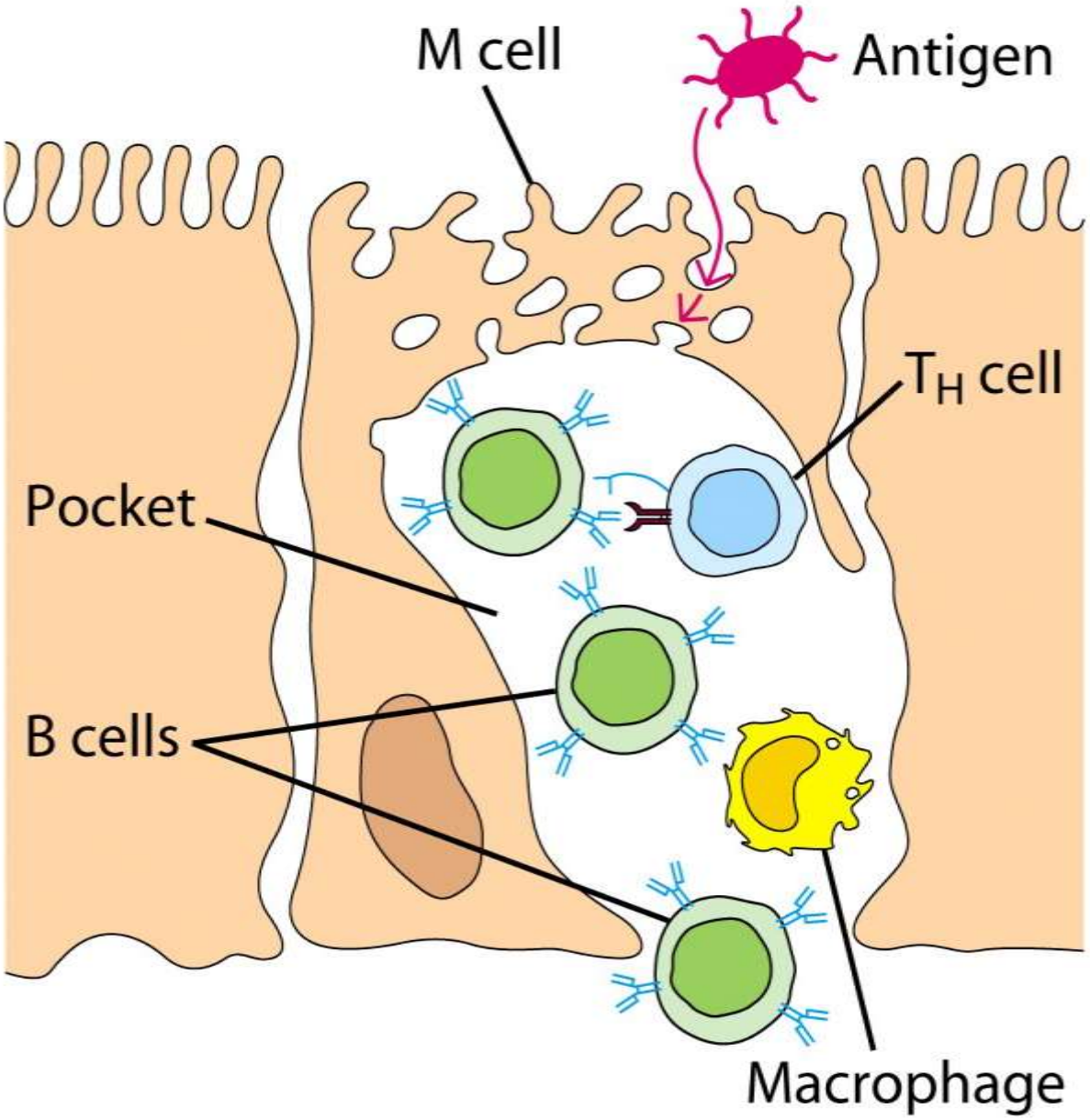
Immune Responses To Infectious Diseases
Chapter 17

Steps Needed To Establish Infection

- Penetrate The Epithelial Barriers-Not Easy
  - Skin
  - GI Lining
  - Respiratory Lining
- Compete With Normal Flora For Binding Sites
  - Lactobacillus Acidophilous
  - Bifidobacterium Bifidus
- Evade Innate Immunity
  - MΦ
  - Neutrophils
  - NK cells

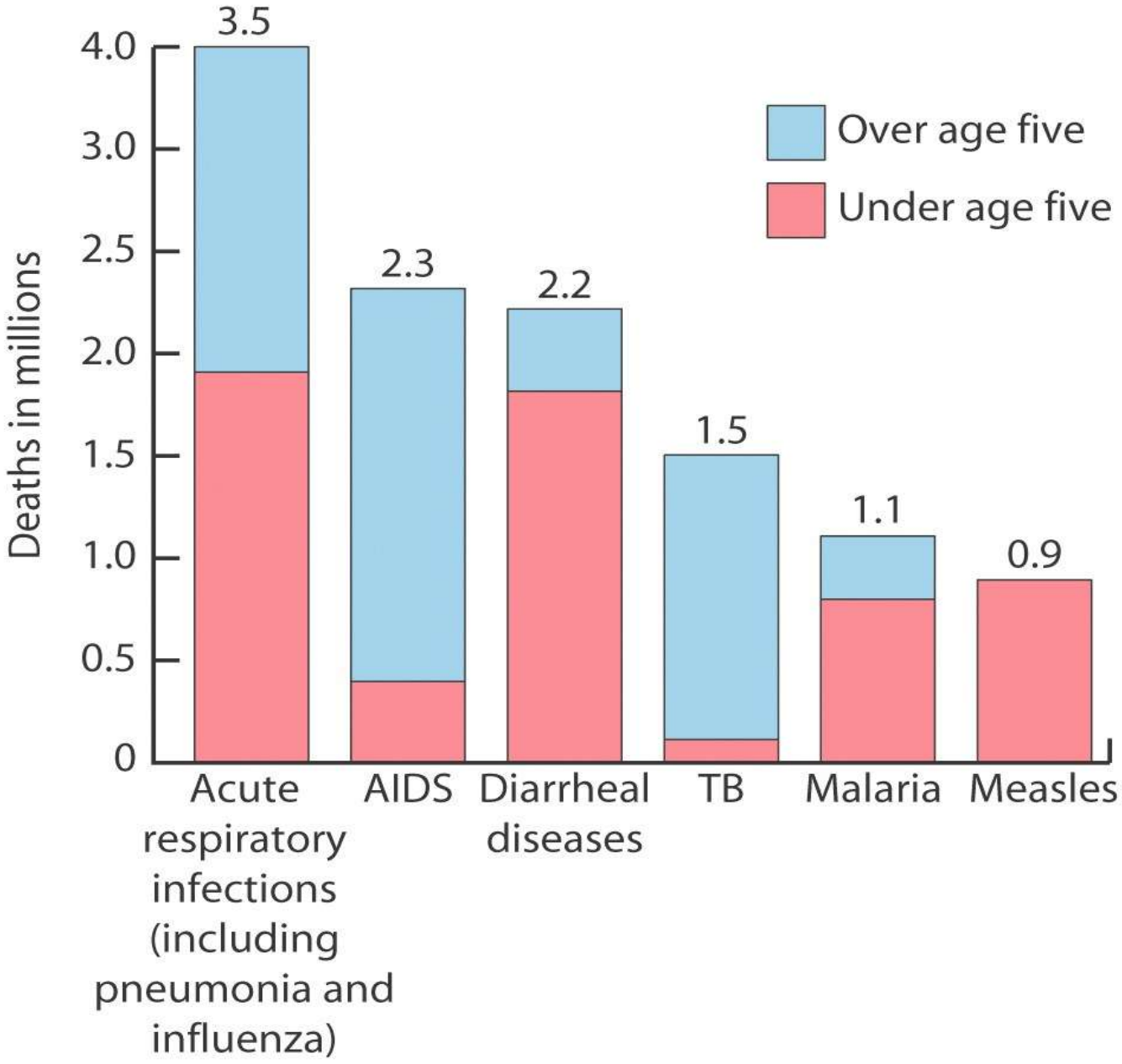

M cell
Antigen
T_H cell
Pocket
B cells
Macrophage

Innate Immunity

- Innate Immunity Cells Express Receptors That Recognize Bacterial Molecules
  - TLR-4 (Recognizes LPS, gram negative bacteria)
  - TLR-2 (Recognizes PGN, gram positive bacteria)
  - TLR-3,7,9 (viral nucleic acids)
- Viruses Induce Production of Interferons (IFN-α, IFN-β and IFNγ)
  - Interferons produce an anti-viral state

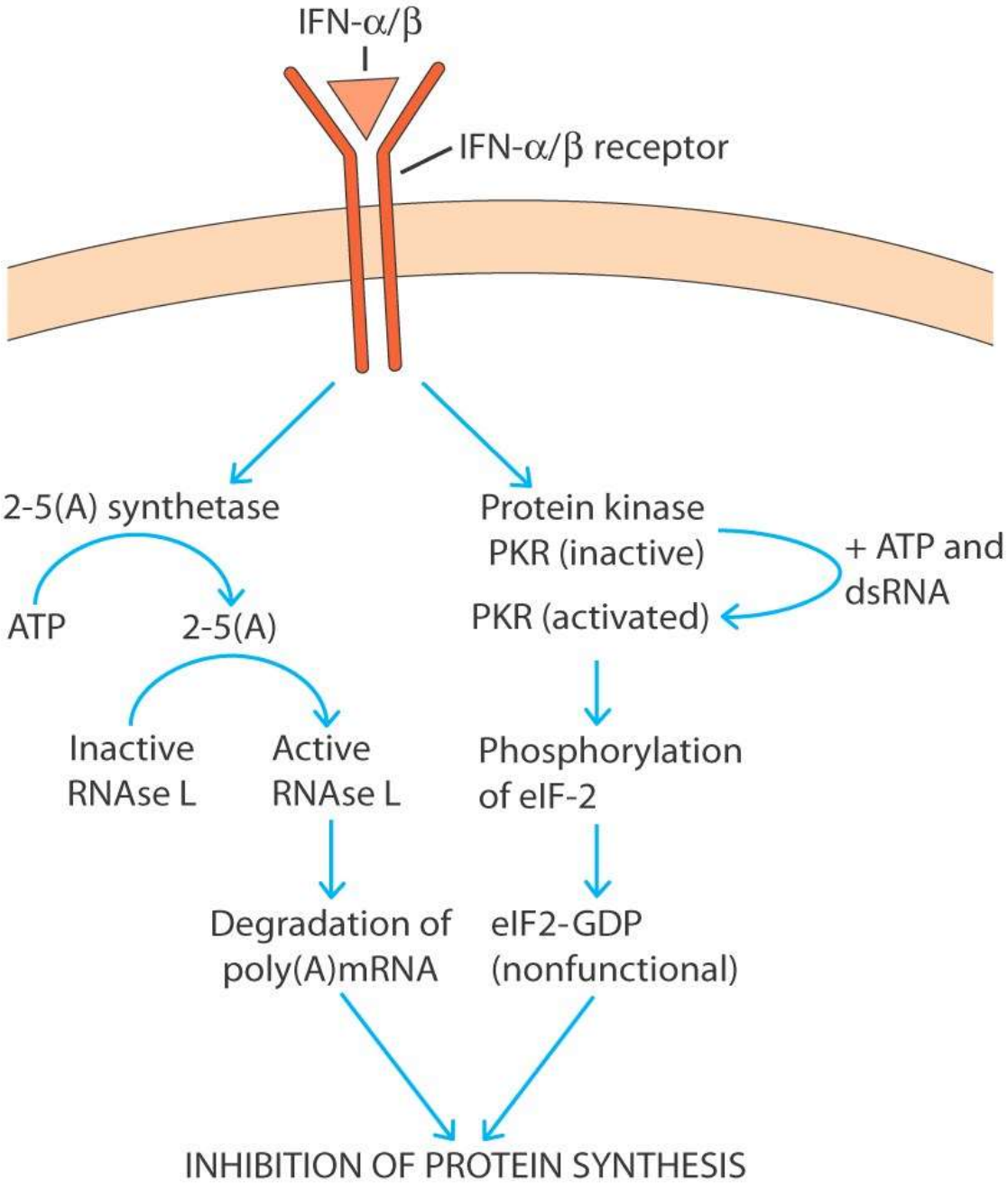
Pathogens Often Succeed

- Pathogens Use Several Tricks To Avoid Immune System
  - Start Living Inside Cells
  - Induce specific type of immunity that allows it to survive
  - Continuous variation of antigens. Ex. HIV
  - Express antigens that resemble our own genes
- Infections Are Prevalent In Developing Countries
  - 4,000,000 of deaths due to respiratory infections


Deaths in millions
4.0
3.0
2.5
2.0
1.5
1.0
0.5
0
3.5
2.3
2.2
1.5
1.1
0.9
Over age five
Under age five
Acute respiratory infections (including pneumonia and influenza)
AIDS
Diarrheal diseases
TB
Malaria
Measles

Viral Infections

- The Immune Response Against Virus Is Primarily Mediated Thru Interferons
  - Double stranded RNA induces production of IFN
  - Main producers of IFNα and IFNβ are pDCs
  - TLR-3 (dsRNA); TLR-7 (ssRNA)
  - Interferons produce an anti-viral state
    - A state that inhibits viral replication
    - A state that inhibits viral infection


IFN-α/β
IFN-α/β receptor
2-5(A) synthetase
ATP
2-5(A)
Inactive RNAse L
Active RNAse L
Degradation of poly(A)mRNA
Protein kinase PKR (inactive)
+ ATP and dsRNA
PKR (activated)
Phosphorylation of eIF-2
eIF2-GDP (nonfunctional)
INHIBITION OF PROTEIN SYNTHESIS

IFN Signaling

- Upon Ligand Binding The Following Events Occur
  - Expression of oligo adenylate synthetase [2-5 (A) Synthetase]
  - Activation of RNAase L
  - Degradation of viral RNA
- In Addition Activation of dsRNA-dependent Protein Kinase (PKR)
  - Phosphorylates eIF-2
  - Protein synthesis is inhibited
  - Viral replication is inhibited
- IFN Signaling Activates NK cells
  - Start eliminating virally infected cells

Antibody Protection Against Viruses

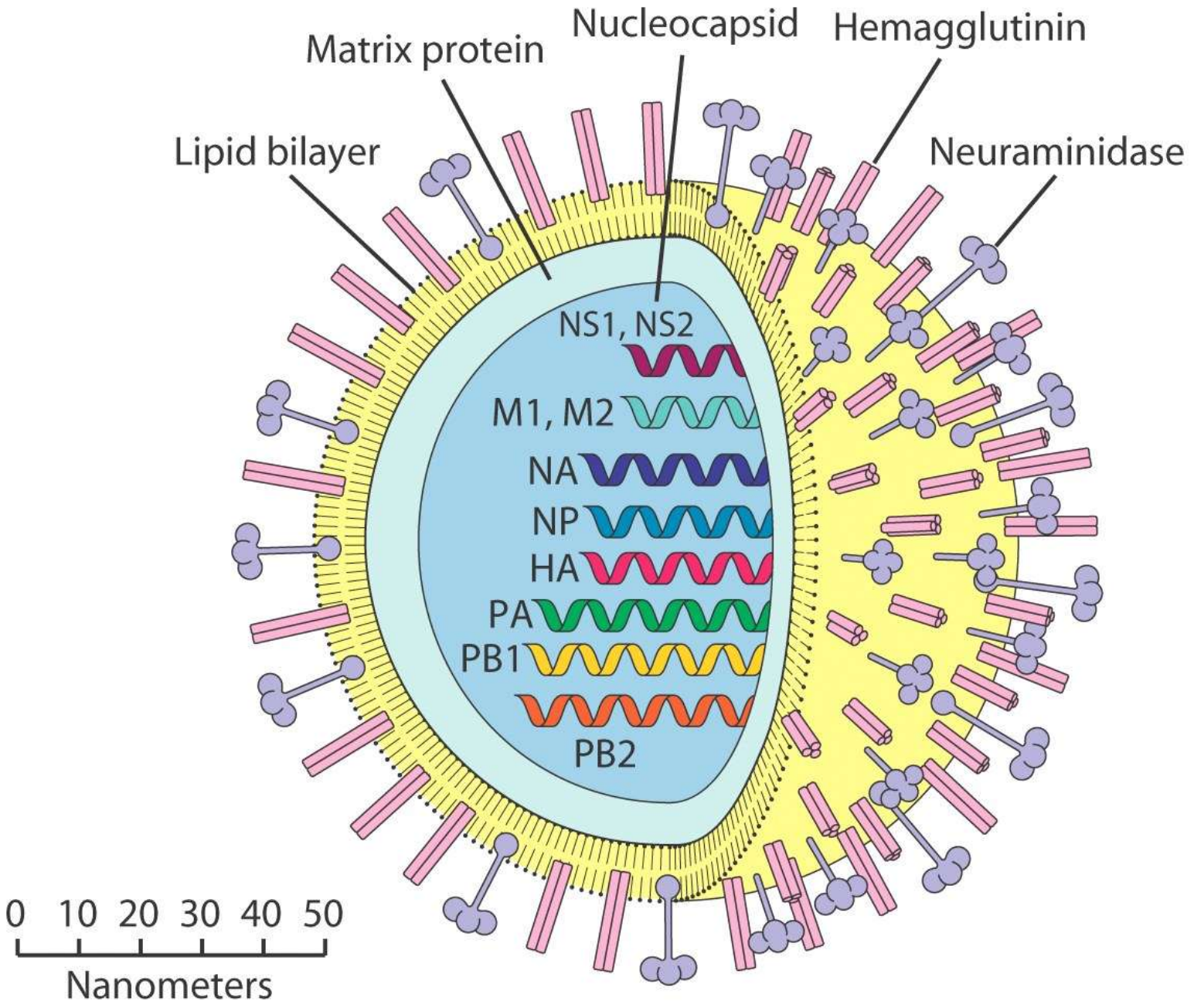
- Antibodies Bind To Viral Surface Antigens
  - Protect againts re-infection
  - Huge amounts of secretory IgA in lumen block viral attachment
- Viral Entry Into Cells Is Mediated Thru Receptors
  - Influenza virus binds to sialic acid on glycoproteins
  - Rhinovirus binds to ICAMs
- If Receptor Is Blocked, Infection Is Blocked
- Oral Polio vaccine Relies On IgA Production

Antibody Protection Against Viruses

- Antibodies Are Efficient In Preventing Infection
- Once Infection Has Occurred, Only Cell Mediated Immunity Can Eliminate Infected Cells
- Examples Of Cell Mediated Immunity
  - T_{H1}, CTL Are the major participants
- T_{H1} Produce IFN-γ, IL-2, and TNF-α
  - IL-2 expands CTL-P
  - IFN-γ induces antiviral state
  - IL-2 and IFN-γ activate NK cells (first line of defense)
- CTL (cytotoxic lymphocytes)
  - Peaks 7-10 days post infection
  - Eliminate virally infected cells

Evading The Immune System

- HCV (Hepatitis C Virus) Evades Anti-viral Effect Of IFNs By Inhibiting Action Of PKR
- HSV (Herpes Simplex Virus) Decreases Expression Of MHC I, Avoids CTL Elimination
- CMV (Cytomegalovirus) Also Decreases Expression Of MHC I
- HIV (Human Immunodeficiency virus) Decreases MCH II Expression, No T_{H1} Support for CTL
- Influenza Virus, Keeps Changing Antigens
  - Antigenic Drift
  - Antigenic Shift

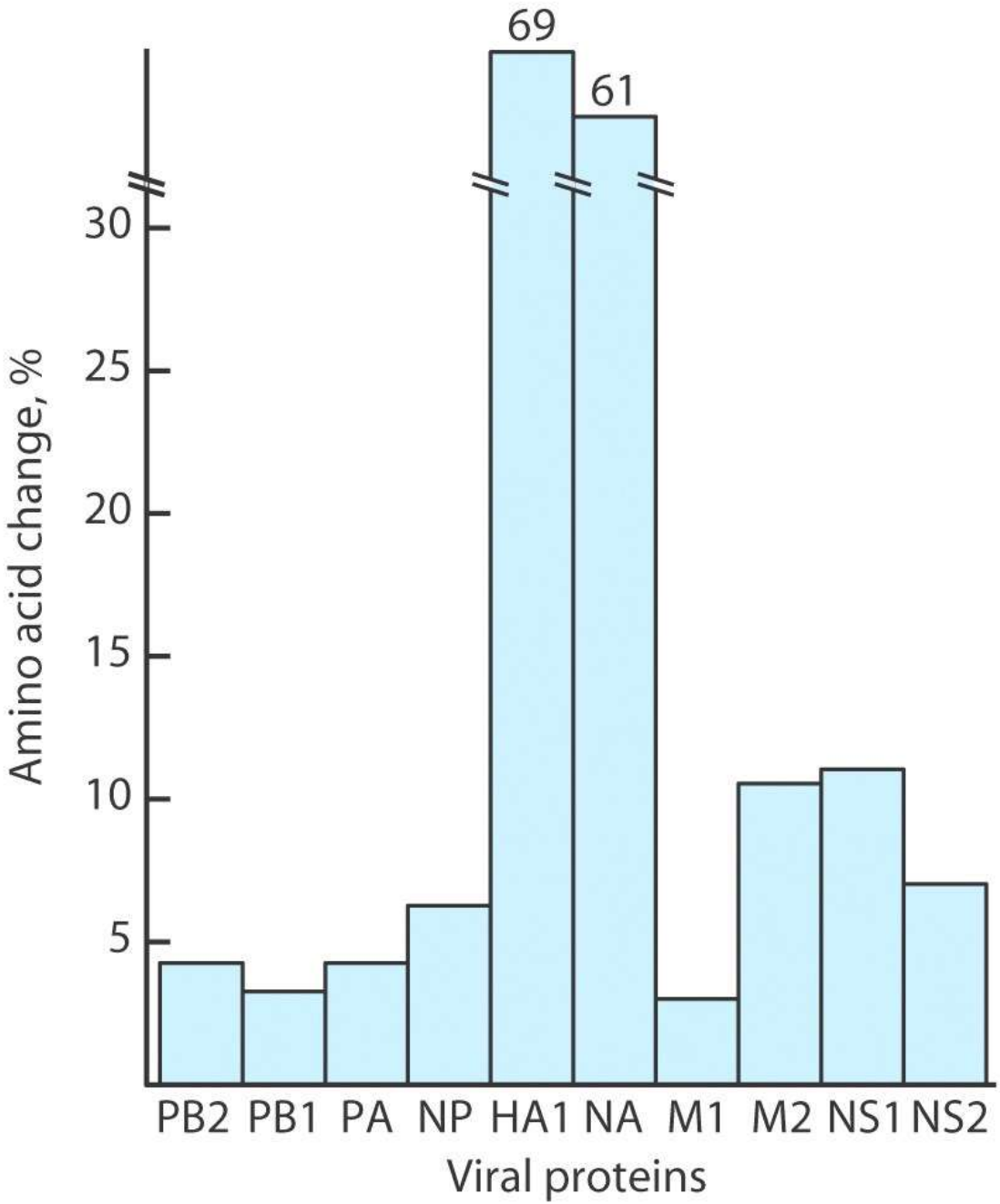

Matrix protein
Nucleocapsid
Hemagglutinin
Lipid bilayer
Neuraminidase
NS1, NS2
M1, M2
NA
NP
HA
PA
PB1
PB2
0 10 20 30 40 50
Nanometers

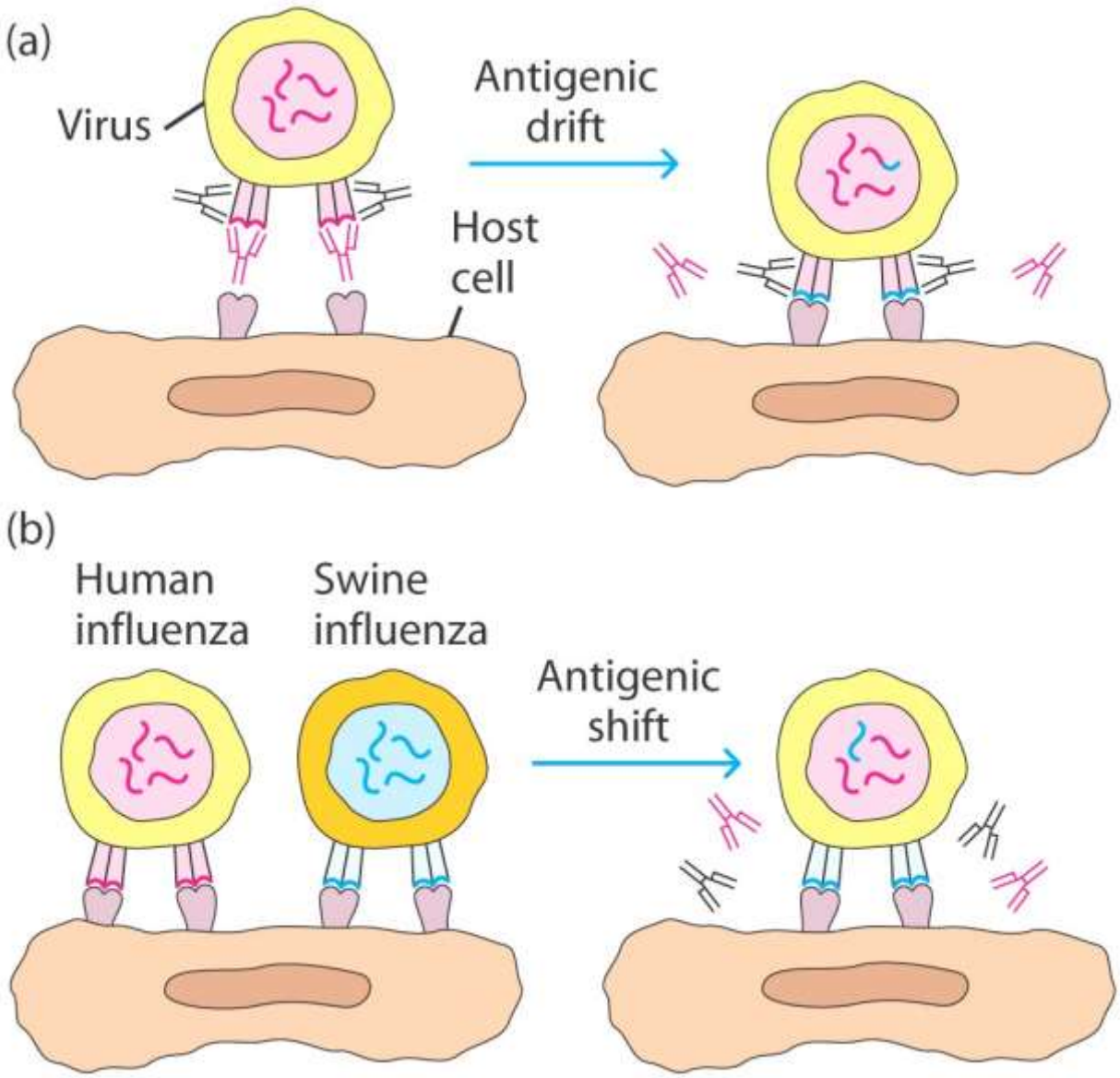
Influenza Virus

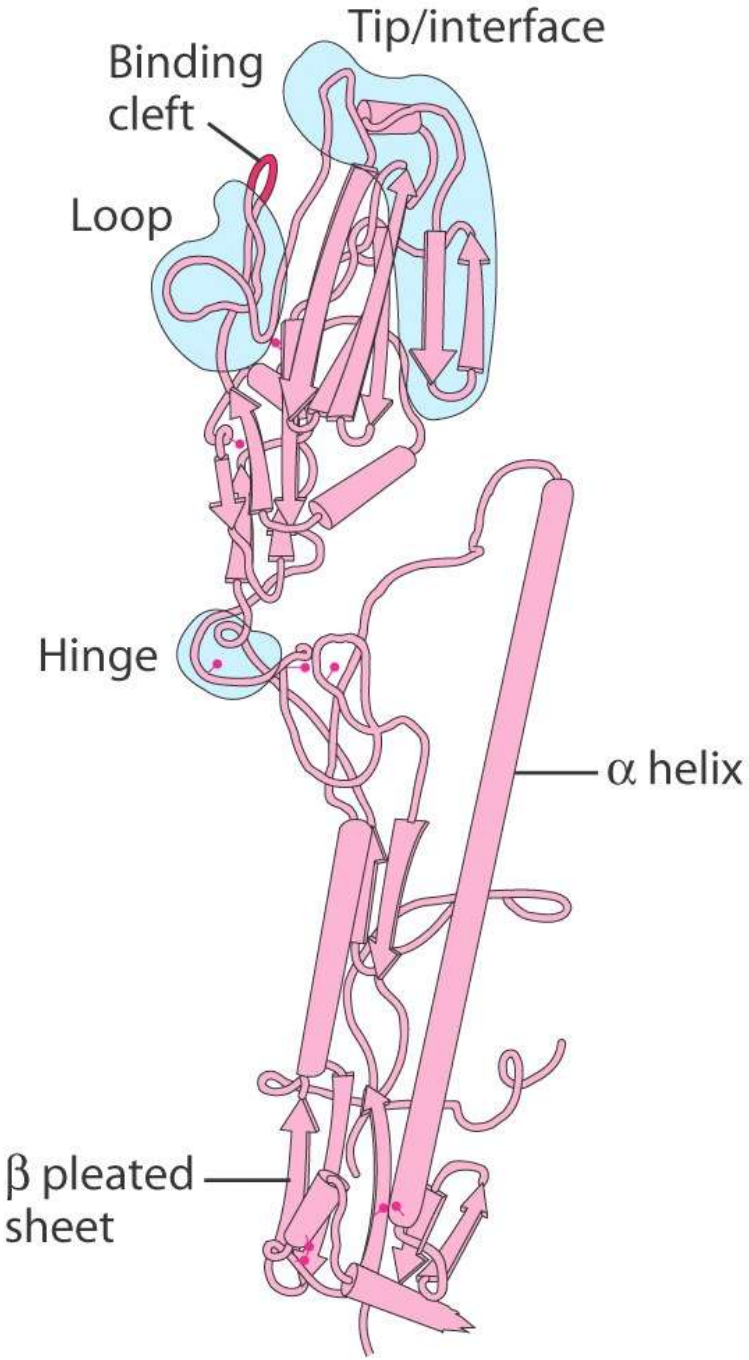
- Size of Virion Is 90-100 nm
- Surrounded By Plasma Membrane Of Host
  - 2 glycoproteins on surface
    - Hemagglutin (HA) and Neuroaminidase (NA)
    - HA is responsible for viral attachment to sialic acid found on glycoproteins
    - NA is responsible for detaching from sialic acid (budding)
- Matrix Protein Beneath Lipid Bi-layer
- Nucleocapsid contains 8 ssRNA
  - ssRNA associates with RNA polymerase and protein
  - Each ssRNA encodes for one or more proteins
- Types of Influenza Virus Are Bases On Protein Matrix Composition and nucleoprotein composition
  - Type A, B, C
  - Type A is responsible for major pandemics in humans
  - Antigenic variation in HA (13 variants) and NA (9 variants) determines subtype
    - Ex. H1N1

TABLE 17-2 Some influenza A strains and their hemagglutinin (H) and neuraminidase (N) subtype

Species	Virus strain designation	Antigenic subtype
Human	A/Puerto Rico/8/34	H0N1
	A/Fort Monmouth/1/47	H1N1
	A/Singapore/1/57	H2N2
	A/Hong Kong/1/68	H3N2
	A/USSR/80/77	H1N1
	A/Brazil/11/78	H1N1
	A/Bangkok/1/79	H3N2
	A/Taiwan/1/86	H1N1
	A/Shanghai/16/89	H3N2
	A/Johannesburg/33/95	H3N2
	A/Wuhan/359/95	H3N2
	A/Texas/36/95	H1N1
	A/Hong Kong/156/97	H5N1
Swine	A/Sw/Iowa/15/30	H1N1
	A/Sw/Taiwan/70	H3N2
Horse (equine)	A/Eq/Prague/1/56	H7N7
	A/Eq/Miami/1/63	H3N8
Birds	A/Fowl/Dutch/27	H7N7
	A/Tern/South America/61	H5N3
	A/Turkey/Ontario/68	H8N4
	A/Chicken/Hong Kong/258/97	H5N1


69
61
30
25
20
15
10
5
Amino acid change, %
PB2
PB1
PA
NP
HA1
NA
M1
M2
NS1
NS2
Viral proteins


(a)
Virus
Antigenic drift
Host cell
(b)
Human influenza
Swine influenza
Antigenic shift

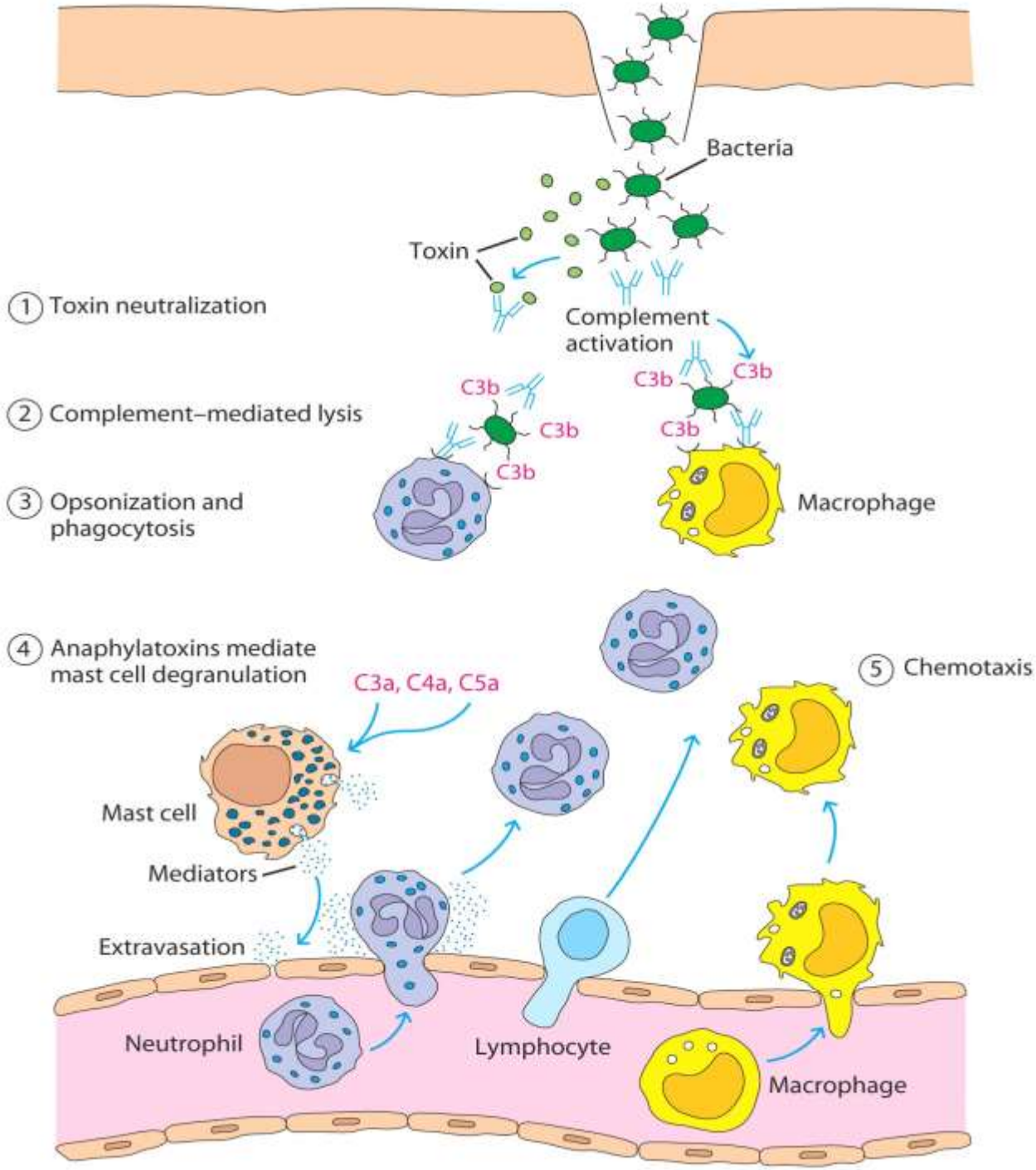

Tip/interface
Binding cleft
Loop
Hinge
α helix
β pleated sheet

Host Response To Influenza Infection

- Humoral Response Is Strain Specific
  - If Antigenic Drift Occurs Protection Is Lost
  - Many Antibodies Are Generated Against Tip And Loop
    - Domains surrounding binding cleft
  - Antibodies Against Tip and Loop Domain Prevent Infectivity
- Antibodies Are NOT Essential For Recovery
  - In Mice Infected With Influenza And Ab Production Is Suppressed There Is Recovery
  - However Can Be Re-infected
- NK, pDC , CTL Are Responsible For Viral Elimination

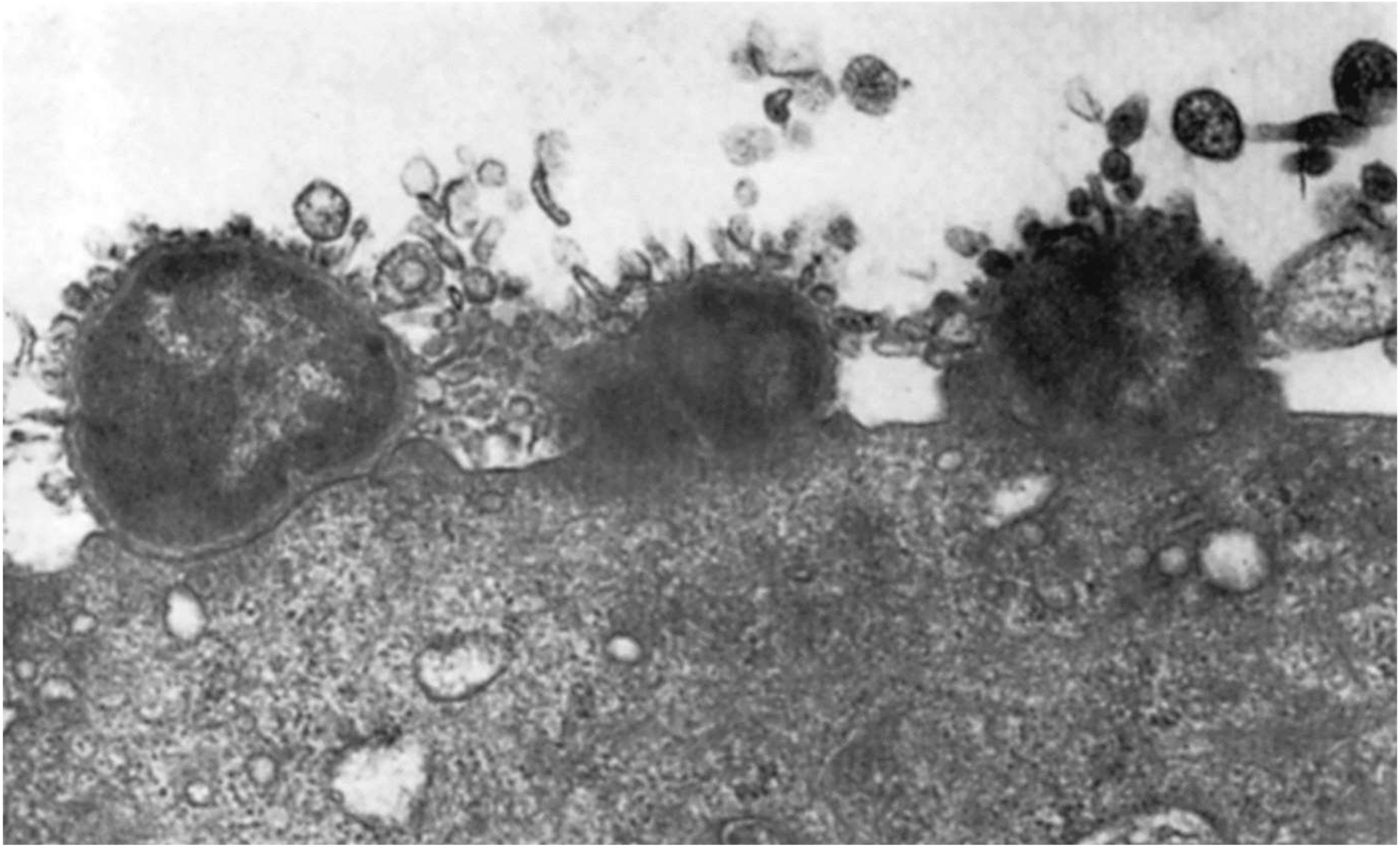
Bacterial Infections

- Bacterial Infections Are Eliminated By Humoral Immunity
  - Exception: intracellular bacteria Ex. TB
  - DTH Is Important In Elimination Of Intracellular Bacteria
  - Antibodies Eliminate Bacteria Or Bacterial Toxins
    - Opsonization Of Bacteria
    - Neutralization Of Toxins
      - Exotoxins (Ex. Diptheria)
      - Endotoxins (Ex. LPS)
    - Lysis Of Bacteria Thru Complement Pathway
    - Complement Activation Thru Mast Cell Activation Results In Localized Inflammation
      - Vasodilation and Extravasation (Neutrophil Accumulation)
- Bacteria Enter Host Thru
  - Respiratory Tract, GI Tract, Genitourinary Tract, Skin


Bacteria
Toxin
1 Toxin neutralization
Complement activation
C3b
C3b
C3b
C3b
C3b
2 Complement–mediated lysis
3 Opsonization and phagocytosis
Macrophage
4 Anaphylatoxins mediate mast cell degranulation
C3a, C4a, C5a
5 Chemotaxis
Mast cell
Mediators
Extravasation
Neutrophil
Lymphocyte
Macrophage

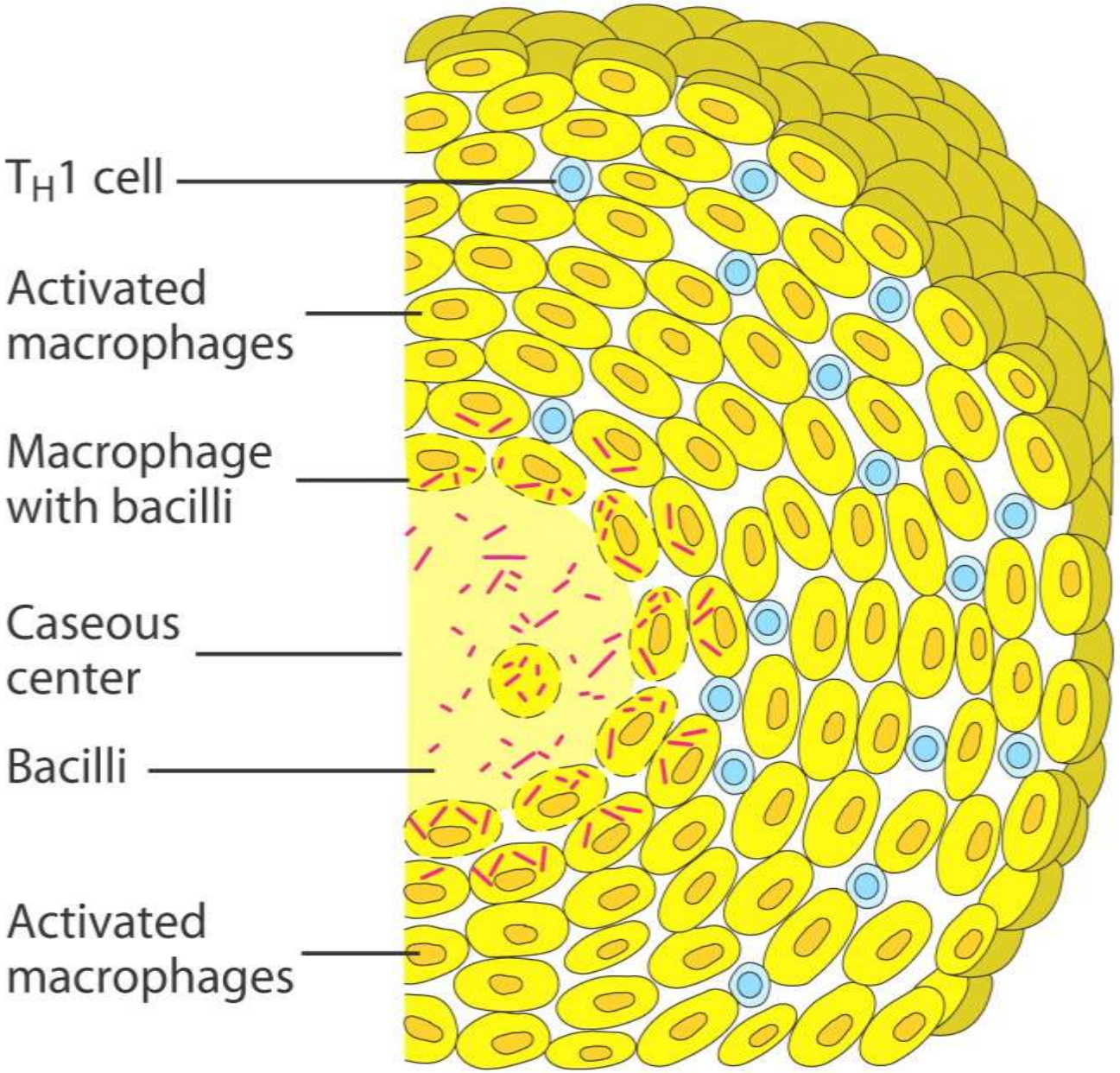
Bacteria Evade Host Defense Mechanisms

- Bacterial Infection Involves 4 Steps
  - Attachment
  - Proliferation
  - Invasion Of Host Tissue
  - Toxin Induced Damage To Host Cells
- Attachment
  - Some Bacteria Hava Pili
  - Some Bacteria Secrete Adhesion Molecules (Bordetella Pertussis)
  - Immune System Response To Attachment Is IgA
    - Prevents Attachment
    - Some Bacterial Evade IgA Thru Proteases That Decrease ½ Life Of IgA
      - Ex. Heamophilus Influenzae
    - Some Bacteria Avoid Phagocytosis By Surrounding Themselves In A Polysaccharide Capsule. Ex. Streptococcus Pneumoniae



Immune Response Against Pathogen Can Cause Pathogenesis

- Overzealous Immune System Can Be Pathogenic
  - Bacterial Septic Shock
    - Predominant Cytokines Involved: IL-1 and TNF-α
    - Source: MΦ
  - Intracellular Bacteria Cause Granulomas
    - Extensive Tissue Damage
    - Ex. Tuberculosis
- Tuberculosis (Mycobacterium Tuberculosis)
  - 3 Million Fatalities Every Year Globally
  - MΦ Ingest M.T But Cannot Digest It
  - Eventually Burst Releasing Bacilli
  - MΦ And T_{H1} Cells Form Granulomatous Lesion, Containment+Destruction Of Healthy Tissue
  - INF-γ and IL-12 Are Crucial In Eliminating Pathogen


T_H1 cell
Activated macrophages
Macrophage with bacilli
Caseous center
Bacilli
Activated macrophages