HIV, SYPHILLIS and TYPHOID

By Dr. Swathi Swaroopa .B


HIV
AIDS

- AIDS is a retroviral disease caused by the 'Human Immuno Deficiency' (HIV) virus

- It is characterized by profound immunosuppression with associated opportunistic infections, malignancies, wasting, and central nervous system (CNS) degeneration

- Retroviruses are unable to replicate outside of living host cells because they contain only RNA and do not contain DNA

- Two types of viruses – HIV type 1 and HIV type 2
- HIV is transmitted from one person to another through sexual contact, blood-to-blood contact, or perinatally.

PATHOPHYSIOLOGY

- HIV selectively attacks the CD4 T lymphocytes, the immune cells responsible for orchestrating and coordinating the immune response to Infection.

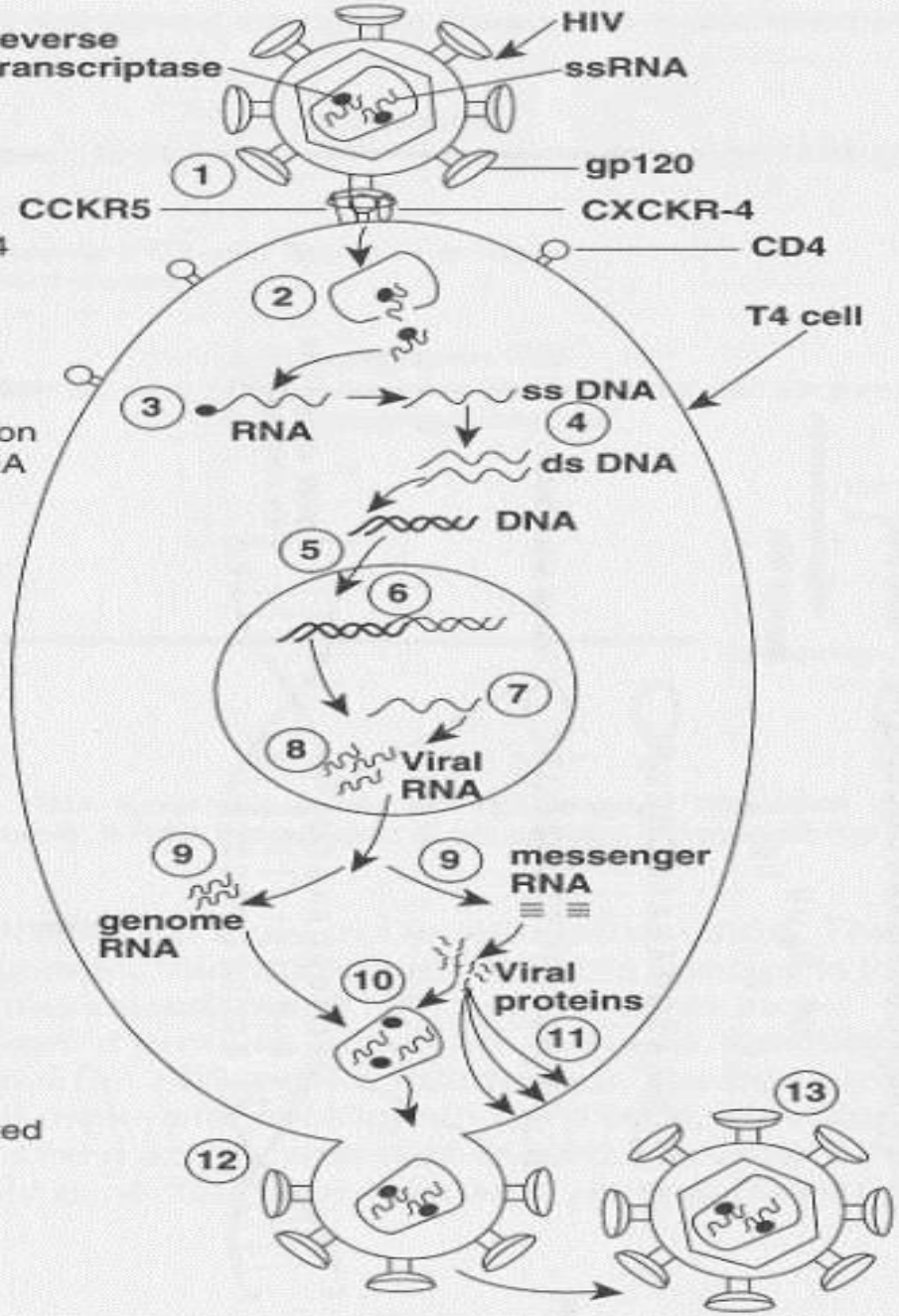
- People with HIV infection have a deteriorating immune system and thus are more susceptible to severe infections with ordinarily harmless organisms.

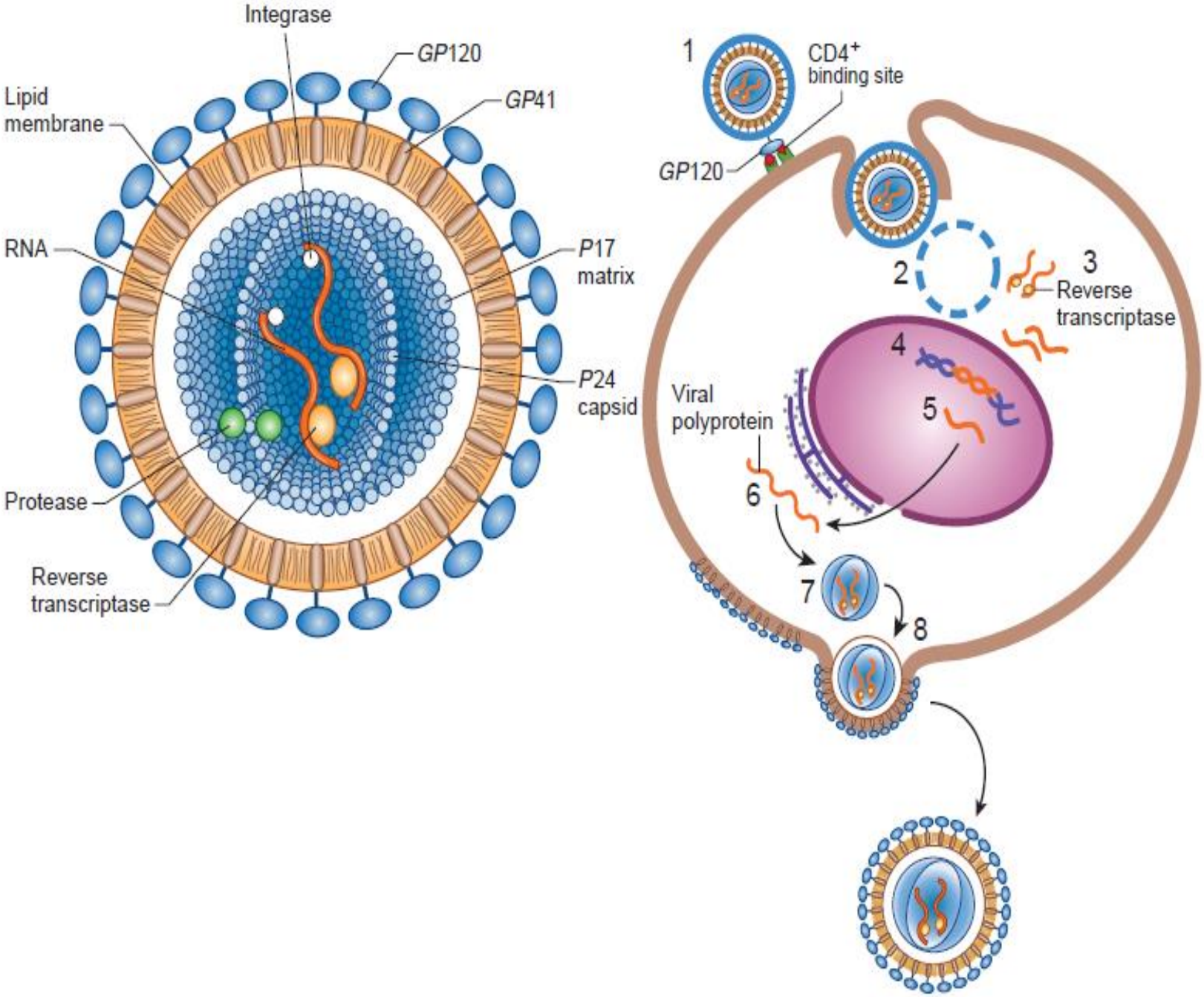
- HIV infects a limited number of cell types in the body, including a subset of lymphocytes called CD4 T lymphocytes also known as(T-helper cells or CD4 T cells), macrophages, and dendritic cells.

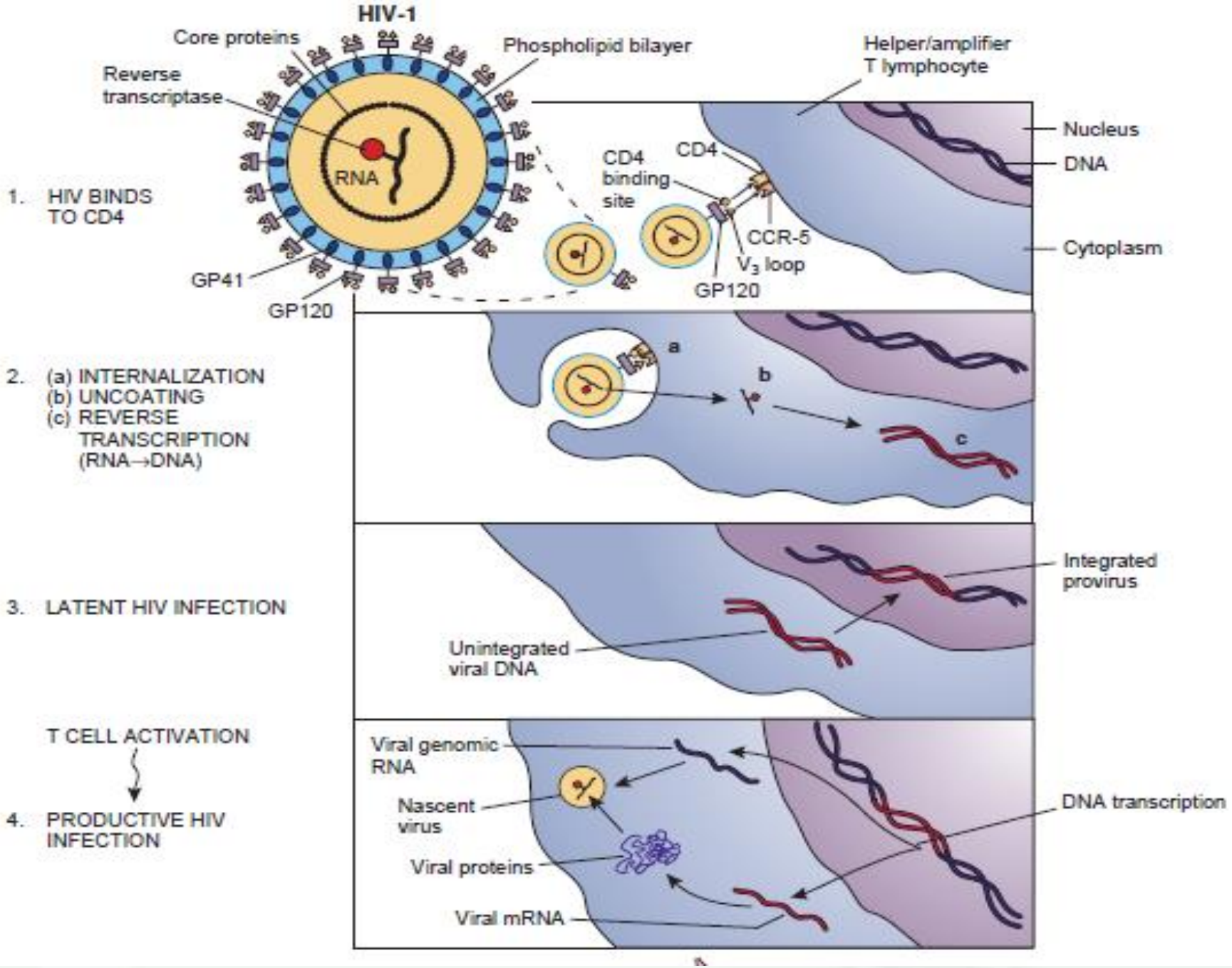
- Once HIV has entered the bloodstream, it attaches to the surface of a CD4 T cell by binding to a CD4 receptor that has a high affinity for HIV.

Steps in viral replication

1. Attachment to CD4
2. Attachment to co-receptor CXCKR4 or CCKR5.
3. Uncoating
4. Reverse transcription of single strand RNA
5. DNA synthesis of second strand
6. Migration to nucleus
7. Integration
8. Viral transcription
9. RNA nuclear transport
10. Protein synthesis
11. RNA packaging and virion assembly
12. Viral proteins move into cell membrane
13. Release of virus
14. Maturation completed




Integrase
GP120
GP41
Lipid membrane
RNA
P17 matrix
P24 capsid
Protease
Reverse transcriptase
1
CD4+ binding site
GP120
2
3
Reverse transcriptase
4
5
Viral polyprotein
6
7
8


HIV-1
Core proteins
Phospholipid bilayer
Reverse transcriptase
RNA
GP41
GP120
Helper/amplifier T lymphocyte
Nucleus
DNA
Cytoplasm
CD4
CD4 binding site
CCR-5
V_3 loop
GP120
1. HIV BINDS TO CD4
2. (a) INTERNALIZATION
(b) UNCOATING
(c) REVERSE TRANSCRIPTION (RNA→DNA)
a
b
c
3. LATENT HIV INFECTION
Integrated provirus
Unintegrated viral DNA
T CELL ACTIVATION
4. PRODUCTIVE HIV INFECTION
Viral genomic RNA
Nascent virus
Viral proteins
Viral mRNA
DNA transcription

- After attachment the viral envelope peptides fuse to the CD4 T-cell membrane results in an uncoating of the virus, allowing the contents of the viral core (the two single strands of viral RNA and the reverse transcriptase, integrase, and protease enzymes) to enter the host cell.

- DNA synthesis from RNA by using reverse transciptase enzyme. The result is double-stranded DNA that carries instructions for viral replication.

- **Integration, the new DNA enters** the nucleus of the CD4 T cell and, with the help of the **enzyme integrase**, is inserted into the cell's original DNA.

- Transcription of the double-stranded viral DNA to form a **single-stranded messenger RNA (mRNA)** with the instructions for building new viruses.

- To finish the cycle ribosomal RNA (rRNA) uses the instructions in the mRNA to create a chain of proteins and enzymes called a polyprotein.

- The cleavage -During cleavage, the protease enzyme cuts the polyprotein chain into the individual proteins that will make up the new viruses.

- Finally the proteins and viral RNA are assembled into new HIV viruses and released from the CD4 T cell.

Pathophysiology of AIDS:

- 2 major targets of HIV infection → CNS
- 2 major targets of HIV infection → immune system

HIV infects T – cells and macrophages

T – cells ⇄ dendritic cells ⇄ macrophages

dendritic cells cause viremia & widespread seeding of lymphoid tissues

depending on host immune response

CLINICAL LATENCY / CHRONIC INFECTION

Replicated HIVs in

T – cells: latent infection, low level infection

follicular dentric cells (HIV reservoir)

macrophages: latent infection, low level infection

T – cells → antigenic stimulation & cytokine stimulation → cause extensive viral replication → lead to CD_4^+ cell lysis → cause severe CD_4^+ cell loss → cause opportunistic infection & 2^0 neoplasms

macrophages → activation of cytokines, TNF, IL – 6 → extensive viral replication → transport to brain

The multiple effects of HIV infection:

Loss of T – cells & macrophages cause,

- **Decreased response to antigens**
- **Disturbed cytokine, IL secretion**
- **Decreased specific cytotoxicity**
- **Decreased killing of tumor cells (cause 2^0neoplasm)**
- **Decreased Ig production in response to new antigens (opportunistic infections)**
- **Decreased chemotoxins (Specific killers of cancer cells,etc)**

Phases of HIV Infection

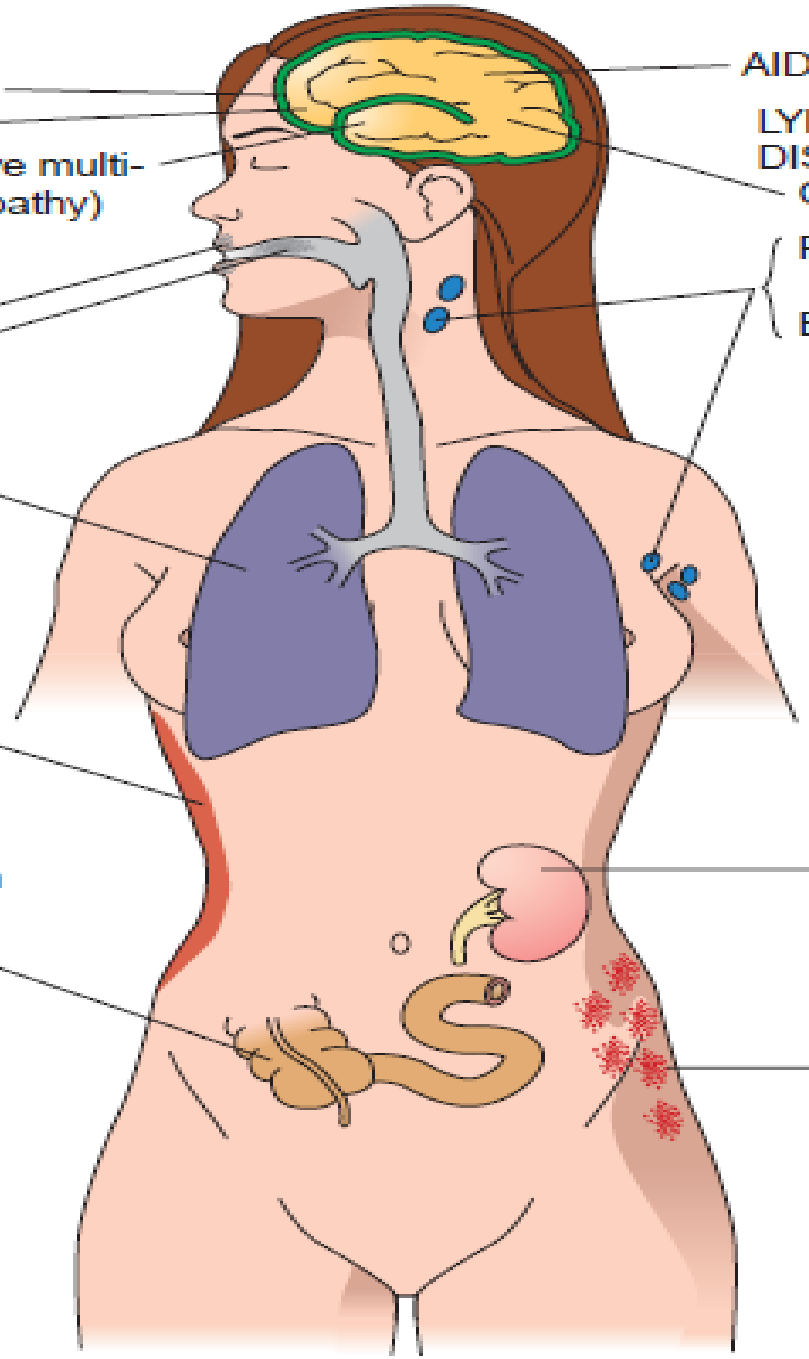
The three phases are

- **Primary infection phase,**
  - **high viral loads, sometimes greater than 1,000,000 copies/ mL, and a decrease in the CD4+ T-cell count.**
- **Chronic asymptomatic Latency phase (10YRS)**
  - **latent period during which the person has no signs or symptoms of illness.**
  - **CD4+ T-cell count 200 cells/µL or lower**
- **Overt AIDS phase**
  - **CD4+ cell count of less than 200 cells/µL or an AIDS-defining illness.**
  - **The risk of opportunistic infections and death increases significantly when the CD4+ cell count falls below 200 cells/µL**

Symptoms of acute HIV infection

- Fever
- Fatigue
- Rash
- Headache
- Lymphadenopathy
- Pharyngitis
- Arthralgia
- Myalgia
- Night sweats
- Gastrointestinal problems
- Aseptic meningitis
- Oral or genital ulcers

OPPORTUNISTIC INFECTIONS



CNS
Cryptococcal meningitis
Toxoplasmosis
Papovavirus (Progressive multi-focal leukoencephalopathy)

MUCOCUTANEOUS
Herpes simplex
Candidiasis

PNEUMONIA
Pneumocystis jiroveci
Mycobacterium avium intracellulare
Cytomegalovirus

SKIN
Staphylococcus
Scabies
HPV
Molluscum contagiosum

DIARRHEA
Protozoa:
Cryptosporidium
Isospora belli
Giardia lamblia
Bacteria:
Mycobacterium avium intracellulare
Viruses:
Cytomegalovirus

AIDS dementia

LYMPHOPROLIFERATIVE DISEASE
CNS lymphoma

Persistent generalized lymphadenopathy
B cell lymphoma

AIDS nephropathy

Kaposi sarcoma

Syphillis

- **Spirochetes are Gram-negative, corkscrew-shaped bacteria with flagella; an outer sheath membrane can mask bacterial antigens from host immune responses.**

- **Syphilis is an infectious venereal disease caused by the spirochete *Treponema pallidum*.**

- **Syphilis is transmissible by sexual contact with infectious lesions, from mother to fetus in utero, via blood product transfusion, and occasionally through breaks in the skin that come into contact with infectious lesions.**

If untreated, it progresses through 4 stages:

- Primary,
- Secondary,
- Latent, and
- Tertiary.

- It can be either acquired or congenital

- **Primary syphilis occurs about 3 weeks after contact:**
- **A firm, non-tender, raised, red lesion (chancre) forms on the penis, cervix, vaginal wall, or anus;**
- **This will heal even without therapy.**
- **Treponemes spread lymphohematogenously throughout the body even before the chancre appears.**

- **Secondary syphilis occurs 2 to 10 weeks later in 75% of untreated patients, with spread and proliferation of spirochetes in skin (including palms and soles) and mucocutaneous tissues (especially mouth)**

- **Lymphadenopathy, mild fever, malaise, and weight loss are common.**

- **Tertiary syphilis occurs in one third of untreated patients, after a long latent period (more than 5 years).**

- **Cardiovascular syphilis (more than 80% of tertiary syphilis) results in aortitis and aortic valve insufficiency.**

- **Neurosyphilis can be symptomatic (meningovascular disease) or asymptomatic (cerebrospinal fluid [CSF] abnormalities only, with pleocytosis, increased protein, and decreased glucose).**

- **“Benign” tertiary syphilis is associated with necrotic rubbery masses (gummas due to delayed type hypersensitivity to the organisms), which form in various sites (bone, skin, oral mucosa).**

- **Congenital syphilis usually occurs when the mother has primary or secondary syphilis.**

- **Intrauterine or perinatal death occurs in 50% of untreated cases.**

- “Early (infantile) congenital syphilis includes nasal discharge, a bullous rash with skin sloughing, hepatomegaly, and skeletal abnormalities (nose and lower legs are most distinctive).

- Diffuse lung or liver fibrosis can also occur.

- Late (tardive) manifestations include notched , deafness, and interstitial keratitis with blindness (Hutchinson triad).

Serologic tests for syphilis:

- **Treponemal antibody tests measure antibodies reactive with T. pallidum.**

- **Non treponemal tests (i.e., VDRL, RPR) measure antibody to cardiolipin, a phospholipid in treponemes and normal tissues.**

Syphilis:

- Syphilis is a chronic venereal infection caused by *'Treponema pallidum'*

T. Pallidum → cutaneous / mucosal lesion (during sexual intercourse) → after 2 - 6 weeks → a primary lesion at the point of entry → failure of immune response → spirochetes of 1^0 inoculation → 2^0 syphilis → lymph node enlargement & mucocutaneous lesion

Immune response stimulate (trepnomeal specific / non specific Ab

2^0 syphilis lead to latent phase after 5 yrs → 3^0 sypilis (CVS, CNS syphilis)

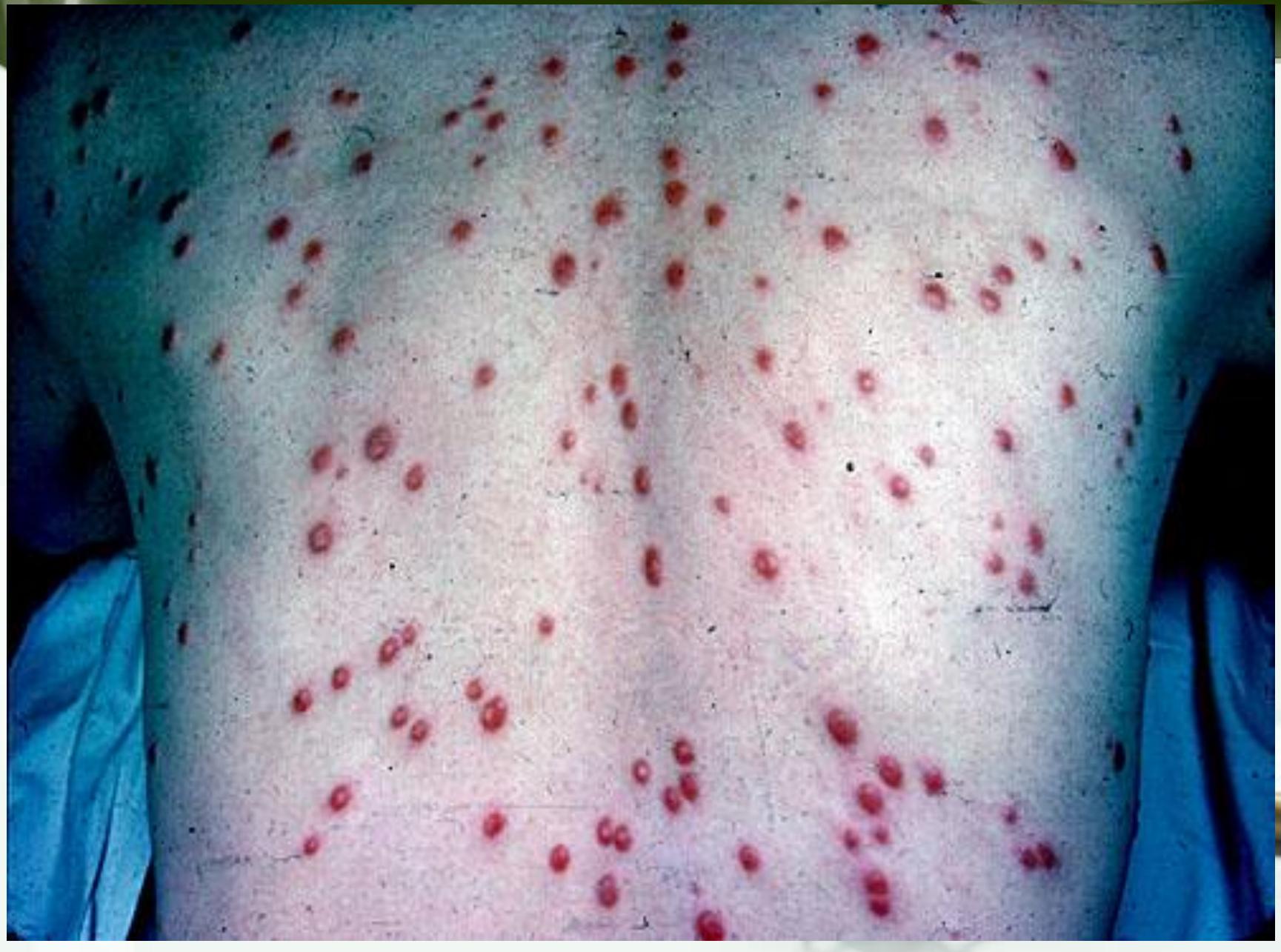
"primary syphilis" symptoms .

- Small, painless sore or ulcer called a **chancre** on the penis, vagina, or around the anus.

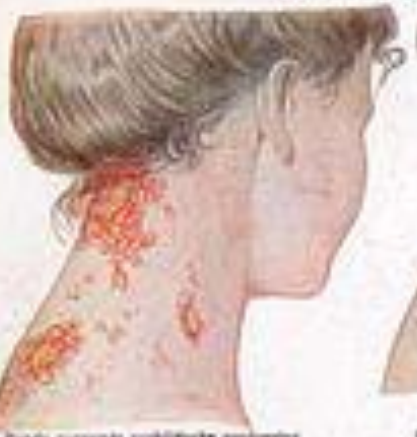
Later symptoms of syphilis

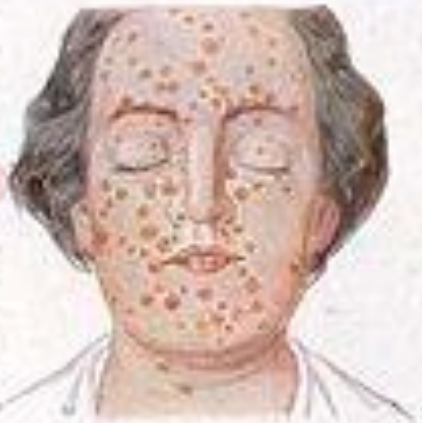
- A **blotchy red rash** that can appear anywhere on the body,
- **Small skin growths** on women these often appear on the vulva and for both men and women they may appear around the anus
- **White patches** in the mouth
- **flu-like symptoms**, such as tiredness, headaches, joint pains and a high temperature (fever) swollen glands occasionally, patchy hair loss

- Complications ?????



Syphilitische Ziekten.





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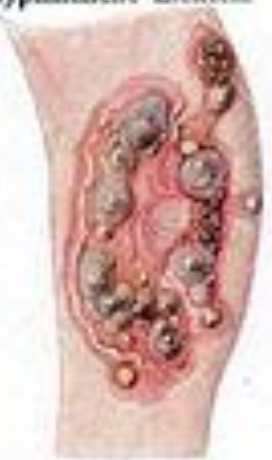
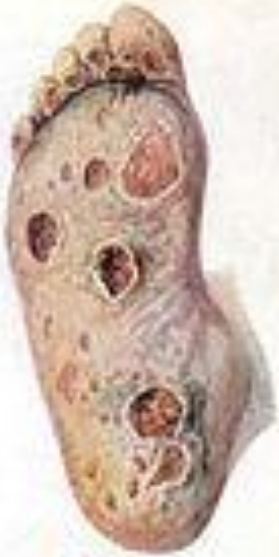
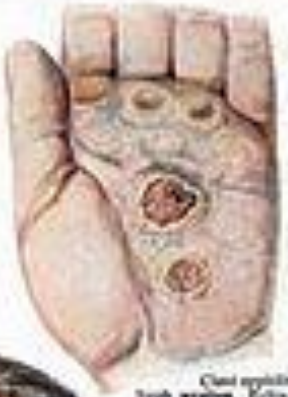






Typhoid

- **Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by *Salmonella* Caused by *S. typhi, S. paratyphi* A, B and rarely C**

- ***Salmonella* – flaggellated, gram negative bacteria**

- **Food borne and water borne**

- ***S. typhi* seen only in human**

Pathophysiology

- *Salmonella* species, when present in the gut are engulfed by phagocytic cells, and present them to the macrophages in the lamina propria.

- With toll-like receptor (TLR)–5 and TLR-4/MD2/CD-14 complex, macrophages recognize pathogen-associated molecular patterns (PAMPs) such as flagella and lipopolysaccharides.

- Macrophages and intestinal epithelial cells then attract T cells and neutrophils with interleukin 8 (IL-8), causing inflammation and suppressing the infection

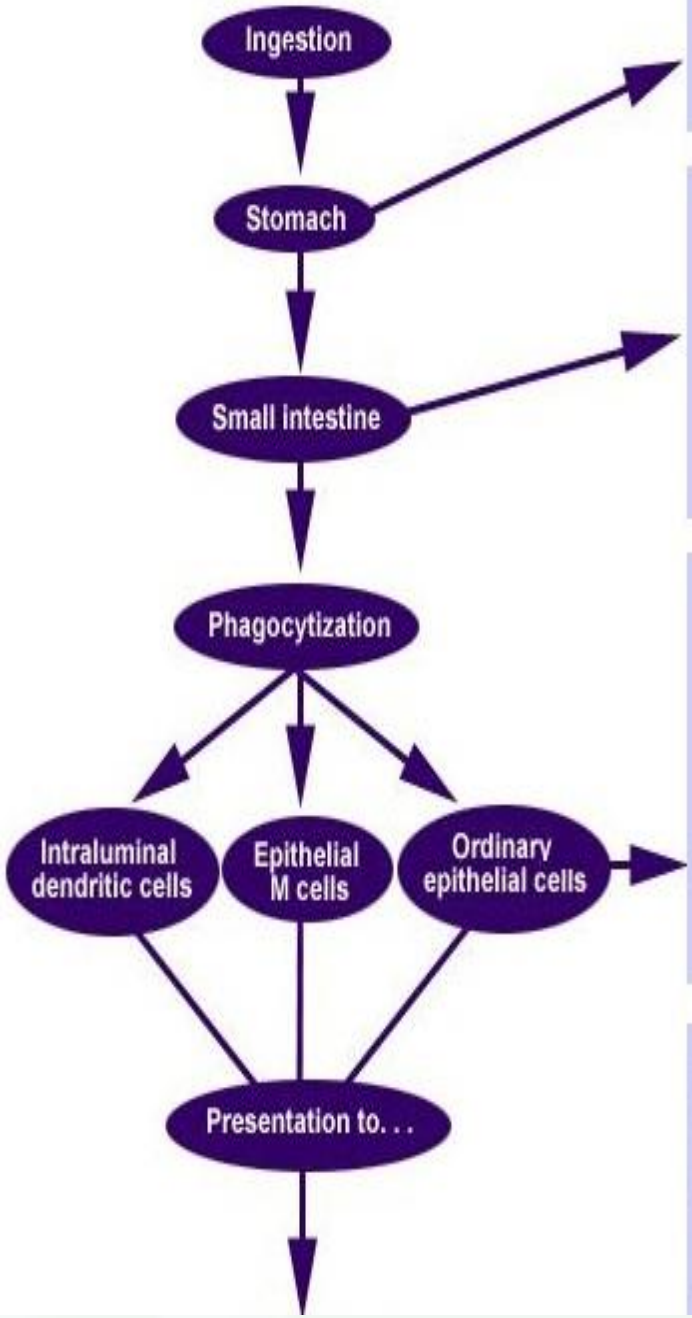
- **Nontyphoidal salmonellae are phagocytized throughout the distal ileum and colon**

- ***S typhi* and paratyphi have specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system.**

- **The bacteria then induce their host macrophages to attract more macrophages.**

- *S typhi* has a Vi capsular antigen that masks PAMPs, avoiding neutrophil-based inflammation
- Typhoidal salmonella co-opt the macrophages' cellular machinery for their own reproduction as they are carried through the mesenteric lymph nodes to the lymphatics and then through to the reticuloendothelial tissues of the liver, spleen, bone marrow, and lymph nodes.
- There, they pause and continue to multiply until some critical density is reached.
- Afterward, the bacteria induce macrophage apoptosis, breaking out into the bloodstream to invade the rest of the body.

- The bacteria then infect the gallbladder via either bacteremia or direct extension of infected bile.
- The result is that the organism re-enters the gastrointestinal tract in the bile and reinfects Peyer patches
- Bacteria that do not reinfect the host are typically shed in the stool and are then available to infect other hosts
- Chronic carriers are responsible for much of the transmission of the organism.



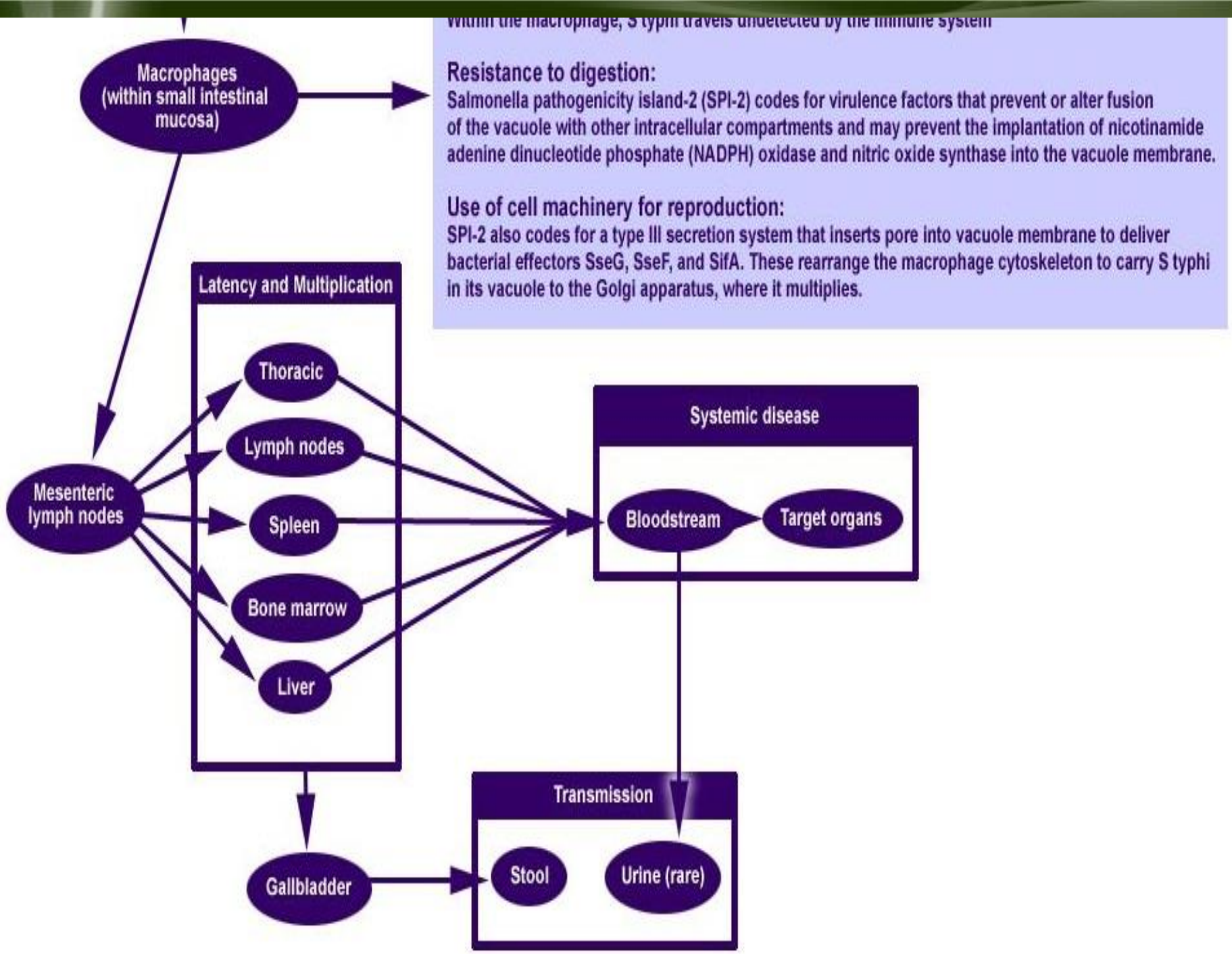
High acid tolerance:
Salmonellae survive a pH as low as 1.5.

Targeting Peyer patches:
Salmonella typhi and a few closely related Salmonella species specifically target grossly visible clusters of lymphatic tissue called Peyer patches. These are the primary pathway for the gut to present antigens to the immune system. S typhi has specialized fimbriae that attach to epithelium over Peyer patches, where the organism may be phagocytized.

Bacterially mediated endocytosis (BME):
Salmonella pathogenicity island-1 (SPI-1) contains the genes for a type III secretion system. This includes macromolecular channels that gram-negative bacteria such as Salmonella species insert into eukaryotic cells and intracellular membrane to inject virulence proteins into the epithelial cell. The proteins disrupt the normal brush border and force the cell to form membrane ruffles, which engulf the bacilli and create vesicles. These carry the bacteria across the epithelial cell cytoplasm and the basolateral membrane, where they are presented to macrophages.

Evasion of immune recognition:
The Vi capsular polysaccharide prevents the recognition of pathogen specific molecular patterns by toll-like receptors and other immune surveillance mechanisms.

Macrophage as vehicle:
Within the macrophage, S typhi travels undetected by the immune system


Within the macrophage, S typhi travels undetected by the immune system
Macrophages (within small intestinal mucosa)
Resistance to digestion:
Salmonella pathogenicity island-2 (SPI-2) codes for virulence factors that prevent or alter fusion of the vacuole with other intracellular compartments and may prevent the implantation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase into the vacuole membrane.
Use of cell machinery for reproduction:
SPI-2 also codes for a type III secretion system that inserts pore into vacuole membrane to deliver bacterial effectors SseG, SseF, and SifA. These rearrange the macrophage cytoskeleton to carry S typhi in its vacuole to the Golgi apparatus, where it multiplies.
Latency and Multiplication
Thoracic
Lymph nodes
Spleen
Bone marrow
Liver
Mesenteric lymph nodes
Systemic disease
Bloodstream
Target organs
Transmission
Gallbladder
Stool
Urine (rare)

The following are modes of transmission of typhoidal salmonella:

- **Oral transmission via food or beverages handled by an often asymptomatic individual—a carrier—who chronically sheds the bacteria through stool or, less commonly, urine**
- **Hand-to-mouth transmission after using a contaminated toilet and neglecting hand hygiene**
- **Oral transmission via sewage-contaminated water or shellfish (especially in the developing world).** [10, 11, 12]

Signs and symptoms

- An initial dysentery is followed by bacteremia (90% of patients),fever, and abdominal pain that can persist for 2 weeks without antibiotic treatment (typhoid fever).

Systemic dissemination can cause extra intestinal complications including:

- Encephalopathy,
- Meningitis,
- Endocarditis,
- Myocarditis,
- Pneumonia, and
- Cholecystitis.