

Lecture 17 – Infectious Disease

Key Terms:

Antigenic drift/shift

- Bacterial Evasion Mechanisms
- Viral evasion mechanisms
- Dengue Fever
- T-cell dependent responses

A. Summary of response to extracellular bacterial infections:

A1: Innate Response:

- Physical Barriers – Skin, mucus, biofilms of non-pathogenic commensal bacteria on mucosal membranes (e.g. vaginal).
- Physiological/Chemical Barriers:
- Cellular Barriers: Local tissue phagocytes clear up small infections. Activation via TLR-4.

A2: Humoral Response:

- Antibody binds to antigens on bacterial surface and opsonizes the organism; phagocytosis in tissue or spleen (blood) clears the bacteria.
- Antibody to bacterial toxins binds to the toxin molecule and **antibody-toxin complex** is cleared by phagocytes like other antigen-antibody complexes.

A3: Complement system

- Activated by binding of specific antibody to bacterium or by the alternative pathway.
- Direct lysis can occur.
- Opsonization by C3b followed by phagocytosis via Mφ, neutrophil.
- Release of split products like C3a and C5a that are anaphylatoxins, inducing mast cell degranulation releasing mediators that cause vasodilation and chemotactic factors that attract lymphocytes, macrophages and neutrophils thereby building up phagocytic cells at the site of infection.

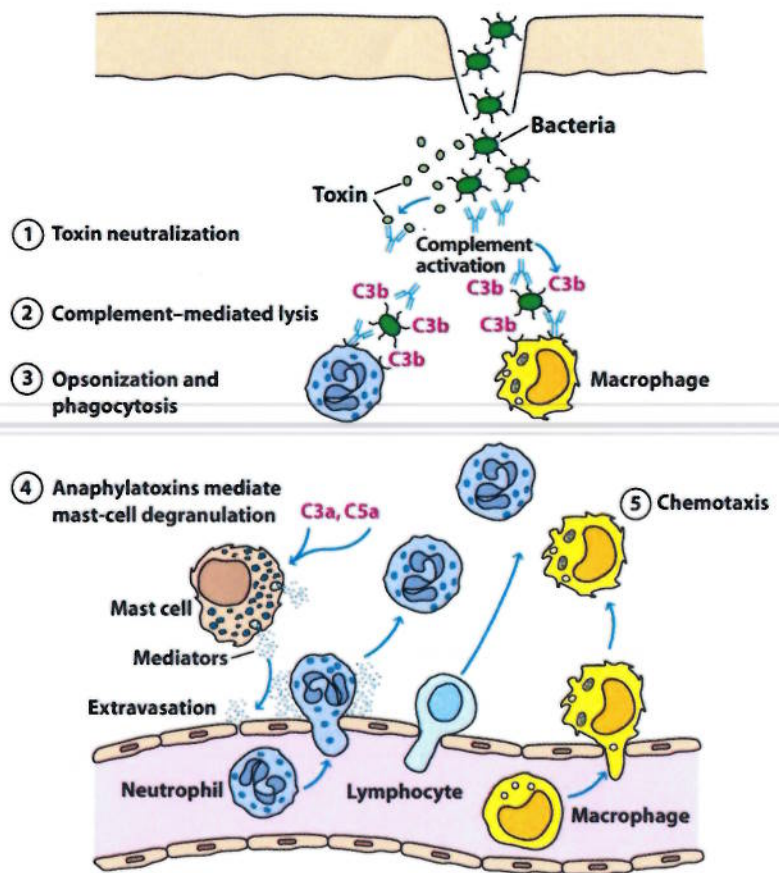
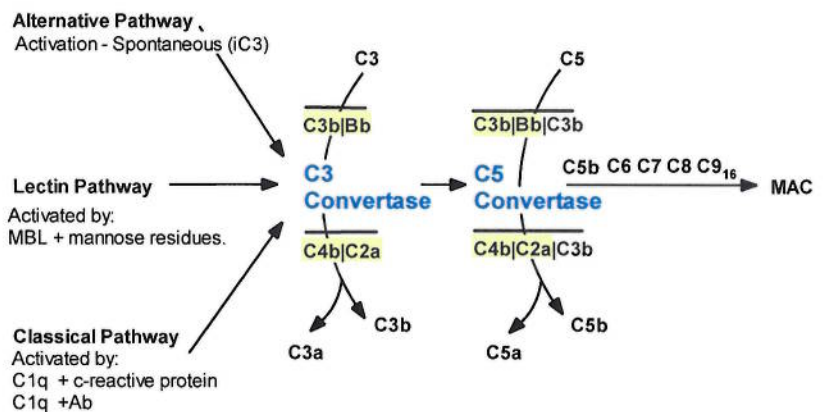
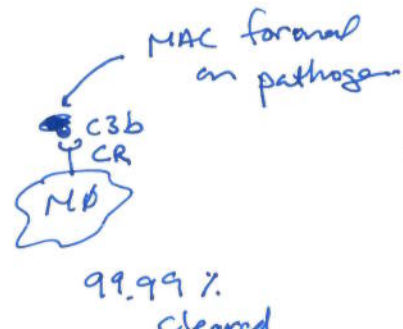
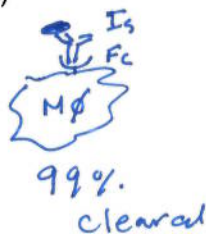


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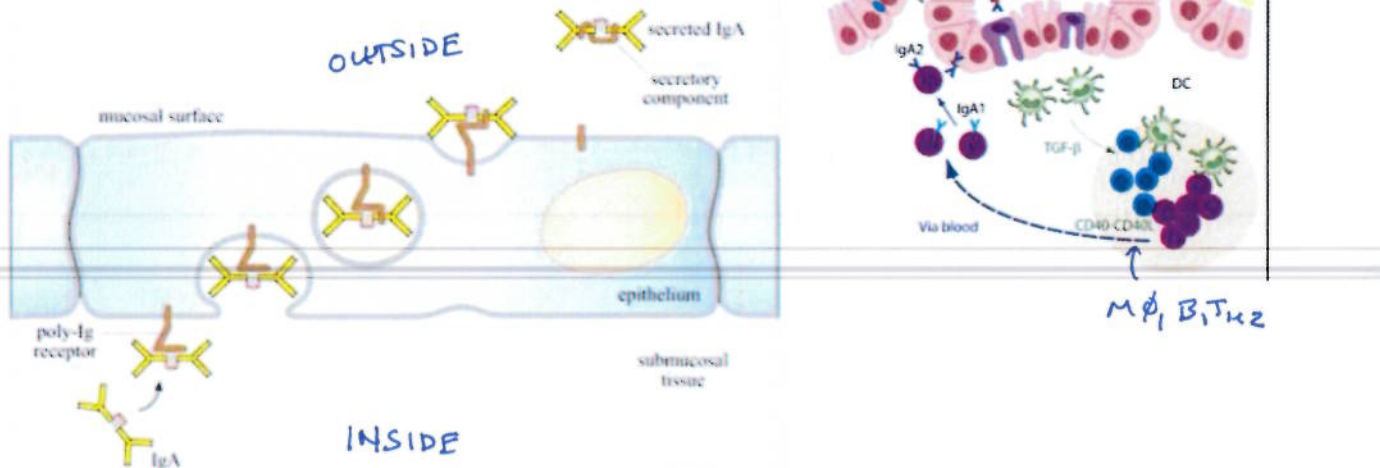
Effectiveness of pathogen clearance:

- Uncoated (90%) — 90% not cleared
- Ab opsonized w/o C3b (1%)
- C3b opsonization + MAC (0.01%)



B. Mucosal Defense System:

Pathogens on the outside of the body are constantly sampled by lymphocytes and dendritic cells in MALT (mucosal associated lymphoid tissue). IgA secreted by B-cells in the MALT tissue prevents entry of pathogen.



Transcytosis of Secretory IgA:

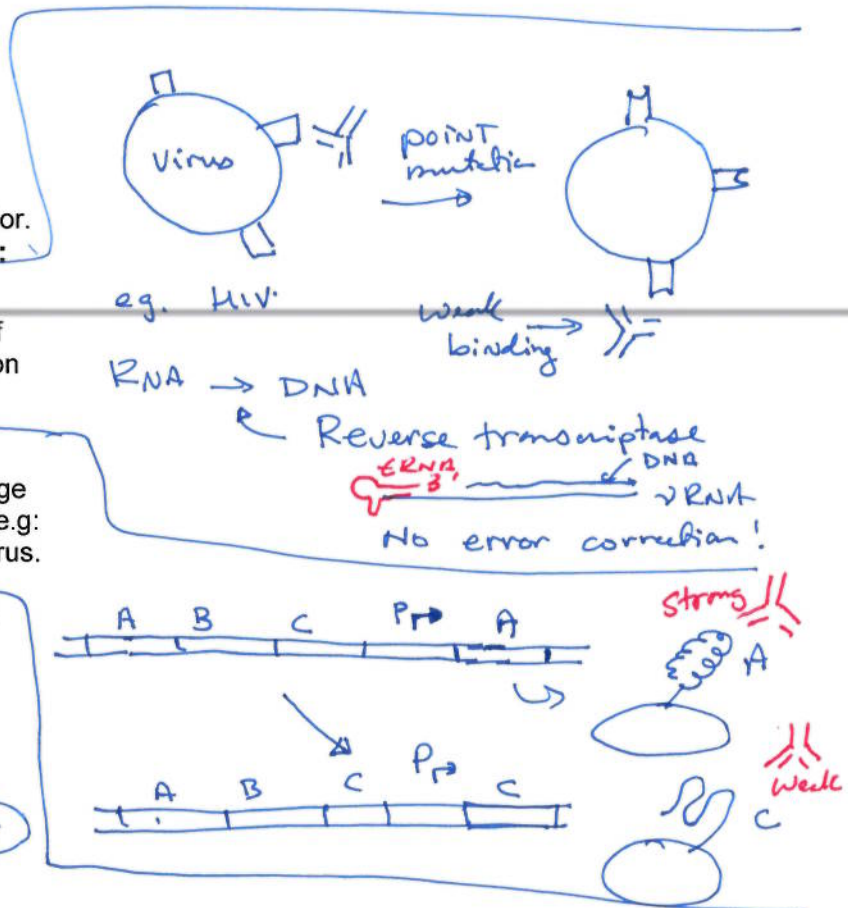
1. IgA binds to poly-Ig receptor
2. Endocytosis occurs
3. Vesicle transported across cell
4. Fusion and release of cargo, containing part of the poly-Ig receptor.

C. Key Concepts for Pathogen Evasion:

C1. Antigenic Drift: Small changes in the structure of surface antigens lead to loss of recognition of antigen, e.g. capsid protein on HIV (human immunodeficiency virus).

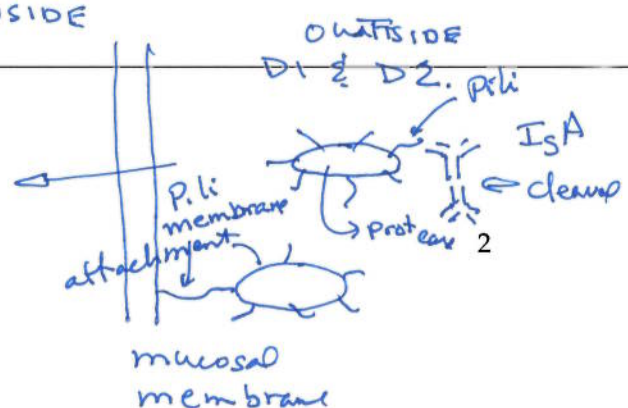
C2. Antigenic Shift: Large changes in antigen. Some pathogens repeatedly change the antigenic composition of their surface. e.g: i) pili on *Neisseria gonorrhoeae*, ii) flu virus.

C3. Multiple Serotypes: Single protein has many different alleles, each of which is antigenically different. No interconversion between serotypes.



D: Some Bacterial Evasion Mechanisms.

D1. Degradation of Secretory IgA. Secretion of a protease that cleaves IgA, rendering it ineffective e.g. *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Hemophilus influenzae*.



D2. Attachment to host cells - bacteria have specialized structures or molecules that enhance the ability to attach to host cells. For example, gram negative bacteria have pili, such as *N. gonorrhoeae*, that enable them to attach to the membrane in intestine and genitourinary tracts.

D3. Interfering with the complement system.

Haemophilus influenzae - inactivates C5a

N. gonorrhoeae produces an outer-membrane protein that inhibits the insertion of C5b-C9. Also enhances degradation of C3 convertase.

Salmonella - projection that binds MAC away from cell membrane.

Staphylococcus - C3 convertase (C3bBb) can't bind.

D4. Bacteria possess surface structures that inhibit phagocytosis. For example, secretion of variant polysaccharide capsule e.g. *Streptococcus pneumoniae*

H. influenzae.
C5a → inactivated
Mast cell degranulation reduced

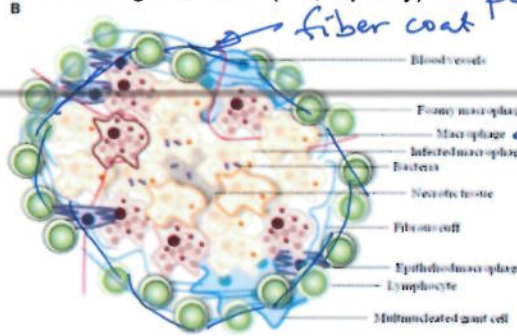
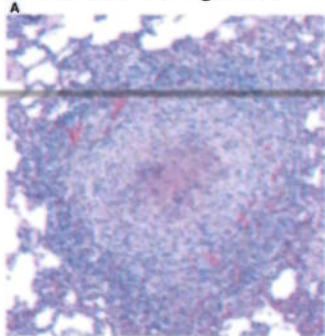
H. gon ← C5b → C9.
No MAC complex

Sam ← MAC forms on projection

Staph ← C3 convertase blocked
poor opsonization.

poly saccharide capsule

D5. Intracellular growth - Formation of granuloma (TB, leprosy)

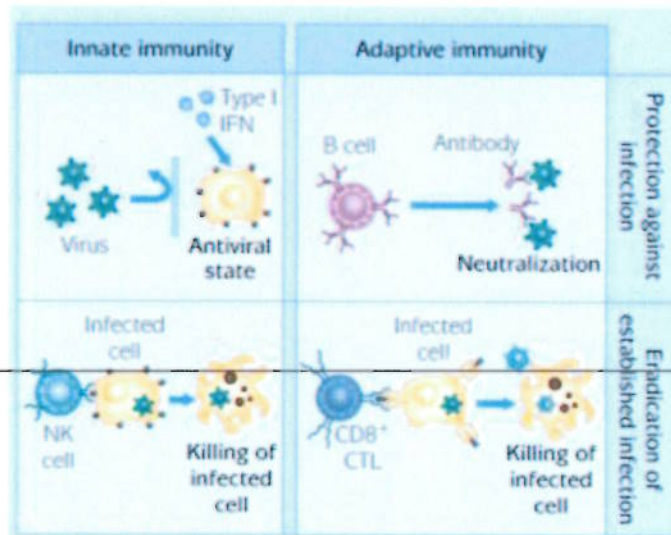


poor antigen presentation
Foamy Mφ (exhausted Mφ)
Mφ (become infected)
infect Mφ

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E. Innate & Adaptive Immune Response to Viruses

- Type I IFNs (alpha, beta) cause neighboring cells to enter anti-viral state
- NK cells kill virally-infected cells.
- B-Cell produce Ab that neutralize virus particles
- CD8+ T_{CTL} cells kill virally infected cells, requiring T_H participation.

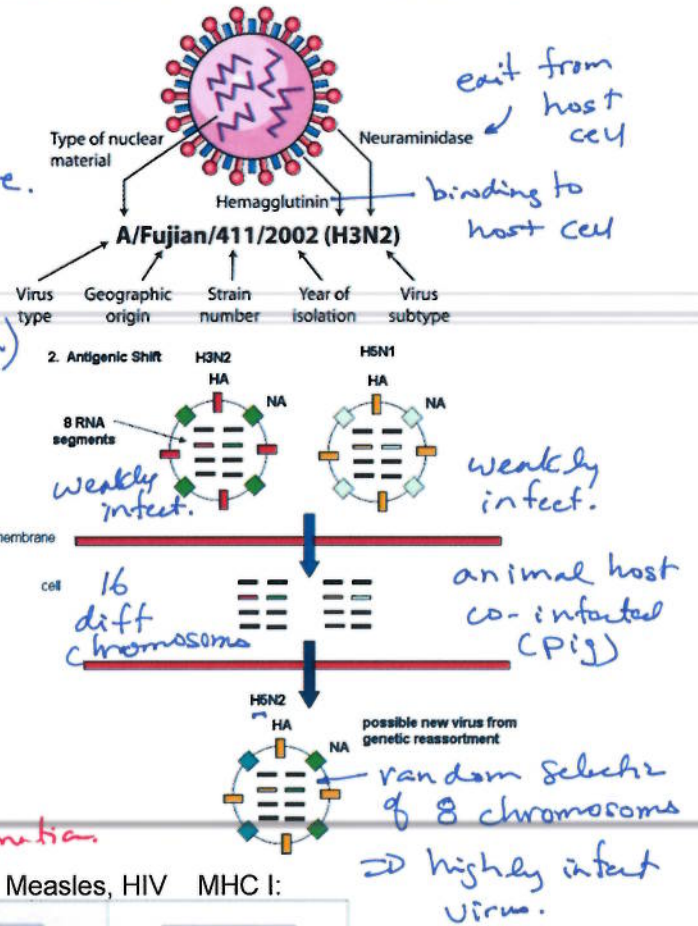


F. Evasion Mechanisms by Viruses:

Antigenic Drift: - Small change
 HIV → Rev Transcriptase.
 Flu (seasonal)

Flu RNA genome → RNA dependent RNA polymerase (proof error correction)

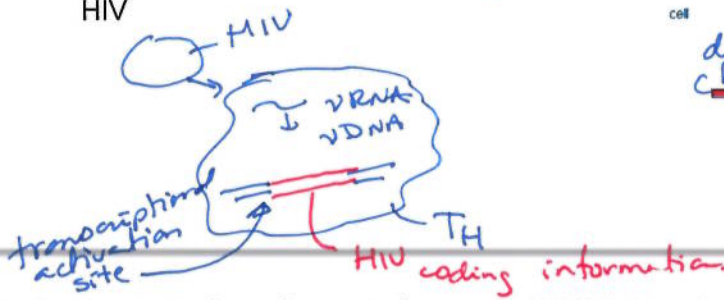
Antigenic Shift: Flu Virus:



Latency state:

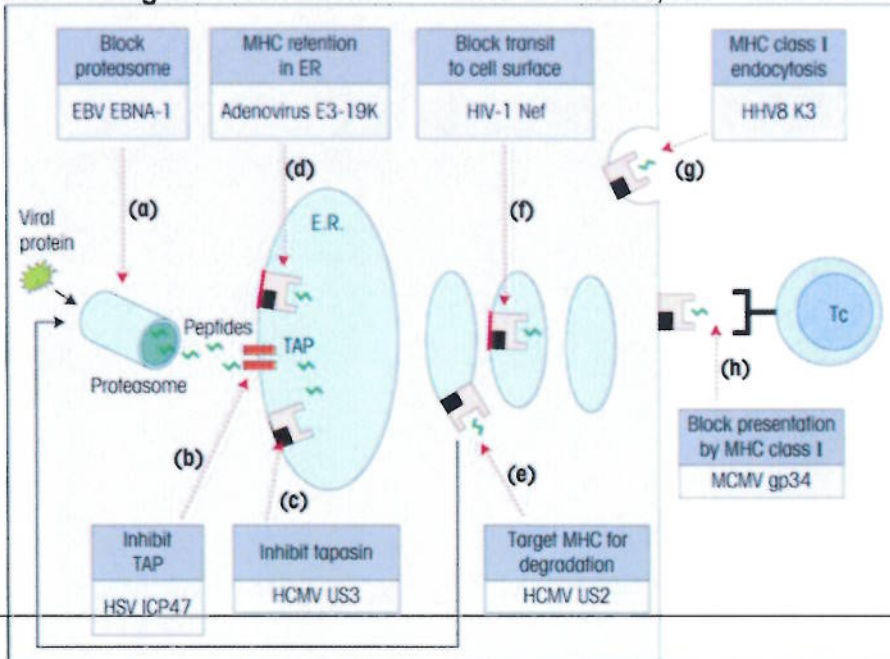
- Herpes simplex (cold sores)
 - Herpes zoster (chicken pox → shingles)
- virus hidden in cytoplasm

HIV



Reduction in Antigen Presentation:

MHC II: Measles, HIV MHC I:

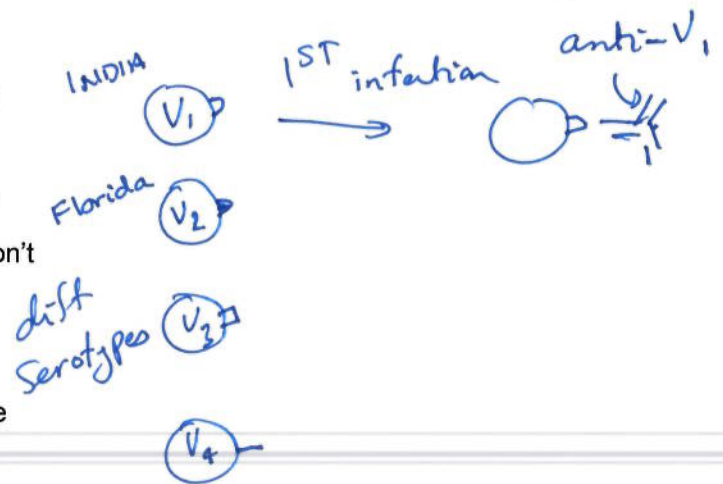


Presentation on class I - each step is inhibited by at least one virus

HSV = herpes simplex virus, EBV = Epstein Barr virus (mono), HCMV = Human cytomegalovirus, HHV8=Kaposi's sarcoma-associated human herpesvirus 8

Dengue Virus:

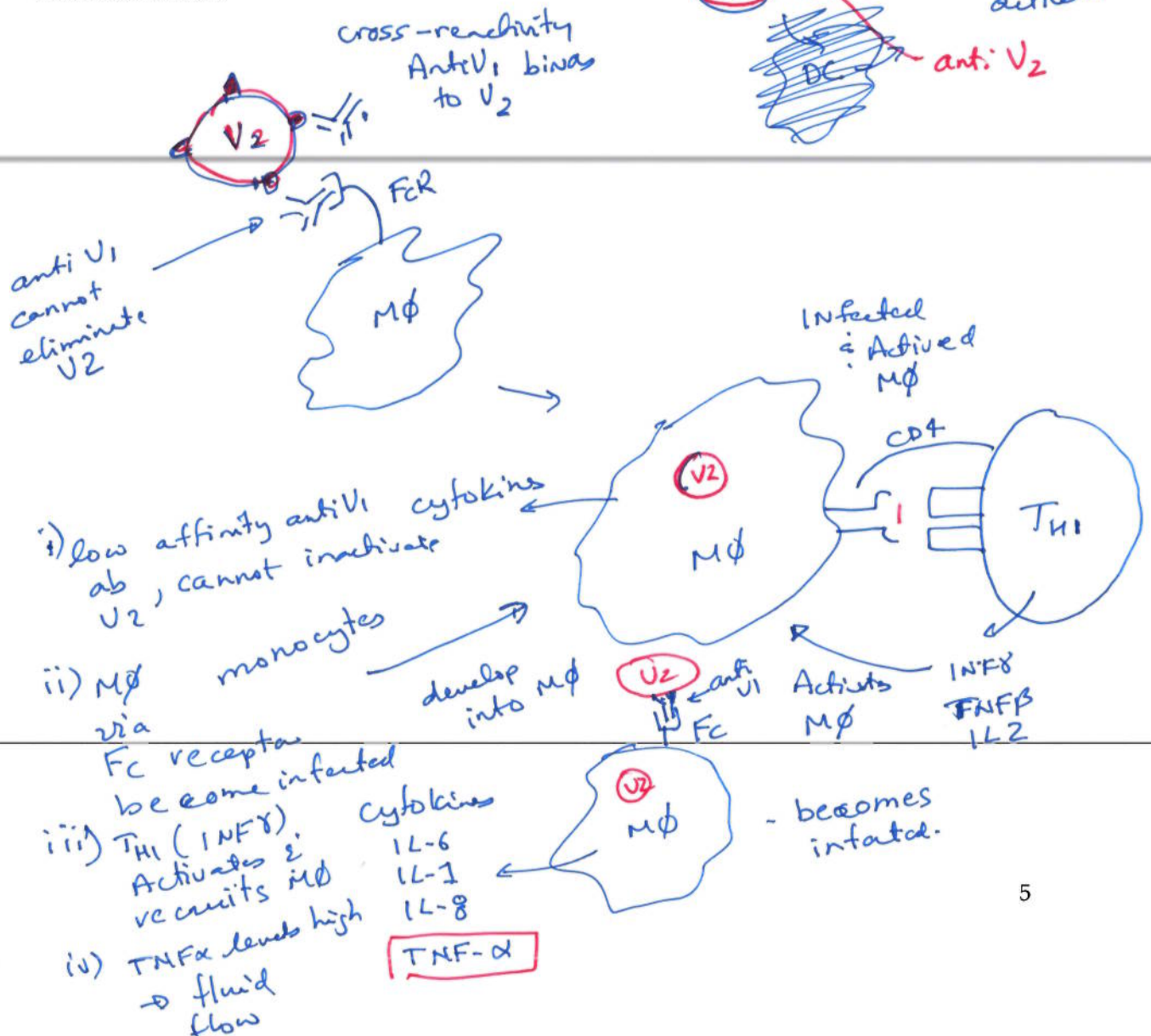
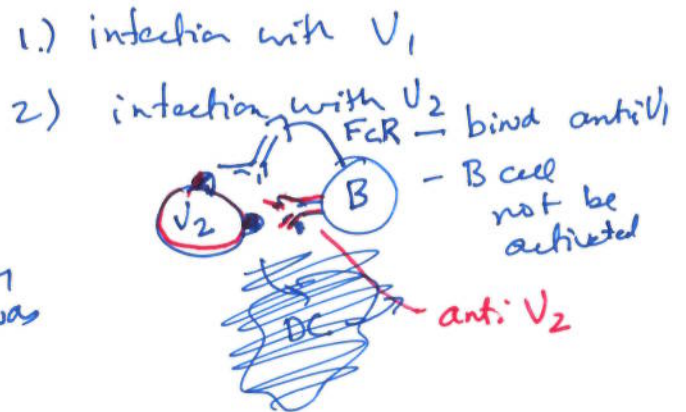
1. Infection via infected mosquitoes.
2. Four different serotypes of virus, each with a distinct genome and geographical location.
3. Distinct Ab are easily raised against each serotype, and these are effective against the particular serotype.
4. They cross-react with other serotypes, but don't neutralize the virus.



Dengue Fever:

Subsequent infection-different serotype

1. Antibodies that recognize one serotype of the virus bind, but do not completely inactivate another serotype.
2. Antibody-virus complex brought into macrophages/dendritic cells via F_C receptor.
3. Cell is now infected and activates T_C and T_H -cells via MHC-viral peptides.
4. $INF-\gamma$, secreted by T_H1 cells recruits more macrophages and activates them. The newly arriving macrophages become infected.
5. $TNF\alpha$ secreted by macrophages, causes severe local inflammation.



Protozoa - African Sleeping Sickness: Antigenic shift.

Chronic debilitating disease transmitted by the bite of the tsetse fly. Caused by a flagellated single celled protozoan parasite e.g. *Trypanosoma brucei*. (medical-dictionary.thefreedictionary.com)

Disease:

In the **systemic phase**, the parasite differentiates in the bloodstream and divides every 4-6 hours. In the **neurologic phase**, the parasite infects the central nervous system (CNS) causing **meningoencephalitis** and eventually loss of consciousness and then death.

Immune response:

During the systemic phase, antibodies are made against a protein on the surface of the parasite - **variant surface glycoprotein (VSG)**. Antibodies eliminate the parasite by complement-mediated lysis or opsonization followed by phagocytosis.

Genetics of evasion of immune response:

1. Each trypanosome carries a large repertoire of VSG genes, each encoding a different VSG primary sequence. A trypanosome expresses only one VSG at a time.
2. Activation of a VSG gene involves duplication of the VSG gene and transposition to a transcriptionally active expression site; the previous gene is displaced.

Evasion of immune response:

1. Most of the parasites are cleared by antibody mediated mechanisms. 1% of the parasites escape killing because they bear an antigenically different VSG. These parasites proliferate and cause another wave of parasitemia.
2. In the course of a single infection, each new wave of parasitemia is able to evade the immune response to the preceding variant

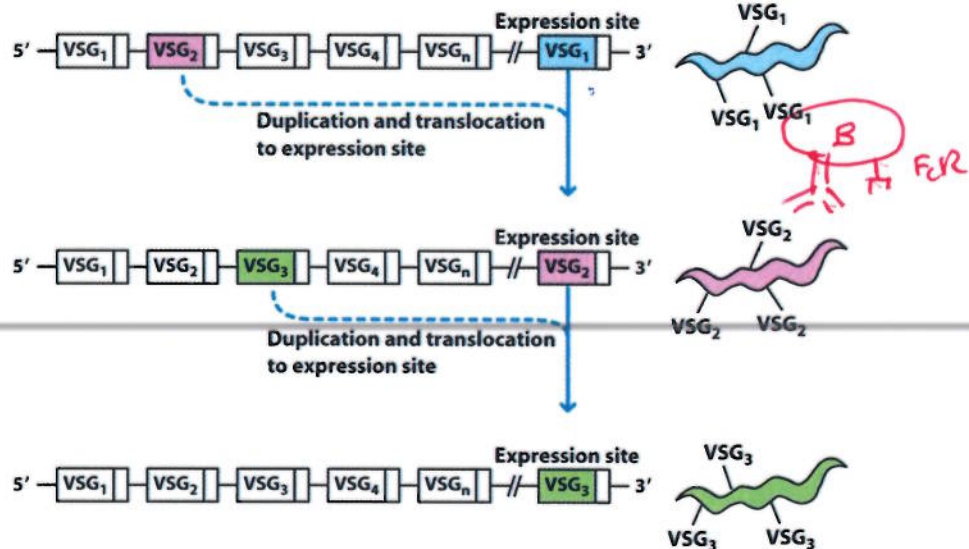
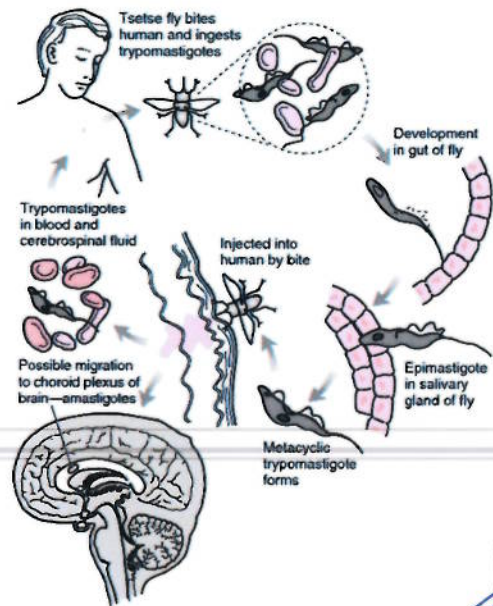


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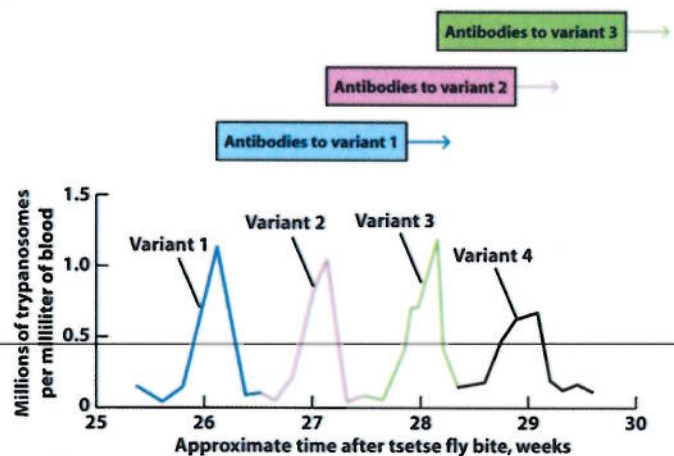


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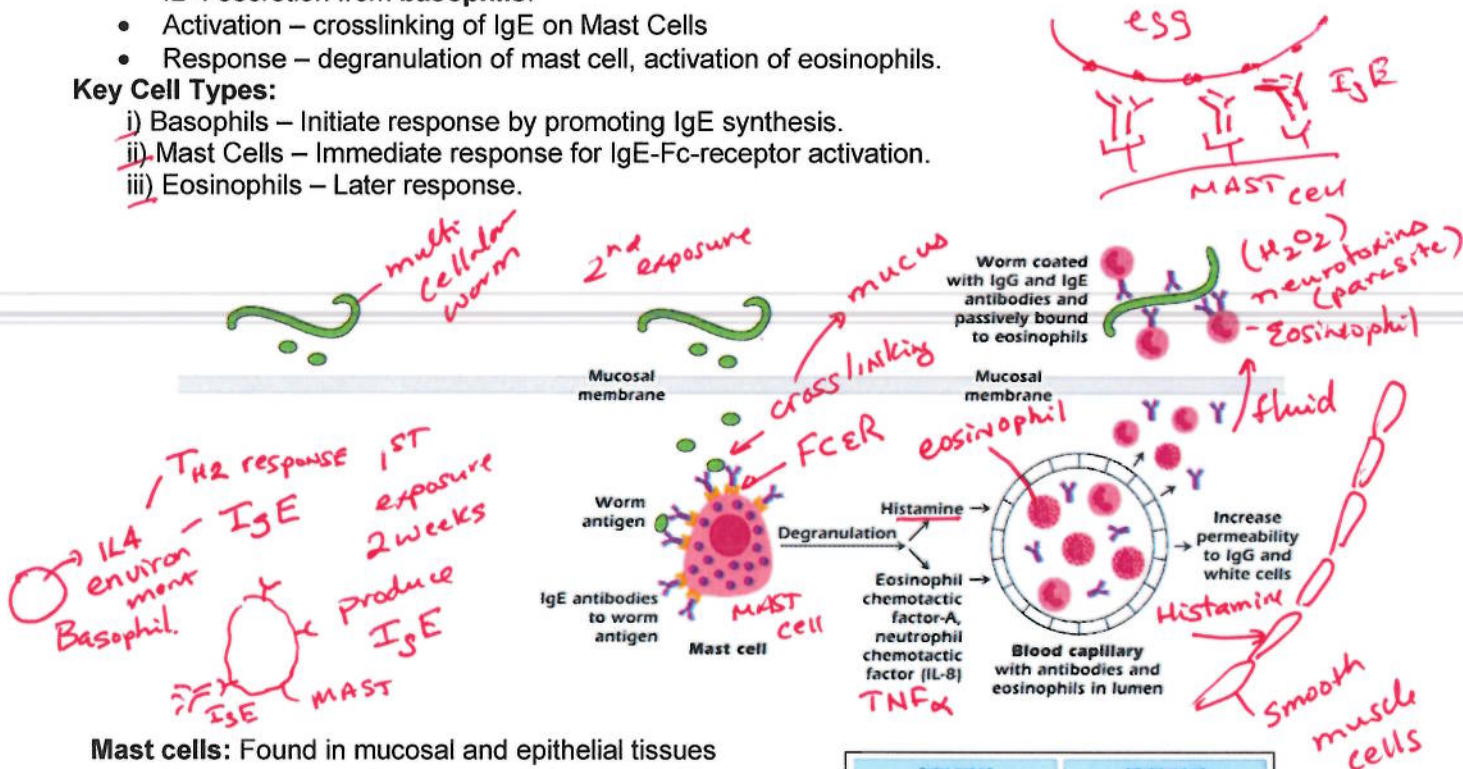
Response to Multi-cellular Parasites – e.g. Schistosomes

T_{H2} response:

- Sensitization results in the production of IgE antibodies, via T_{H2} dominated response due to IL-4 secretion from **basophils**.
- Activation – crosslinking of IgE on Mast Cells
- Response – degranulation of mast cell, activation of eosinophils.

Key Cell Types:

- Basophils – Initiate response by promoting IgE synthesis.
- Mast Cells – Immediate response for IgE-Fc-receptor activation.
- Eosinophils – Later response.



Mast cells: Found in mucosal and epithelial tissues

- Have constitutively expressed high affinity Fc receptors on surface.
- Anti-parasite IgE antibodies bind to surface of mast cell.
- Crosslinking of IgE/Fc receptor complex activates mast cell, releasing:
 - Proteolytic enzymes: ✓
 - Histamine**, heparin: ✓
 - TNFα: ✓
 & long-term inflammatory mediators. ✓

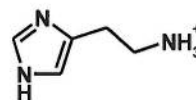
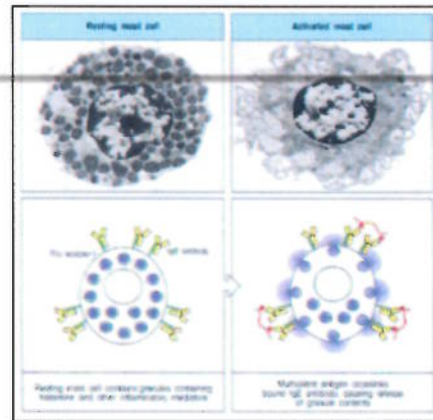
Histamine binds to histamine receptors causing:

- Increase in permeability of blood vessel, allowing fluid and other immune cells to enter tissue.
- Smooth muscle contractions
- Increase of mucus flow from epithelium
- Fluid flow across epithelium

Result is fluid/mucus flow outside the body + coughing, sneezing, vomiting, diarrhea.

Eosinophils: Similar to mast cells in response.

- Fc receptors up-regulated in response to inflammation.
- IgE-antigen interactions cause release of:
 - Collagenase, ii) Peroxidase, iii) Proteins that are neutrotoxic to parasites.



T_{H1} Response – More effective than T_{H2} response.

- INFγ production activates macrophages that are effective at killing parasites.

Immune Evasion - Schistosomes may induce T_{H2} cells to produce cytokine that suppresses T_{H1} formation.