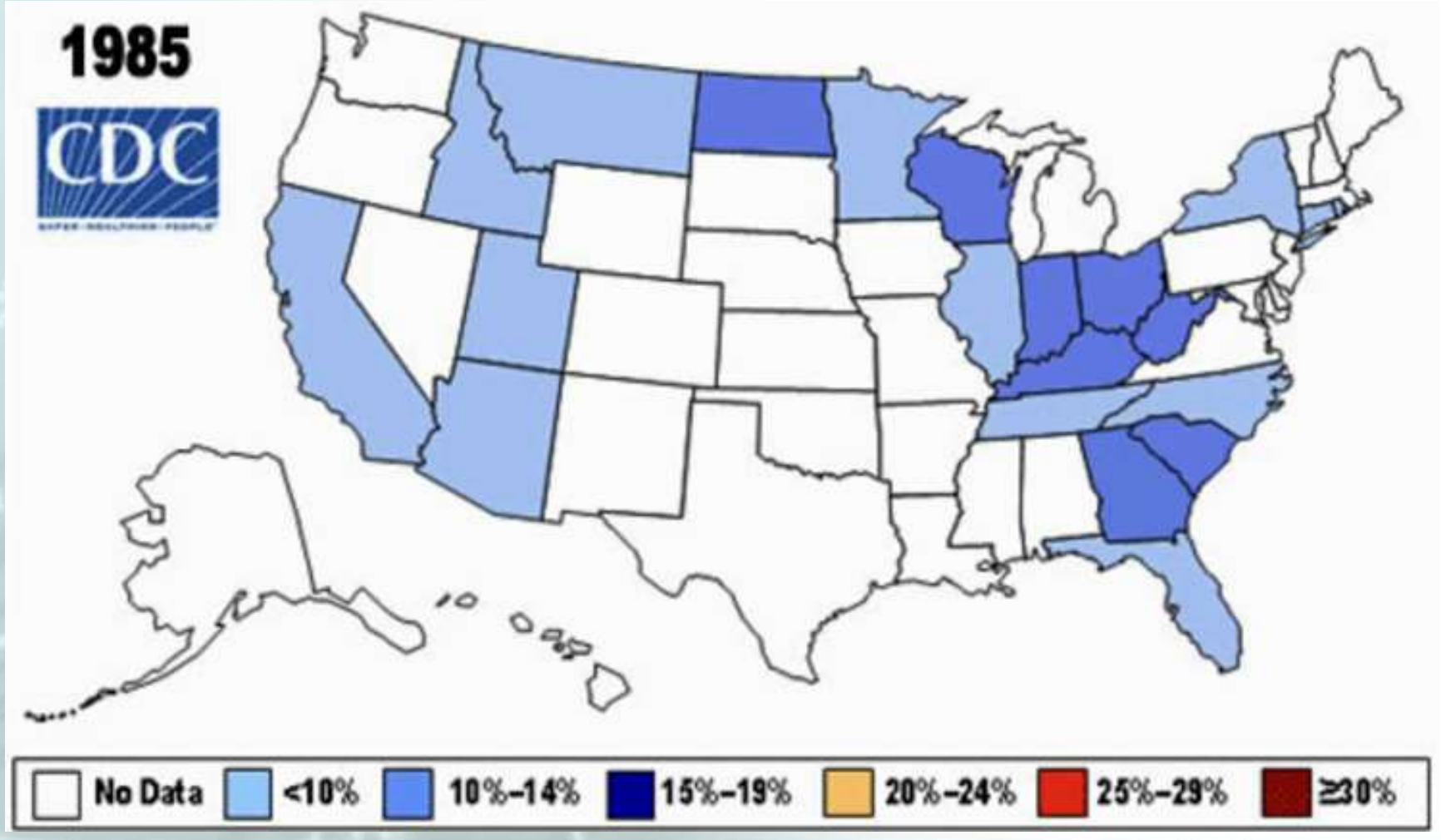
- Joy Milne, a retired nurse living in Perth near Edinburgh
  - Decades earlier, she had noticed a sudden onset of a strange odor in her now-late husband – he was diagnosed with Parkinson's disease many years later
  - To a super smeller like Milne, Parkinson's disease has a distinct odor - more importantly, the odor is present long before physical symptoms appear
- The second-most common neurodegenerative disease after Alzheimer's, Parkinson's affects about 1% of the population at age 60, and 4% of the population by age 80
  - Current treatments can help alleviate some of the physical effects — like muscle tremors — though they don't actually slow the progression of the disease – there is no cure
- It takes complicated brain imaging to confirm that certain brain cells, the neurons that produce dopamine, have been damaged or destroyed
  - But a much simpler test might be on the way
  - Volatile compounds in sebum — the oily substance produced on your face and back — might soon be used to identify the disease very early on

Microbiomes – Disorders

- Obesity – human gene analysis 57% accuracy whether a person is obese, but 90% accuracy by microbiome genetic analysis!
- Human genes are fixed, but microbiome genes are modifiable
- A lean – germ free mouse – can be transformed into an obese mouse by microbiome transplant from an obese human
- A lean – germ free mouse – still remains lean after a microbiome transplant from a lean human
- In some studies the altered microbiome changed the mouse's metabolism so it processed it's food more efficiently hence it became obese
- In other studies the altered microbiome changed the mouse's behaviour so that it was hungrier and it ate more and became obese

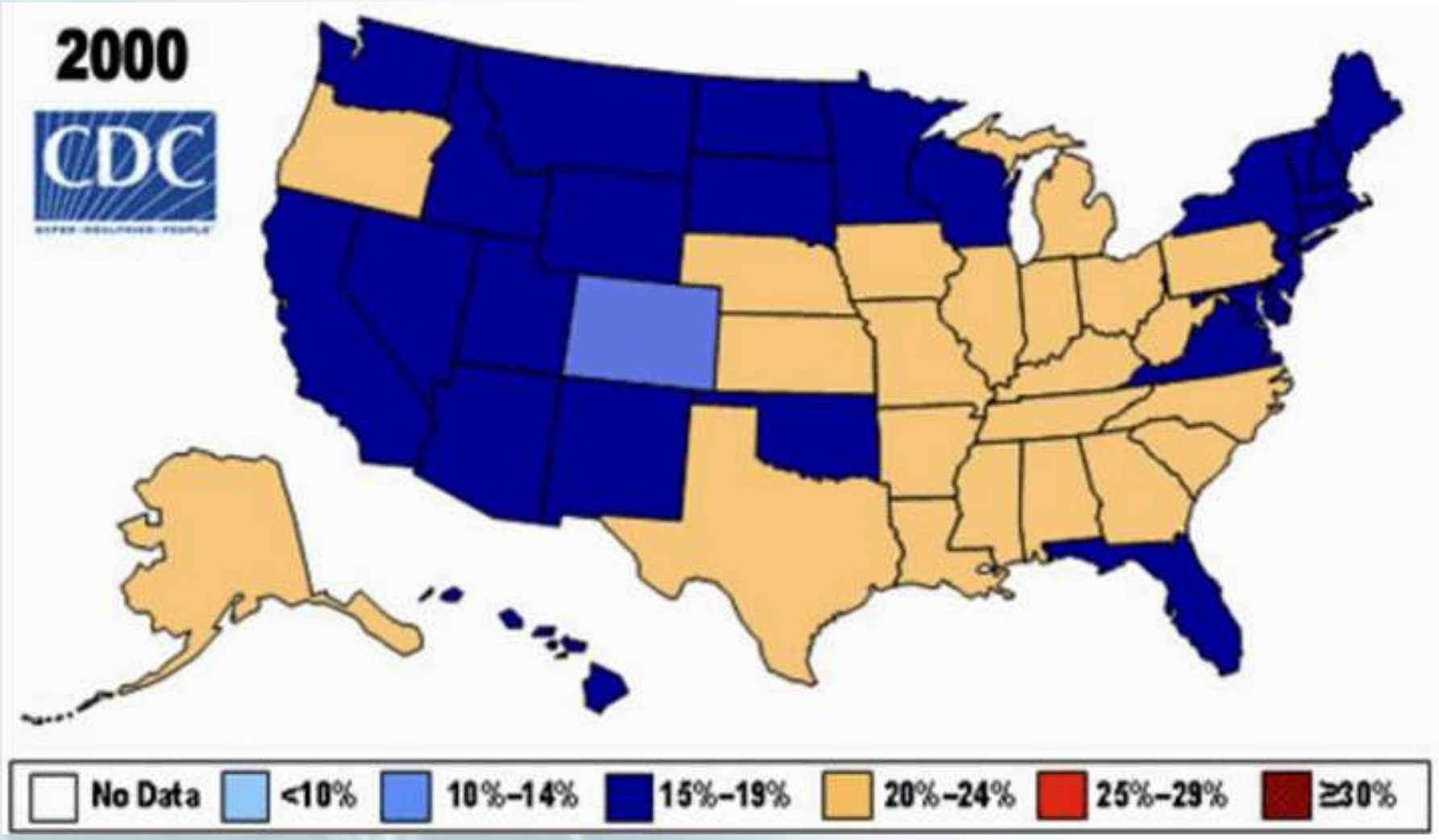
Microbiomes – Disorders

- US CDC has been tracking the US obesity epidemic from 1985 to 2010 a period of 25 years
- In 1985 there were a few States with 10% obesity or below and light blue



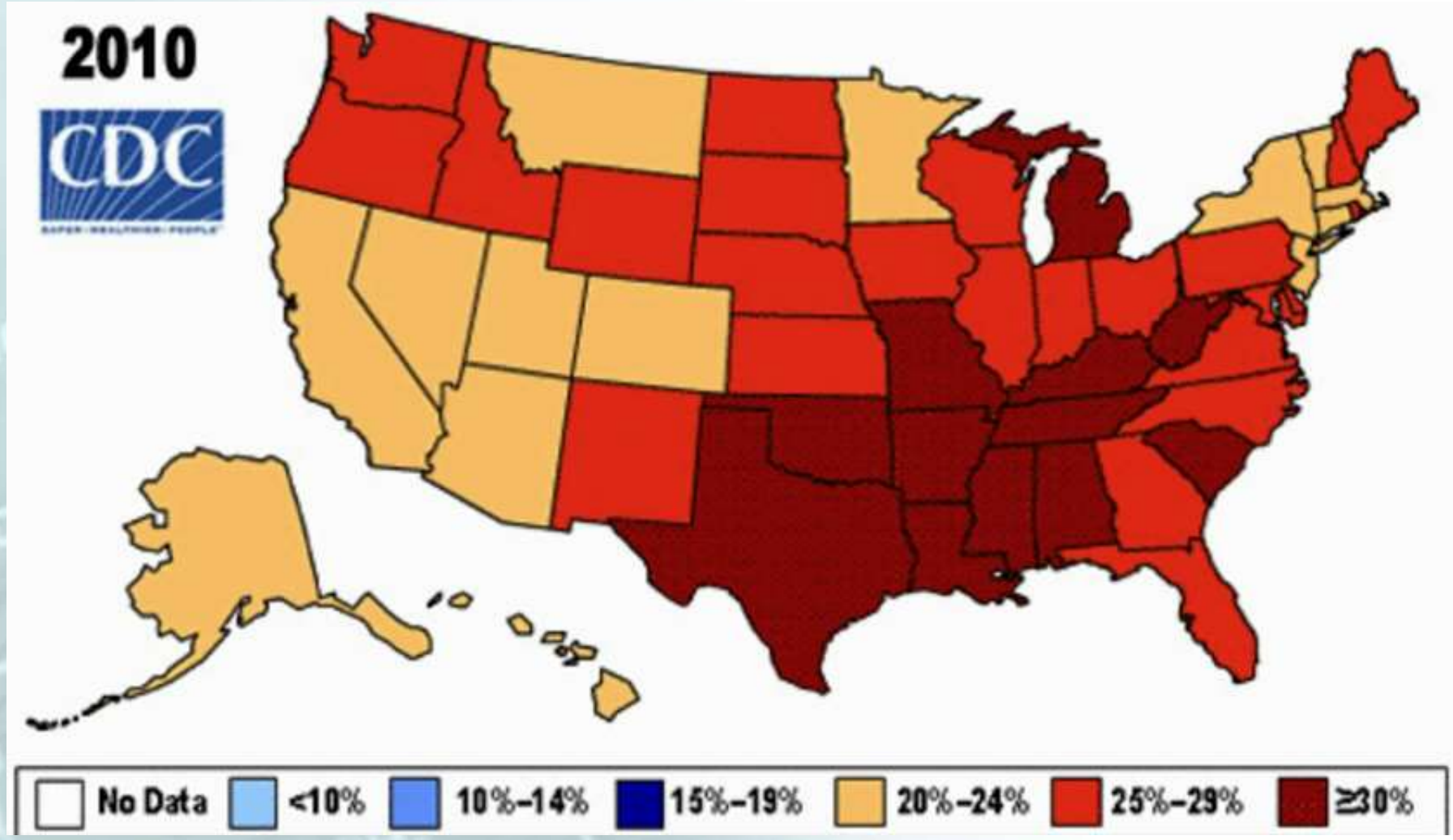
Microbiomes – Disorders

- Here at 15 years the difference is huge



Microbiomes – Disorders

- Over the span of 25 years you can see it spreading throughout the United States until it becomes the public health issue it is today

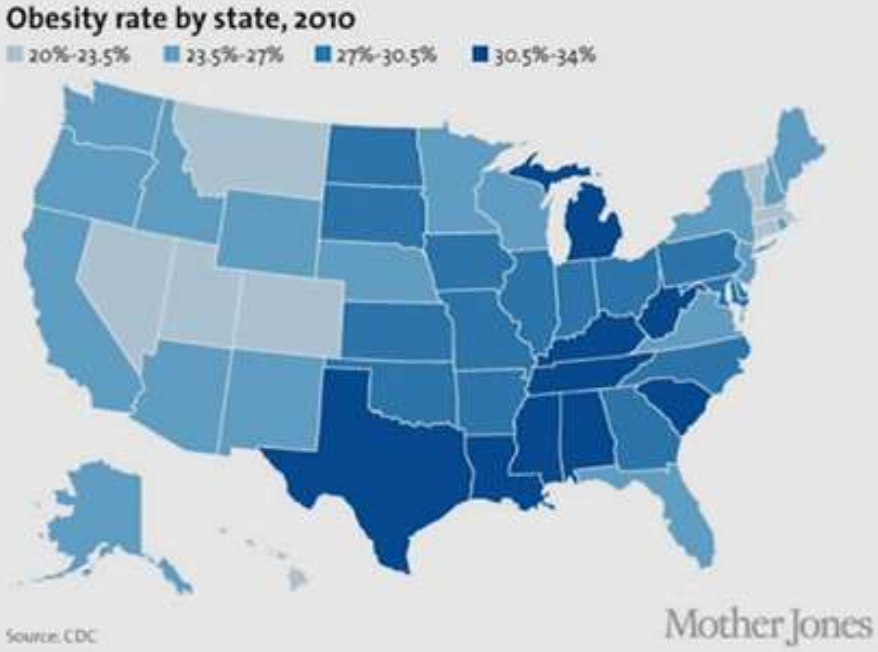


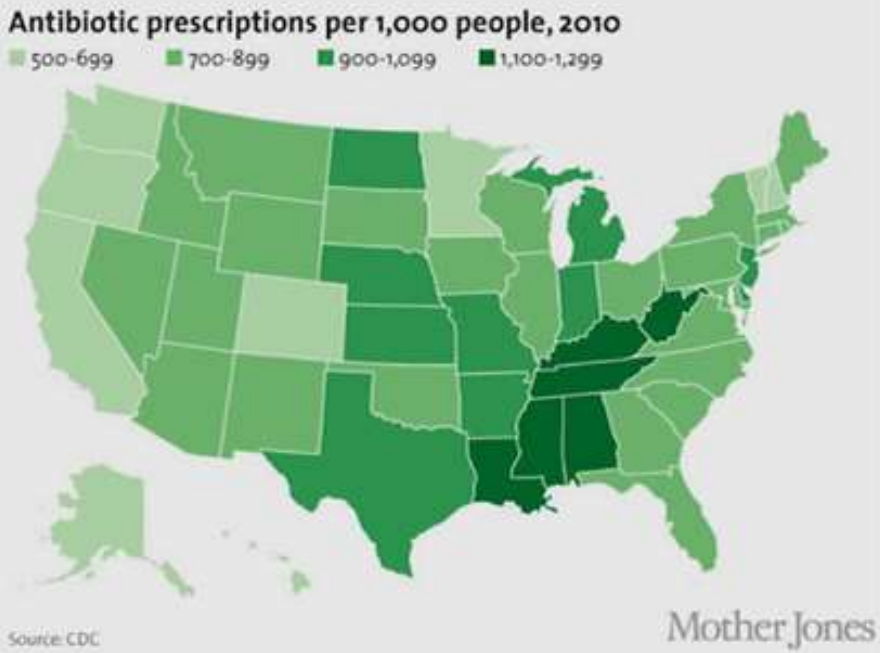
Microbiomes – Disorders

- It can be pinned on something other than changes in human genes
  - Because for human genes to change that rapidly over a span of 25 years and within just one generation
  - Either all of the lean people would have had to have had essentially no kids
  - All of the obese people would have had to have had a tremendous number of kids and it would have been very obvious just from a demographic perspective
  - So that's why scientists are looking for an environmental causes
- One particularly exciting possibility is that the obesity epidemic is literally an epidemic in terms of transmitting an obesogenic microbiome from human to human
- Just as it has been shown that it can be transmitted from humans to mice and even from mouse to mouse

Microbiomes – Disorders

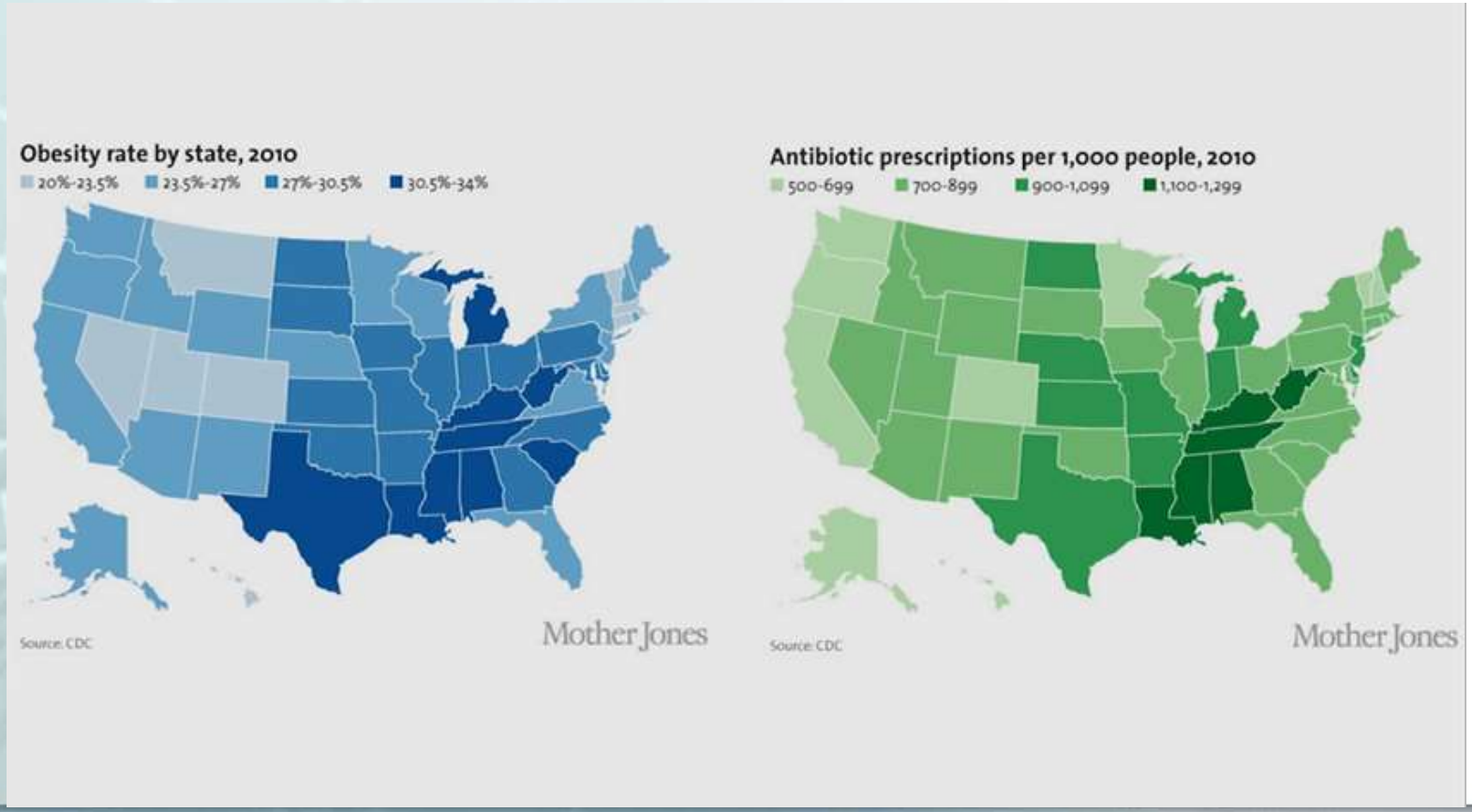
- Antibiotic utilisation in the United States in 2010
- You can probably see a visual similarity between the antibiotic map and the obesity map





Microbiomes – Disorders

- Scientist Martin Glaser has done a tremendously elegant series of experiments in mice with sub-therapeutic antibiotic doses
  - Low doses like you might get from the environment from eating antibiotics in food and also with therapeutic doses of antibiotics
  - This does not prove causality but it needs investigating



Microbiomes – Disorders

- Transmitting traits like obesity and things like Inflammatory Bowel Disease via microbiome transfers is proven
- It's also possible to transmit behaviour between different kinds of mice by transmitting their microbes
  - For example a group at McMaster University in Canada was able to show that you can make a bold mouse timid or timid mouse bold that by changing their microbiomes
- It also extends to neurological disorders
  - Mice with a genetic defect a similar to a change in human genes that has been associated with Parkinson's disease
  - By transmitting into those mice faecal content of people with Parkinson's, the mice develop symptoms very reminiscent of human Parkinson's disease
  - In contrast if they transfer the microbiome from someone who is healthy, they did not develop any of these symptoms
- This is very strong evidence that suggests the microbiome could be linked to not just to diseases that occur early in life but to diseases that occur later in life like Parkinson's & Dementia

Microbiomes – Disorders

- Patients with hemorrhagic brain disease have disordered gut microbiomes
  - Investigators at University of Chicago Medicine and published May 27 2020 in Nature Communications
  - Examined the gut bacteria of patients with cavernous angioma (CA), a disease where blood vessel abnormalities develop in the brain and cause strokes, seizures and serious neurologic complications
- Changes in gut mucus may contribute to Alzheimer's, Parkinson's, and other neurological disorders
  - Researchers noted changes in types of gut mucus bacteria in those with a range of neurological disorders compared to their healthy peers
  - Findings suggest those with reduced gut mucus protection may be more susceptible to gastrointestinal problems, Source: RMIT University – pub Front. Cell. Infect. Microbiol., 28 May 2020
- The gut microbiome is more malleable in the first two years after birth, allowing probiotics to make their mark
  - Can we exploit this to improve infants' health? Pub Dec 2017, Am Soc Microbiol
    - Jennifer Smilowitz is the associate director of the Human Studies Research Program at the Foods for Health Institute and a research scientist in the Department of Food Science and Technology at the University of California, Davis. Diana Hazard Taft is a postdoctoral research fellow in David Mills's lab in the Department of Food Science and Technology and a member of the Foods for Health Institute at UC Davis.

Microbiomes – Disorders

- In mice, altered microbiomes have been linked to all kinds of additional conditions, including things like multiple sclerosis, motor neurone disease and even depression

- Autism Spectrum Disorders (ASD)
  - Altered microbiome in ASD patients - increased: Clostridia and Desulfovibrio in stools
  - Increased SCFAs in ASD patients: acetic, propionic, and butyric acid
    - Adding PPA (propionic acid) induces repetitive behaviour in mice
  - Probiotics improved ASD in mice
    - Ref Ceymi Doenyas, Neuroscience 374, Pages 271-286
  - Small US FMT trial recently done is ASD children has seen improvements in neurobehavioural symptomology in those children – now moving on to a much bigger clinical trial

Microbiomes – Differences

- For an individual adding a particular food item to your diet or cutting one out of your diet can have a very large or very small effect for you

- A ground breaking study by an Israeli group at the end of 2015 really revolutionized our understanding of why these individual differences exist and what they are linked to

Microbiomes – Differences

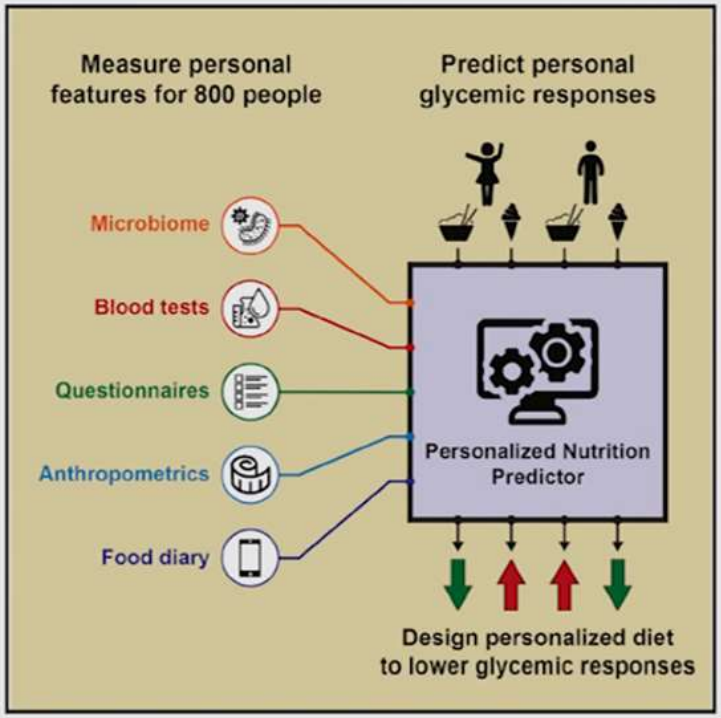
- Israeli study of 800 people connected to continuous glucose monitors to continuously monitor and record their blood glucose levels

Article

Cell

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract



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In Brief

People eating identical meals present high variability in post-meal blood glucose response. Personalized diets created with the help of an accurate predictor of blood glucose response that integrates parameters such as dietary habits, physical activity, and gut microbiota may successfully lower post-meal blood glucose and its long-term metabolic consequences.

Microbiomes – Differences

- Gave them standard sequence diets so that they could tell the exact effect of each individual food item on blood glucose for each one of those 800 people, over a two-week period
- The average results for each food item for all of those 800 people together perfectly recaptured the glycemic index for each of those foods
- But when they calculated individual glycemic indexes for each food, for each individual, they found the same food had totally different effects on different people
- For some people it is actually better to eat a bowl of ice cream that it is to eat a bowl of white rice
- Amazingly almost the whole of this variation was not due to human genes and not due to their physiology
- Rather it was just due to differences in their microbiomes
- There was one subject who's blood glucose spiked every time he ate tomatoes, by cutting tomatoes out of his diet that individual brought his blood glucose under control

Microbiomes – Differences

- So is there a test to tell if you're in the ice cream category rather than the rice category
- Right now it only works if you're Israeli
- Urgently need to test this in other populations where the microbiome backgrounds are very different, and where the background in terms of dietary choices is very different as well
- Also supposed you found out that you were in the rice category, and you wanted to be in the ice cream category, could you actually change your microbiome to achieve that?
- Can you look at what your microbiome should look like in the future and can you make the right changes to move your microbiome from where you are now towards that ideal?
- Currently this is unknown but being studied intensely – it's a big potential market

Microbiomes – Differences

- The American gut project - hundreds of people (250) had their microbiome genomes sequenced over three time points
- Can tell many things about them for example:
  - Age
  - If you have IBD
  - Antibiotic use
  - Male or female
  - How much sleep you get at night (need to get enough - lifespan)
  - How much you weigh / BMI
  - How much alcohol you drink
  - What sort of plants you eat
  - The season of the year
  - Even how much you exercise - how much they said they exercised since all of this was self-reported data
- The largest effect was brought about by the number of plant types eaten
- Lifestyle factors like diet can have an even bigger impact on your microbiome than things you have less control over like diseases and medications

Microbiomes - In Summary

- We Humans are the newbies on the block
  - Microbes predate animals by over 3.3 billion years
  - They predate Humans by 3.8 billion years
- At all stages of our evolution we were immersed in microbes
- Our microbiomes are critically important to our health and wellbeing
- They are usually cooperative, but can become our worst enemies
- We can, and need, to look after them
- Only very recently have we begun to realise their importance, functions and influences
- Much more work is needed and is ongoing

Microbiomes – Further Reading

Book,

I Contain Multitudes,

The microbes within us and a grander view of life

by Ed Yong

Thank You

Any questions?

Microbiomes – Sourdough Bread

- While most store-bought bread is made using one of a few kinds of wheat and only a single species of yeast, many bakeries and home bakers continue to make new starters and keep old ones alive, resulting in a very wide spectrum of tastes
- Nearly all traditional leavened bread tastes at least a little bit sour, and this sourness is often due to the same bacteria found in yogurt, species of Lactobacillus
- But more than 60 different lactic acid-producing bacterial species and a half dozen species of yeasts have been found in one or another starter from different bakeries in different places
- No one really knows why there are so many variations
- The Starter microbes come from – the soil the wheat was grown in, from the grain, from the flour, from the environment where the starter was cultured, from the hands of the Bakers (e.g. species of Saccharomyces yeast) and even the water used
- But all the starters studied were unique in terms of the yeasts and the bacteria found

Microbiomes – A Noah's Ark

- Scientists want to build a Noah's Ark for the human microbiome
- The project aims to safeguard the beneficial microbes living in and on the human body
- Inspired by initiatives the Svalbard Global Seed Vault