

# **Pathogenesis of microorganisms & Host Defense Mechanisms**

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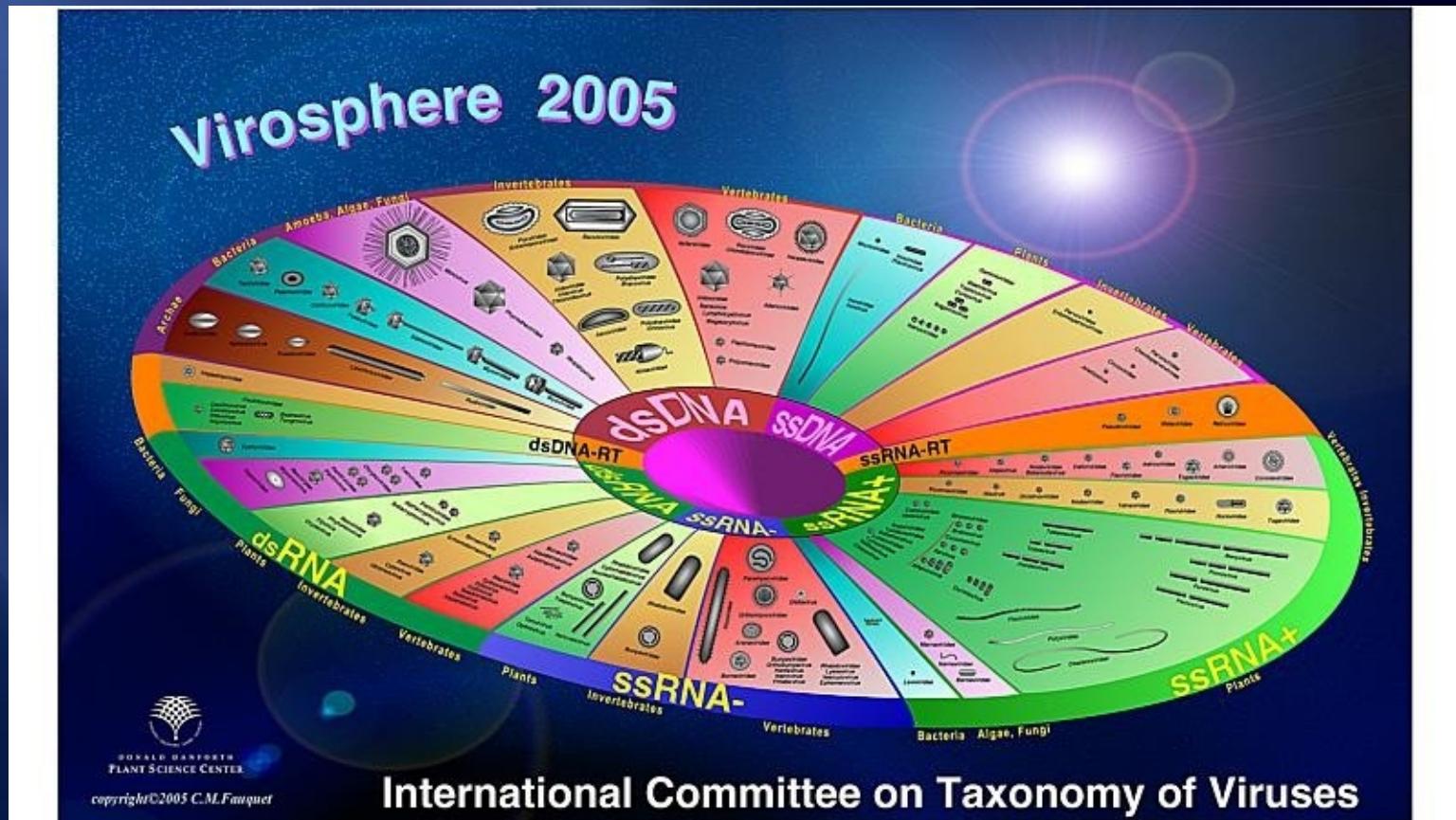
## *Learning Objectives:*

- 1. Understand definitions and classification of infectious agents**
- 2. Study the spread of the infection: reservoirs, transmission of disease, and exit**
- 3. Microbial pathogenesis: entry into the host, penetrate host defense and damage the host**
- 4. Understand nonspecific host defense, specific host defense, and antibody-mediated immunity vs. cell-mediated immunity**

## Infectious agents

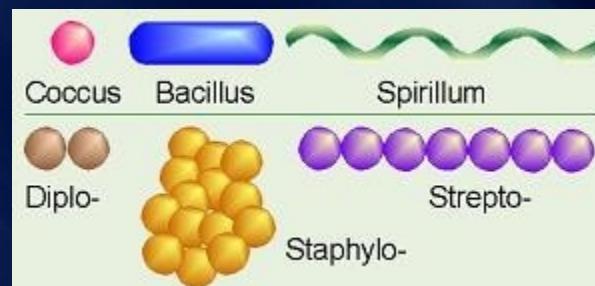
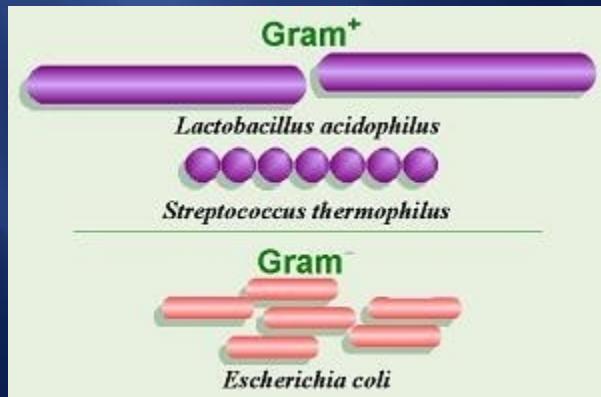
## a) Viruses

- the smallest organisms that can only be seen under an electron microscope
  - contain only one type of nucleic acid (DNA or RNA)
  - can only grow and replicate in a living cells

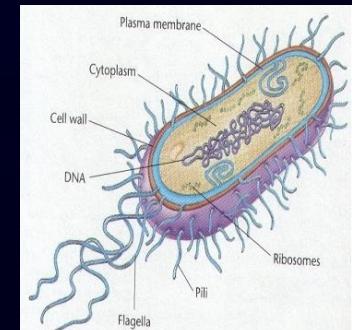


## b) Bacteria

- small single-celled organisms;
  - simple cellular structures and without membrane bound organelles (prokaryotic organisms)
  - contain cell wall that is made up of a mixture of carbohydrates and amino acids (peptidoglycan)
- can be classified by 3 categories:
- i) Gram-staining properties
  - ii) Shapes
  - iii) Requirements for oxygen



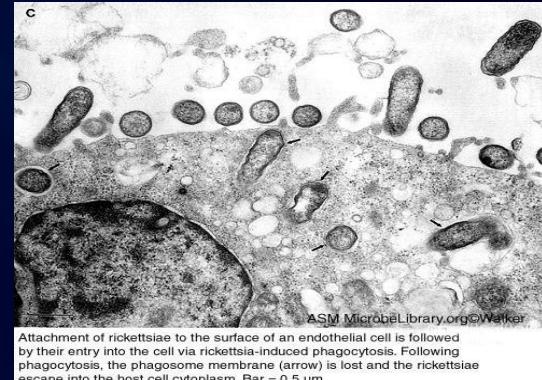
Aerobic  
Anaerobic



## c) Unusual bacterial pathogens

### i) Rickettsia

- a group of parasitic bacteria that live in arthropods (e.g. ticks and mites)
- obligate intracellular parasites
- rod or round-shaped bacteria
- transmitted by bites of insects



### ii) Mycoplasmas

- very small organisms without the ability to form cell walls

### iii) Chlamydia

- obligate intracellular pathogens without a cell wall

## d) Protozoa

- unicellular eukaryotic microbes
- belongs to the animal kingdom
- live by ingesting food



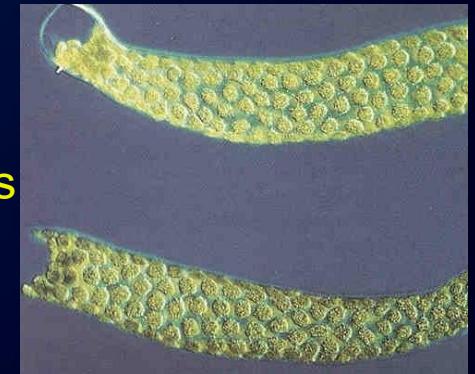
## e) Fungi

- eukaryotic cells with nucleus
- consist of yeast and mold
- acquire food through absorption



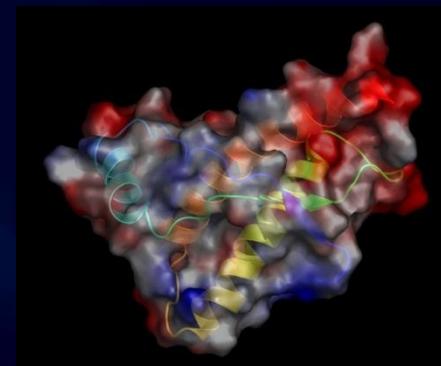
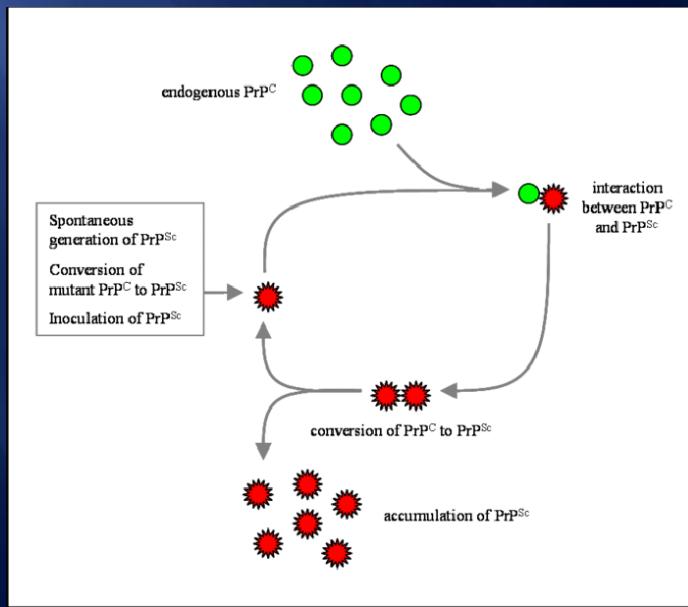
## f) Helminths

- can be further classified as roundworms, flatworms or flukes
- large multi-cellular organisms;
- with complex body structure

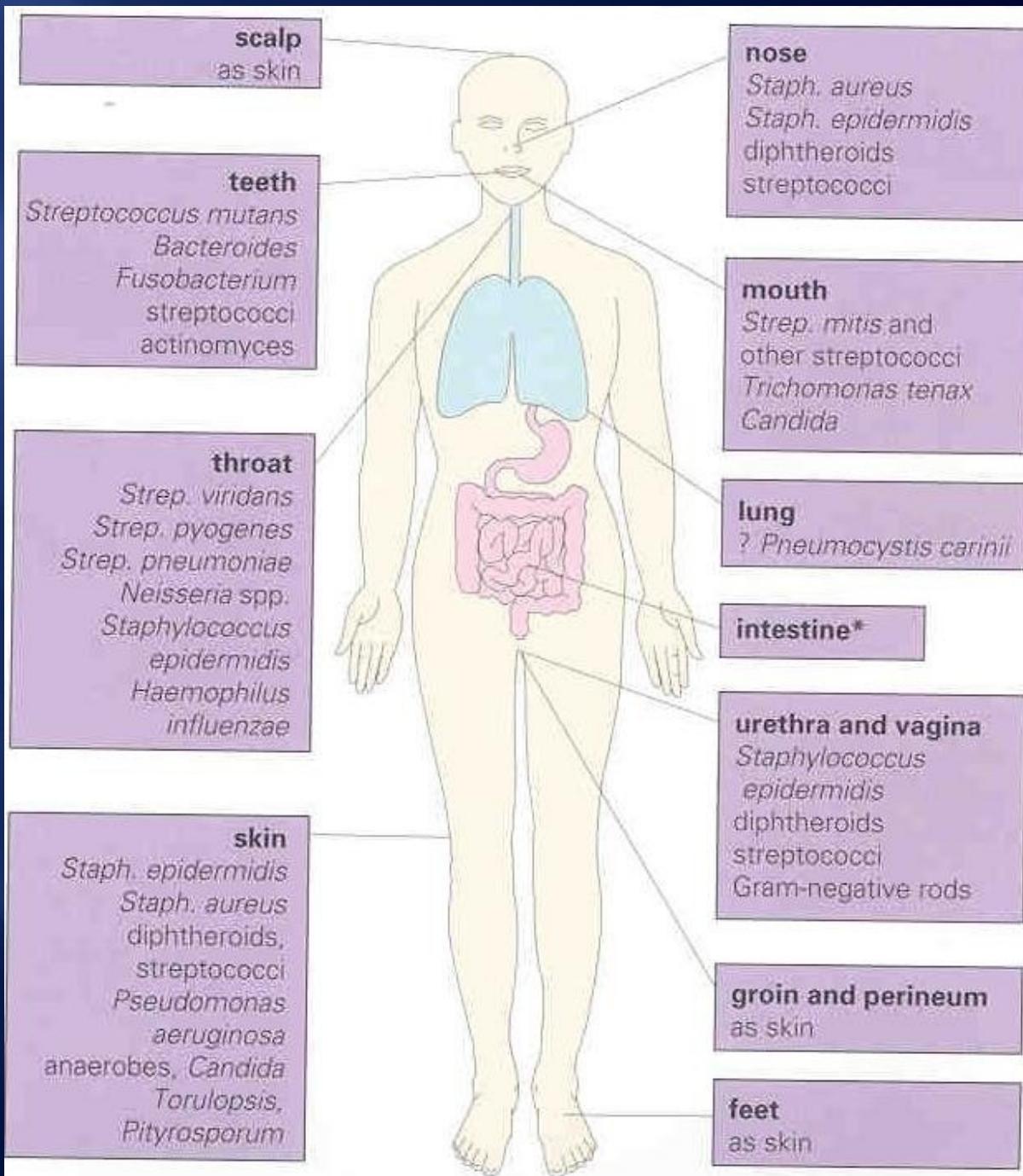


## g) Prions

- considered to be a rare disease caused by misfolded proteins
- protein-only vs. viral hypothesis
- could be caused by spontaneous mutation or by consuming contaminated food.



# Normal Flora



# Normal flora

- colonize on certain parts of the body without causing diseases under normal conditions
- begin their colonization in and our on the surface of the body soon after birth. A human body contains  $10^{13}$  human cells and  $10^{14}$  bacterial cell
- prevent colonization and infection by pathogens
- sometimes, bacterial normal flora can be beneficial to the host
  - In large intestine, *E.coli* produces bacteriocins that can inhibit the growth of other bacteria
  - *E.coli* synthesizes vitamin K and B that are absorbed into the blood stream
- Under certain conditions, normal flora can cause diseases (e.g. dental plaque) caused by *Streptococcus mutans*

# Opportunistic Pathogens

An infectious microorganism that is normally a commensal or does not harm its host but can cause disease under specific conditions.

Examples:

1. Gain of entry to other parts of body

- infective endocarditis caused by *Streptococcus mutans*

2. Patients with a compromised immune system

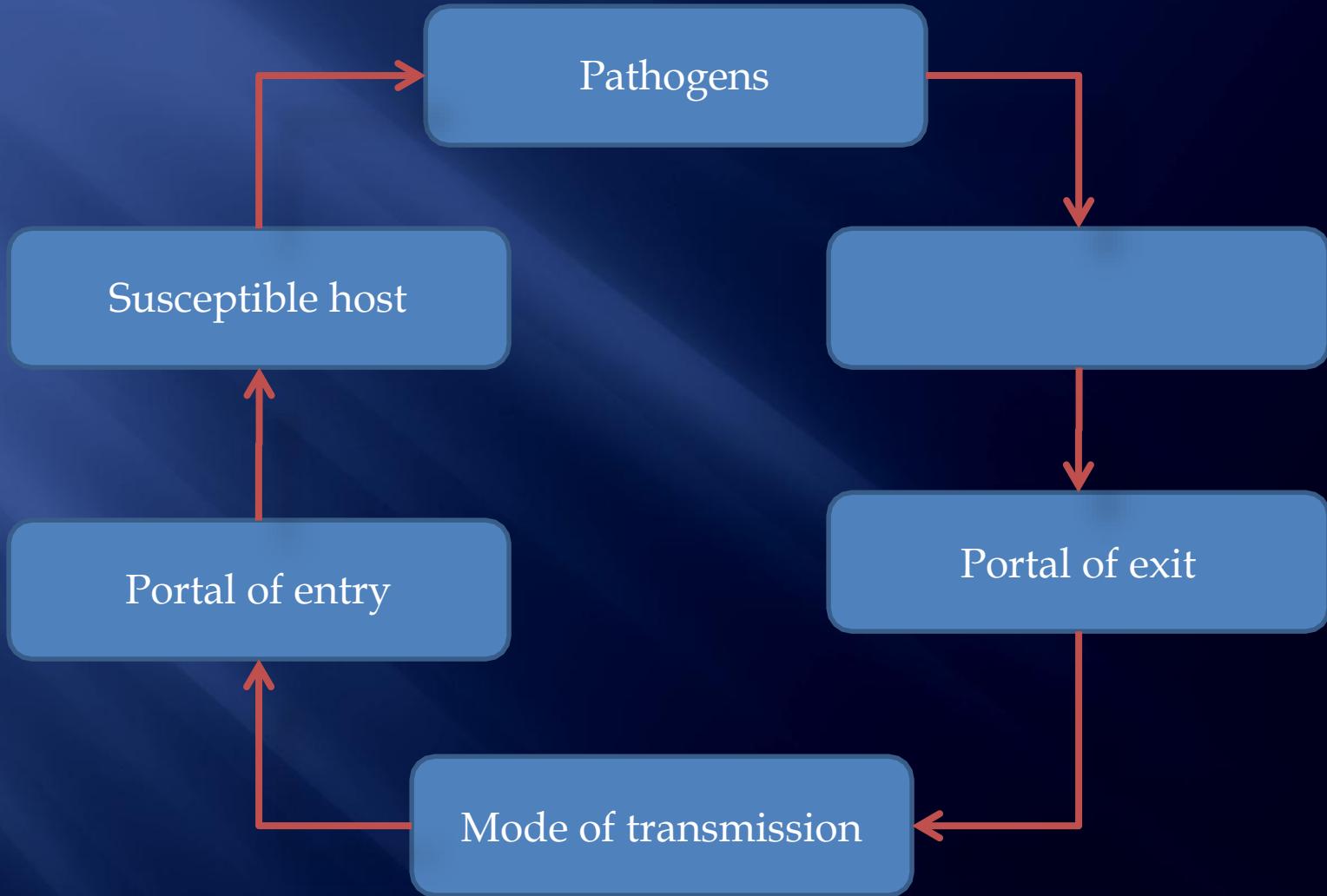
- aspergillosis caused by *Aspergillus fumigatus*



# Koch's Postulations for a Pathogen of a Given Disease

- The microbe must be present in every case of the disease
- The microbe must be isolated from the diseased host and grown in pure culture
- The cultured microorganism should cause disease when introduced into a healthy organism
- The microbe must be recovered from an experimentally-infected host

# The Infection Chain



# The Infection Chain (1)

## 1) Pathogens

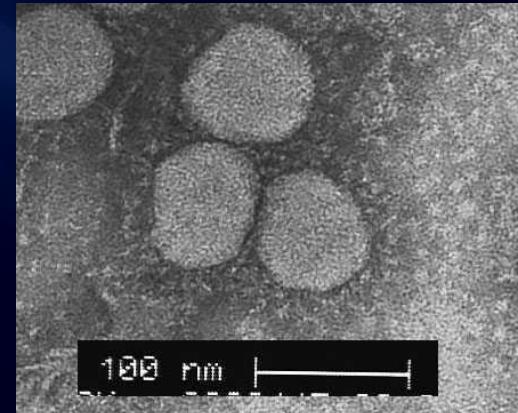
Bacteria, viruses, fungi etc

Clinical interventions used to break the chain

- Rapid identification of organisms

## *SARS – Koch' Postulates proved.*

- Novel coronavirus identified from fluids of patients.
- Virus cultured in Vero cell line.
- Sera of patients have antibodies to virus.
- Cultured virus produces disease in Macaque monkeys.
  - -produces specific immune response
  - -isolated virus is SARS CoV
  - -pathology similar to human
- 



# The Infection Chain (2)

## 2) Reservoir

Animate reservoirs:

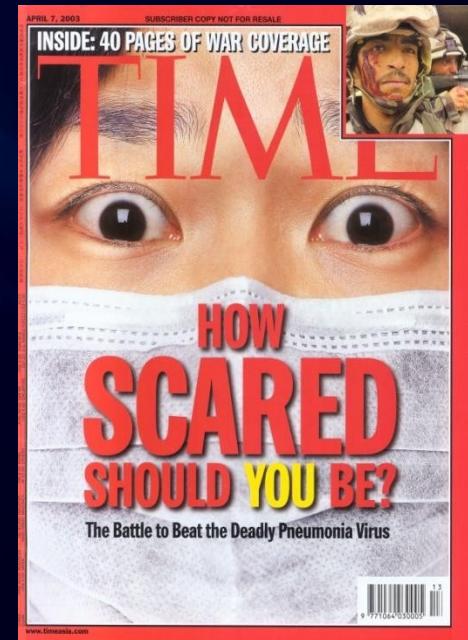
Human (patients or carriers), animals and insects

Inanimate reservoirs:

Soil, water, and other nonliving objects

Clinical interventions used to break the chain

- Health surveillance
- Environmental sanitation
- Disinfection/sterilization



# The Infection Chain (3)

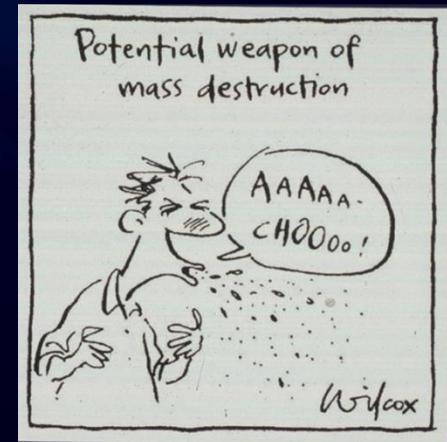
## 3) Portal of exit

- Excretions
- Secretions
- Skin
- Droplet



## Clinical interventions used to break the chain

- Hand hygiene
- Control of excretions and secretion
- Trash and waste disposal



# The Infection Chain (4)

## 4) Mode of transmission

- Direct contact
- Ingestion
- Fomites
- Airborne
- Vector
- Transfusion

## Clinical interventions used to break the chain

- Hand hygiene
- Sterilization
- Standard precautions
- Airflow control
- Food handling
- Isolation
- Pest control

*Lancet* 2003; **361**: 1519–20

 **Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS)**

W H Seto, D Tsang, R W H Yung, T Y Ching, T K Ng, M Ho, L M Ho, J S M Peiris, and Advisors of Expert SARS group of Hospital Authority\*

\*Members listed at end of report

# The Infection Chain (5)

## 5) Portal of entry

- Mucous membrane
- GI tract
- GU tract
- Respiratory tract
- Broken skin

Clinical interventions used to break the chain

- Aseptic technique
- Catheter care
- Wound care

# The Infection Chain (6)

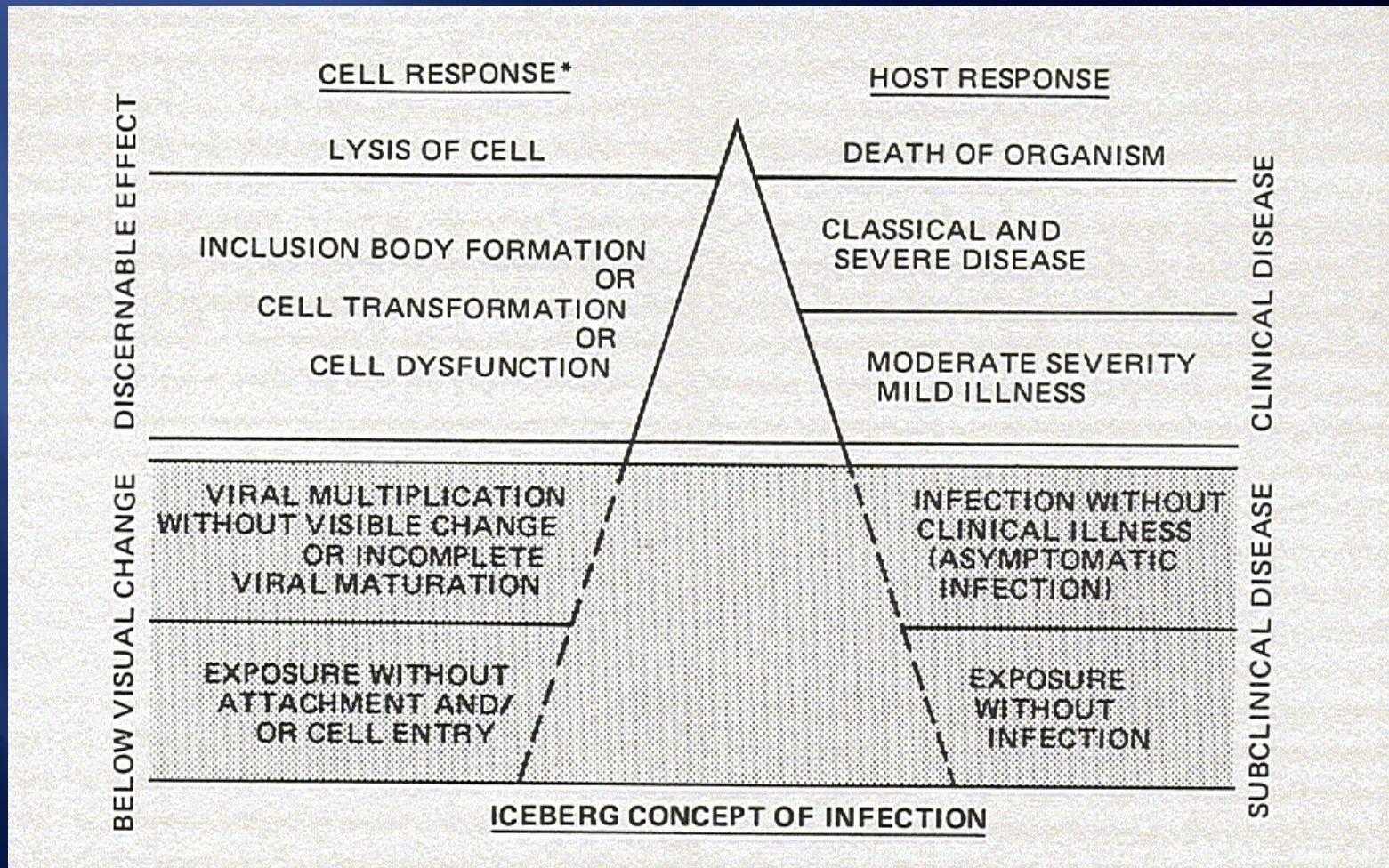
## 6) Susceptible host

- Immunocompromised patients
- Surgical patients
- Elderly
- etc

Clinical interventions used to break the chain

- Treatment of underlying diseases
- Recognition of high-risk patients

# The iceberg concept of infectious disease



# Severity and Duration of a Disease

- **Acute:** develops rapidly but last only a short time. Example: influenza and hepatitis A
- **Chronic:** develops slowly but is likely to be continual or recurrent for a long time. Example: tuberculosis, hepatitis B and HIV
- **Latent:** inactive for the time being but can be reactivated to cause symptoms of the diseases. Example: herpes simplex virus

# **Extent of the Infection**

- **Local infection** is limited to a relative small area of the body
- **Systemic infection**, the microorganisms or their products are spread throughout the body via the circulatory system

# Predisposing Factors

- A predisposing factor is one that makes the body more susceptible to disease.
  - **gender**
  - **genetic background**
  - **climate**
  - **age**
  - **fatigue**
  - **stress**
  - **inadequate nutrition**

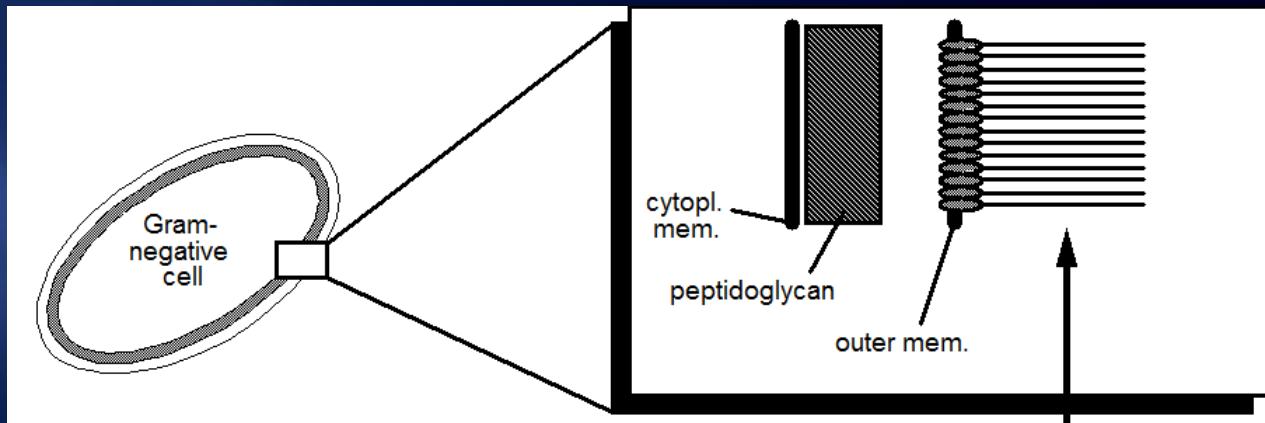
# Development of Disease

- **Period of incubation:** the period between infection and the first sign of symptoms
- **Illness:** the person exhibit symptoms: fever, chills, muscle pain, sensitive to light, sore throat, lymph node enlargement, and gastrointestinal disturbances
- **Decline:** symptoms subside
- **Convalescence,** person regains the strength and returns to the state of health

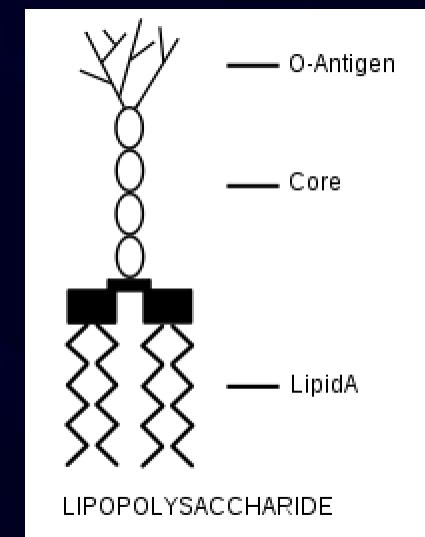
# Bacterial Pathogens Damage the Host

- Bacterial cells directly damage the host tissue through the production of specific tissue-degrading enzymes (e.g. collagenases)
- Bacterial cells produce toxins that are poisonous substances to the host. They are frequently the primary factor contributing to the pathogenesis.
- Exotoxins, diffusible proteins secreted into external medium.
- Endotoxins, components of the outer membrane of Gram -ve bacteria.

# Endotoxin of Gram-negative bacteria



- They are a part of the cell wall of gram-negative bacteria --
  - lipopolysaccharides (LPS, also pyrogen)
- They are released when the gram-negative cell dies and its cell wall undergoes lysis
- Activate cytokines production
- Cause septic shock that can be presented in fever, leukopenia, hypotension (SHOCK), impaired organ perfusion, disseminated intravascular coagulation and death eventually
- Attempts at therapy using anti-endotoxin or anti-TNF antibodies



# Exotoxin

- cause damage to the host by destroying cells or disrupting normal cellular processes

Action:

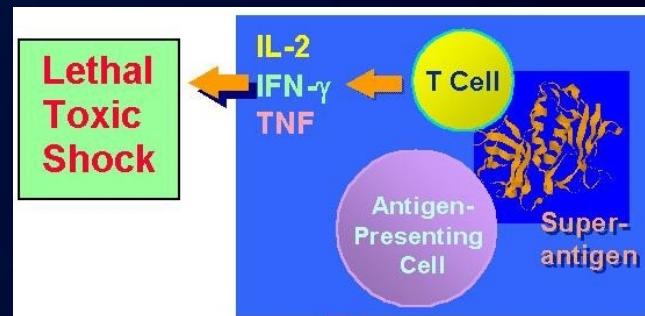
Type 1) cell surface

e.g. superantigens of *Staphylococcus aureus* bind to a receptor on the cell surface and stimulate intracellular signaling pathways

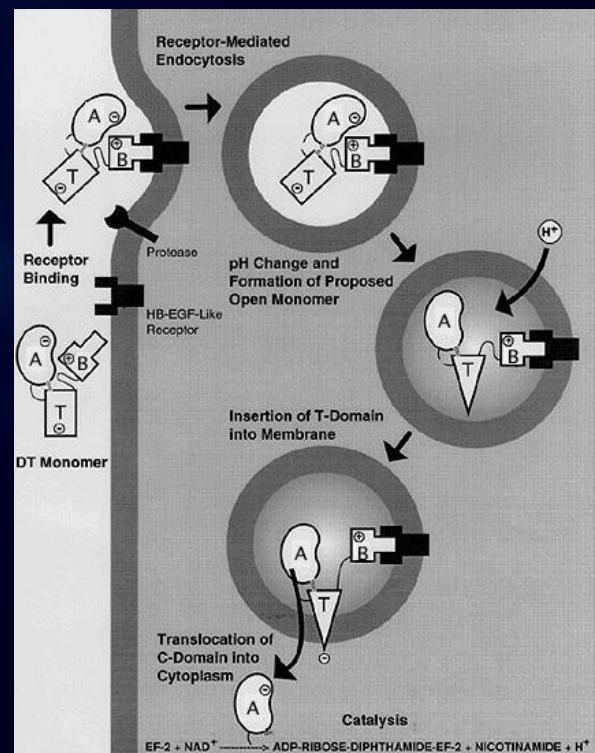
Type 2) membrane damaging  
e.g. Alpha toxin of *C. perfringens* with phospholipase C activity

Type 3) intracellular  
e.g. AB toxins (A: active, B: binding) of *Corynebacterium diphtheriae*

Massive secretion of proinflammatory cytokines



Action of diphtheria toxin



# Exotoxin can be classified by its mode of action

**Cytotoxins** kill cells or affect their functions: Diphtheria Toxin, produced by *Corynebacterium diphtheriae*, inhibits protein synthesis of host cells.

**Neurotoxins** interfere with normal nerve impulse transmission: Tetanus toxin, produced by *Clostridium tetani*, leads to uncontrollable muscle contraction and a symptom called “lockjaw”.

**Enterotoxins** affect epithelia cell lining of the gastrointestinal tract: Vibrio enterotoxin, produced by *Vibrio cholerae*, binds to epithelial cells of the small intestine to lead to severe diarrhea.

# Host Defense Mechanism

## *Learning Objectives*

- Understand nonspecific vs. specific host defense.
- Understand antibody-mediated immunity vs. cell-mediated immunity

# Non-specific defense vs. Specific host dense

## Barriers

- Physical
- Chemical
- Biological

## Innate immunity

- inflammatory response
- fever
- complement system
- interferon
- phagocytosis
- natural killer cells
- nature resistance

## Adaptive immune immunity

- Cell-mediated response
- Humoral response

# Physical barriers

- **Intact skin:** barrier against the penetration of any microorganism
- **Saliva:** washes microorganisms from teeth and gums
- **Mucus:** traps microorganisms that enter into respiratory and gastrointestinal tracts
- **Ciliate:** moves the mucus up and out in the lower respiratory tract

# Chemical barriers

## Bactericidal substances in body fluids/secretions

- Production of fatty acid (sebum) from sebaceous glands of the skin
- Lysozyme in tears and saliva that dissolves bacterial cell wall
- Hydrolytic enzymes in saliva, acid in stomach, degradative enzymes in small intestine

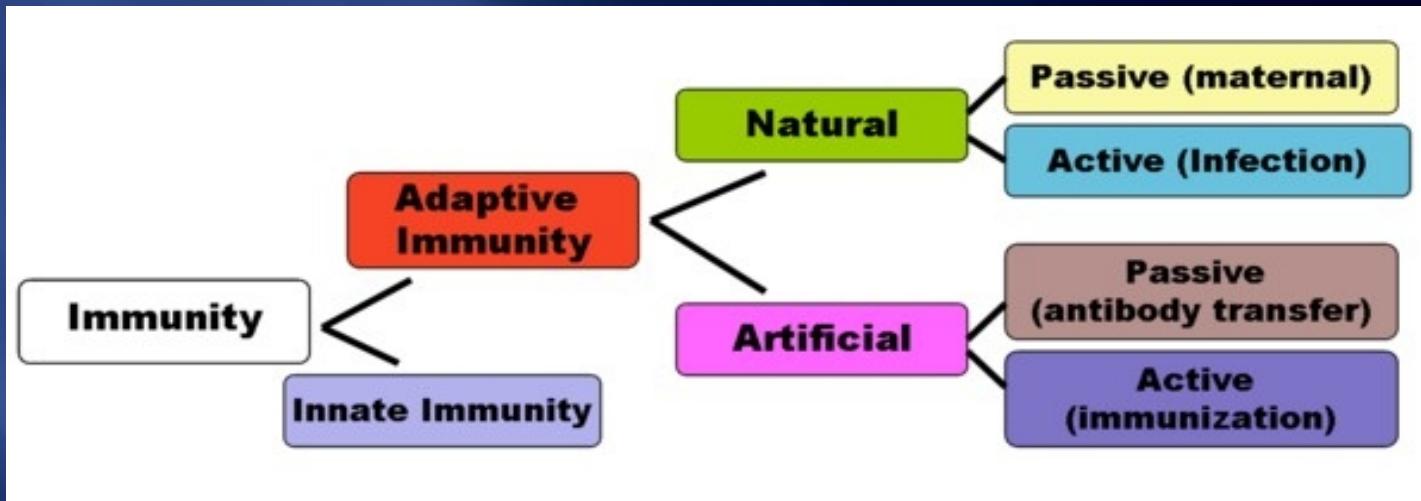
# Biological barriers

- **Normal flora:** prevent colonization and infection by pathogens

# Immunity

## What is Immunity?

- resistance of an organism to infection, disease, or other unwanted biological invasion



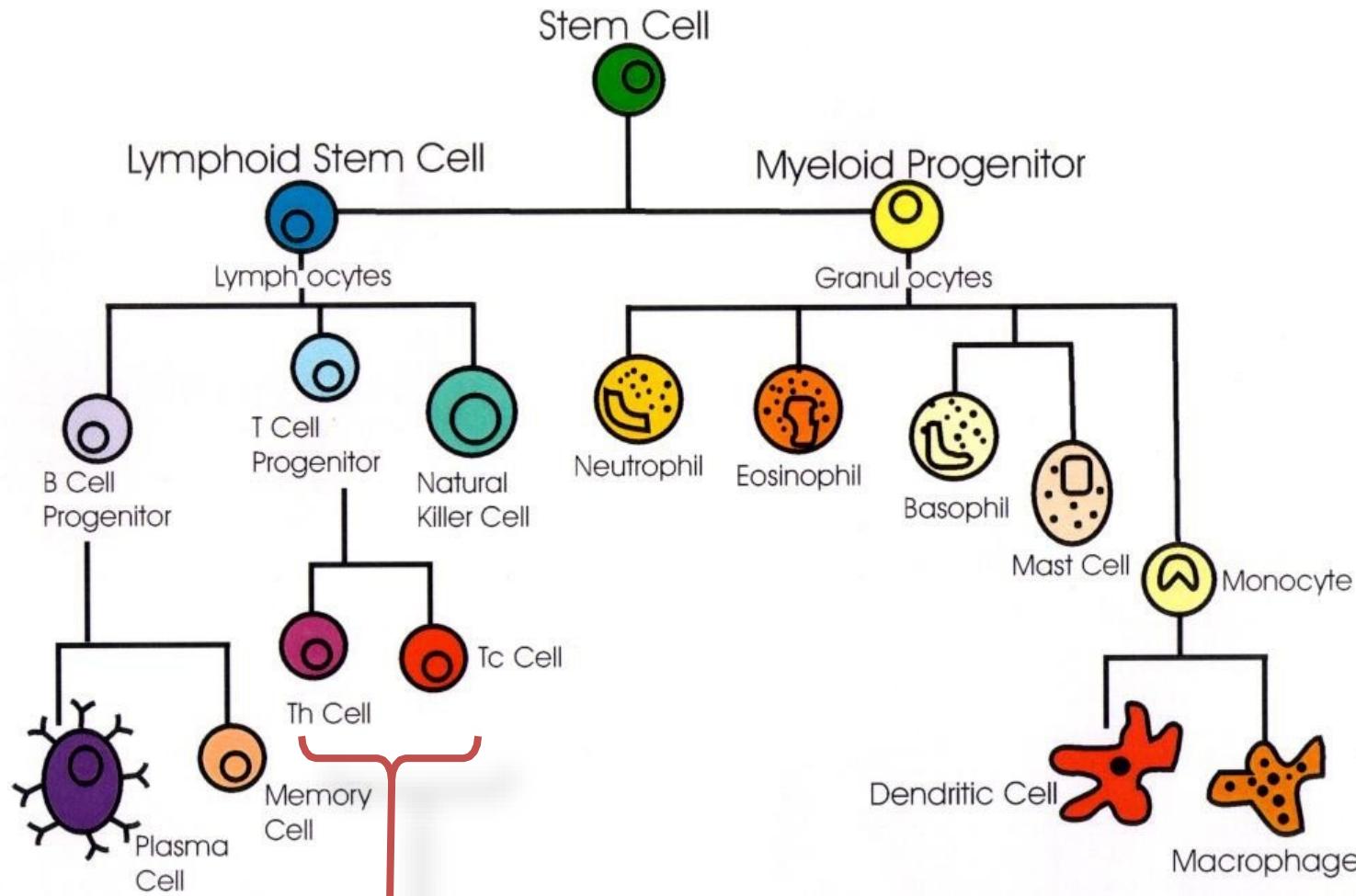
### Innate immunity:

- non-specific
- no change with repeat exposure
- immediate defense against infections

### Adaptive immunity:

- specific
- able to generate long-lived memory cells against a specific pathogens
- take sometime to active the memory cells

# Cells of the Immune System



Humoral response Cell-mediated response

T cells (T for thymus, where they mature)

B cells (B for bone marrow, where they originate)

# Innate immunity

# Inflammatory Response

- Body response to cell damage. It is characterized by redness, pain, heat, and swelling
- Vasodilation and increased permeability of blood vessels by the release of histamine and prostaglandin by mast cells
- Phagocytic cells squeeze through endothelial linings
- Phagocytosis of the invading pathogens, resulting in dead microbes and granulocytes and macrophages
- Facilitate tissue repairing by removing invading pathogens

# Fever

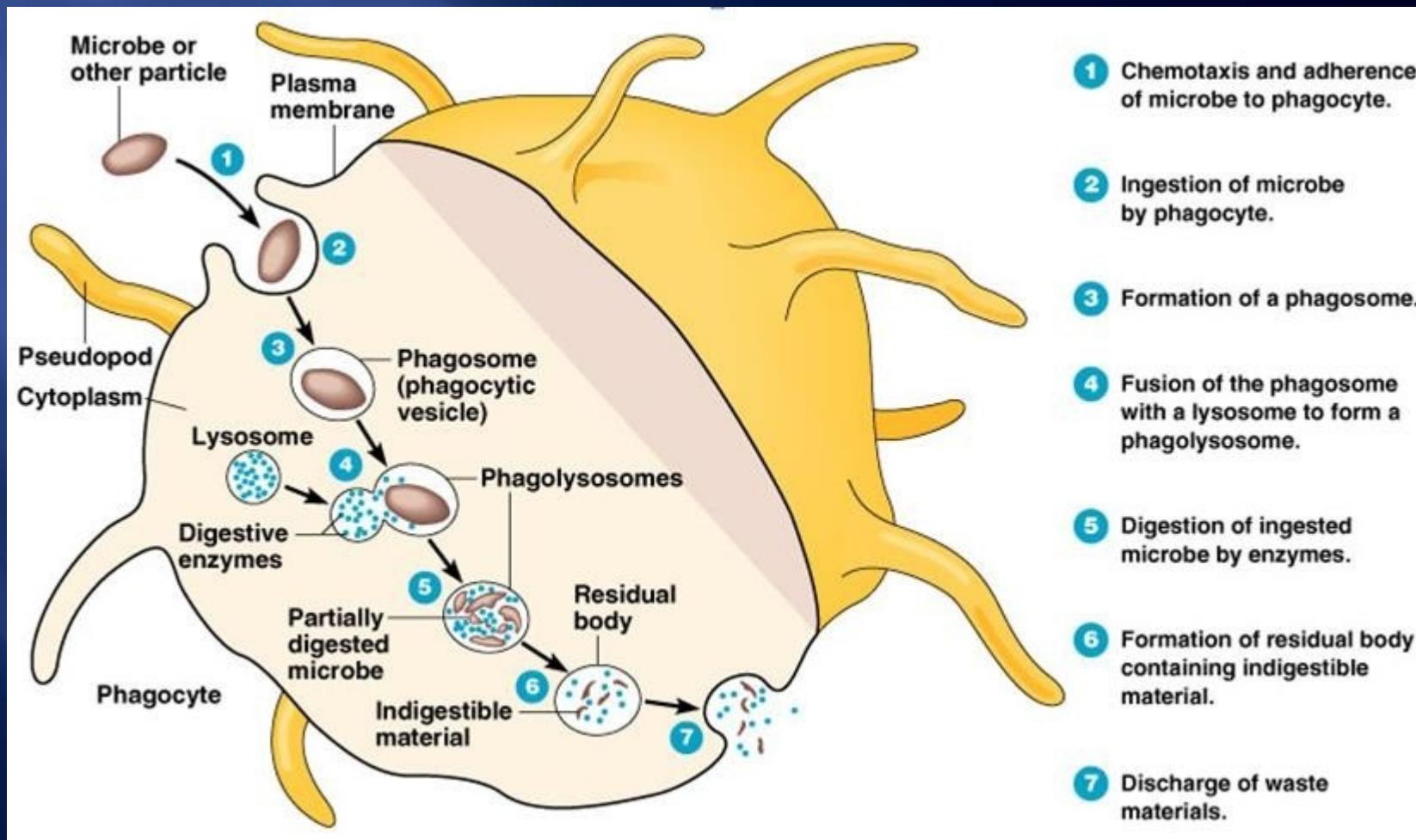
- Fever is abnormal high body temperature produced in response to infections
- Infections induce the release of interleukin-1 that resets the temperature of hypothalamus resulting in fever
- No consistent benefits for fever in the control of infection in human. Suppression of fever by drugs is not harmful during infection and often makes patients more comfortable

# Antimicrobial Substances

- Complement system (with >20 different proteins)
  - a biochemical cascade that attacks the surfaces of foreign cells
  - enhance phagocytosis or puncture bacterial cell membranes
  - facilitate inflammation
- Interferons (IFNs)
  - Antiviral proteins produced in response to viral infection
  - Three types:**IFN- $\alpha$** , **IFN- $\beta$**  (**Innate immune response**) and**IFN- $\gamma$**  (**Acquired immune response only**)
  - Work by inducing uninfected cells to produce antiviral proteins
  - Modulate immune response to the infected cells

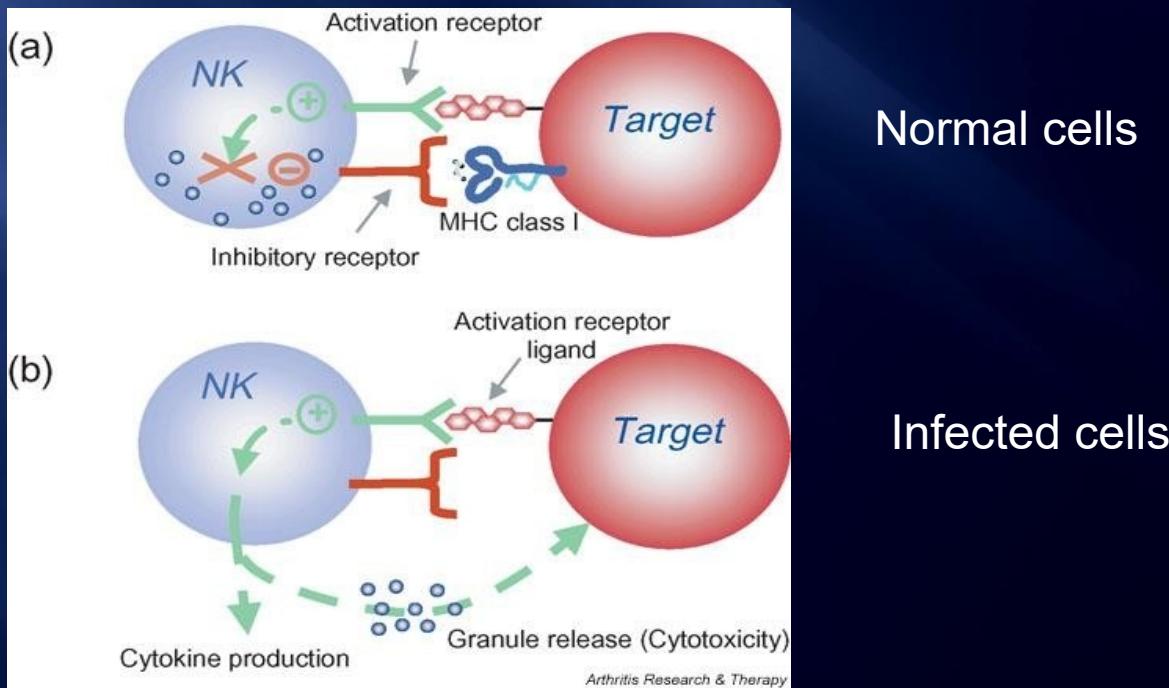
# Phagocytosis

- Engulfment, killing and digestion of microbes by phagocytes
- 3 commonly founded phagocyte cells of the immune system (macrophages, neutrophils, and dendritic cells)



# Natural killer cells

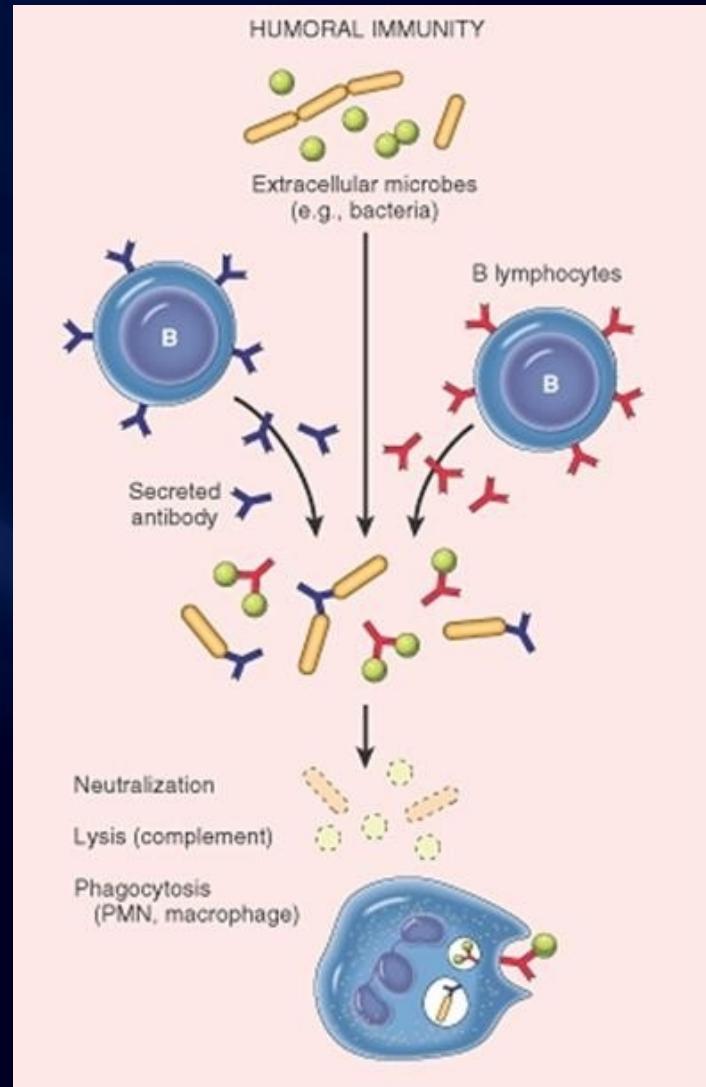
- NK cells attack host cells that have been infected by microbes, but do not directly attack invading microbes.
- NK cells attack and destroy infected cells, through a process known as "missing-self."



# Adaptive immunity

# B Cells and Antibodies-mediated Immunity (Humoral)

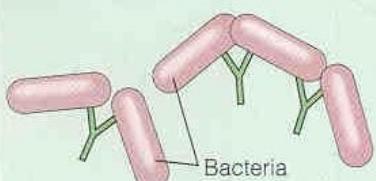
- Bone marrow cells give rise to B cells that are then **migrate into lymphoid tissues**
- When challenged by foreign antigens, the B cells **become mature plasma cells to produce antigen specific antibodies**
- Some activated B cells persist as **long-living memory cells**. Upon re-stimulation by the same antigens years later, they rapidly multiply and differentiate into antibody producing plasma cells (**secondary immunity**)



## PROTECTIVE MECHANISM OF BINDING ANTIBODIES TO ANTIGENS

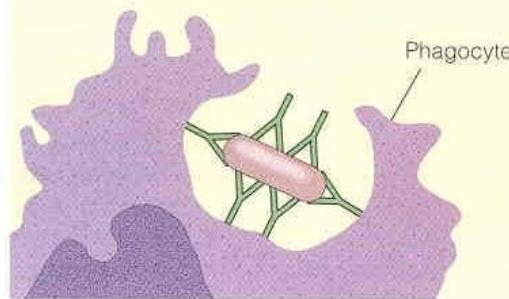
### Agglutination

Enhances phagocytosis and reduces number of infectious units to be dealt with



### Opsonization

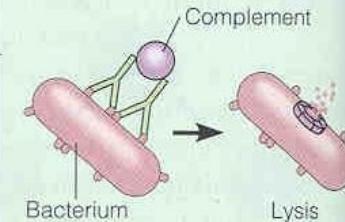
Coating antigen with antibody enhances phagocytosis



Phagocyte

### Activation of complement

Cell lysis

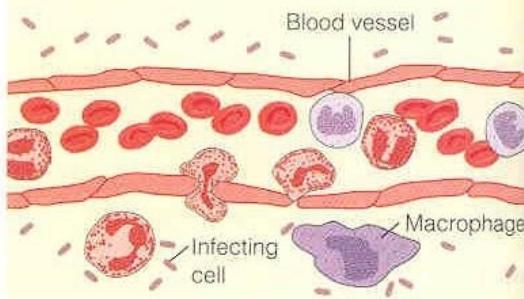


Bacterium

Lysis

### Inflammation

Disruption of cell by complement/reactive protein attracts phagocytic and other defensive immune system cells



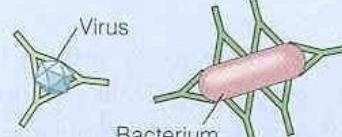
Blood vessel

Macrophage

Infecting cell

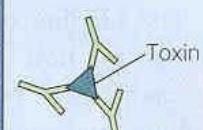
### Neutralization

Blocks adhesion of bacteria and viruses to mucosa



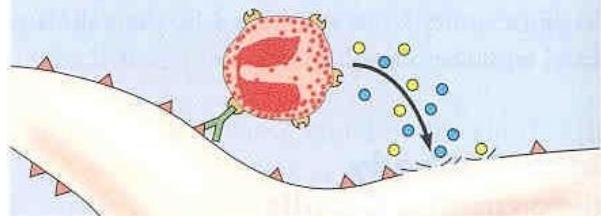
Bacterium

Blocks active site of toxin



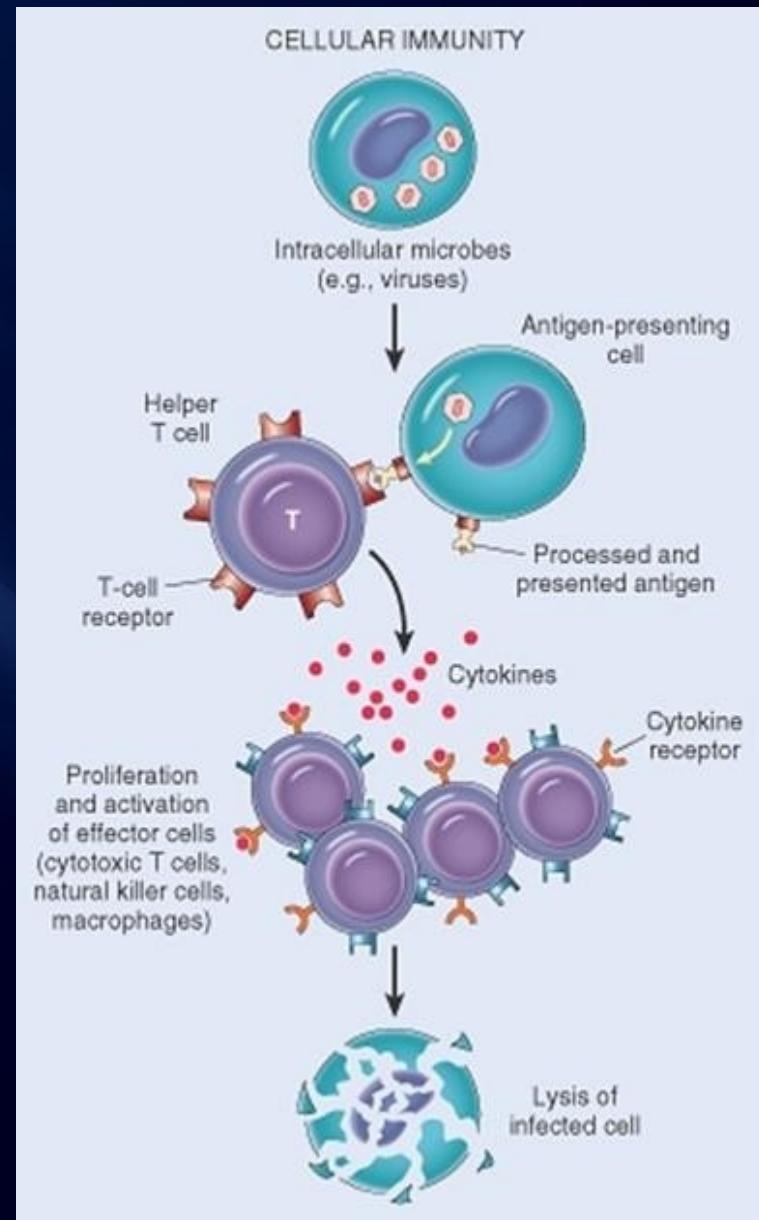
### Antibody-dependent cell-mediated cytotoxicity

Antibodies attached to target cell cause destruction by non-specific immune system cells

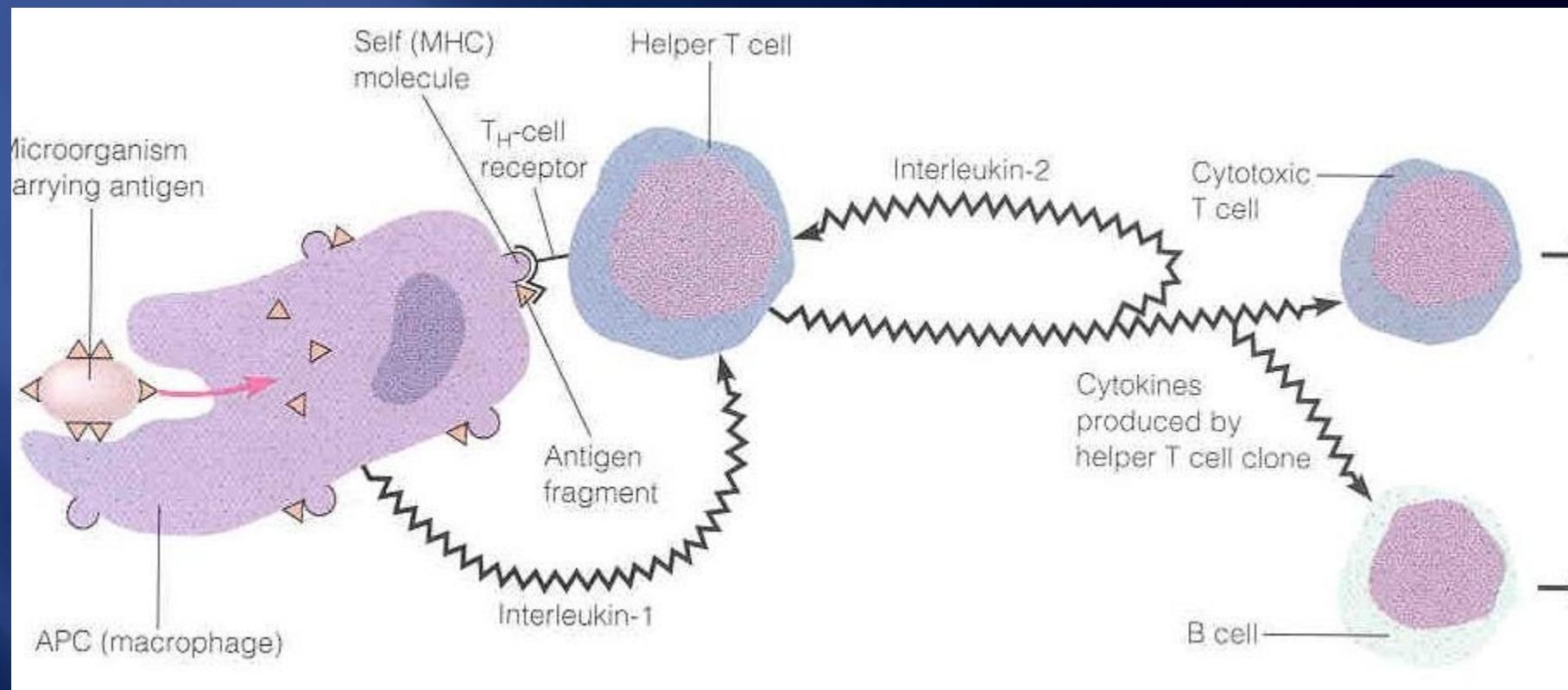


# T Cells & Cell-mediated Immunity

- Cell mediated immunity associated with T lymphocytes responding to intracellular antigens
- They are developed in thymus and then migrate to lymphoid tissue
- There are 2 major and 2 minor types of T cells
  - Helper T cells (CD4+), modulate both T and B cell immunity
  - Cytotoxic T cells (CD8+) destroy target cells on contact
  - Memory T cells that are responsible for secondary immunity
  - Naturally kill cells (NK) that are responsible for antibody-mediated cytotoxicity



# Helper-T cells



# Cytotoxic T cells (CD8+)

