How your body decides if bacteria are friends or foes
Would you:

• Let you child eat food that dropped on the ground?

• Let your child suck their thumbs?

• Take antibiotics without knowing the true reason you are feeling sick?
Humans and Microbes

• Leeuwenhoek’s discovery of microorganisms in 17th century led people to suspect they might cause diseases

• Robert Koch (1876) offered proof of what is now considered germ theory of disease; showed *Bacillus anthracis* causes anthrax

• Today, we now know that most of the bacteria we associate with are not pathogens, and many are critical for our health.
Bacteria Are Ubiquitous

- We contact numerous microorganisms daily
  - Every surface on earth is covered!
    - Even clouds have microbes
      - Could play a role in seeding rain..
  - Some have tremendous commercial value
    - Yogurts, wine, cheese, vinegar, pickles, etc.
  - Our bodies:
    - Breathe in, ingest, pick up on skin
    - Vast majority do not make us sick, or cause infections
    - Some colonize body surfaces; or slough off with dead epithelial cells
    - Most that are swallowed die in stomach or are eliminated in feces
    - Relatively few are pathogens that cause damage
Most microbes are harmless
  • Many are beneficial
  • Normal microbiota (normal flora) are organisms that routinely reside on body’s surfaces
    • Relationship is a balance, and some can cause disease under certain conditions—opportunistic infections
    • Weaknesses in innate or adaptive defenses can leave individuals vulnerable to invasion
      – malnutrition, cancer, AIDS or other disease, surgery, wounds, genetic defects, alcohol or drug abuse, and immunosuppressive therapy
Human commensals and mutualistic microbes

**Resident microbiota** inhabit sites for extended periods

**Transient microbiota** inhabit temporarily

- Important to human health
- Relatively little is known
- Human Microbiome Project aimed at studying

http://en.wikipedia.org/wiki/Human_Microbiome_Project
The Normal Microbiota

The Protective Role of the Normal Microbiota

• Significant contribution is protection against pathogens
  • Covering of binding sites prevents attachment
  • Consumption of available nutrients
  • Production of compounds toxic to other bacteria

• When killed or suppressed (e.g., during antibiotic treatment), pathogens may colonize, cause disease
  • Some antibiotics inhibit *Lactobacillus*
  • Oral antibiotics can inhibit intestinal microbiota, allow overgrowth of toxin-producing *Clostridium difficile*
The Normal Microbiota

- The Dynamic Nature of the Normal Microbiota
  - Healthy human fetus sterile until just before birth
    - Exposure during birth and through contact with people, food, and environment lead to microbes becoming established on
  - Find that families often share similar microbial populations, and important gut microbes are acquired from the mother
  - Critical for proper gut development—first colonizers from mom

- Composition of normal microbiota is dynamic
  - Changes occur over the life of a person. Younger people tend to have different compositions than older people.
  - Responses to physiological changes (e.g., hormonal changes), activities and diet (e.g., consuming food)
Microbiota alter the chemistry of your gut

- Obese mice had 50% fewer Bacteroidetes and 50% more Firmicutes in their bowels than their lean counterparts.

The link between the microbiota and obesity became even clearer when Gordon looked at a special strain of mice with no microbiota of their own.

When the team transplanted the microbiota from fat and lean mice into the germ-free strains, those colonized by microbiota from fat donors packed on far more weight than those paired with lean donors.

**Fat Bacteria**
- More Firmicutes
  -- break down carbohydrates better
- More Bacteroidetes
  -- trigger biochemical pathways to store fat

**Thin bacteria**
PROBIOTICS, ADHD, AND AUTISM

Your Gut Bacteria Linked to Anxiety and Depression. Here's What to Do to Stay Mentally Healthy

Gut Bacteria May Play Role in Crohn's Disease

CAN BACTERIA Talk To Your YOUR BRAIN?

Our brain and our digestive system are intricately linked. So closely linked, in fact, that some experts say it should be viewed as one system, with the gut often being referred to by scientists as "the second brain"...and the contents of this second brain can profoundly affect our first!

CHEMOTHERAPY AND THE MICROBIOME

NEWBORN GUT MICROBIOME LINKED TO ALLERGY & ASTHMA RISK IN LATER LIFE

- Gut microbes in infancy increase the risk of asthma and allergies in childhood
- Avoid situations or substances that trigger attacks of asthma
- Monitor lung function closely
Microbiome

- So far... more questions than answers

- But there are major indications that the microbiome (the combination of all microbes living in and on us) may be thought of as an organ
Principles of Infectious Disease

Colonization—microbe establishes on body surface

- **Infection** usually refers to pathogen
  - **subclinical**: no or mild symptoms
  - **Infectious disease** shows noticeable impairment
    - **Symptoms** are subjective effects experienced by patient (e.g., pain and nausea)
    - **Signs** are objective evidence (e.g., rash, pus formation, swelling)
- Initial infection is **primary infection**
Pathogenicity

- **Primary pathogen** is microbe or virus that causes disease in otherwise healthy individual
  - Diseases such as plague, malaria, measles, influenza, diphtheria, tetanus, tuberculosis, etc.
- **Opportunistic pathogen** (opportunist) causes disease only when body’s innate or adaptive defenses are compromised or when introduced into unusual location
- **Virulence** refers to degree of pathogenicity
- **Virulence factors** are traits that allow microorganism to cause disease
Distribution of Pathogen

- **Localized infection**: microbe limited to small area (e.g., boil caused by *Staphylococcus aureus*)
- **Systemic infection**: agent disseminated throughout body (e.g., measles)

- **Suffix** -emia means “in the blood”
  - **Bacteremia**: bacteria circulating in blood
    - Not necessarily a disease state (e.g., can occur transiently following vigorous tooth brushing
  - **Toxemia**: toxins circulating in bloodstream
  - **Viremia**: viruses circulating in bloodstream
  - **Septicemia or sepsis**: acute, life-threatening illness caused by infectious agents or products in bloodstream
Mechanisms of Pathogenesis—how do pathogens make us sick?

- General patterns
  - Produce toxins that are ingested
  - Colonize mucous membranes, produce toxins
  - Invade host tissues, avoid defenses
  - Invade host tissues, produce toxins
  - Pathogens and hosts usually evolve toward balanced pathogenicity (e.g., myxoma virus and rabbits)
Invasion—Breaching the Anatomical Barriers

- **Penetrating the Skin**
  - Difficult barrier to penetrate; bacteria rely on injuries
    - *Staphylococcus aureus* enters via cut or wound; *Yersinia pestis* is injected by fleas, Lyme’s disease by tick bite

- **Penetrating Mucous Membranes**—respiratory and gut tracts
  - Common Entry point pathogens
  - Directed Uptake by Cells
    - Pathogen induces cells to engulf via endocytosis

*Borrelia burgdorferi* *(Lyme’s disease)*
Avoiding the Host Defenses

- **Hiding Within a Host Cell**
  - Allows avoidance of complement proteins, phagocytes, and antibodies
    - *Shigella* directs transfer from intestinal epithelial cell to adjacent cells by causing host cell actin polymerization
    - *Listeria monocytogenes* (meningitis) does the same

- **Avoiding Killing by Immune System**
  - Serum resistant bacteria resist
https://youtu.be/sF4BeU60yT8
Infection – your options

- What happens when a pathogen invades our bodies?

- There are two options:
  - It may be detected and removed by our immune system
  - It avoids our immune systems and takes hold (an infection ensues)
    - Antibiotics is the only option then
To microbes, human body is nutrient-rich

• But most of our internal systems are sterile (except the gut)

• **Innate immunity** is routine protection
  • Skin, mucous membranes prevent entry
  • Sensor systems detect invaders, general microbe pattern recognition

• **Adaptive immunity** develops
  • throughout life:
    • **Antigens** cause response, system
    • Produces antibodies to bind
      • Can also destroy host cells
Overview of Innate Defense System

First-line defenses
Prevent microbial entry

Sensor systems
Detect microbial invasion

Pattern recognition receptors
(surfaces, endosomes, and phagosomes of sentinel cells)

Pattern recognition receptors
(cytoplasm of many cell types)

Complement system
(blood and tissue fluids)

Innate effector actions
Destroy invader

Inflammatory response

Inflammatory response

Interferon response

Inflammatory response
Opsonization
Membrane attack complexes

Microbial invasion
First lines of Defense

- Physical Barriers
  - Skin
  - Mucous membranes

- Antimicrobial substances
  - Lysozyme
  - Peroxidase enzyme
  - Lactoferrin
  - Defensins

- Normal Flora
Physical Barriers: body’s borders

Skin

- Difficult to penetrate
- **Dermis**: tightly woven fibrous connective tissue
- **Epidermis**: many layers of epithelial cells
  - Outermost are dead, filled with **keratin**
    - Repels water, continually slough off along with any attached microbes
Skin as the first line of defense

- Intact skin protects
  - Epidermis
  - Dermis
First-Line Defenses

- Physical Barriers (continued…)
- Mucous Membranes line the inside of the body
  - Digestive, respiratory, genitourinary tracts
  - Constantly bathed in secretions (e.g., mucous)
  - Peristalsis of intestines, mucociliary escalator of respiratory tract remove microbes

![Diagram of human body systems with labeled mucous membranes and other organs.](image)
Antimicrobial Substances

- Protect skin, mucous membranes
- Salt on skin
- Lysozyme degrades peptidoglycan
- Peroxidase enzymes break down hydrogen peroxide
- Lactoferrin binds iron
- Defensins form pores in microbial membranes
**Microbial Barriers**

- Normal flora (biota) play a role in keeping the body protected

- Competitive exclusion—take up spaces, and nutrients

- Toxic compounds
  - *Propionibacterium* degrade lipids, produce fatty acids
  - *E. coli* may synthesize colicins in intestinal tract
    - Kill Salmonella and Shigella
  - *Lactobacillus* in vagina produce low pH—prevents infections
Sensor systems in the blood, tissues and cells

- Can detect signs of tissue damage or microbial invasion
- Respond by
  - Detecting parts of bacteria/viruses using pattern recognition receptors (PRRs)
  - Directly destroy bacteria using complement
  - Recruit other components of host defense
Pattern Recognition Receptors (PRRs)

- Pattern recognition receptors (PRRs) detect pathogen-associated molecular patterns (PAMPs), “see” signs of microbial invasion

- Cell wall (lipopolysaccharide, peptidoglycan, lipoteichoic acid, lipoproteins), flagellin subunits, viral RNA molecules

- Also called MAMPs (for microbe-associated)

- Some are DAMPs (for danger-associated), which indicate host cell damage
Types of Pathogen-Associated Molecular Patterns (PAMPs)

- Lipopolysaccharide layer of Gram (-) Microorganisms
- Lipoteichoic Acid and Peptidoglycan of Gram (+) Microorganisms
- Flagellin
- DNA and RNA from bacteria and viruses
Pattern Recognition Receptors

- Toll-Like receptors (TLRs)
  - Membrane bound receptors which detect bacterial parts

- NOD-like receptors (NLRs)
  - Cytoplasmic proteins detect bacterial parts
Pathway Activation

- PAMP binds to a TLR to activate cell signaling
Pattern Recognition Receptors (PRRs)  
Toll-like receptors (TLRs) in membranes of sentinel cells

(e.g., macrophages, dendritic cells, cells lining sterile body sites)

Cells “see” PAMPs in extracellular environment
-signal transmitted to nucleus
-Induces gene expression, e.g. inflammatory response, antiviral response
Pattern Recognition Receptors (PRRs)

- **NOD-like receptors (NLRs found in cytoplasm)**
  - Detect bacterial components -- cell invasion; some detect damage
  - Unleash series of events to protect host
    - Some at expense of cell
  - Some NLRs join cytoplasmic proteins to form an inflammasome
    - Activates inflammatory response

NLR - Detects flagellin
NLR - Detects peptidoglycan
NLR - Detects compounds that indicate cell damage
Antibody Recruitment Assay Design

- Utilized fluorescent anti-DNP antibodies to determine if bacteria were being opsonized
- Analysis could be performed using flow cytometry