Chapter 6: Introduction to host-bacteria interaction

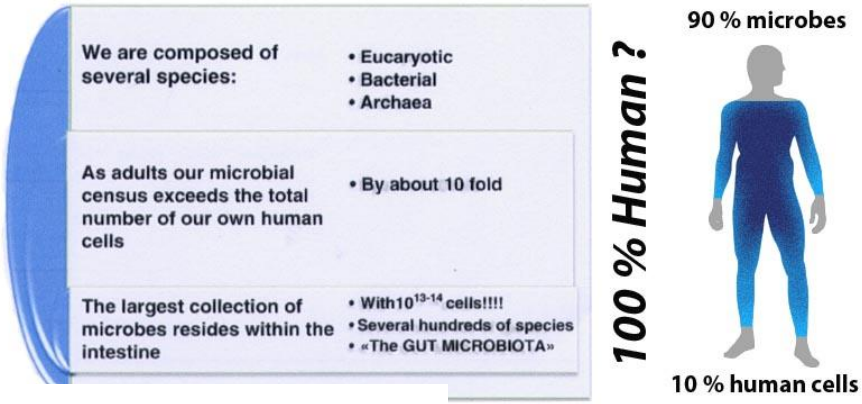
aa 2017-18

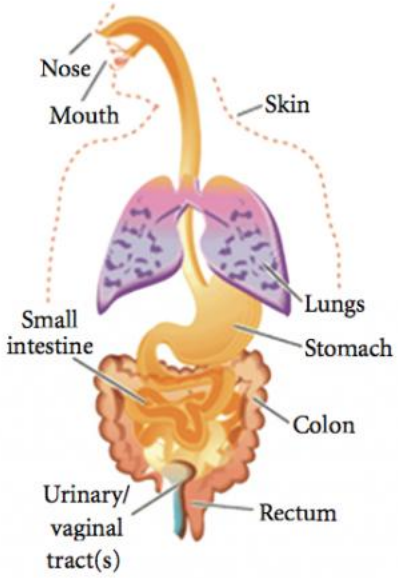
100% Human?

Bacteria are consistently associated with the body of animals.

Bacteria-human host is an ecosystem comprising 10^{14} microbs and only 10^{13} mammalian cells!

The bacteria and other microbes that are consistently associated with an host are called the **microbiota** (**microflora**) of the animal.





Human body 10^{13} cells 23,000 genes

Normal flora 10^{14} microbial cells on the human body. 3.3 million genes

Amount of bacteria per gram of cellular component

- Stomach–10^{1} to 10^{2} cells
- Duodenum–10^{3} cells
- Jejunum–10^{4} cells
- Ileum 10^{4} to 10^{7} cells
- Proximal colon 10^{10} to 10^{11} cells
- Transverse colon 10^{11} to 10^{12} cells
- Distal colon >10^{12} cells

In a healthy animal, the internal tissues, e.g. blood, brain, muscle, etc., are normally free of microorganisms. However, the surface tissues, i.e., skin and mucous membranes, are constantly in contact with environmental organisms and become readily colonized by various microbial species.

The human microbiota

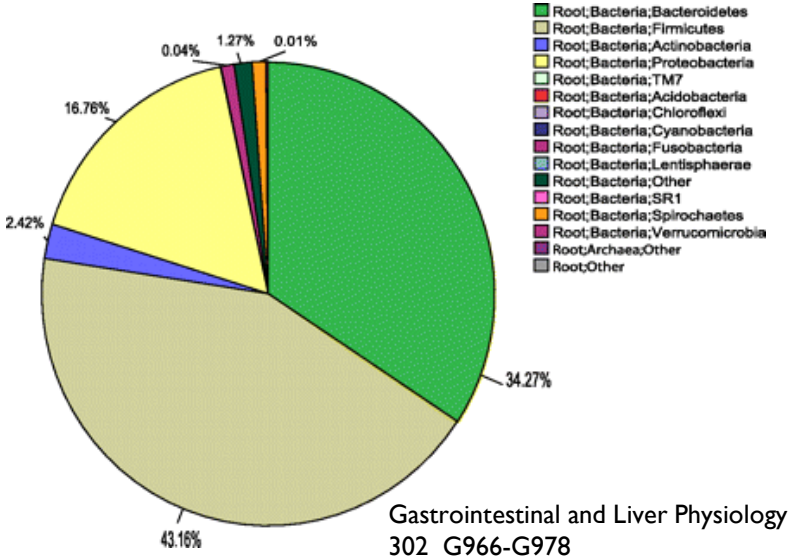
Microbial population consists of hundreds species. Bacteria are the most numerous but few eukaryotic fungi and protists are also present. Methods to characterize the human microbiota:

1) Lab cultivation

2) Nucleic acid-based approaches. PCR to amplify 16S RNA probes to detect the diversity of bacteria. Example: in dental plaque only 1-5% of the total species found have ever been cultivated. Similar observations have been made with the intestinal microbiota.

3) Massively parallel methods of DNA sequencing (metagenomics).

Intestine **microbiome**: about **60000 different genes** representative of 1000 bacterial species have been sequenced. 3-4 phyla are dominant: Firmicutes, Bacteroidetes Proteobacteria and Actinobacteria



Gastrointestinal and Liver Physiology 2012 Vol. 302 G966-G978

Pie chart pyrosequencing data analyzed at the phylum level. Uncommon phyla that are a very small fraction of the total are not visible in the chart but they are present in the legend.

Human microbiome

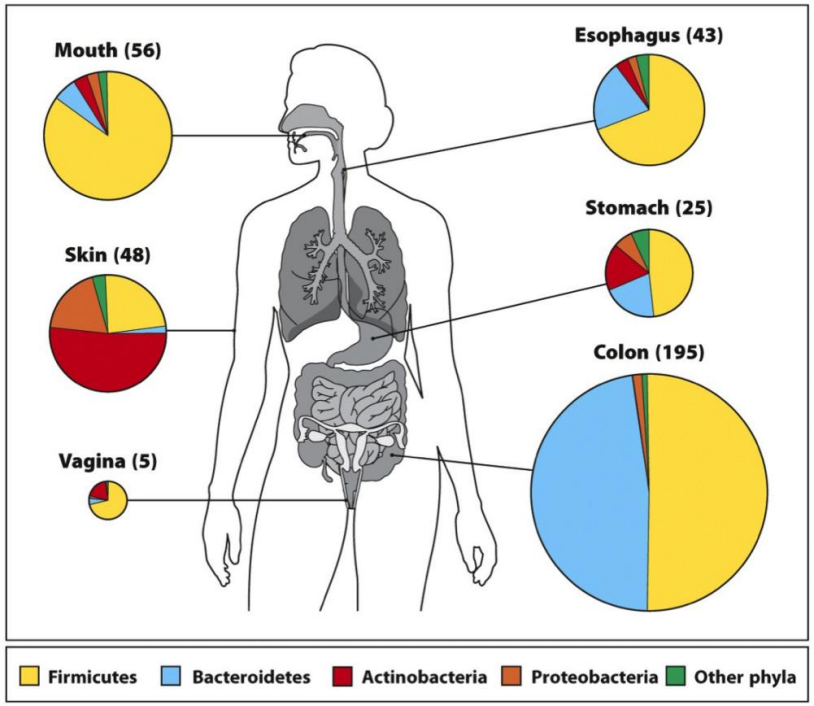


Figure 12.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Nature 486, 207–214 (14 June 2012)

Present Aim: to decrypt the whole human **"microbiome":** the genomes of all micro-organisms that live in our body (our **microbiota**).

Published in final edited form as:
Nature. 2017 October 05; 550(7674): 61–66. doi:10.1038/nature23889.

Strains, functions, and dynamics in the expanded Human Microbiome Project

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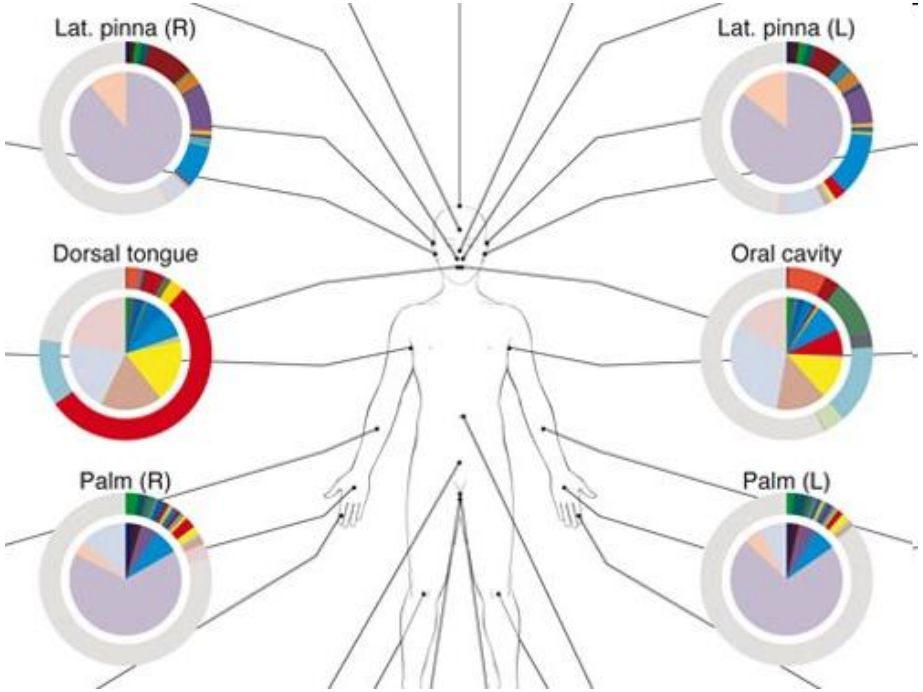
cultured and uncultured bacteria, plus several viral and small eukaryotic microbes isolated from human body sites.

- Different organs are colonized by different bacteria.
- Healthy individuals differ remarkably in the microbes that occupy habitats such as the gut, skin and vagina.
- Diet, environment, host genetics and early microbial exposure have all been implicated in individual diversity
- Metagenomic carriage of metabolic pathways was stable among individuals despite variation in community structure

Bacterial Community Variation in Human Body Habitats Across Space

To obtain an integrated view of the spatial and temporal distribution of the human microbiota, bacteria were collected and examined from up to 27 sites in seven to nine healthy adults on four occasions.



New Scientist Nov. 2009 Elizabeth K. Costello

For each region of the body, a pie chart shows the microbial community living there. Each color corresponds to one of the 40 microbial groups found in the bodies sampled.

- Several skin locations harbored more diverse communities than the gut and mouth. Within habitats, interpersonal variability was high.
- Transplantation from one site to a different one often has not been success: that skin chemistry exerts a strong control over community growth.

Community composition was determined primarily by body habitat and is personalized.

The Nature of Bacterial Host-Parasite Relationship in Humans

These bacteria have a full range of **symbiotic interactions** with their animal hosts:

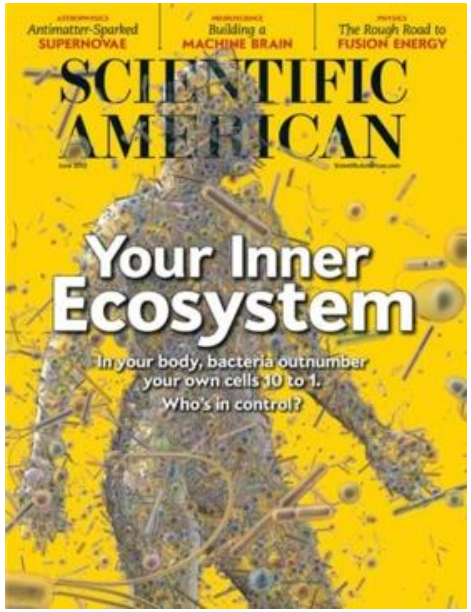
- **mutualism:** both members of the association benefit
- **commensalism:** there is no apparent benefit or harm to either member of the association
- **parasitism:** one member grows, feeds and is sheltered on or in a different organism while contributing nothing to the survival of its host.

Interactions sometimes are not fully understood (neither for *E. coli*).

The host obtains from the normal microbiota:

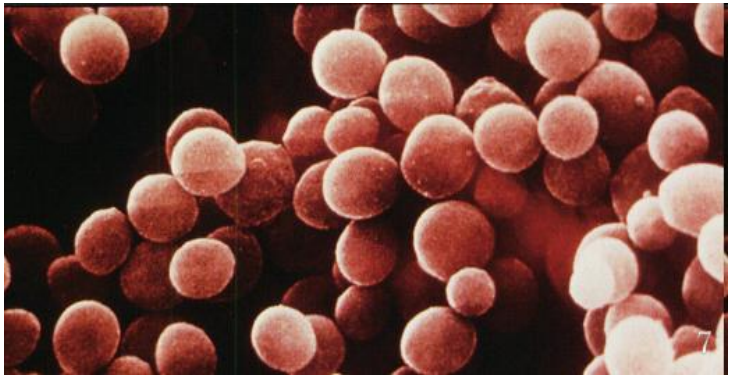
1. Certain nutritional and digestive benefits.
2. Stimulation, development and activity of immune system.
3. Protection against colonization and infection by pathogenic microbes.

Normal microbiota obtains from the host a warm, moist, nutrient-rich environment.



Pathogens and pathogenesis

A **pathogen** is a microorganism (bacterium or virus, fungus or protist) that is able to damage its host:
e.g. the interruption of normal tissue structure and/or function of the host that applies at the cellular (necrosis, apoptosis, synaptic blockage), tissue (granulomatous inflammation, fibrosis), and organ (ductal obstruction) levels producing a disease.



S. aureus, likely the most prevalent pathogen of humans, may cause up to one third of all bacterial diseases

Pathogenicity (virulence) is the ability to produce damage in a host organism under certain conditions.

Virulence factor a component of a pathogen that contributes to virulence

Primary and secondary pathogens

Pathogens can be classified as either primary or secondary (also known as opportunistic) pathogens (accordly to https://www.cdc.gov/).

Primary pathogens infect a normally healthy body. They normally do not associate with their host except in the case of disease. When this occurs, the result is a parasitic relationship in which the prokaryote exogenous pathogen causes damage to its host.

Several members of the normal microbiota are potential pathogens: **opportunistic pathogens (secondary pathogens).** They cause disease in their host when they have an opportunity to do it.

*Clostridium tetani **
*Legionella pneumophila**
*Bacillus Anthracis**
*Yersinia spp.**
*Vibrio cholerae**
Salmonella typhi
*Brucella spp.**
Mycobacterium tuberculosis
Corynebacterium diphtheriae
Neisseria Gonorrhoeae
Shigella spp.
*Listeria monocytogenes**
Bordetella pertussis

Staphylococcus aureus
Enterococcus faecalis
Streptococcus pneumoniae
Neisseria meningitidis
Enterobacteriaceae
E. coli (some strains)
Klebsiella pneumoniae
Haemophilus influenzae
*Pseudomonas aeruginosa**

Opportunities:

- Weakness in the host's anatomical barriers: damage of the epithelium, presence of foreign body.
- Suppression of immune system (drugs or radiation), co-infections of an exogenous pathogen.
- Alterations of microbiota (by antibiotics).

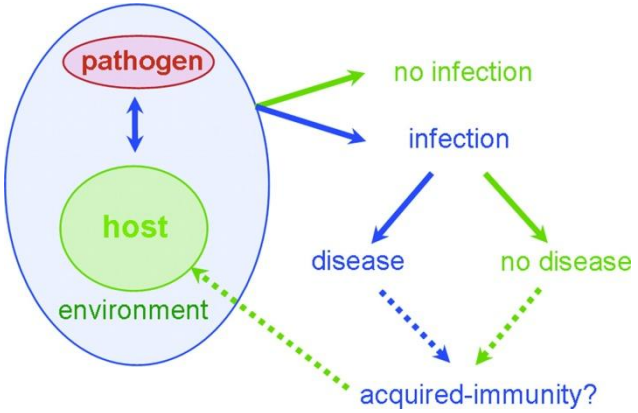
*Accidental pathogens: non associated with humans but with animals or soil or water.

Views of the microbe-human interaction

Host-microbe interaction is a very complex process: there are difference in susceptibility from person to person and also variation among different strains of the same bacterial species

Three different views:

- Disease-causing bacteria evolved specifically to cause human disease.
- Disease-causing bacteria are actually trying to achieve an equilibrium with humans that does not result in disease, but often this equilibrium does not develop.
- Humans are only accidental host of bacteria that have evolved to occupy some other niches.



Riny Janssen et al. Clin. Microbiol. Rev. 2008;21:505-518

Probably each of these views is correct for a subset of bacteria.

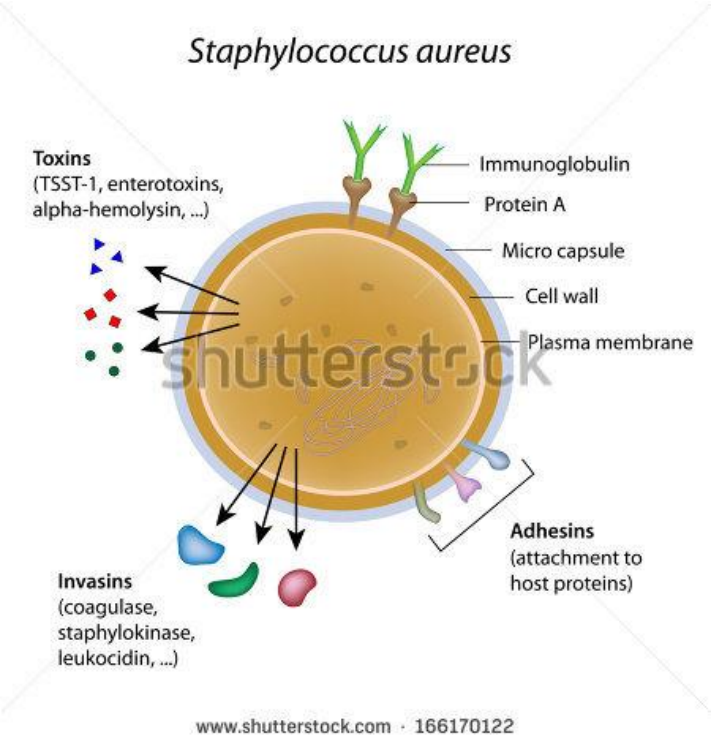
Virulence factors and multifactorial nature of virulence

Genes that contribute to the ability of an organism to become virulent are **virulence genes** and their product are **virulence factors.**

Few pathogens have a main single gene of virulence: E.g. *Clostridium tetani* and *Corynebacterium diphtheriae*, are able to produce disease, the symptoms of which depend on a single genetic trait: the ability to produce a toxin.

Most pathogens possess a large repertoire virulence genes. They are able to produce a more complete range of diseases that affect different tissues in their host.

Bacterial virulence factors could be classified into different groups:



1. Factors are related to the **invasiveness**: adhesins, invasins (exoenzymes), impedins (capsule).
2. Factors related to **toxigenesis:** aggressins (toxins), modulins (effector proteins).

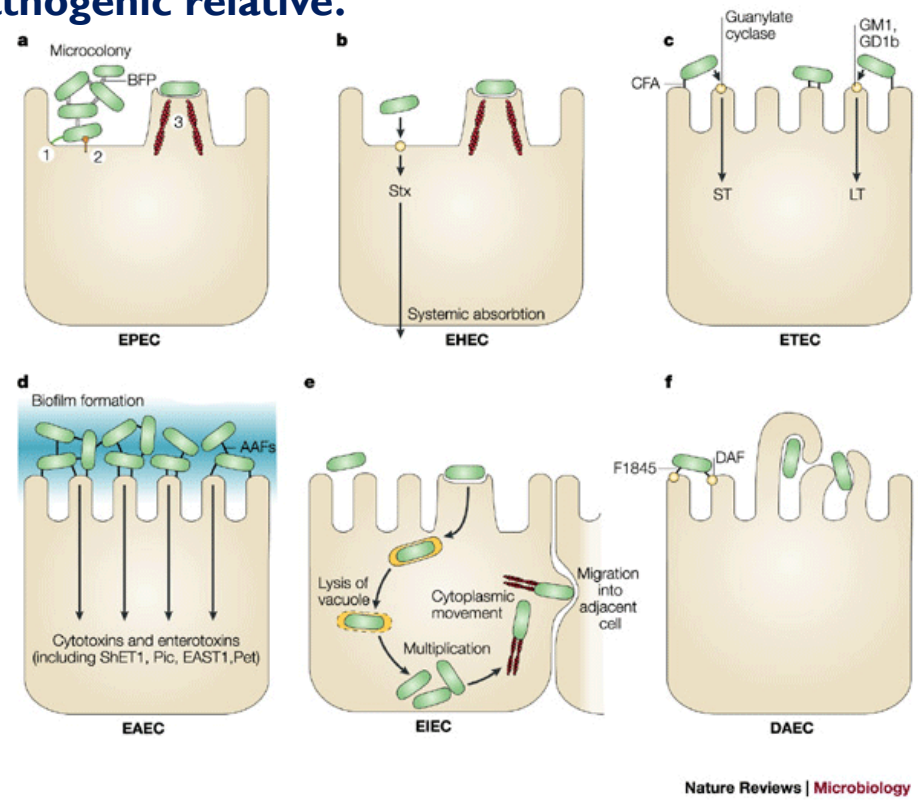
Different types (virotypes) of Escherichia coli

A relatively small number of genes causes the significant differences between a virulent pathogenic bacterium and its closest **non-pathogenic relative.**

As a pathogen, *E. coli* is best known for its ability to cause intestinal diseases. Different classes (**virotypes**) of *E. coli* that cause diarrheal diseases (DEC) are now recognized:

enteropathogenic *E. coli* (EPEC)
enterohemorrhagic *E. coli* (EHEC)
enterotoxigenic *E. coli* (ETEC)
enteroaggregative *E. coli* (EAEC)
enteroinvasive *E. coli* (EIEC)
Diffusely adherent E. coli (DAEC)

The DEC virotypes differ regarding their preferential host colonization sites, virulence mechanisms, and the ensuing clinical symptoms and consequences

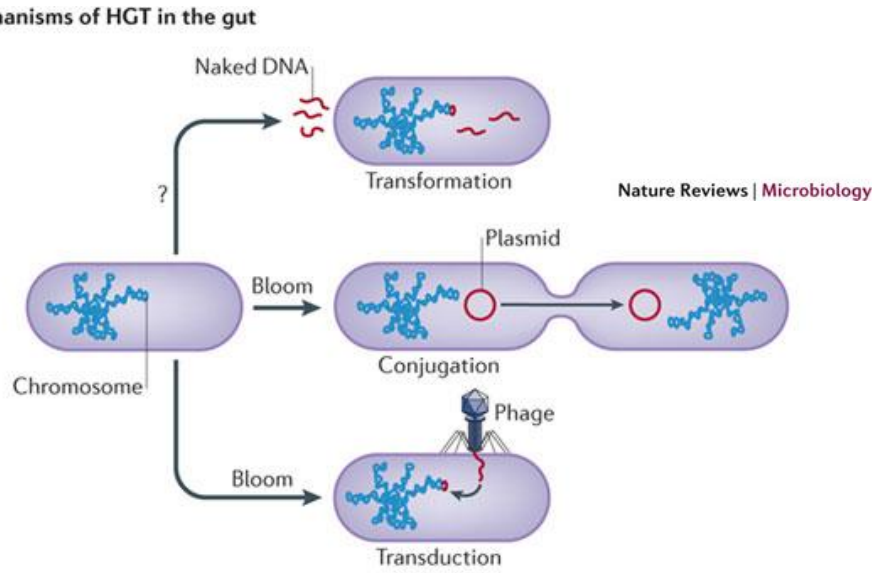


Gut epithelia damaged by different diarrheagenic *E. coli* virotypes.

Genetics of virulence genes

Virulence genes are frequently clustered together, either in groups on the bacterial chromosome called *pathogenicity islands* or on extrachromosomal *virulence plasmids*. These genes may also be carried on mobile *bacteriophage*s (bacterial viruses).

New pathogen may arise when groups of virulence genes are transferred together into a previously avirulent bacterium.



Acquisition of large pieces of DNA and other large chromosomal changes have contributed to bacterial evolution (***horizontal gene transfer, HGT***), enabling bacterial species to inhabit new ecological and nutritional niches, as well as to cause disease. Even within a single bacterial species, the amount of chromosomal variation is astonishing (25%).

Acquisition of virulence genes

Genetic differences between pathogenic and nonpathogenic *E. coli* exist: