Host Pathogen Interaction

→ All microbes are not pathogen – sometimes they prevent growth of harmful pathogen, help in digestion, or produce certain vitamins

Microbial Symbiosis
Mutualism – benficial to both
Commensalism – +/0
Parasitism – +/–

Pathogen – A microorganism that causes or can cause a disease

Infection ≠ Disease

Because of host resistance, an organism that can cause a disease in one organism might not cause disease in another.
How do we differentiate b/w infection and disease?

Infection is the invasion, colonisation and multiplication of pathogenic microorganisms in the host, with or without the manifestation of disease

Disease is an abnormal condition of body function(s) or structure that is considered to be harmful to the affected individual (host)

Koch's postulates for microbial pathogenesis

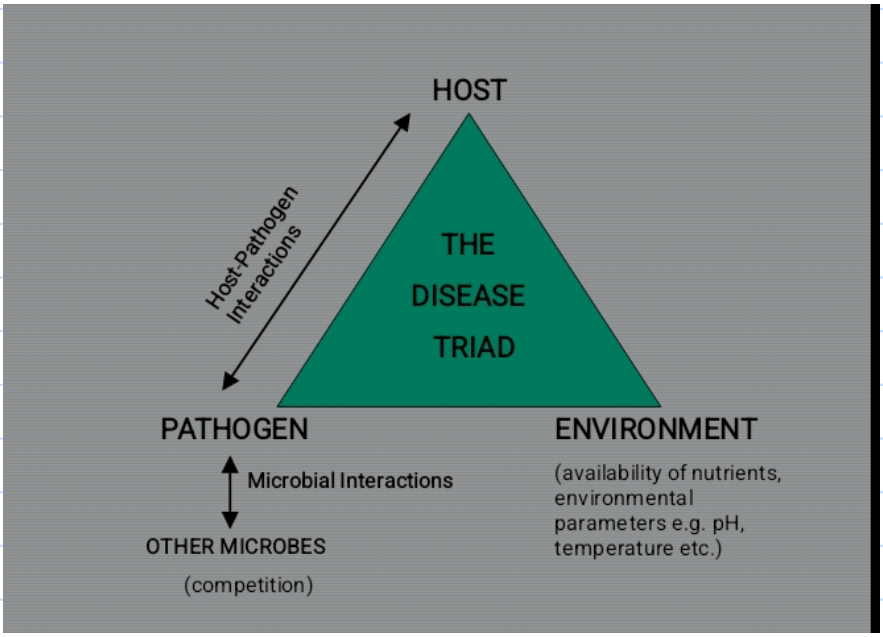
1. microorganism must be found in abundance in all organisms suffering from the disease but should not be found in healthy animals.
2. The microorganism must be removed from a diseased organism and grown in a pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original, specific causative agent.

Limitations of Koch's postulates

1. Viruses can't be grown in pure culture
2. Due to host resistance, a person might get infected by host but never show signs of disease.

Finally we arrive at the definition of a pathogen.

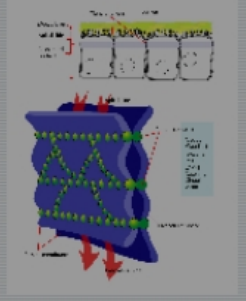
A pathogen is a microorganism that causes disease in a susceptible host.



Steps in pathogenesis:

1. Encounter – Pathogen meets the host
2. Entry – Pathogen gains access to the main host cells
3. Spread – Movement from the entry site
4. Replication – Production of progeny
5. Damage – Causes host cell abnormality or cell death
6. Outcome – Either pathogen wins or host wins. Or they coexist.

Surface barriers



	Skin	Gut	Lungs	Eyes/nose
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH		Enzymes in tears (lysozyme)
		Enzymes (pepsin)		
	Antibacterial peptides			
Microbiological	Normal flora			

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Antimicrobial peptides and the skin immune defense system

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Encounter

① Inhalation ② Ingestion ③ Physical/Sexual transmission ④ Insect bites
⑤ Organ transplants ⑥ Blood/Needle transfusions

As we saw, the surface barriers must be breached for pathogen entry

① Faults in the surface barriers (opportunistic pathogens)

② Active penetration (primary pathogens)

Faults in the surface barrier:

① Wounds in the skin
② Damage of the mucosal surface of nose, throat & lungs
③ Flushing action of urine is disrupted
④ Depletion of resident microbes

What is necessary for active penetration?

↳ the pathogen must adhere to surface of host cell and secrete substances that damages those cells

How do pathogens (adhere)?

With the help of bacterial adhesins:

① Pilus (fimbria) ② Non-pilus (afimbrial) adhesins

Characteristics of Pilus (fimbria):

① Hair-like protein appendage found on surface of many bacteria.
② Appx. diameter 3-10 nm
③ Typical str. comprise a scaffold like rod anchored to the bacterial outer membrane and adherence factor located at the tip of the scaffold

Non-pilus (afimbrial adhesins)

① presence implied by capability of bacteria that lack visible pili of binding to eukaryotic cells

Examples:
- Fibronectin binding protein of *Staphylococcus aureus*
- Integrin receptor binding protein of *Mycobacterium avium*
- Sialic acid binding protein of *Helicobacter pylori*

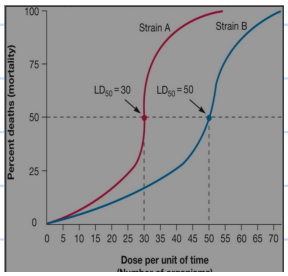
Adhesins give rise to the specificity of infection

Virulence and Pathogenicity

Pathogenicity is the capability of a microscopic organism to cause pathologic changes to a tissue or disease.

Virulence is a measure of pathogenicity as indicated by severity of the diseases produced. It is often ascertained by determining the dosage reqd. to cause a specific degree of pathogenicity, e.g., by measuring LD_{50} (lethal dose 50%) values.

LD_{50} is measured by determining the number of pathogens who will kill 50% of an experimental group of hosts in a specified time.



Too much damage to the host is not good for the pathogen - why?

① because if the parasite regularly does this, it will deplete the host species eventually

② Ideally it should cause as little damage as possible

③ only a small proportion of microbes infecting humans give rise to significant disease

④ causing a disease is not a required for the pathogen to survive

Why are some pathogens highly virulent than well-behaved?

In some cases, human host is not necessary for the survival of the pathogen, or they might not have had enough time to become adapted to the host.

Trade off between Transmission and death

Myxomatosis in australian rabbits - an example of ongoing evolution arms race, answers the question of whether viruses become more or less virulent as they adapt to the host.

- it was shown that original, highly lethal strain was replaced by less virulent strains.
- But then, genetic resistance evolved rapidly in this rabbit population, and caused the same viral strain to have reduced mortality rates
- In response, viral lethality began to climb, and the strains became immunosuppressive

In trypanosomiasis, B cell - apoptosis is induced → leading to loss of antibody and memory responses.

Bacterial pathogens might also have the ability to inhibit apoptosis in eukaryotic cells during infection, because it enables bacteria to replicate inside host cells.

Bacterial pathogens prevent apoptosis by
- protecting mitochondria and preventing cytochrome C release
- activating cell survival pathways
- preventing caspase activation

Mechanical influence of microbe replication

① Host cell lysis by mechanical influence

→ In some diseases like rickettsia, bacterial cells after infection, continue to multiply until the cell is packed with organisms and then bursts.

→ Same happens for lytic viruses, which also induce lysis to release newly synthesised viral particles.

② The host injures itself

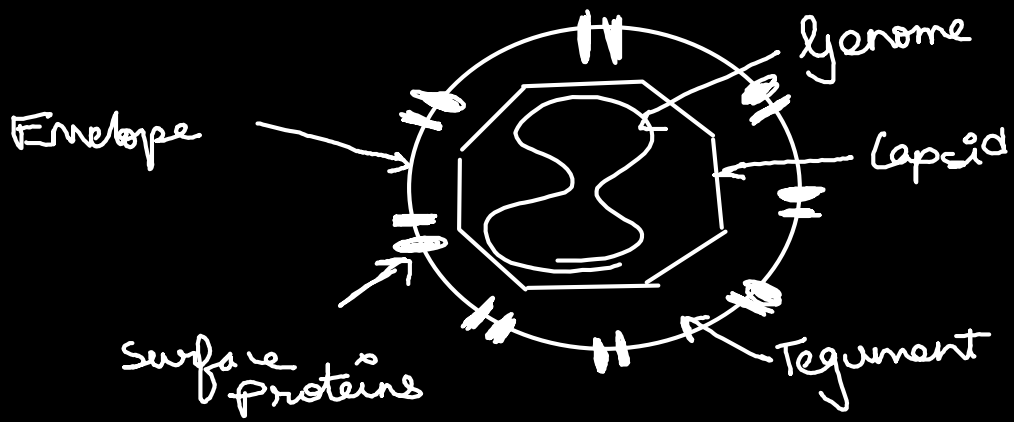
→ in many microbes, the disease is largely due to the host's own immune and inflammatory response to the infection.

→ general mechanisms include:
- (a) deregulated host inflammatory response
- (b) overwhelming activation of complement system
- (c) autoimmune response
- (d) uncontrolled cell-mediated immunity

Virology

- A virus is defined as a nucleoprotein complex which replicates
- one of the smallest known infective agents
- metabolically inert – must enter host cell to replicate
- most are highly species specific.

Virus structure



- Genome – The RNA or DNA that carries genetic information
- Capsid – A protein shell surrounding and protecting the genome
- Envelope – a lipid bilayer surrounding and protecting the capsid. Viral surface glycoproteins are embedded in the envelope.
- Tegumen –

Lecture 3

First, we go over steps in pathogenesis:

1. Encounter with pathogen
2. Entry of pathogen into host cells
3. Spread of pathogen from entry site
4. Replication of pathogen
5. Damage to cell causing host cell abnormality and death.
6. Outcome - Host/pathogen wins/they learn to coexist

Surface barriers for pathogens

- can be mechanical, chemical or microbiological
  - epithelial cells
  - cilia
  - fluid flow
  - fatty acids
  - low pH
  - enzymes
  - antimicrobial peptides
  - normal flora.

Encounter of pathogen and host

① Inhalation ② Ingestion ③ Physical contact / sexual transmission
④ Insect bites ⑤ Organ transplants ⑥ Blood / needle transfusions.

How are surface barriers breached?

Can be due to ⓐ faults in surface barriers (opportunistic pathogens)
ⓑ active penetration (primary pathogens)

What are the faults in our surface barriers that opportunistic pathogens make use of?

① wounds in the skin ② damage of the mucosal surface of nose, throat & lungs
③ flushing action of the urine is disrupted ④ depletion of resident microbes.

Active penetration

→ pathogen must adhere to the surface of the host cell and secrete substances that damages those cells

In order to adhere to host cells, bacteria make use of proteins called **adhesins**

Adhesins have Two major groups: ⓐ pilus (fimbria)
ⓑ Non-pilus (afimbrial) adhesins

Characteristics of Pilus / fimbria

- hair-like protein appendage found on the surface of many bacteria
- approx. diameter 3-10 nm.
- typical structure comprise a scaffold-like rod anchored to the bacterial outer membrane and adherence factor (adhesin) located at the tip of the scaffold.

Non-pilus (afimbrial) adhesins

- bacteria that lack visible pili are capable of binding to eukaryotic cells — non-pilus adhesins must be present.
- e.g., fibronectin binding protein of *S. aureus*.
  integrin receptor binding protein of *M. avium*

Adhesins give rise to the specificity of infection.

Tropism

- Bacteria and other pathogens have a restricted range of host tissues and cell types they are able to colonise.
  - Tropism
- determined by availability of host cell receptors for a given adhesin

Pathogen entry

For successful infection, adherence should be followed by penetration.

However penetration is not necessary for all cells, some pathogens are extracellular and cause damage while adhering and replicating on the surface.

Active penetration

In order to breach surface defenses, several approaches can be taken:

① Secretion of invasins (locally acting enzymes that damage host cells)

e.g., hyaluronidase, collagenase, neuraminidase, phospholipases

Pathogens encounter immune barrier

Initially, the host immune system responds to an infection by:

① employing phagocytes
② switching on inflammation
③ recruiting interferons & complement factors.

Pattern Recognition Receptors

- responsible for recognising pathogen associated molecular patterns (PAMPs)
- recognition of pathogen induces inflammation.
- macrophages, which have these receptors, are strategically placed in skin, lungs, lymphnodes, etc.

Neutralisation of Pathogens

How do you actually kill it?

Methods include acidification, ROS, NO, and microbial peptides, enzymes, competition

Things that go wrong in the immune system

- Defects in pattern recognition (mutation in the receptors) can impair proper immune response.
- Faulty phagocytes – Chronic granulomatous disease (CGD)
  - ↳ diverse group of hereditary diseases in which phagocyte fails to kill engulfed pathogen because of defects in enzymes that produce free radicals or toxic small molecules (NADPH oxidase)
- Defects in antibody production – Agammoglobulinaemia
  - ↳ do not generate mature B cells due to mutation in B+k gene → no antibody/memory
- Defects in cell mediated immunity –
  - DiGeorge syndrome → impaired thymus development & T-cell deficiency
  - HIV – T_H cells are reduced in population

- Bubble baby disease (SCID) - both B and T cells are impaired

Evasion of the immune system

① Outmaneuvering the phagocytic defense
- → microbe kills the phagocyte by releasing toxin
- → prevents chemotaxis
- → Prevents phagocytosis & opsonisation by virtue of surface properties
- → avoid being killed by phagocytic cell by stopping fusion of phagosome with lysosome
  - by escaping early from phagosome
  - living and replicating inside acidic phagosome.
  - entering the phagocyte through a different route

② Camouflage
- hiding the antigenic surface with host molecules

③ hiding in non-phagocytic cells

Pathogens can undergo antigenic variations

some pathogens frequently vary their surface antigens by carrying many slightly varying copies of genes to encode their surface antigens

Viruses undergo antigenic shift / drift

error prone polymerases are used to replicate leading to an abnormal accumulation of mutations in their surface antigens — viruses from different sources can infect the same cell and recombine, giving rise to hybrid progeny

Diverting the immune response

① Diversion of lymphocyte function by superantigens (these stimulate the immune system in a non-productive way, e.g., stimulating a non-specific T cell response)

Subverting the immune response

① Proteolysis of antibodies and complement factors (inactivating antibodies with the help of proteases)

Latent Infection

some pathogen stay dormant for a long period of time during which they are unrecognised by immune system

Microbial toxins

Many microbes (x viruses) release toxins into host body as they multiply → can be endotoxins / exotoxins

Endotoxin	Exotoxin
◦ LPS (↓ MW, membranous)	◦ Protein (↑ MW, extracellular)
◦ low potency	◦ high potency
◦ low specificity	◦ high specificity
◦ poor antigenicity	◦ good antigenicity

cholera toxin

◦ enterotoxin
◦ secreted by Vibrio cholerae → causes diarrhoea
◦ cholera vaccine does not provide 100% immunity

G protein coupled receptor signalling

- membrane proteins involved in a broad range of biological processes
- regulate ion channels
- about 40% of medications target the GPCRs

Pertussis toxin

- potent virulence factor → causative agent of whooping cough
- in unvaccinated infants, symptoms include whooping cough and vomiting
- antibiotics are not very helpful in later stages

Diptheria toxin

- single polypeptide chain consisting of two subunits linked by disulfide bridges
- vaccine available but immunity decreases over time
- toxin enters host cells by receptor-mediated endocytosis and inhibits protein synthesis

Cholera and pertussis toxins target GPCRs by modifying G-proteins through ADP ribosylation → ↑ cAMP levels.
On the other hand, Diptheria toxin targets EF2 & blocks elongation during proteins. synthesis

Tetanus toxin

- highly pathogenic → causes tetany
- normally glycine released from inhibitory interneurons stops acetylcholine release & causes muscle relaxation
- tetanus binds to inhibitory interneurons, stops glycine release → tetany

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Inducing cell death

① Pathogen induced host cell apoptosis

e.g., Shigella induces apoptosis in infected macrophages, so does Salmonella typhimurium

Such induction can be through extrinsic & intrinsic pathway

ⓐ Extrinsic pathway – pathogens induce expression of death ligands like FasL → binds to death receptors on neighbouring cells → DISC formation → caspase 8 activation → apoptotic cascade

ⓑ Intrinsic pathway – virulence factors disrupt mitochondrial membranes → cytochrome C release → Caspase 9 activation → executioner caspase → apoptosis