
بسم الله الرحمن الرحيم

Bacterial Pathogenesis

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LECTURE OBJECTIVES

At the end of lecture, students of 3rd year MBBS should be able to

1. Define various terms related to infectious diseases.

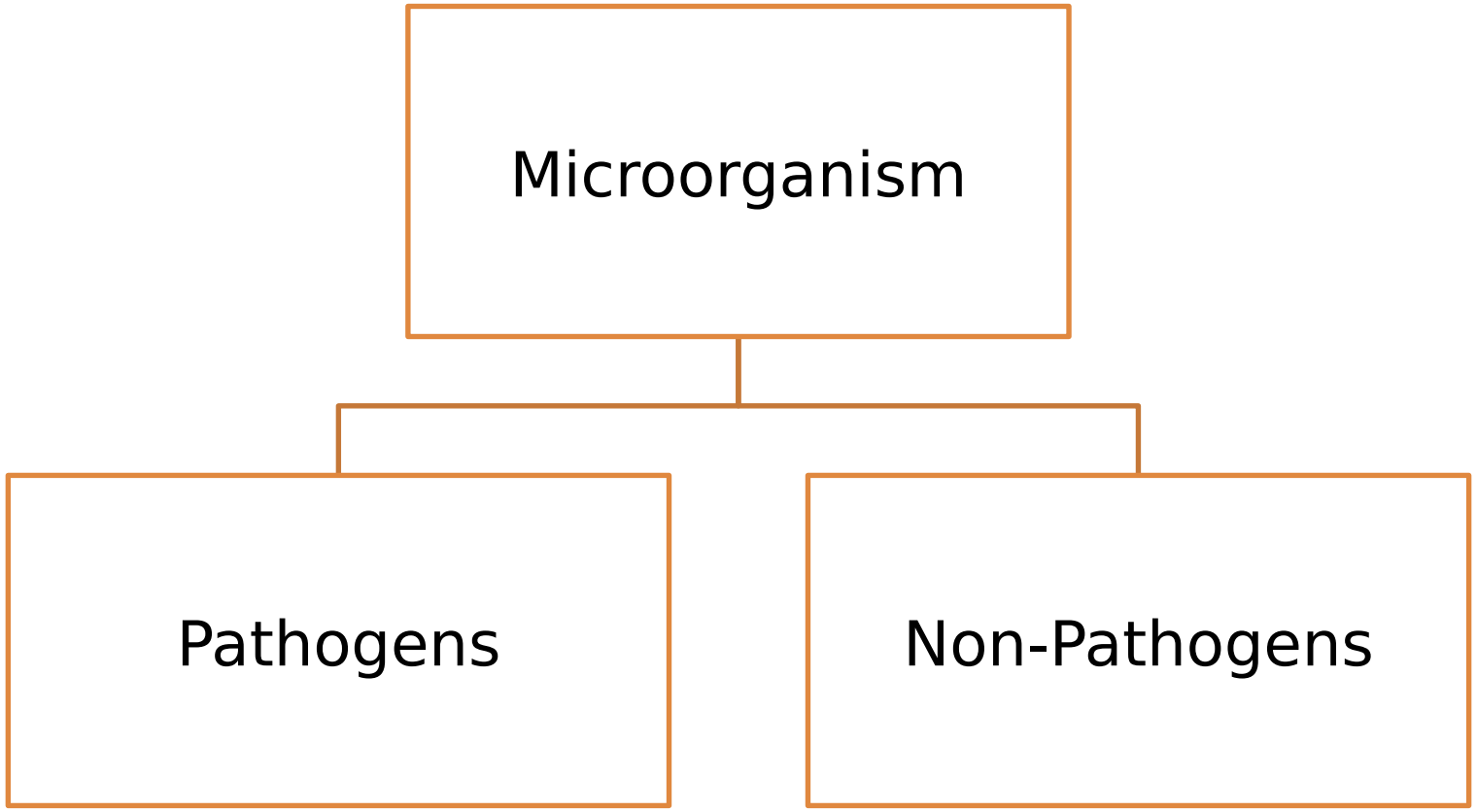
   Infection, virulence, communicable, endemic, epidemic, pandemic, carrier, pathogens, opportunistic, commensals, and colonizers.

2. Describe stages / determinants of bacterial pathogenesis
3. Describe colonization, invasion, toxins, immunopathogenesis.
4. Differentiate between exotoxins and endotoxins
5. Describe various modes of action of endotoxins and exotoxins.
6. Describe four stages of typical infectious disease and Koch's postulates.

INFECTION

- It is the entry of microorganism in the host.
- The outcome of an infection may be
  - No disease when microorganisms are overpowered or killed by host defenses.
  - clinically asymptomatic disease
  - symptomatic disease

  depending on the virulence of the invading pathogen and the relative degree of immunity or susceptibility of the host



Microorganisms capable of causing a disease in host

Definitions

- **Communicable:** (Infectious or transmissible) are the disease that spread from host to host (an individual human or animal (i.e. cholera, TB, enteric fever).
- **Endemic:** an infection constantly present at expected and low level in specific population or area (i.e. measles, chickenpox).
- **Epidemic:** a widespread occurrence of an infection than usual in a community or area at a particular time (i.e. cholera epidemic).
- **Pandemic:** outbreak of an infectious disease involving wide geographical area or world-wide distribution (multiple countries or continents are involved).

Definitions

- **Carrier:** A person or an animal that carries / holds an infectious agent without having the disease symptoms i.e. “Typhoid Mary”
- **Commensals:** microbes that reside on either surface of the body or at mucosa without harming human health. It is 10 times more than the cells present in our body (normal flora of the body).
- **Opportunistic:** Microorganism cause diseases in immunocompromised hosts.
- **Colonizers:** are the new organisms that are neither members of the normal flora nor the cause of symptoms.

Definitions

Pathogenicity

the capability of microbe to cause disease in host. Microbes express their pathogenicity by their **virulence.**

Virulence

quantitative measure of pathogenicity of the microbe and is measured by the number of organisms required to cause disease.

THE DOSE OF ORGANSIM

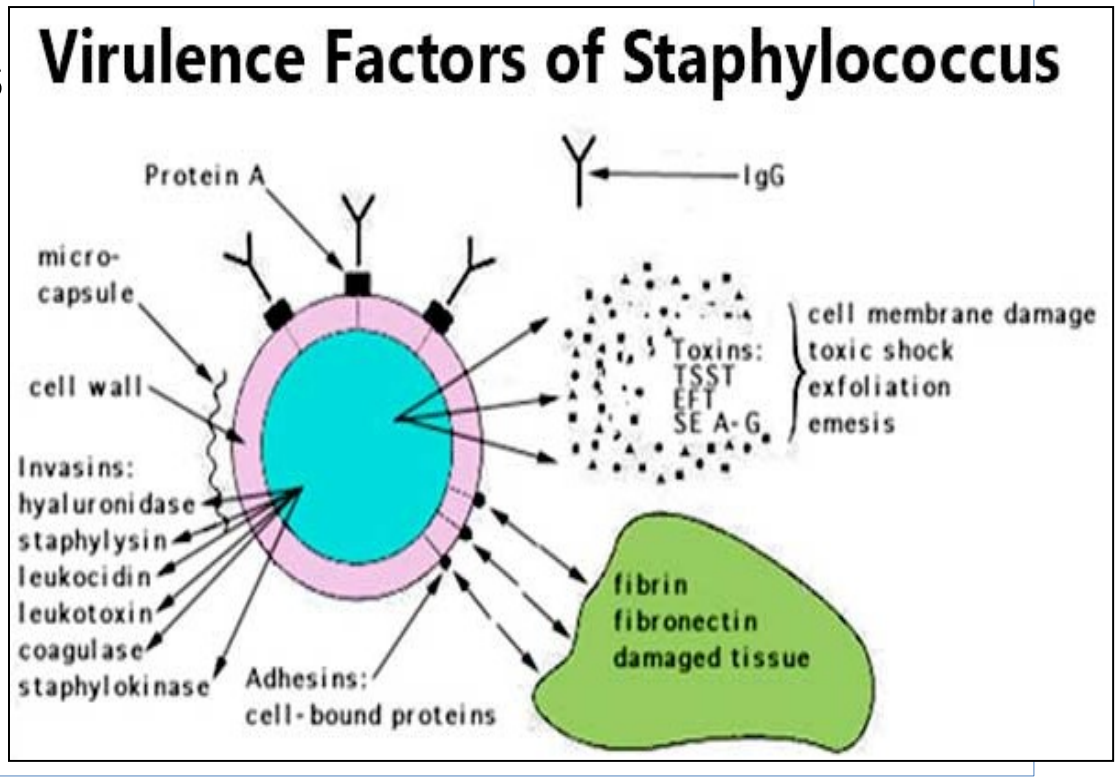
- The dose means number of organism that must be entering the host in order to establish a disease.
  - i.e. one million *S. typhi* are required in contaminated water for disease
- It is obvious that more severe infection is produced by more organisms.

Stages of bacterial pathogenesis

1. Transmission from external source into portal of entry
2. Evasion of host defenses like skin, stomach acid.
3. Adhesion to mucous membrane by pili
4. Colonization by multiplication at the site of adhesion
5. Toxin production or invasion leading to inflammation & disease symptoms
6. Host response (non- specific/ specific) immunity
7. Progression or resolution of the disease

Virulence factors

- Virulence factors are the genetic or biochemical or structural features of pathogen that produce disease in a host e.g. toxins, adhesins, invasins, antiphagocytic factors, hemolysins, proteases, lipases and DNAses.
- They help pathogens in colonization, immuno-evasion, immunosuppression, and entry or exit from cell.



Virulence factors

- Some of the virulence factors are chromosomally encoded and intrinsic to the bacteria (e.g. capsules and endotoxin), some are extrinsic / acquired from mobile genetic elements like plasmids and bacteriophages (e.g. some exotoxins).

Virulence factor

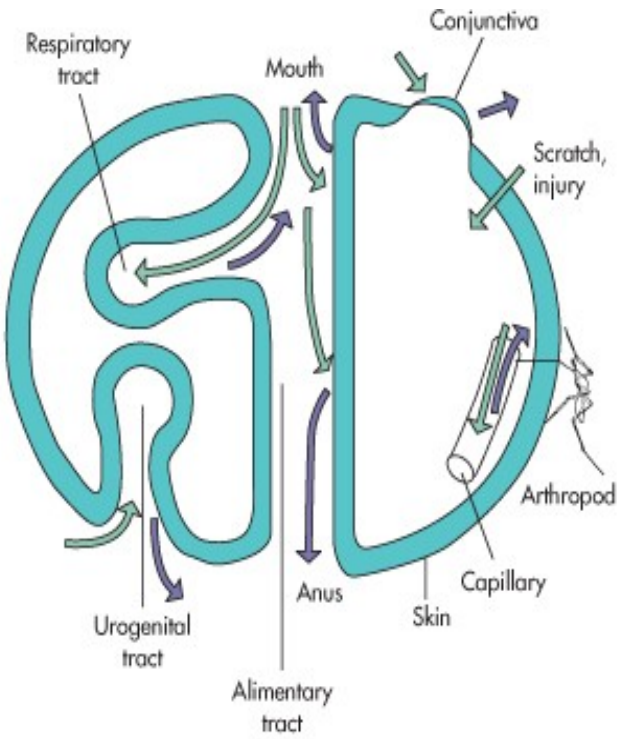
- Virulence factors range from
  - simple molecules (e.g. heat-stable toxin of *E. coli*, urease of *Helicobacter pylori*),
  - complexes of molecules (e.g. pili of bacteria),
  - transport mechanisms (e.g. iron acquisition in many bacteria)

Falkow's Postulates

1. The gene(s) encoding the phenotype of virulent factor shall be associated with pathogenic strains.
2. Inactivation of the virulent-trait gene(s) results in loss of or reduction in virulence.
3. Reversion or replacing the mutation leads to restoration of virulence.

Falkow, S. 1988 Rev Infect Dis. 1988, vol. 10 Suppl 2:S274-6

Virulence factors



- **Colonization factors**

  Pathogens produce virulent factors to colonize, survive and replicate in host.

- **Adherence factors ("adhesins")**

  Adhesin helps pathogens to attach to receptors at the surface of host cells.

- **Invasion factors ("invasins")**

  These proteins either disrupt host cell membranes to help invasion, or stimulate endocytosis.

Virulence factors

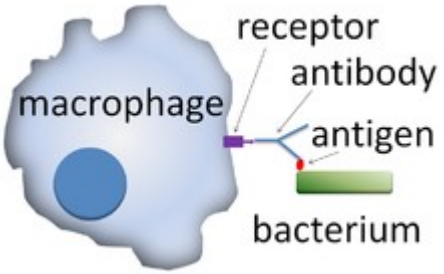
- **Toxins**

  Pathogens may produce toxins that poison host cells & cause tissue damage.

- **Immune evasion factors**

  Many pathogens produce virulence factors that inhibit or fool host immune defenses.

  Capsule protects bacteria and inhibits phagocytosis, immunoglobulin (Ig) proteases prevent opsonization and phagocytosis.



Action of opsonins: a phagocytic cell recognises the opsonin on the surface of an antigen

- **Motility**

  Pathogens need to swim toward targets, or swim away from host defenses;

- **Iron acquisition**

  Host iron is tightly bound to proteins or cofactors; pathogens have proteins that can extract iron from these complexes to fulfill their own nutritional requirements

- **Biofilms** (Slimy extracellular polymeric substance matrix)

  many pathogens can form biofilms that allow them to survive in the environment and sometimes in the host; bacteria within biofilms may be inaccessible to antibiotics; biofilm formation is key to the catheter associated infections.

Bacteria

cause disease by two mechanisms

- Invasion & inflammation
- Toxin production,

Portal of entry of infectious agent

Pathogens may be acquired through

- **Skin and mucous membrane**

  Direct contact e.g. STD / by fomites / by vector .

  Wound contamination e.g. tetanus (RTA).

- **By injection**

  Syringes, transfusion, vector borne

  Operation and implantation

- **By ingestion**

  Contaminated water and food e.g. typhoid, cholera.

- **By inhalation**

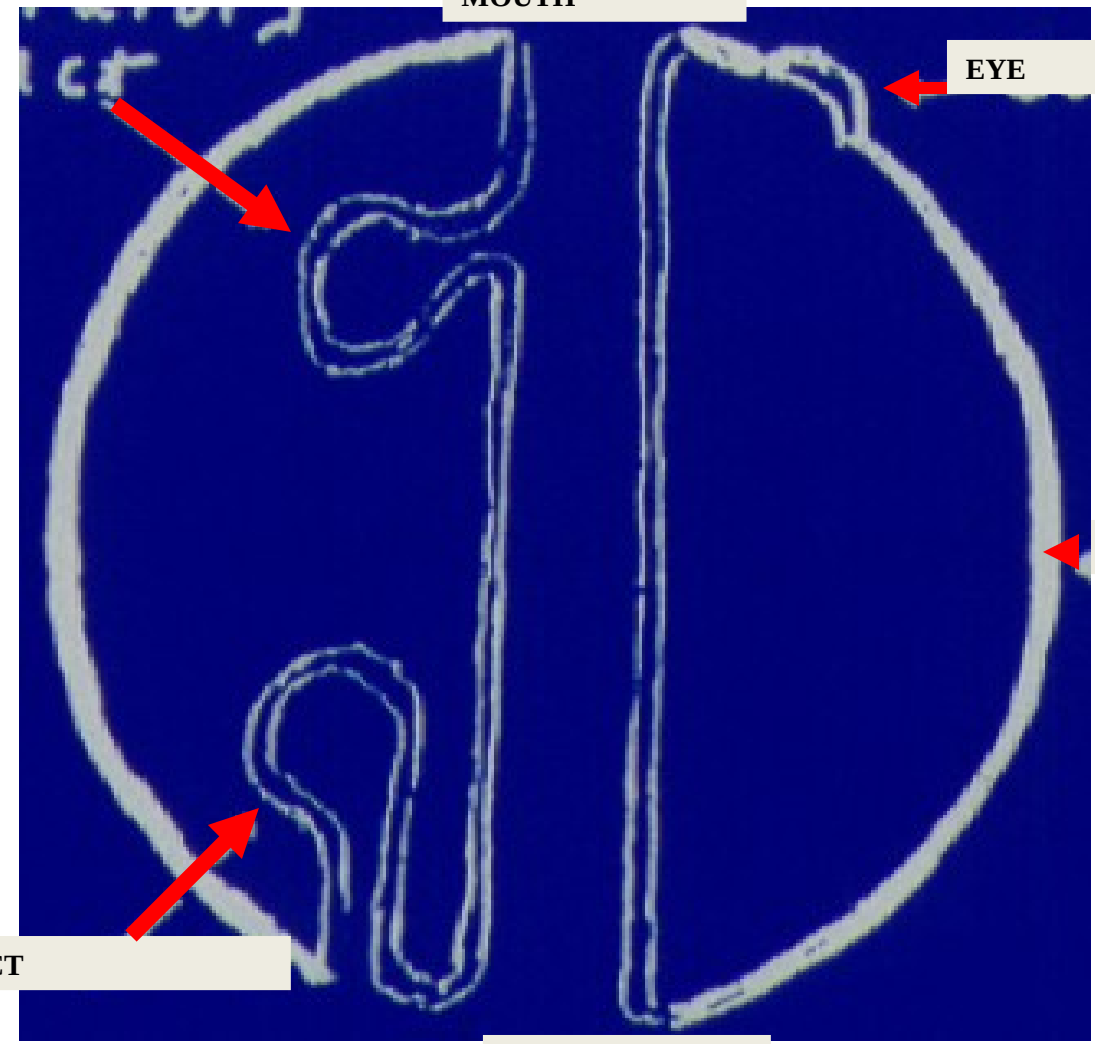
  Dust and droplets e.g. tuberculosis.

TABLE 7–1 Important Modes of Transmission

Mode of Transmission	Clinical Example	Comment
I. Human to human		
A. Direct contact	Gonorrhea	Intimate contact (e.g., sexual or passage through birth canal)
B. No direct contact	Dysentery	Fecal–oral (e.g., excreted in human feces, then ingested in food or water)
C. Transplacental	Congenital syphilis	Bacteria cross the placenta and infect the fetus
D. Blood-borne	Syphilis	Transfused blood or intravenous drug use can transmit bacteria and viruses; screening of blood for transfusions has greatly reduced this risk
II. Nonhuman to human		
A. Soil source	Tetanus	Spores in soil enter wound in skin
B. Water source	Legionnaire's disease	Bacteria in water aerosol are inhaled into lungs
C. Animal source		
1. Directly	Cat-scratch fever	Bacteria enter in cat scratch
2. Via insect vector	Lyme disease	Bacteria enter in tick bite
3. Via animal excreta	Hemolytic-uremic syndrome caused by *E. coli* O-157	Bacteria in cattle feces are ingested in undercooked hamburger
D. Fomite source	Staphylococcal skin infection	Bacteria on an object (e.g., a towel) are transferred onto the skin

PORTAL OF ENTRY

1. SKIN
2. HAIR
3. NAILS
4. RESPIRATORY TRACT
5. GI TRACT
6. URINARY TRACT

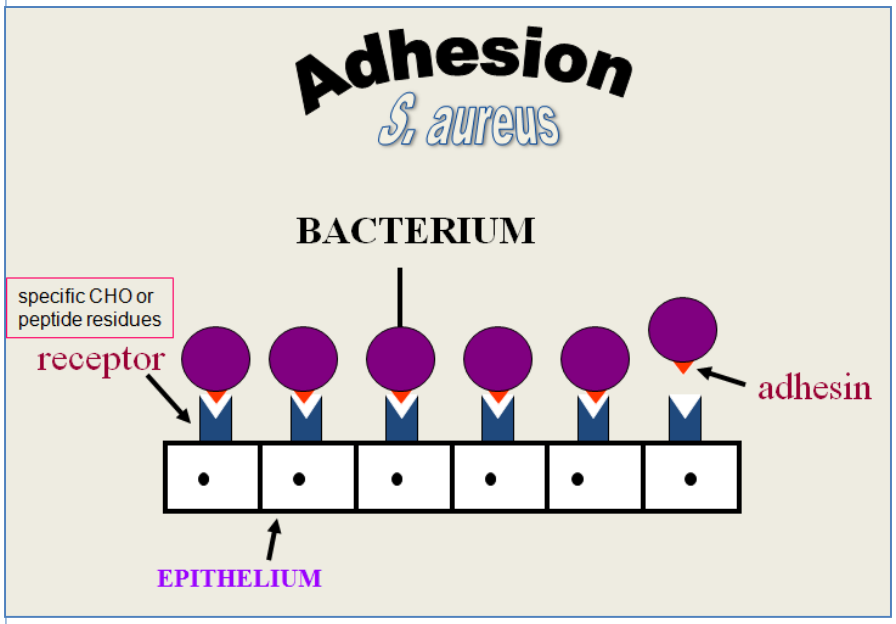


Bacterial Adherence to Mucosal Surfaces

requires the participation of two factors:

- A **receptor** is usually a specific carbohydrate or peptide residues on the eukaryotic cell surface.

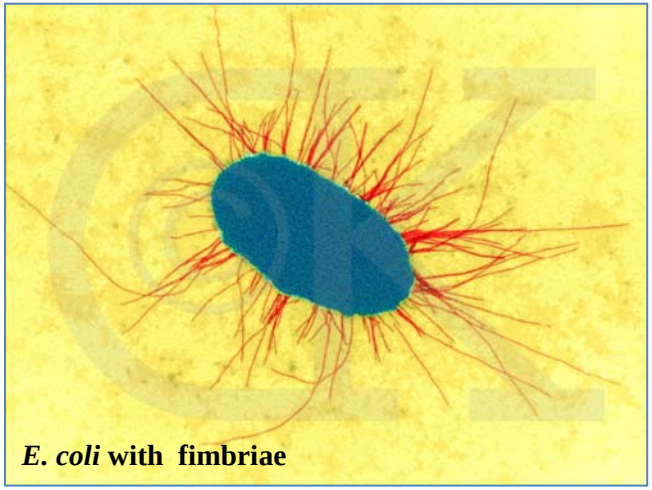
- The **bacterial adhesin** is typically a macromolecular component of the bacterial cell surface that binds bacterium to a specific host cell receptor.
  - Fimbrial adhesins
  - Afimbrial adhesins



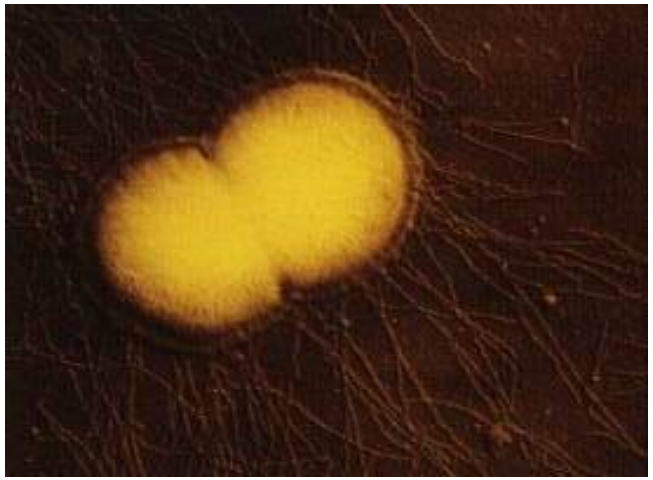
ADHERENCE FACTOR	DESCRIPTION
Adhesin	A surface structure or macromolecule that binds a bacterium to a specific surface receptors.
Fimbriae (pili)	Filamentous proteins on the surface of bacterial cells that may behave as adhesins for specific adherence
Glycocalyx	A layer of exopolysaccharide fibers on the surface of bacterial cells which may be involved in adherence to a surface
Capsule	A polysaccharide layer (rarely polypeptide) on the surface of a bacterial cell which may mediate attachment
Lipopolysaccharide (LPS)	A component of the outer membrane of Gram-negative bacteria with the potential to mediate specific adherence
Teichoic acids and lipoteichoic acids	Cell wall components of Gram-positive bacteria that may be involved in nonspecific or specific adherence

Bacterial Pili (fimbriae)

- These are hollow, hair like structures on the surface of gram negative bacteria (pilins), that allow bacteria to attach to other cells.



***E. coli* with fimbriae**



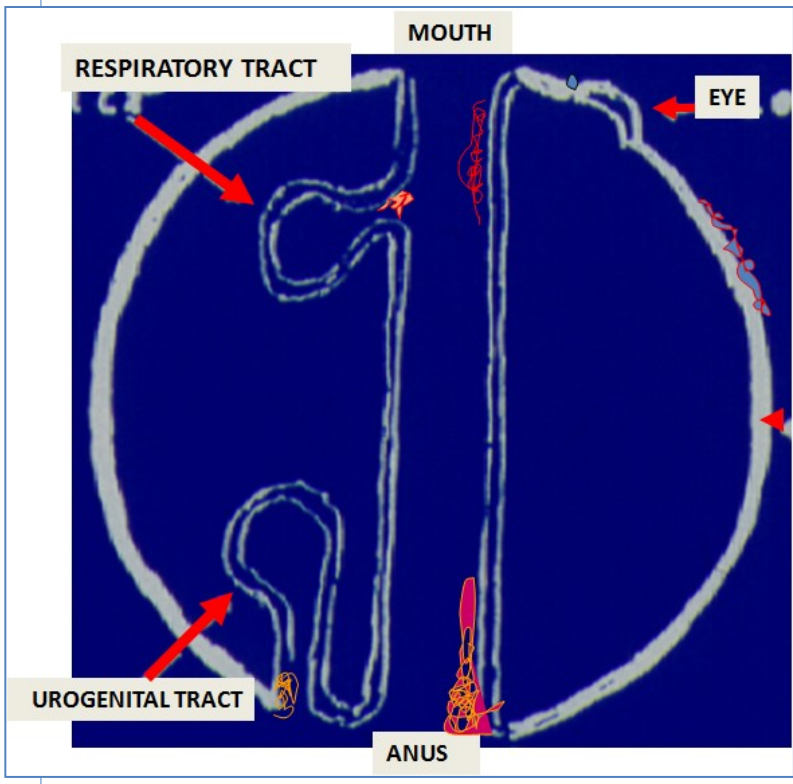
Neisseria gonorrhoeae

- The mechanisms for adherence to cell or tissue surfaces may involve two steps:
  - **nonspecific adherence or reversible attachment** of the bacterium to the eukaryotic surface (sometimes called "docking")
  - **specific adherence or irreversible permanent attachment** of the microorganism to the surface (sometimes called "anchoring").
- The usual situation is that reversible attachment precedes irreversible attachment

Colonization

- The establishment and multiplication of the pathogen at appropriate portal of entry.

- Pathogens usually colonize host tissues that are in contact with the external environment.



- After entering the portal of entry,
- adhesion to the epithelial cells,
- evasion of the local defenses, and colonization
- the progression of process depends on the ability of the pathogenic bacteria to
  - **<u>invade tissues:</u>** **Invasiveness**

    &
  - **<u>produce toxins:</u>** **Toxigenesis**

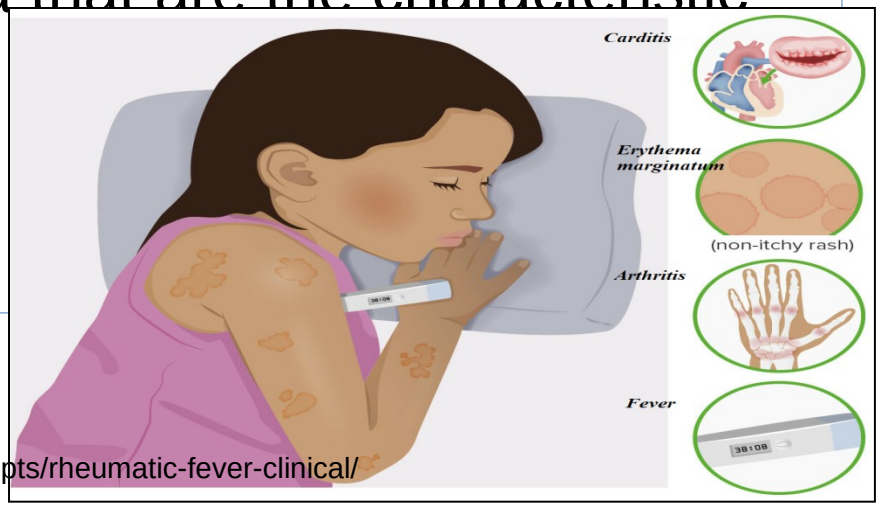
- **<u>The ability to invade tissues: Invasiveness</u>**

  which encompasses mechanisms for

  - **colonization** (adherence and initial multiplication),
  - **ability to bypass or overcome host defense mechanisms**, and
  - **the production of extracellular substances which facilitate invasion**.

- The invasion of a host cell by a pathogen may be aided by inflammation & production of bacterial extracellular enzymes (INVASINS),
  - **Collagenases & hyaluronidases** (degrade collagen & hyaluronic acid),
  - Coagulases (accelerate fibrin clot from fibrinogen to wall off infected area)
  - IgA protease (degrades IgA) *H. influenzae, S. pneumoniae, N. gonorrhoeae, N. meningitidis*
  - Leukocidins (destroy neutrophils & macrophages)

- **Immunopathogenesis.**
- It is the immune mediated symptoms of disease, induced in the body against a pathogen.
- In rheumatic fever, antibodies are formed against the M protein of *Streptococcus pyogenes*, which cross-react with joint, heart, and brain tissue. Inflammation occurs, resulting in arthritis, carditis, and chorea that are the characteristic findings in rheumatic disease



https://www.lecturio.com/concepts/rheumatic-fever-clinical/

The severity & establishment of the disease depend upon

1. **Route of transmission**
2. **Number of invaders & inoculum size (dose)**
3. **Immunity and state of health**
4. **Virulence of pathogen and production of toxins**

Bacterial inflammation

Bacteria can cause two types of inflammation:

- **In Pyogenic** (pus-producing) inflammation, neutrophils are the predominant cells. (*S pneumoniae, S pyogenes, S aureus, Neisseria miningitidis*).
- **In granulomatous** inflammation, macrophages and T cells predominate. (*Mycobacterium tuberculosis*).

Toxin Production

- These are poisonous substances produced by bacteria that may act locally or distantly.

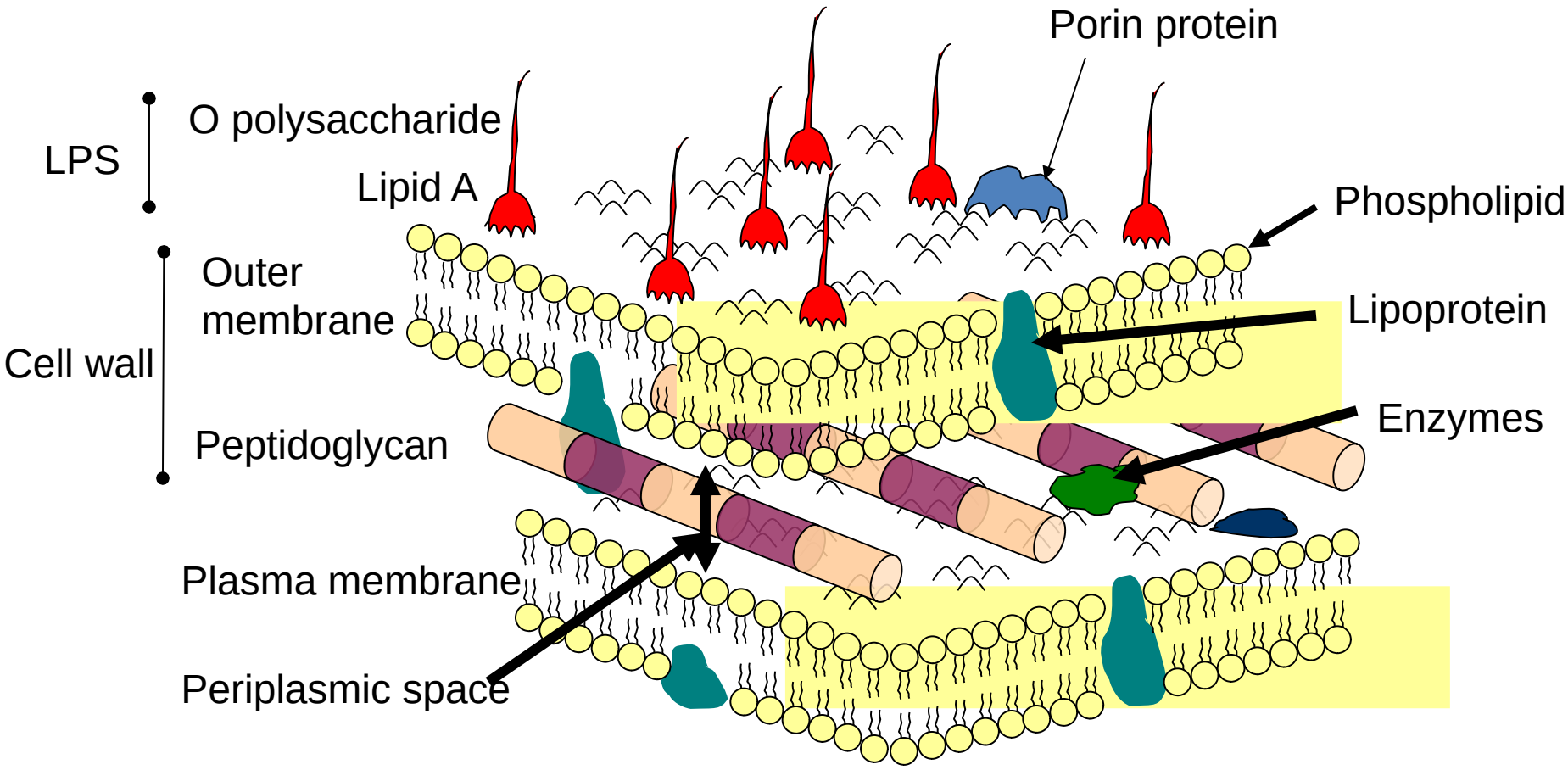
ENDOTOXIN

- It is the lipopolysaccharide component of the outer membrane of the cell wall of gram negative bacteria, that is released when bacterial cell disintegrates.
- LPS is composed of Lipid A + Core Polysaccharide + O Antigen (O side chain); Lipid A carries the endotoxin activity; O side chain is the antigenic portion of LPS
- When this LPS is liberated into the body system, symptoms of infection are produced (for example: fever, septic shock etc)

EXOTOXIN

- Polypeptide secretions produced and diffuses out of the living bacterial cell into surrounding body tissues and generally affects only certain cells at a distance.

Gram-negative Cell Wall



PROPERTY	ENDOTOXIN	EXOTOXIN
CHEMICAL NATURE	Lipopolysaccharide (mw = 10kDa)	Polypeptides (soluble protein) (mw = 50-1000kDa)
RELATIONSHIP TO CELL	Part of outer membrane	Secretions, diffusible
DENATURED BY BOILING	No (Heat stable)	Usually (Heat labile)
ANTIGENIC	Yes	Yes
FORM TOXOID	No	Yes
POTENCY	Relatively low	Relatively high
SPECIFICITY	Low degree	High degree
ENZYMATIC ACTIVITY	No	Usually
PYROGENICITY	Yes	Occasionally
Location of genes	Bacterial chromosome	Plasmid or bacteriophage
	Are neutralized by specific antibodies	Not neutralized by antibody

Mode of Actions

EXOTOXIN	ENDOTOXIN
Often have specific and localized enzyme activity and may act on specific organs or tissues, i.e. diphtheria toxin has lethal action on cardiac muscle while tetanus toxin on nervous system	Non-specific and generalized action. Action of all endotoxins are usually similar. In small amount they damage micro-vasculature and the coagulation system and increase in temperature, while in larger doses cause cell necrosis and endotoxin shock.
Secreted mostly by gram + bacteria Tetanus, botulism, diphtheria	Possessed mostly by gram negative bacteria Meningococcemia, sepsis by gram-negative rods

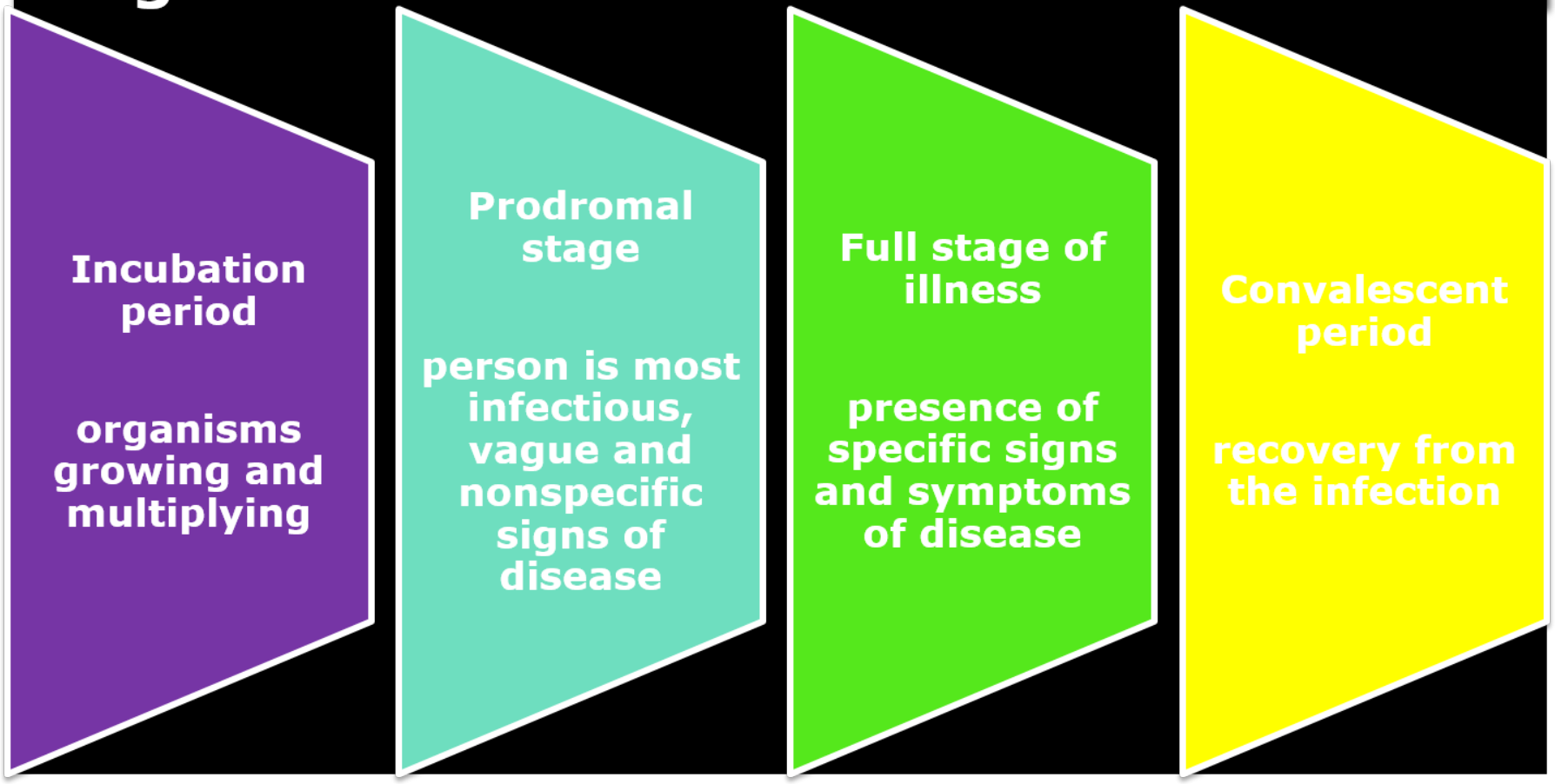
EXOTOXIN	ENDOTOXIN
Most pathogens produce more than one exotoxins	Not so
Bacteria free filtrate can produce symptoms of disease due to presence of exotoxins.	Filtrate are free of endotoxins.
Highly potent and toxic and a small amount can kill an organism, fatal dose of tetanus toxin for a human is estimated to be less than 1 µg	Less potent and larger amount is required for clinical infection,
Highly antigenic, i.e. antisera are easily prepared to neutralize the toxins,	Weakly antigenic, i.e. antisera are not easily prepared and not usually effective,
Toxoids can be prepared which are antigenic but not toxic	Toxoids are not prepared.

TYPICAL STAGES OF AN INFECTIOUS DISEASE

A typical acute infectious disease has four stages:

1. **Incubation period,** which is the time between the acquisition of the organism (or toxin) and the beginning of symptoms (this time varies from hours to days to weeks, depending on the organism).
2. **Prodromal period,** during which nonspecific symptoms such as fever, malaise, and loss of appetite occur.
3. **Specific-illness period,** during which the overt characteristic signs and symptoms of the disease occur.
4. **Recovery period,** also known as the **convalescence period** , during which the illness abates and the patient returns to the healthy state.

Stages of Infection



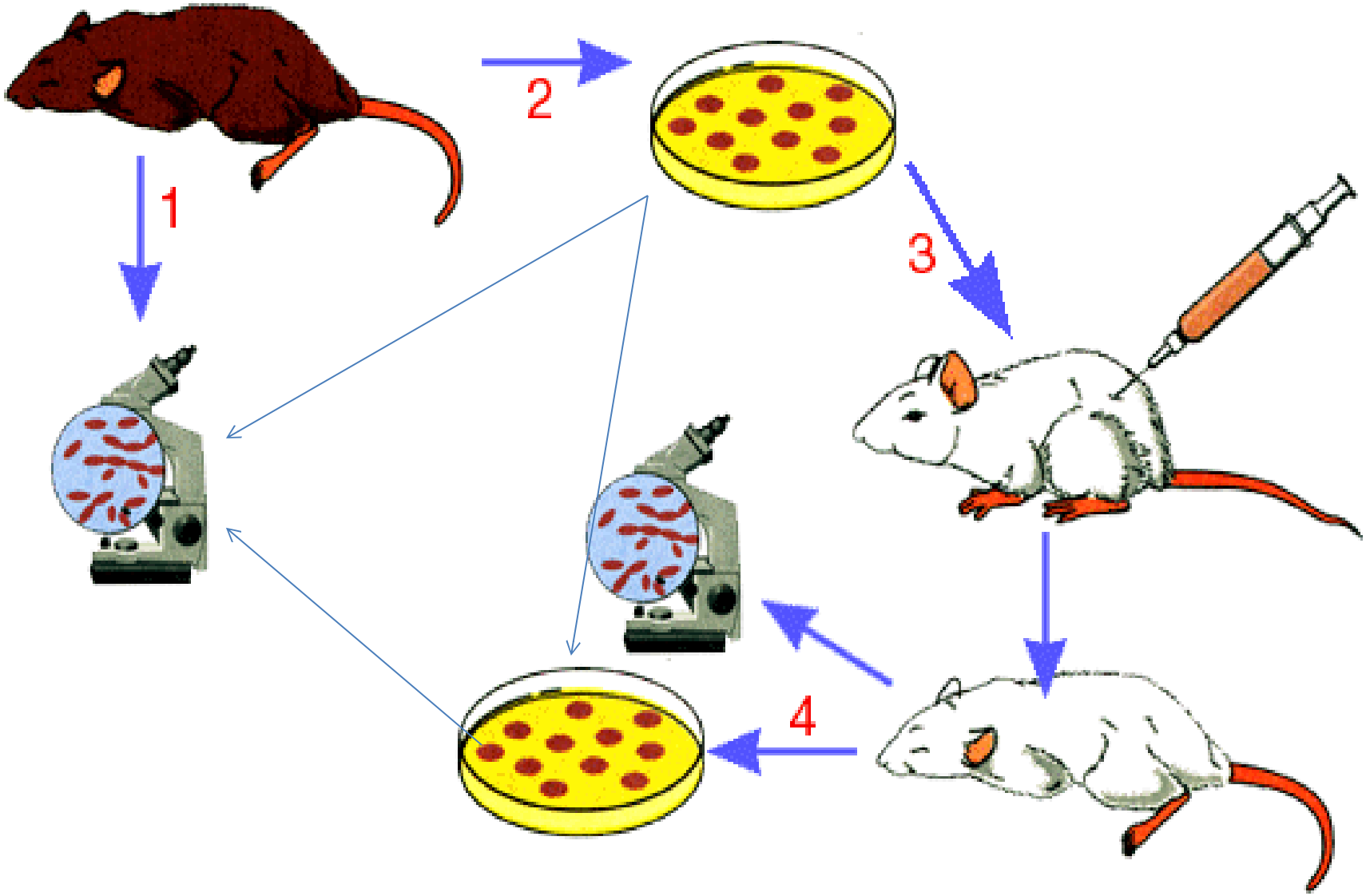
Koch’s Postulates

Germ theory of disease

- These are the principles for recognition of a microorganism as the contagious factor and a causative agent of a disease.

Germ theory of disease

1. The organisms should be present in diseased individuals but not in healthy individuals
2. Cultures must isolate the organisms.
3. When this culture is inoculated into susceptible animals, it should initiate the characteristic disease symptoms.
4. The organisms should be re-isolated from these experimental animals and cultures in the laboratory still isolate the same original organism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