Pharmaceutical Microbiology

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Of

Immunology And Microbiology

Course outlines of pharmaceutical microbiology and parasitology .

- Dr. Mohammad Hussein Taleb

- **Marks distribution:**

- Quizez 30%. ..... Midterm exams 30%........ , Final exam .... 40 %
- Textbook : Essentials of Medical Microbiology .. Fourth Edition Rajesh Bhatia
- Email.....

- Week 1 Chapter1. Introduction to microbiology (General Bacteriology)
- Week2. Chapter2. Pathogenesis of Bacterial Infection
- Week3 Chapter 3.Classification of bacteria
- Week4 and Week5 Chapter4 and Chapter 5. G-positive cocci bacteria (staphyllococci and Streptococci
- Week 6 Chapter 6. G-negative cocci bacteria

- Week7 Chapter 7. Gram-Positive Bacilli: Aerobic Non–Spore-Forming
- Week 8 Chapter 7. Gram-Positive Bacilli: Aerobic Non–Spore-Forming
- Week 9Chapter 8. Gram-negative Bacilli
- Week 10 Chapter 9. General Mycology (Fungi as Human Pathogens)
- Week 11 & week 12 Chapter 10 . Major subjects in Parasitology
- Week 13 Chapter 11 General Virology (Viruses as Human Pathogens)
- Week 14. Chapter 12 . General Aspects in Immunology

Instructions for 95%

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أهم عوامل التفوق الدراسي

1. التفوق في الدراسات السابقة في المــراحل السابقة .
2. التفرغ للدراسة .
3. الإلتحاق بالتخصص عن رغبة أكيدة .
4. المذاكرة من بداية العام الدراسي .
5. زيادة عدد ساعات المذاكرة اليومية .
6. تشجيع الأسرة على الدراسة وعــلى وجه خاص تشجيع الوالدين .
7. تشجيع الأساتذة على الدراسة والـمذاكرة والتفوق .
8. تشجيع المدارس والكليات على التفوق .
9. التشجيع على المنافسة في التــفوق بين الطلاب على مستوى المدارس والجامعات.
10. توجيه الميول إلى الدراسات المناسبة .
11. إستخدام القـيم الموجــهة لإثارة الهـمم العالية وتحفيزها .
12. إتخاذ الأهداف العليا من التــعلم مــثل خدمة الدين والأمة .
13. تخصيص أماكن خاصة ومناسبة للدراسة والسكن سواء في نطاق الأسرة أو المدرسة والجامعة .

Chapter 1

Week 1

Fundamentals

Of

Microbiology

Introduction

- **Microbiology** is the study of microorganisms, **a large and diverse group of microscopic organisms** that exist as **single cells** or **cell clusters**; it also **includes viruses**, which **are microscopic but not cellular.**
- They are **responsible for cycling the chemical elements essential for life**, including **carbon, oxygen, nitrogen, sulfur, and hydrogen**; **more photosynthesis is carried out by microorganisms than by green plants.**

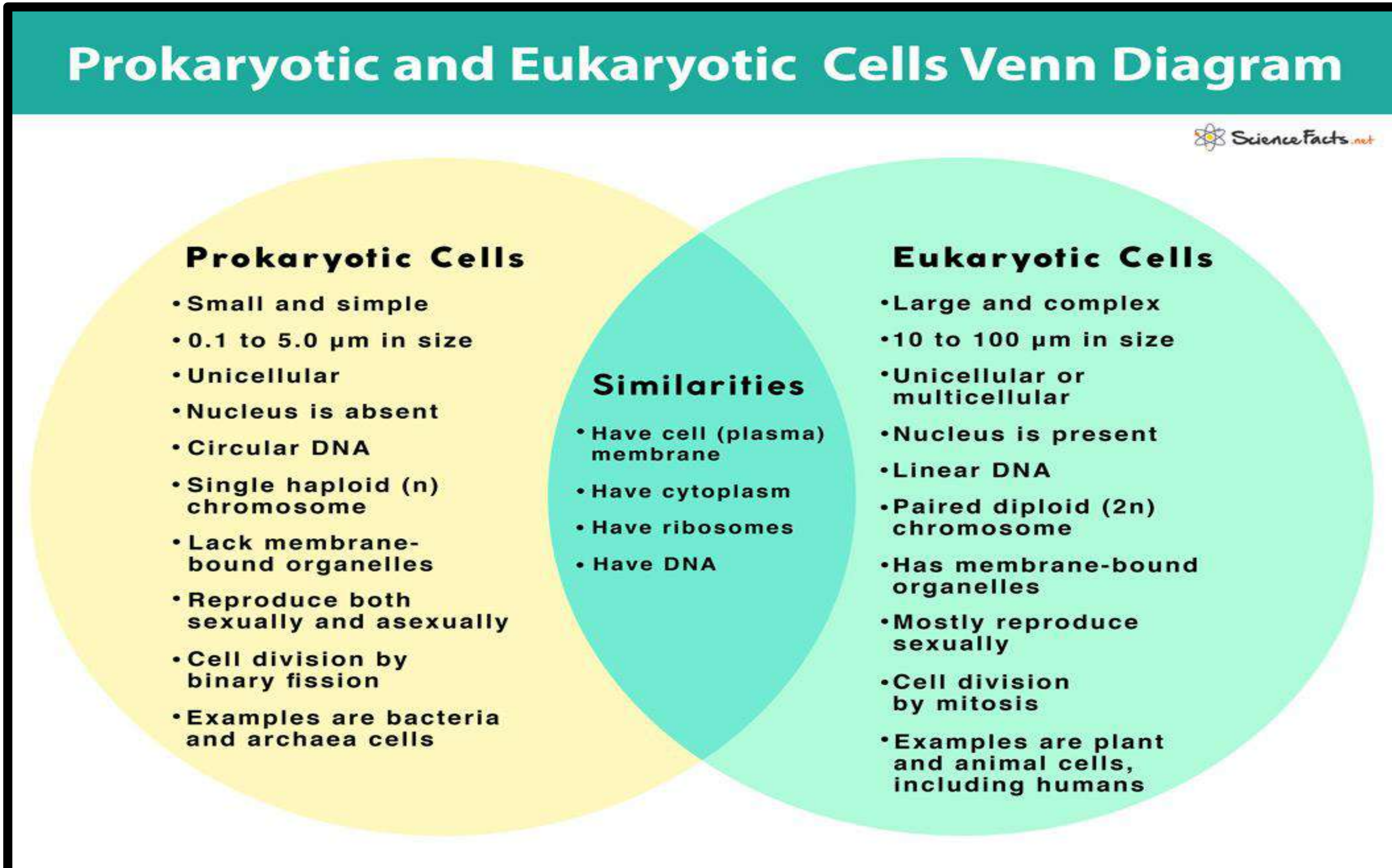
- In fact, **Robert Koch** bagged the most prestigious **Nobel prize in the year 1905** for his spectacular and wonderful discovery for the isolation and characterization of the *bacteria* that cause **anthrax***** and **tuberculosis**.****

Scope of microbiology

Microbial world

- **Scope of medical microbiology:**
  - Bacteriology → Bacteria
  - Mycology → Fungi
  - Parasitology → Parasites (protozoons and helminths)
  - Virology → Viruses
  - Immunology → Immune system

Comparison between Prokaryotic and Eukaryotic cells



General information

About

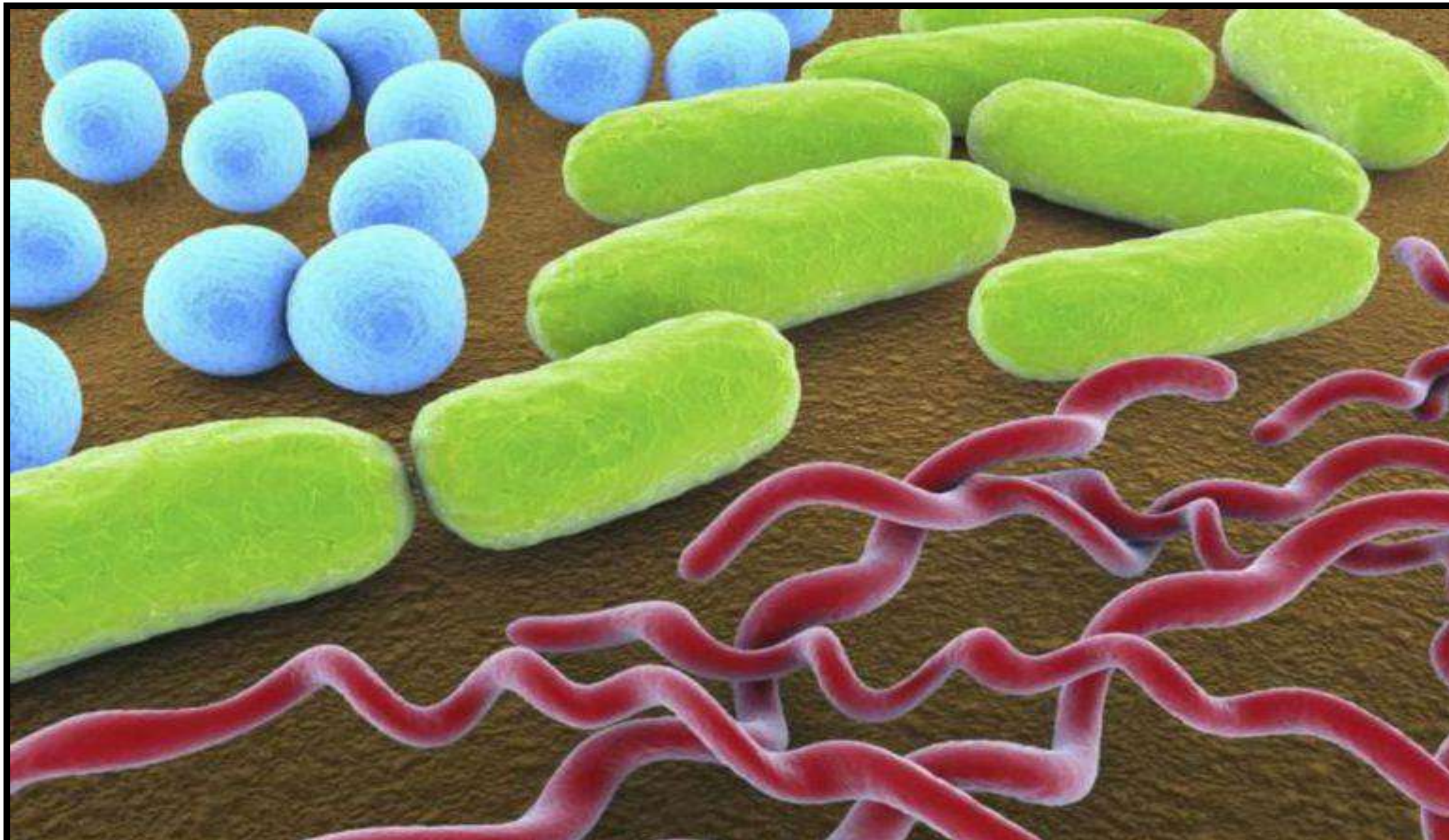
bacteria

Bacteria infection types

Bacteria

- Bacteria; common noun bacteria, singular bacterium) are ubiquitous, **mostly free-living organisms often consisting of one biological cell.**
- They constitute a **large domain of prokaryotic microorganisms.**
- **Typically a few micrometres in length, bacteria were among the first life forms to appear on Earth, and are present in most of its habitats.**

Bacterial forms

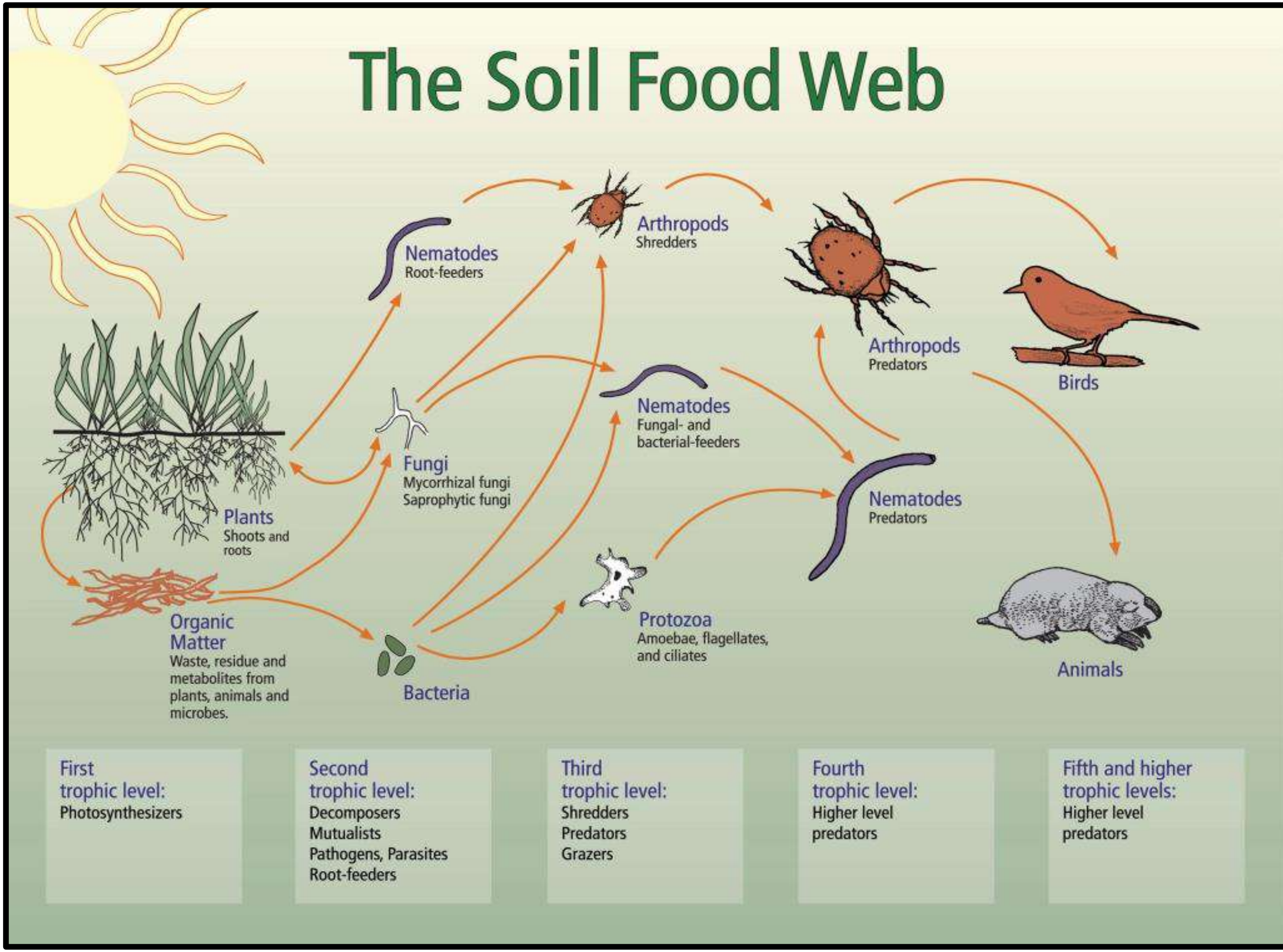


Bacteria

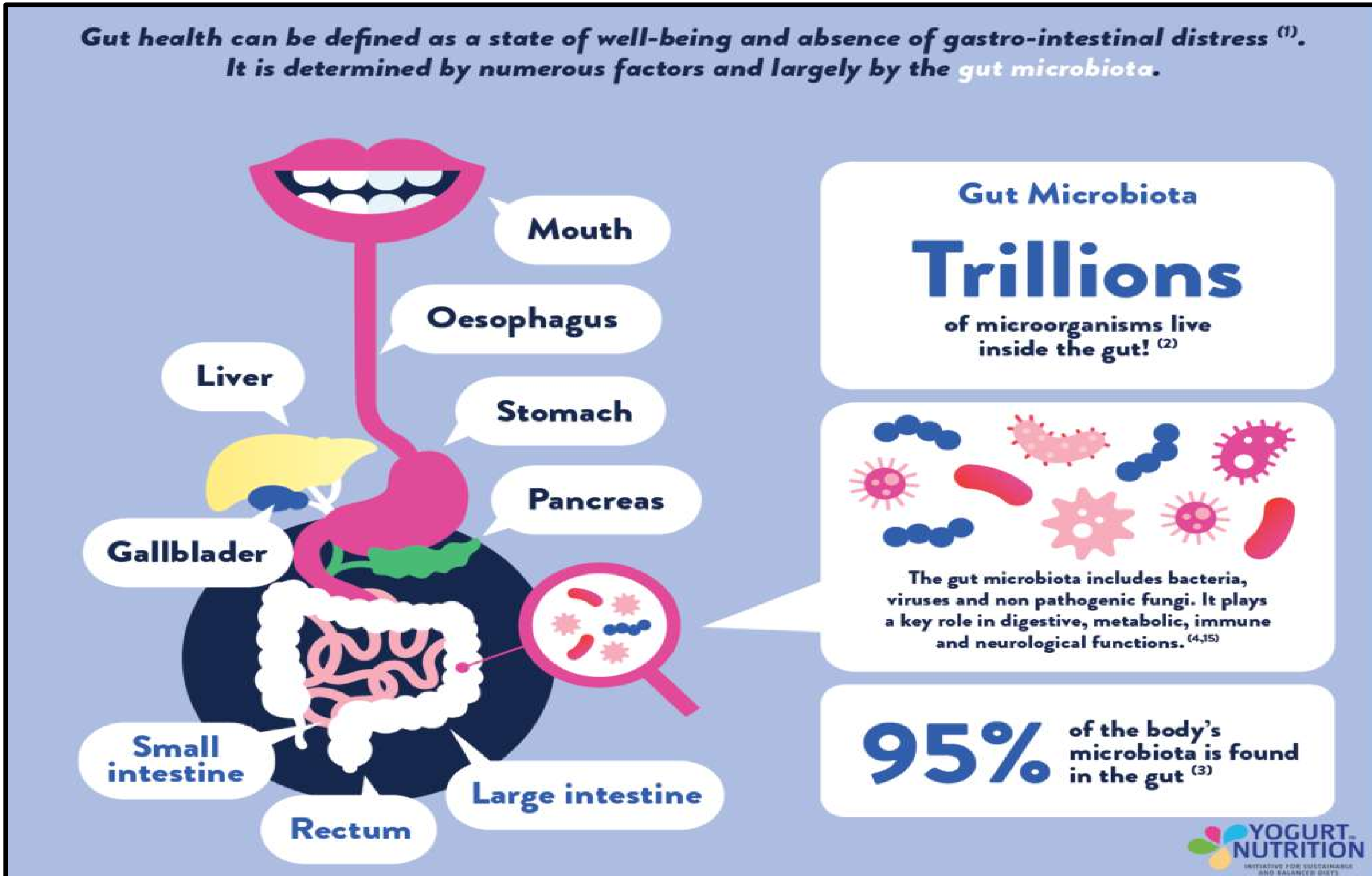
- Bacteria inhabit soil, water, acidic hot springs, radioactive waste, and the deep biosphere of Earth's crust.
- Bacteria are vital in many stages of the nutrient cycle by recycling nutrients such as the fixation of nitrogen from the atmosphere.
- The **nutrient cycle includes the decomposition of dead bodies**; **bacteria are responsible for the putrefaction stage in this process.**

- **There are typically 40 million bacterial** cells in a gram of soil and a million bacterial cells in a milliliter of fresh water.
- There are approximately 5×10^{30} bacteria on Earth, forming a **biomass which exceeds that of all plants and animals.**

- There are **approximately 39 trillion bacterial cells in the human microbiota as personified by a "reference" 70 kg male 170 cm tall.**
- The largest number exist in the gut flora, and a large number on the skin.
- The **vast majority of the bacteria in the body are rendered harmless** by the protective effects of the immune system, though many are beneficial, **particularly in the gut flora**.


The Soil Food Web
Nematodes
Root-feeders
Arthropods
Shredders
Arthropods
Predators
Birds
Fungi
Mycorrhizal fungi
Saprophytic fungi
Nematodes
Fungal- and bacterial-feeders
Nematodes
Predators
Plants
Shoots and roots
Organic Matter
Waste, residue and metabolites from plants, animals and microbes.
Bacteria
Protozoa
Amoebae, flagellates, and ciliates
Animals
First trophic level:
Photosynthesizers
Second trophic level:
Decomposers
Mutualists
Pathogens, Parasites
Root-feeders
Third trophic level:
Shredders
Predators
Grazers
Fourth trophic level:
Higher level predators
Fifth and higher trophic levels:
Higher level predators

Gut microbiota



- However, **several species of bacteria are pathogenic and cause infectious diseases, including cholera, syphilis, anthrax, leprosy, and bubonic plague. The most common fatal bacterial diseases are respiratory infections, with tuberculosis alone killing about 2 million people per year, mostly in sub-Saharan Africa.**

- In developed countries, antibiotics are used to treat bacterial infections and are also used in farming, making antibiotic resistance a growing problem.
- In industry, bacteria are important in sewage treatment and the breakdown of oil spills, the production of cheese and yogurt through fermentation, the recovery of gold, palladium, copper and other metals in the mining sector, as well as in biotechnology, and the manufacture of antibiotics and other chemicals.

Taxonomy of bacteria

- **Taxonomic ranks** form the basis for the organization of bacteria. **Linnaean taxonomy** is the system most familiar to biologists. It uses the formal taxonomic ranks of **kingdom, phylum, class, order, family, genus, and species.**

Taxonomic ranks Formal rank example

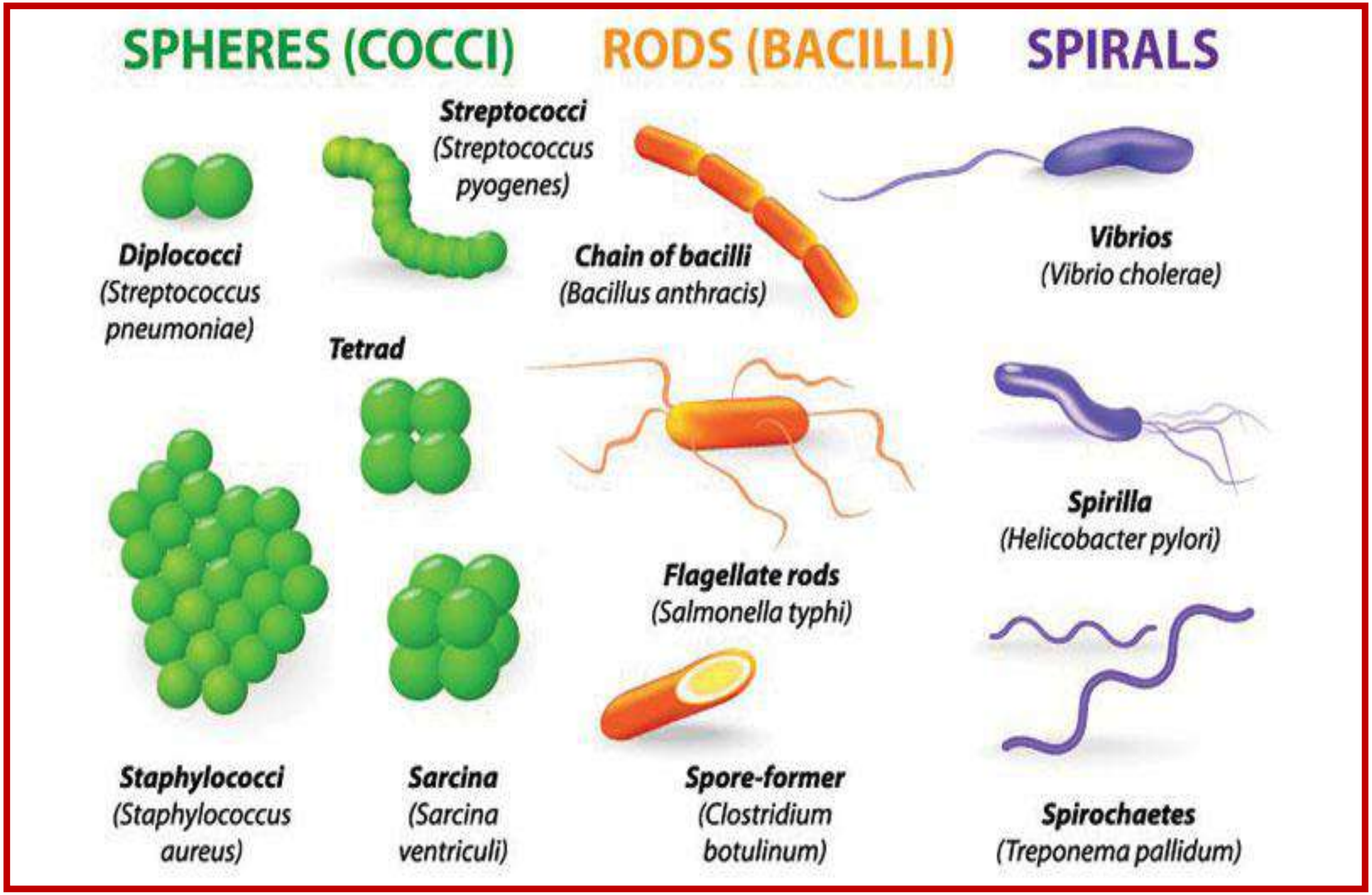
- **Kingdom**: Prokaryotae
- **Division**: Gracilicutes
- **Class:** Scotobacteria
- **Order:** Eubacteriales
- **Family:** Enterobacteriaceae
- **Genus:***Escherichia*
- **Species:** *coli*
- **Subtype:** *Escherichia coli* O157: H7

Classification of bacteria

- Classification of bacteria depends on

1. Shape
2. Oxygen demand
3. Resistance of temprature
4. Gram staining
5. Growth on different media
6. Biochemical tests
7. Immunological tests

1-Shapes of bacteria



2-Based on Oxygen demand

Classification of bacteria based on Oxygen requirement:

Based on Oxygen requirement, bacteria may be classified as:

- **Obligate aerobes:** they require O_2 for growth. They use O_2 as a final electron acceptor in aerobic respiration.

- **Obligate anaerobes** : they do not need or use O_2 . In fact, O_2 is a toxic substance for them, which either kills or inhibits their growth.

- **Facultative anaerobes** : these are bacteria that can switch between aerobic and anaerobic types of metabolism.
  - Under anaerobic conditions, they generate energy mainly by fermentation .
  - In the presence of O_2 they switch to aerobic respiration.

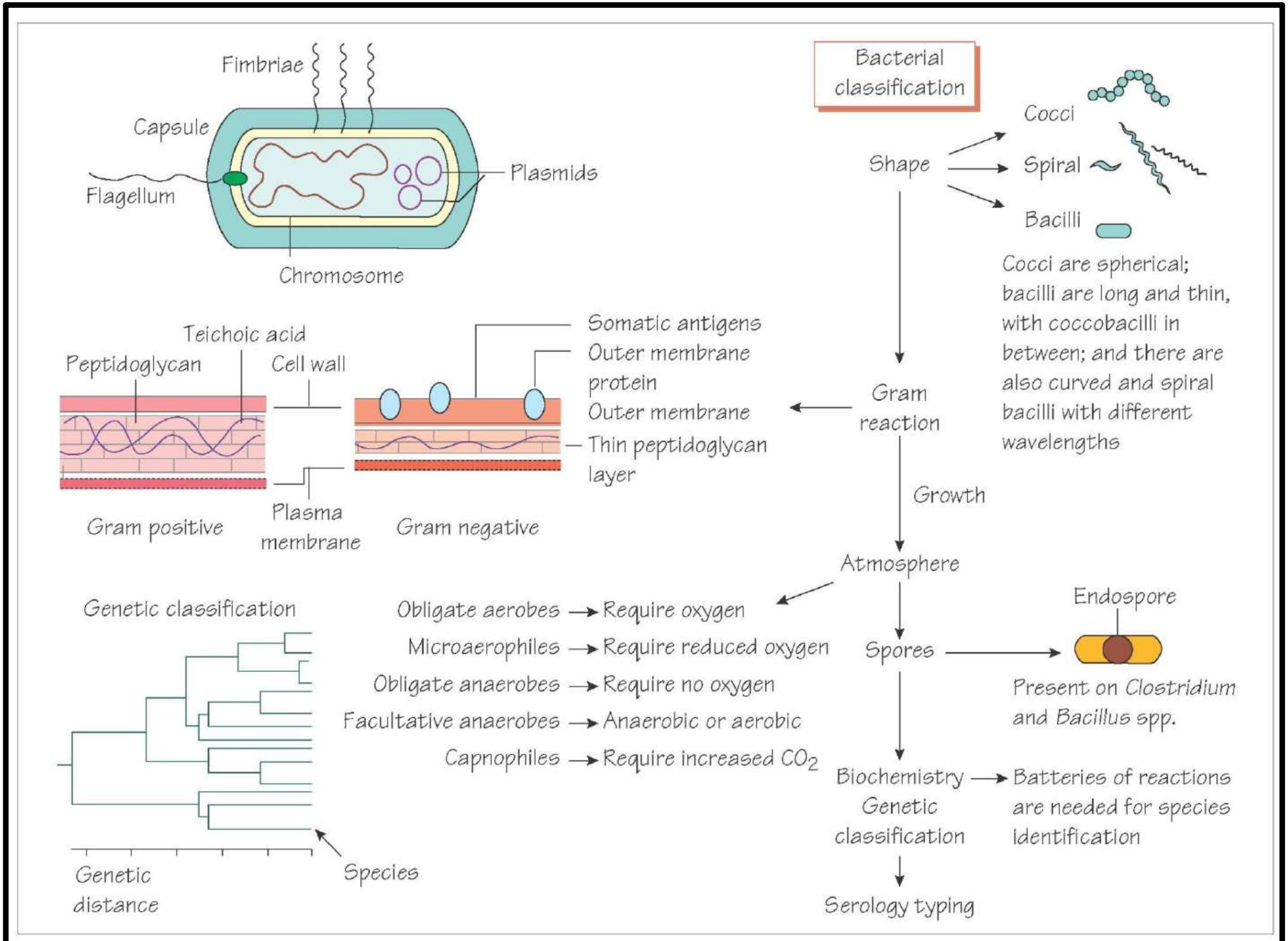
- **Aerotolerant anaerobes:** these are bacteria that are exclusively anaerobic (fermentative). However, they are insensitive (not killed) to the presence of O_2. They live by fermentation alone whether or not O_2 is present in their environment

- **Microaerophilic**: these bacteria need O2 in low concentration

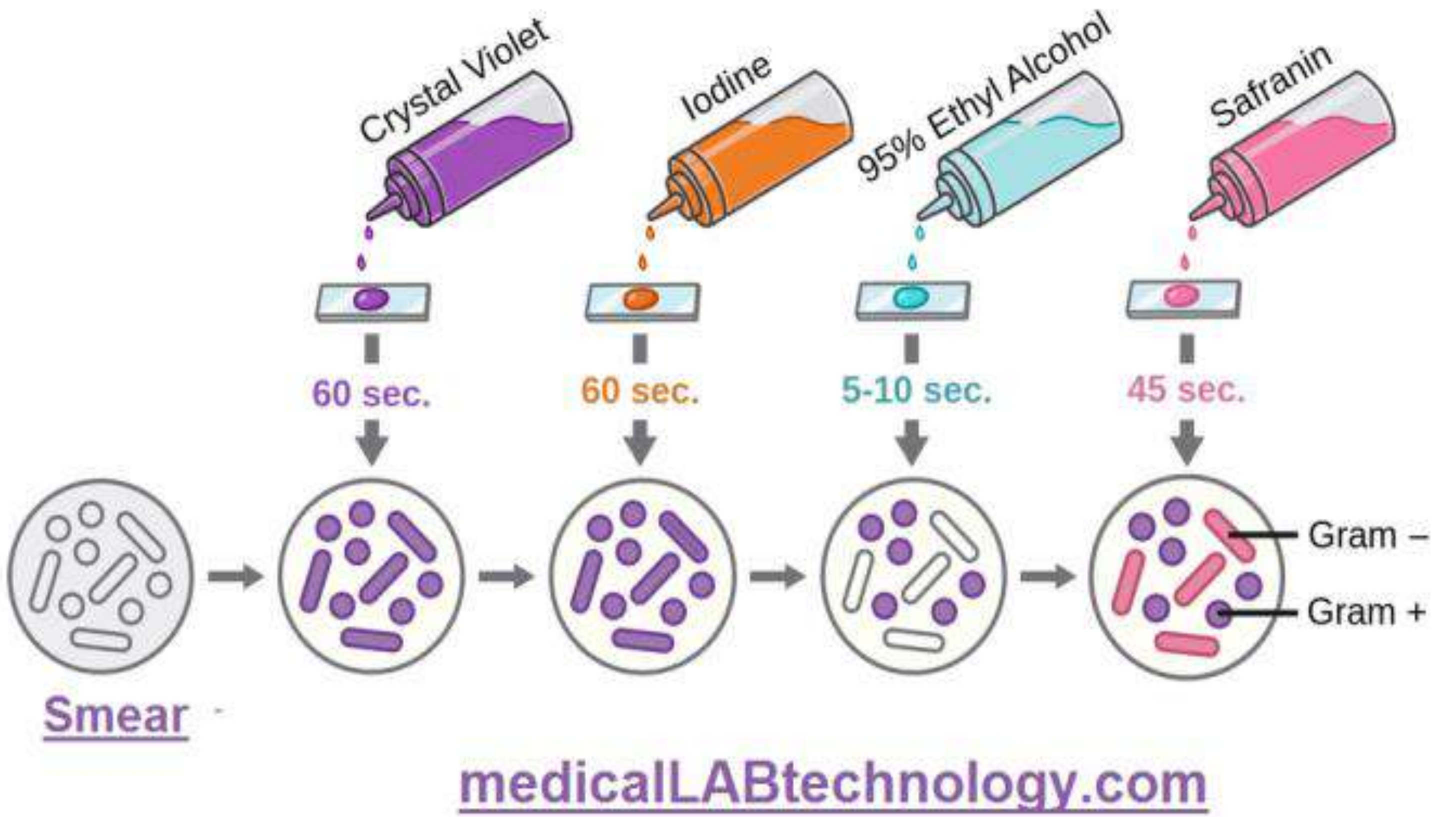
3-On the bases of temprature

ON THE BASIS OF TEMPERATURE

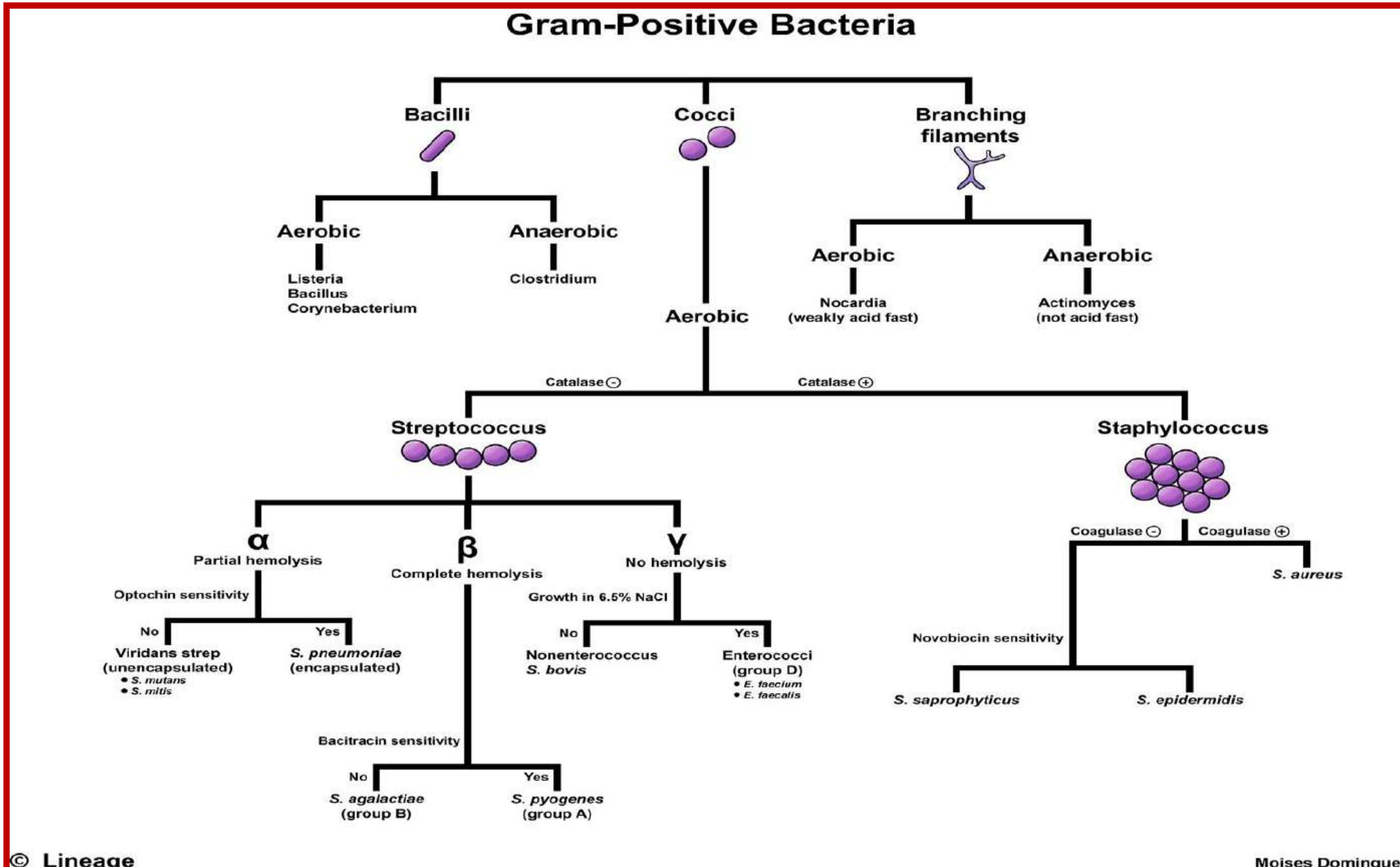
- **Psychrophiles** e.g Bacillus psychrophilus
- **Psychrotrophs** e.g Listeria monocytogenes
- **Mesophiles** e.g E.coli
- **Thermophiles** e.g Bacillus stearothermophiles
- **Hyperthermophiles** e.g Sulpholobus

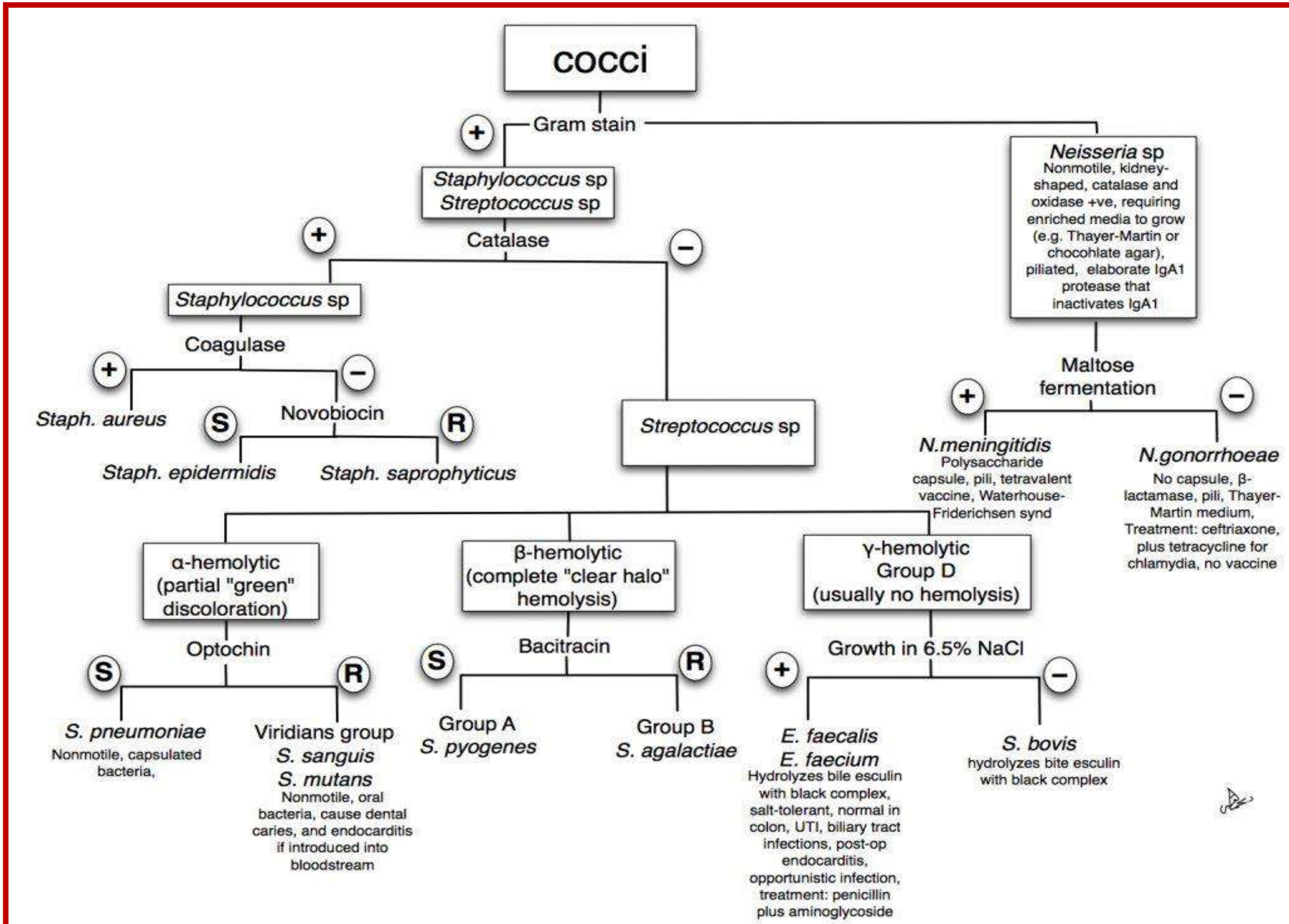

Fimbriae
Capsule
Flagellum
Plasmids
Chromosome
Bacterial classification
Cocci
Spiral
Bacilli
Shape
Cocci are spherical; bacilli are long and thin, with coccobacilli in between; and there are also curved and spiral bacilli with different wavelengths
Teichoic acid
Peptidoglycan
Cell wall
Somatic antigens
Outer membrane protein
Outer membrane
Thin peptidoglycan layer
Gram reaction
Plasma membrane
Gram positive
Gram negative
Growth
Atmosphere
Genetic classification
Obligate aerobes → Require oxygen
Microaerophiles → Require reduced oxygen
Obligate anaerobes → Require no oxygen
Facultative anaerobes → Anaerobic or aerobic
Capnophiles → Require increased CO_2
Spores
Endospore
Present on Clostridium and Bacillus spp.
Biochemistry → Batteries of reactions are needed for species identification
Genetic classification
Serology typing
Genetic distance
Species

4-On the bases of Gram staining

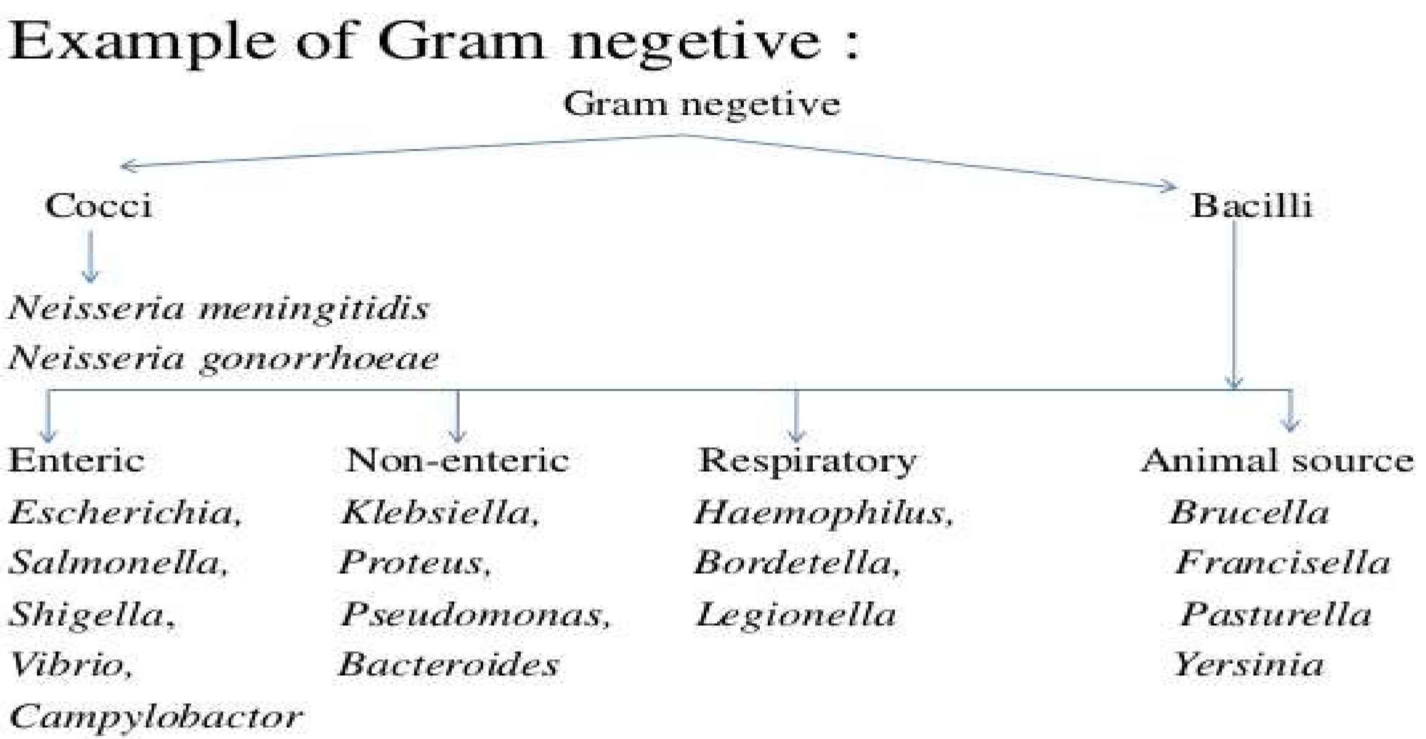


4-Gram staining




cocci
Gram stain
+
Staphylococcus sp
Streptococcus sp
Catalase
+
−
Staphylococcus sp
Coagulase
+
−
Staph. aureus
Novobiocin
S
R
Staph. epidermidis
Staph. saprophyticus
Streptococcus sp
α-hemolytic (partial "green" discoloration)
Optochin
S
R
S. pneumoniae
Nonmotile, capsulated bacteria,
Viridians group
S. sanguis
S. mutans
Nonmotile, oral bacteria, cause dental caries, and endocarditis if introduced into bloodstream
β-hemolytic (complete "clear halo" hemolysis)
Bacitracin
S
R
Group A
S. pyogenes
Group B
S. agalactiae
γ-hemolytic Group D (usually no hemolysis)
Growth in 6.5% NaCl
+
−
E. faecalis
E. faecium
Hydrolyzes bile esculin with black complex, salt-tolerant, normal in colon, UTI, biliary tract infections, post-op endocarditis, opportunistic infection, treatment: penicillin plus aminoglycoside
S. bovis
hydrolyzes bite esculin with black complex
Neisseria sp
Nonmotile, kidney-shaped, catalase and oxidase +ve, requiring enriched media to grow (e.g. Thayer-Martin or chocohlate agar), piliated, elaborate IgA1 protease that inactivates IgA1
Maltose fermentation
+
−
N.meningitidis
Polysaccharide capsule, pili, tetravalent vaccine, Waterhouse-Friderichsen synd
N.gonorrhoeae
No capsule, β-lactamase, pili, Thayer-Martin medium, Treatment: ceftriaxone, plus tetracycline for chlamydia, no vaccine

Gram negative bacteria



- **Clinical samples** from normally **nonsterile sites** (eg, the throat or the colon) contain multiple species of organisms, including **potential pathogens and resident microbial flora**.

- Media can be **nonselective** or **selective**; the latter are used **to distinguish among the various bacteria in a clinical sample containing many different organisms.**

5- Depends on growth on Media

- In contrast to viruses and most parasites, many **bacterial pathogens can be isolated on solid agar-containing media.** The general **cultivation of most bacteria requires media rich in metabolic nutrients.**
- These media generally include **agar, a carbon source, and an acid hydrolysate or enzymatically degraded source of biologic material (eg, casein).** Because of the undefined composition of the latter, these types of media are referred to as **complex media**.

A. Nonselective Media

- **Blood agar** and **chocolate agar** are examples of complex, **nonselective media**, which support the growth of many different bacteria.
- These media are **intended to cultivate as many species as possible, thus giving rise to numerous types of bacterial colonies.**

B. Selective Media

- **Because of the diversity of microorganisms** that typically reside at some sampling sites (e.g, **the skin, respiratory tract, intestines, vagina**), **selective media are used to eliminate (or reduce) the large numbers of irrelevant bacteria in these specimens**.

- The **basis for selective media is the incorporation of an inhibitory agent that specifically selects against the growth of irrelevant bacteria.**

- .

- **Examples of such agents are:**
- **Sodium azide**—selects for gram-positive bacteria over gram-negative bacteria
- **Bile salts** (sodium deoxycholate)—select for gram-negative enteric bacteria and inhibit gram-negative mucosal and most gram-positive bacteria

Colistin and nalidixic acid—inhibit the growth of many gram-negative bacteria

- Examples of selective media are **MacConkey agar** (**contains bile**) that selects for the Enterobacteriaceae and **CNA blood agar** (contains colistin and nalidixic acid) that selects **for Staphylococci and Streptococci**.

C. Differential Media

- **Upon culture**, some bacteria produce characteristic pigments, and others can be differentiated on the basis of their complement of extracellular enzymes; the activity of these enzymes often can be detected as zones of clearing surrounding colonies grown in the presence of insoluble substrates (e g, **zones of hemolysis in agar medium containing red blood cells).**

- Many of the members of the **Enterobacteriaceae** can be differentiated on the **basis of their ability to metabolize lactose**. For example, whereas pathogenic salmonellae and shigellae **do not ferment lactose on a MacConkey plate form white colonies**, **lactose-fermenting members of the Enterobacteriaceae (eg, *E coli*)** form red or pink colonies.
- However, it should be noted **that biochemical identification is an important means to classify microbial pathogens**.

6-Biochemical Tests

- Tests such as the **oxidase test**, which uses an **artificial electron acceptor**, can be used to distinguish organisms on the **basis of the presence or absence of a respiratory enzyme**, **cytochrome C**, the lack of which differentiates **the Enterobacteriaceae from other gram-negative rods**.
- Similarly, **catalase** activity can be used, for example, to differentiate between the gram-positive cocci; the **species staphylococci are catalase positive** whereas the **species streptococci are catalase negative**. If the organism is demonstrated to be catalase positive (*Staphylococcus* spp.), the species can be **subdivided by a coagulase test** into ***Staphylococcus aureus*** **(coagulase positive) or** ***Staphylococcus epidermitidis*** **(coagulase negative)**

7-Immunologic Tests—Serotypes, Serogroups, and Serovars

- The designation **"sero"** simply indicates the use of antibodies (**polyclonal or monoclonal**) that **react with specific bacterial cell surface structures such as lipopolysaccharide (LPS), flagella, or capsular antigens.**

- The terms "**serotype,**" "**serogroups,**" **and** "**serovars**" are, for all practical purposes, identical—they all use the specificity of **these antibodies to subdivide strains of a particular bacterial species**.
- This has been described earlier in this chapter as it relates to the relationship ***E coli* O157:H7** and HUS.

End of part 1 of Chapter 1

Chapter 1

Part 2

Pharmaceutical

Microbiology

Dr . Mohammed Hussein Taleb

A-Additional methods of Classification of Bacteria

Additional methods of classification of bacteria rarely used in differntiation between types of bacteria

1-Based on Pressure

- Based on pressure classified into
- Barotolerant ..
- Barophilic…
- Barosensitive ….

Variations in Pressure

- Barophiles
  - Adapted to high pressures
    - Up to 1,000 atm
- Barotolerant organisms
  - Grow at high, but not very high pressure
- Barosensitive organisms
  - Die at high pressure
    - Most "typical" bacteria, all mammals

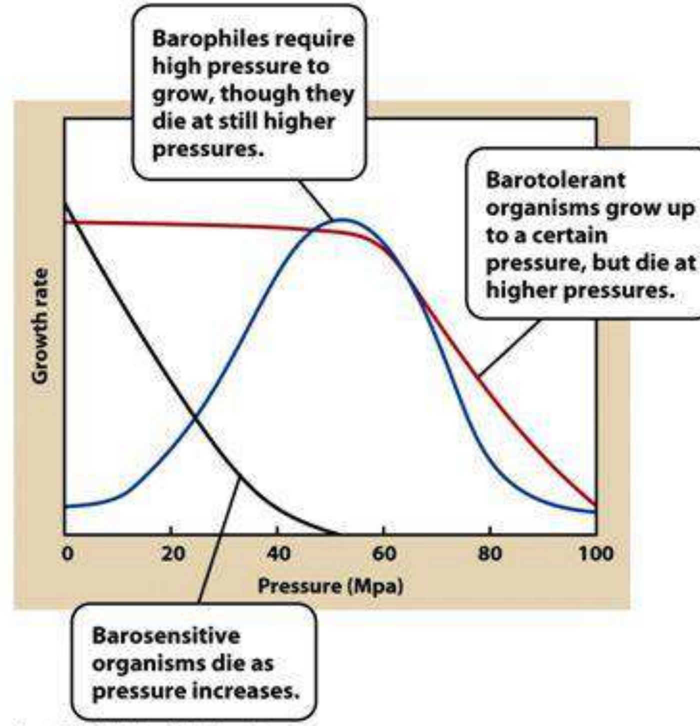


Figure 5.7 Microbiology: An Evolving Science

2-Based on Osmotic pressure

- Osmotolerant: S. aureus
- Halophiles: H.pylori

3-Based on PH

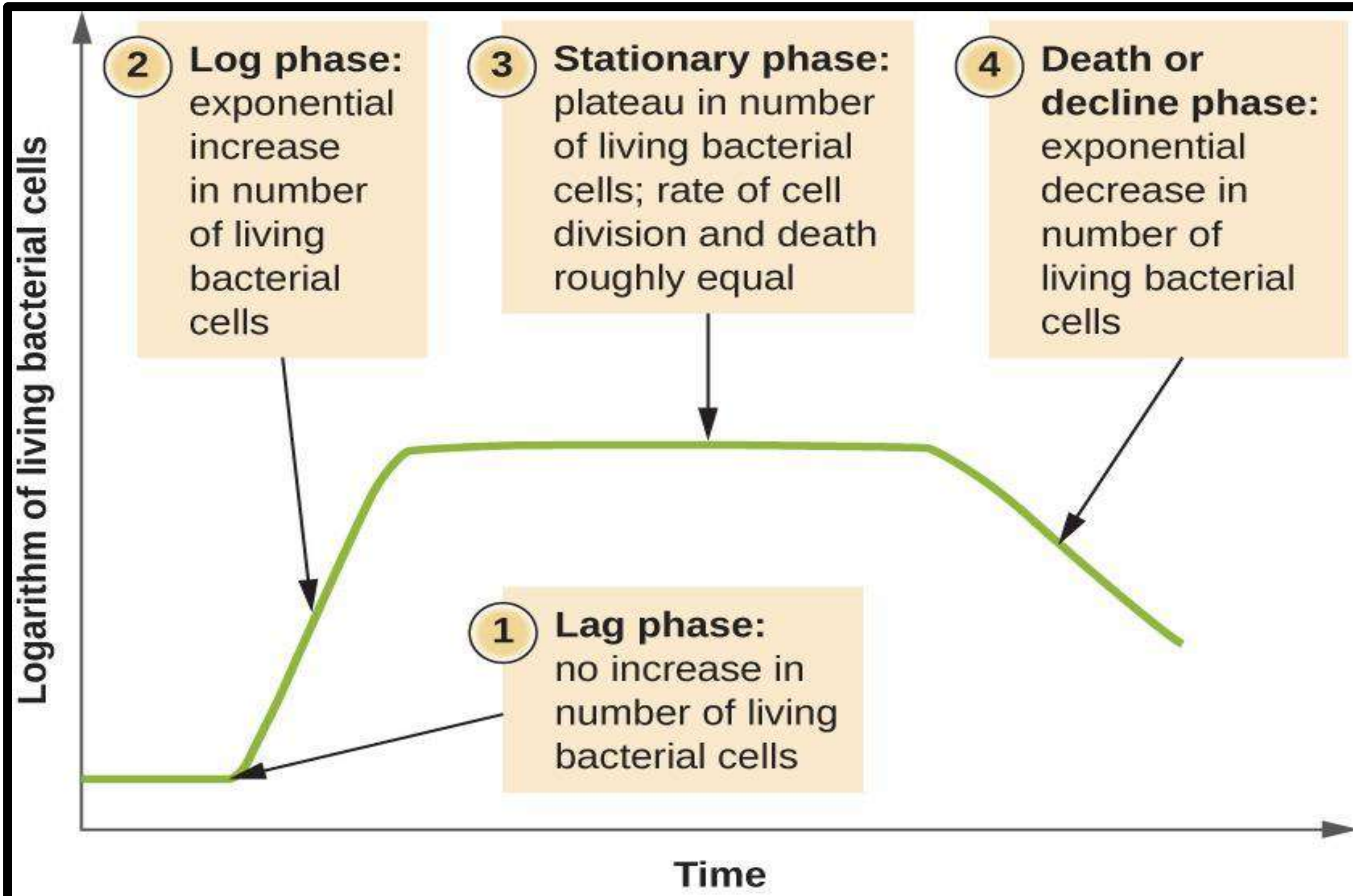
- **Acidophiles** e.g Sulpholobus — PH : 1- 5.5
- **Neutrophiles** e.g Escherichia — PH : 5.5 - 8
- **Alkalophiles** e.g Bacillus alkalophiles — PH : 8 - 11.5

B-Microbial growth curves

Phases of the Microbial Growth Curve

- Lag Zero
- Exponential Constant
- Maximum stationary Zero
- Decline Negative (death)

Phases of bacterial growth curve



Curve of bacterial growth

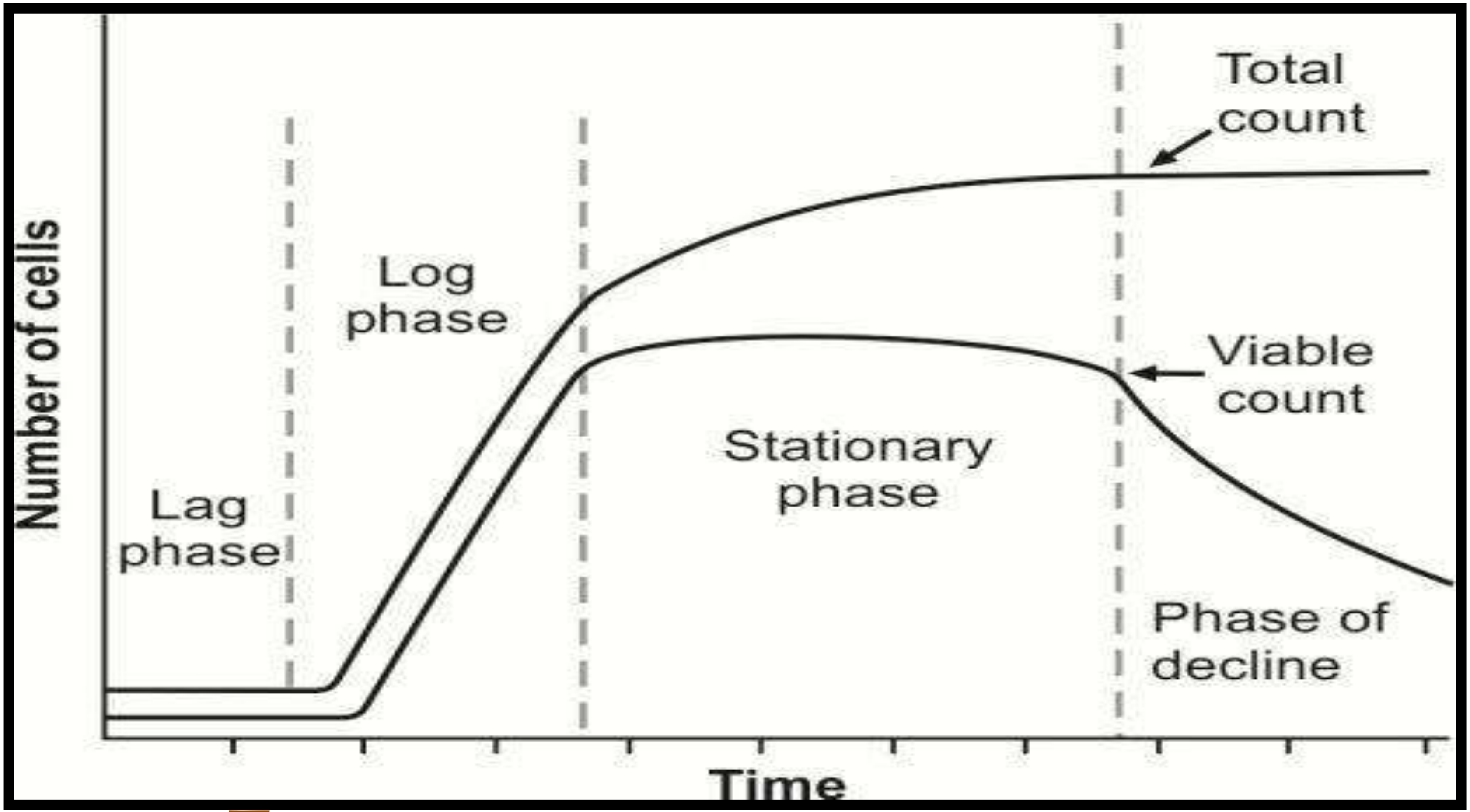


Figure 4-2

1-The Lag Phase

- The lag phase represents a **period during which cells, depleted of metabolites and enzymes as the result of the unfavorable conditions that existed at the end of their previous culture history, adapt to their new environment.**

- **Enzymes and intermediates are formed and accumulate until they are present in concentrations that permit growth to resume.**

- If the **cells** are **taken from an entirely different medium, it often happens that they are genetically incapable of growth in the new medium.**
- In such cases, **a long lag in growth may occur, representing the period necessary for a few mutants in the inoculum to multiply sufficiently for a net increase in cell number to be apparent.**

2-The Exponential Phase

- During the exponential phase, the cells are in a steady state.
- **New cell material is being synthesized at a constant rate, but the new material is itself catalytic, and the mass increases in an exponential manner.**
- This **continues until one of two things happens**: **either one or more nutrients in the medium become exhausted or toxic metabolic products accumulate and inhibit growth.**

The Maximum Stationary Phase

- Eventually, the exhaustion of nutrients or the accumulation of toxic products causes growth to cease completely.
- In most cases, however, cell turnover takes place in the stationary phase:
- **There is a slow loss of cells through death, which is balanced by the formation of new cells through growth and division.**
- When this occurs, the **total cell count slowly increases, although the viable count stays constant.**

4-The Phase of Decline: The Death Phase

- After a period of time in the stationary phase, which varies with **the organism and with the culture conditions, the death rate increases until it reaches a steady level**.
- The mathematics of steady-state death is discussed below.
- In most cases the rate of cell death is much slower than that of exponential growth.

The Mathematics of Growth

- Growth rate studies contribute to basic physiological and ecological research and the solution of applied problems in industry. Therefore the quantitative
- During the exponential phase
- Each microorganism is dividing at constant intervals. Thus the population will double in number during a specific length of time called the generation time or doubling time.

- This situation can be illustrated with a simple example. Suppose that a culture tube is inoculated with one cell that divides every 20 minutes . **The population will be 2 cells after 20 minutes, 4 cells after 40 minutes, and so forth.** Because the population is **doubling every generation, the increase in population is always 2^n where n is the number of generations.** The resulting population increase is exponential or logarithmic

:

Growth Rate and Generation Time

- As mentioned above, bacterial growth rates during the phase of exponential growth, under standard nutritional conditions (culture medium , temperature, pH, etc.), define **the bacterium's generation time**. Generation times for bacteria vary from about 12 minutes to 24 hours or more.

- **The generation time** for ***E. coli*** in the laboratory is **15-20 minutes, but in the intestinal tract, the coliform's generation time is estimated to be 12-24 hours.** For most **known bacteria that can be cultured , generation times range from about 15 minutes to 1 hour.**

C - Bacteria and its relation with another organisms

- Bacteria are consistently associated with the body surfaces of animals.
- There are **many more bacterial cells on the surface of a human (including the gastrointestinal tract) than there are human cells that make up the animal.**
- The bacteria and other microbes that are consistently associated with an animal are called the **normal flora,** or more properly the "**indigenous microbiota**", of the animal.

- **These bacteria have a full range of symbiotic interactions with their animal hosts.**
- In biology, **symbiosis** is defined as **"life together"**, i.e., that two organisms live in an association with one another. Thus, there are at least three types of relationships based on the quality of the relationship for each member of the symbiotic association.

Types of Symbiotic Associations

1- Mutualism. Both members of the association benefit.

- **For humans, one classic mutualistic association is that of the the lactic acid bacteria that live on the vaginal epithelium of a woman.**
- The bacteria are provided habitat with a constant temperature and supply of nutrients (glycogen) in exchange for the production of lactic acid, which **protects the vagina from colonization and disease caused by yeast and other potentially harmful microbes.**

2. **Commensalism** describes a relationship between two living organisms where one benefits and the other is not significantly harmed or helped.

- **A problem with *commensal relationships* is that if you look at one long enough and hard enough, you often discover that at least one member is being helped or harmed during the association.**

- Consider our relationship with ***Staphylococcus epidermidis***, a **consistent inhabitant of the skin of humans**.

- Probably, the bacterium produces lactic acid that protects the skin from colonization by harmful microbes that are less acid tolerant.
- But it has been suggested that other metabolites that are produced by the bacteria are an important cause of body odors (good or bad, depending on your personal point of view) and possibly associated with certain skin cancers.
- "Commensalism" best works when the relationship between two organisms is unknown and not obvious.

3. Parasitism.

- In biology, the term **parasite** refers to **an organism that grows, feeds and is sheltered on or in a different organism while contributing nothing to the survival of its host.**

- **In microbiology, the mode of existence of a parasite implies that the parasite is capable of causing damage to the host.**

- Some **parasitic bacteria live as normal flora of humans while waiting for an opportunity to cause disease**.

- Other **nonindigenous parasites generally always cause disease if they associate with a nonimmune host.**

Normal flora

Bacterial Flora in a Normal Person in the Community

Upper Respiratory Tract

- *Staphylococcus* spp.
- *Streptococcus* spp.
  - *Streptococcus pneumoniae*
  - Alpha-haemolytic *Streptococcus* spp.
- *Haemophilus* spp.
- Anaerobes

Skin

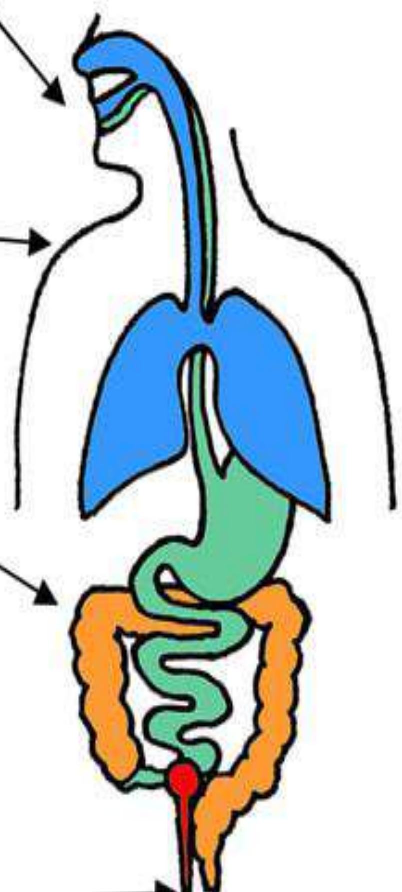
- *Staphylococcus* spp.
- Coryneform bacteria or "Diphtheroids"
- *Cutibacterium* spp.

Gastrointestinal Tract

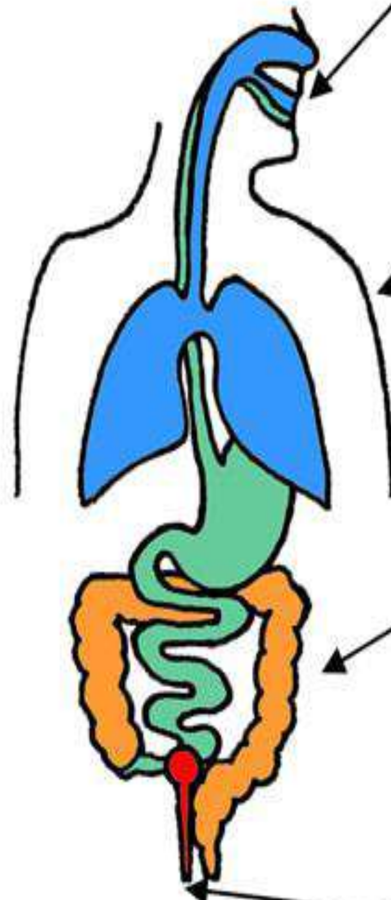
- Anaerobes
- *Enterococcus* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.
- *Streptococcus* spp.
  - *Streptococcus anginosus* group
- *Lactobacillus* spp.
- *Candida* spp.

Genital Tract

- *Lactobacillus* spp.
- *Streptococcus* spp.
  - *Streptococcus agalactiae*



Bacterial Flora in a Normal Person in a Hospital or Long-term Care Facility



Upper Respiratory Tract

- *Staphylococcus* spp.
- Anaerobes
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.
- *Candida* spp.
- *Pseudomonas* spp.

Skin

- *Staphylococcus* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.

Gastrointestinal Tract

- Anaerobes
- *Enterococcus* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.
- *Candida* spp.
- *Pseudomonas* spp.

Genital Tract

- *Candida* spp.

Beneficial Effects of the Normal Flora

1. **The normal flora synthesize and excrete vitamins** in excess of their own needs, which can be absorbed as nutrients by their host. For example, **in humans, enteric bacteria secrete Vitamin K and Vitamin B12, and lactic acid bacteria produce certain B-vitamins.**

Germ-free animals may be deficient in Vitamin K to the extent that it is necessary to supplement their diets.

2. The normal flora prevent colonization by pathogens

- by **competing for attachment sites or for essential nutrients.**
- This is thought to be their most important beneficial effect, which has been demonstrated in the oral cavity, the intestine, the skin, and the vaginal epithelium.
- In some experiments, **germ-free animals can be infected by 10 *Salmonella* bacteria**, while the **infectious dose for conventional animals is near 10^6 cells.**

- **3. The normal flora may antagonize other bacteria through the production of substances which inhibit or kill nonindigenous species.** The intestinal bacteria produce a variety of substances ranging from relatively nonspecific fatty acids and peroxides to highly specific bacteriocins, which inhibit or kill other bacteria.

  4. The normal flora stimulate the production of natural antibodies. Since the **normal flora behave as antigens in an animal, they induce an immunological response, in particular, an antibody-mediated immune (AMI) response**.

5-The normal flora stimulate the development of certain tissues,

i.e., the caecum and certain lymphatic tissues (Peyer's patches) in the GI tract.

- **The caecum of germ-free animals is enlarged, thin-walled, and fluid-filled, compared to that organ in conventional animals.**
- Also, based on the ability to undergo immunological stimulation, **the intestinal lymphatic tissues of germ-free animals are poorly-developed compared to conventional animals.**

Harmful Effects of the Normal Flora

1-Bacterial synergism between a member of **the normal flora and a potential pathogen**. This means that one organism is helping another to grow or survive.

1. There are examples of a **member of the normal flora supplying a vitamin or some other growth factor that a pathogen needs in order to grow**.
2. This is called **cross-feeding** between microbes. Another example of **synergism** occurs during treatment of **"staph-protected infections"** when a **penicillin-resistant staphylococcus** that is a component of the **normal flora shares its drug resistance with pathogens that are otherwise susceptible to the drug.**

- **2. Competition for nutrients :**Bacteria in the gastrointestinal tract must absorb some of the host's nutrients for their own needs.

3. Induction of a low grade toxemia: Minute amounts of bacterial toxins (e.g. endotoxin) may be found in the circulation. Of course, it is these small amounts of bacterial antigen that stimulate the formation of natural antibodies.

4. The normal flora may be agents of disease: Members of the normal flora may cause **endogenous disease** if they reach a site or tissue where they cannot be restricted or tolerated by the host defenses. Many of the normal flora are potential pathogens, and if they gain access to a compromised tissue from which they can invade, disease may result.

- **5. Transfer to susceptible hosts :**

- **Some pathogens of humans that are members of the normal flora may also rely on their host for transfer to other individuals where they can produce disease.** This includes the pathogens that colonize the upper respiratory tract such as ***Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*** **and** ***Staphylococcus aureus.***

End of part 2 of chapter 1