Primary Immunodeficiencies for USMLE Step One

Part I

Part II

Lymphocyte Disorders:
SCID
Bruton's X-Linked Agammaglobulinemia
CVID

Wiskott-Aldrich
Neutrophil Disorders
Chronic Granulomatous Disease
Chediak-Higashi
Leukocyte Adhesion Deficiency

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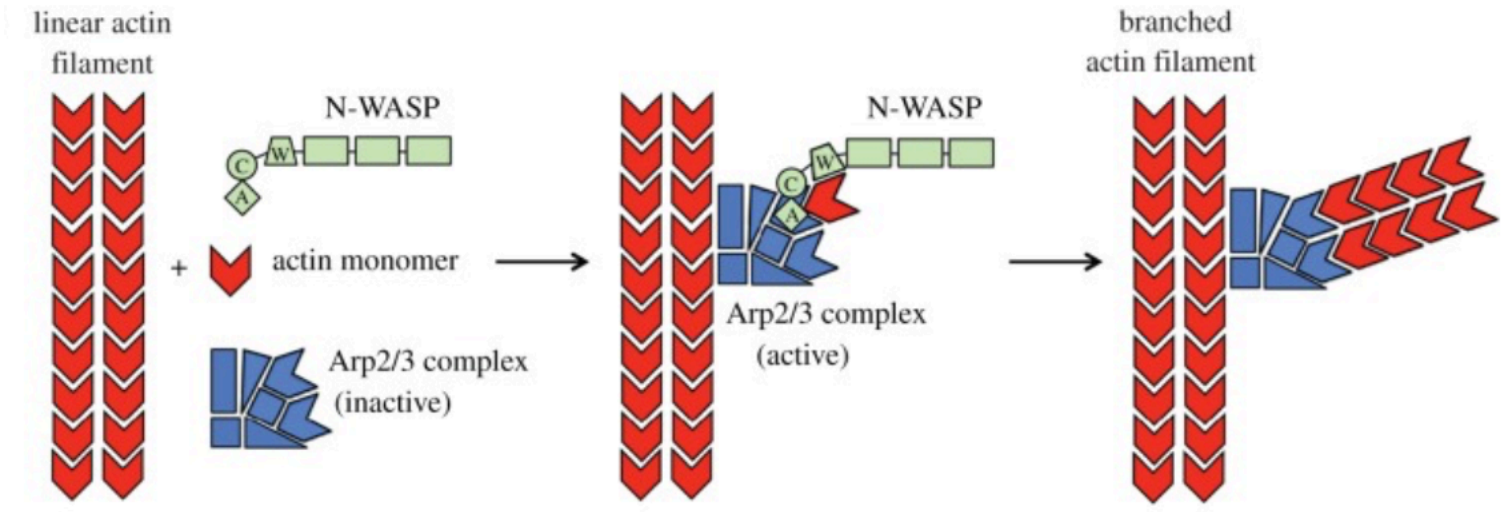
Wiskott-Aldrich: Cytoskeleton

- Background
  - Defect in cytoskeleton of hematopoietic cells



Failure of actin polymerization

Wiskott-Aldrich: Cytoskeleton

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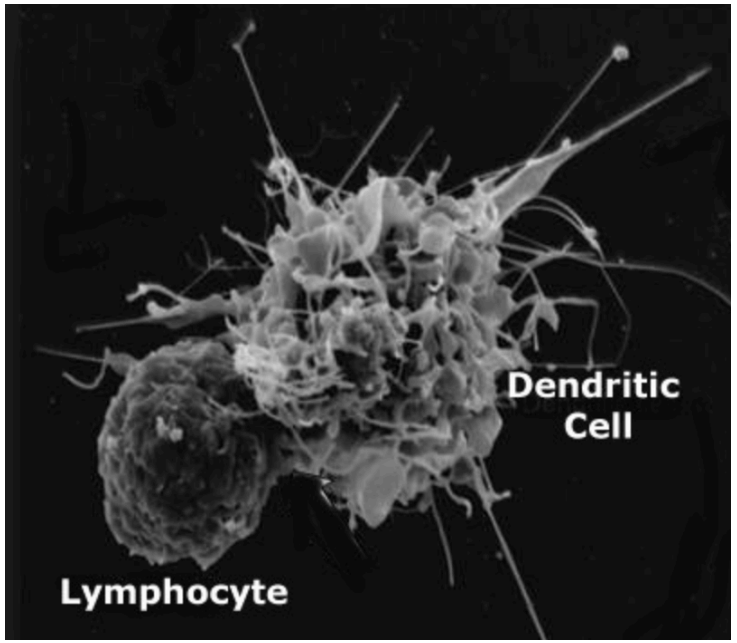
    - T-cells: failure of immunologic synapse (with dendritic cells) immunodeficiency and immune dysregulation (eczema)



Failure of this communication explains the immune dysregulation associated with this syndrome

Failure of 'immunologic synapse'

Wiskott-(B)Aldrich: Cytoskeleton

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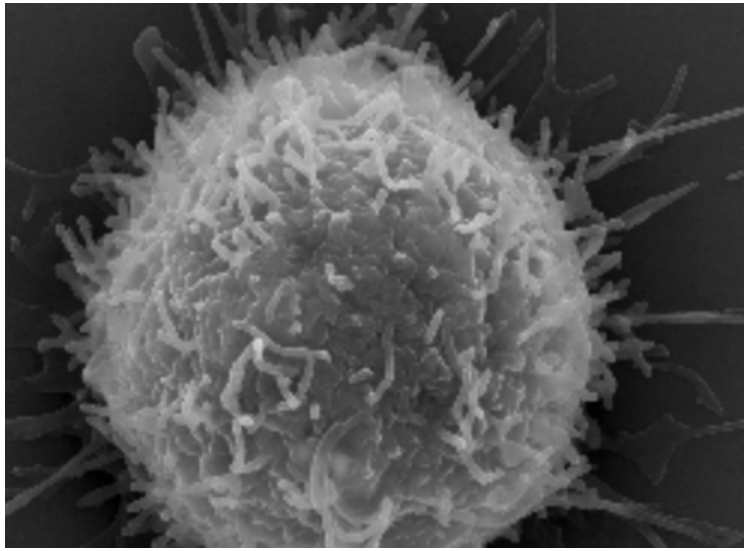
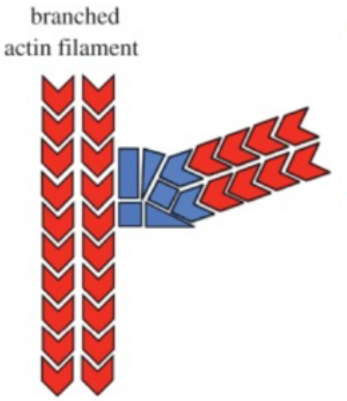


Actin-dependent villous projections



'Bald' Lymphocyte

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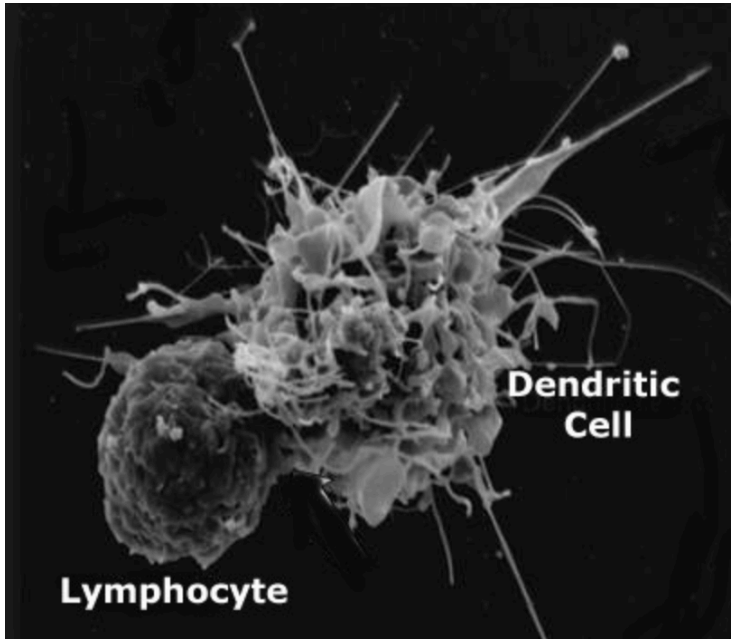
Eczema:
Inadequate T-cell Regulation



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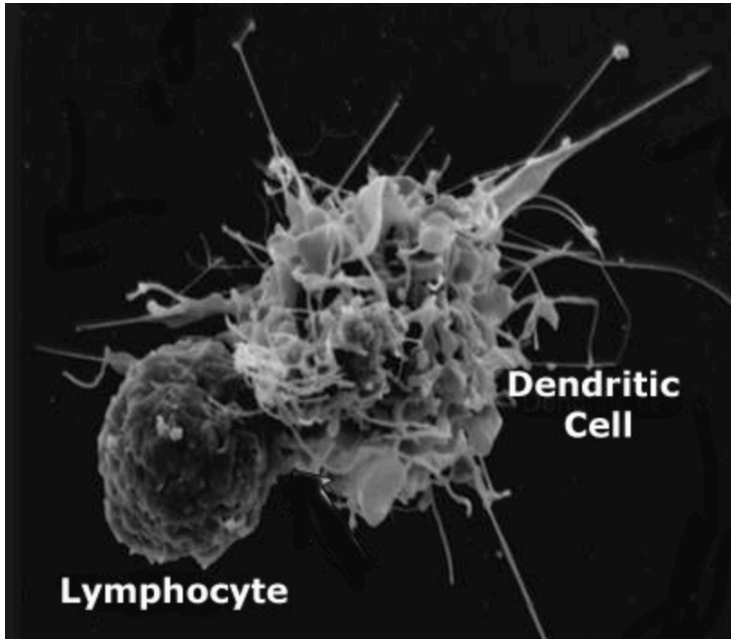
Eczema:
Inadequate T-cell Regulation

Dry, Erythematous, Itchy



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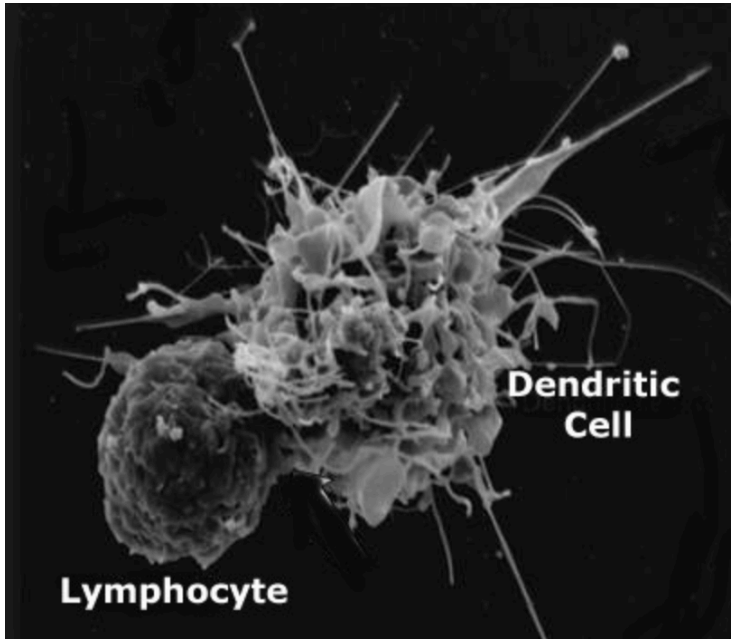
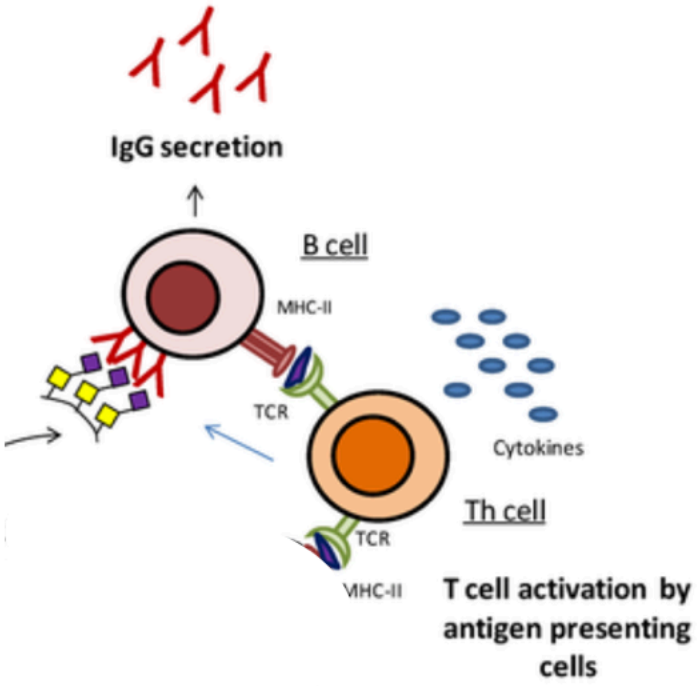


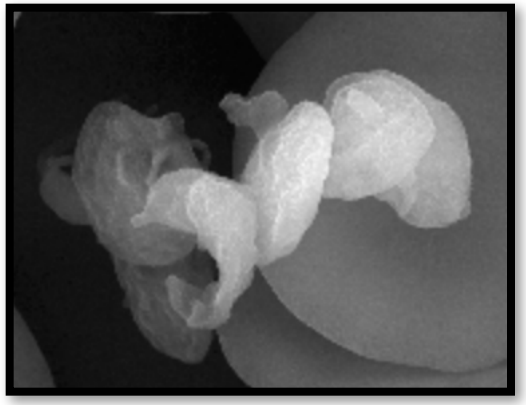
Failure of 'immunologic synapse'

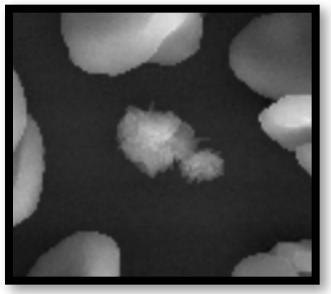
T cell-dependent
B cell activation



Wiskott-(B)Aldrich: Cytoskeleton

- Background
  - Defect in cytoskeleton of hematopoietic cells
    - T-cells: failure of immunologic synapse (with dendritic cells) immunodeficiency and immune dysregulation (eczema)
    - Platelets: increased clearance of puny sized platelets → bleeding





Cytoskeleton of hematopoietic cell: PLTS
Few in number and size

Wiskott-(B)Aldrich: Cytoskeleton

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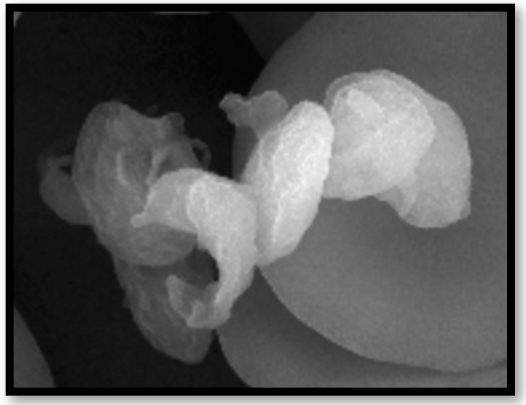

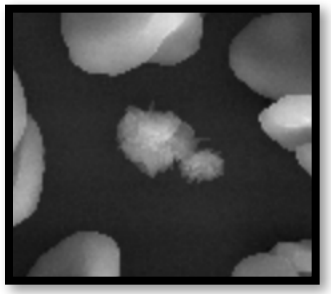

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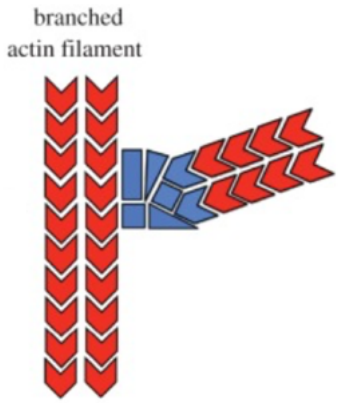
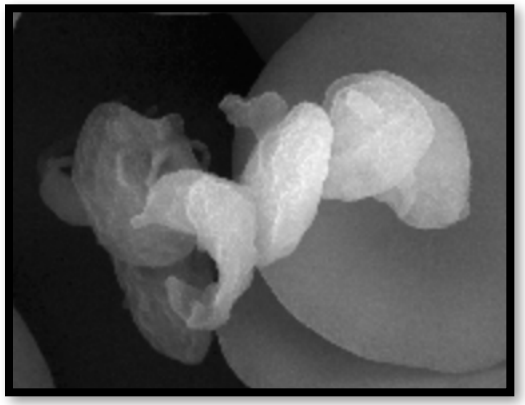
Wiskott-(B)Aldrich: Cytoskeleton

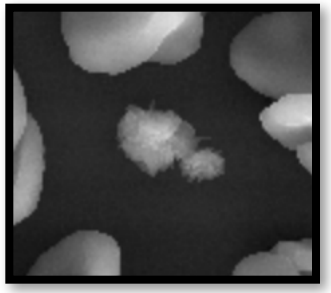
- Background
  - Defect in cytoskeleton of hematopoietic cells
    - T-cells: failure of immunologic synapse (with dendritic cells) immunodeficiency and immune dysregulation (eczema)
    - Platelets: increased clearance of puny sized platelts; Presentation: bleeding
- Pathogenesis
  - WASp (Wiskott-Aldrich syndrome protein): genetic defect leading to failure of actin polymerization/cytoskeleton rearrangement.
  - Lymphocytes are described as 'bald' lacking projections (filopodia)
- Distinguishing Clinical Features
  - Immune dysregulation: Eczema (dry, pruritic, erythematous/papular rash) – face, diaper region
  - 'Abnormal platelet membrane': increased clearance of small sized platelets with significant bleeding (<50k)
  - Dysfunctional T-cells (virus, fungus) failure to of B-cell (encapsulated bugs)
- Dx: WAS protein screening (flow cytometry)
- Rx:
  - Prophylactic/Supportive: Bactrim (PCP), acyclovir (virus), PLT transfusion (bleeding), IVIG
  - HSC transplant
- Notes:
  - Cause of Death: Bleeding
  - Elevated IgA/IgE: increased synthesis versus clearance

WAS protein → Bald Lymphocytes



Eczema:
Inadequate T-cell Regulation





Cytoskeleton of hematopoietic cell: PLTS
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Chronic Granulomatous Disease

- Background
  - Neutrophil, Enzyme Failure (NADPH oxidase)
- Pathogenesis
  - Failure of 'respiratory burst' generation of ROS and subsequently HOCl
  - Implication: catalase (+) organisms
    - Catalase metabolizes bacteria/fungi derived H2O2 so host myeloperoxidase can't convert to HOCL.
    - Hypochlorite is needs to facilitate microbe killing in the phagolysosome.
- Distinguishing Clinical Features
  - Catalase (+) organisms: Staph, Serratia, Nocardia, Aspergillus, Burkholderia.
  - Granulomas: they are response to organism, not the cause.
    - Granulomas, however, are destructive.
- Dx: NBT (nitroblue tetrazolium), DHF (dihydrorhodamine fluorescence) by flow cytometry
- Notes:
  - Normal host response to viral infection; elevated globulins (humoral response intact)
  - Rx: antibiotic and azole prophylaxis

Chediak-Higashi Syndrome (CHS)

- Background:
  - Neutrophil, failure of trafficking protein (in lysosomal membrane+); think granules.

California Highway System (CHS)
Traffic in Los Angeles

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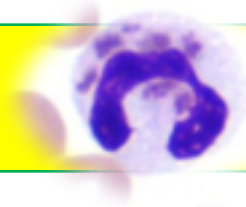
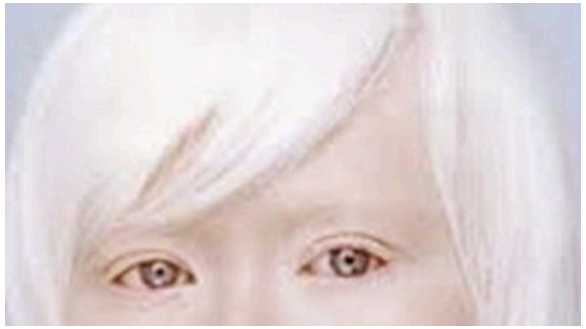
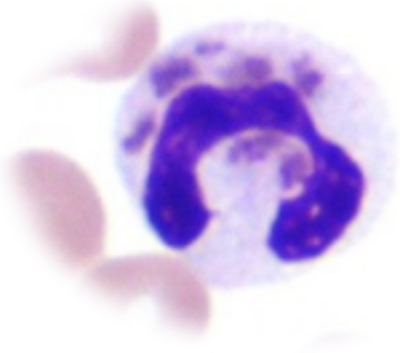


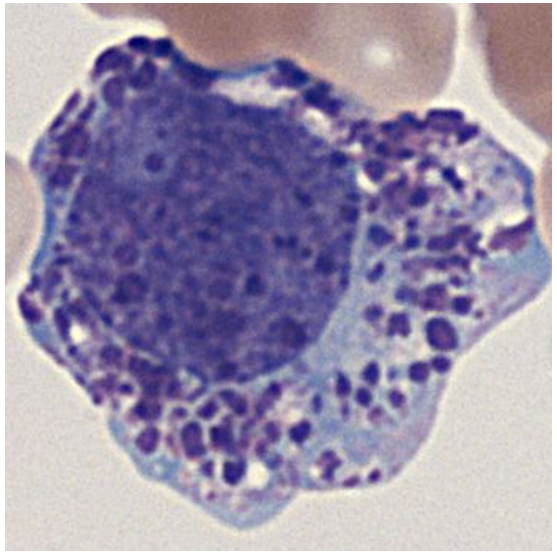
- Background:
  - Neutrophil, failure of trafficking protein (in lysosomal membrane+); think granules.
- Pathogenesis (LYST gene defect):
  - PMN: can't transport lysosome to phagosome (no phagolysosome to kill microbes)
  - Melanocytes: can't transport melanin
  - Nervous system: granule accumulation in Schwann cells

Chediak-Higashi Syndrome (CHS)





- Distinguishing Clinical Features
  - PMN: giant cytoplasmic granules (pathognomonic) - infections, especially of skin
  - Skin: partial albinism (oculocutaneous)
    - Normal melanoctyes with failure of melanin transport
  - Neuro: Schwann cell dysfunction yields to atrophy of brain, spine and cranial neuropathies
- Rx: HSC transplant



Melanin

Cytoplasmic Granules

Schwann

Chediak-Higashi
LYST: Lysosomal transport disorder
No phagolysosome

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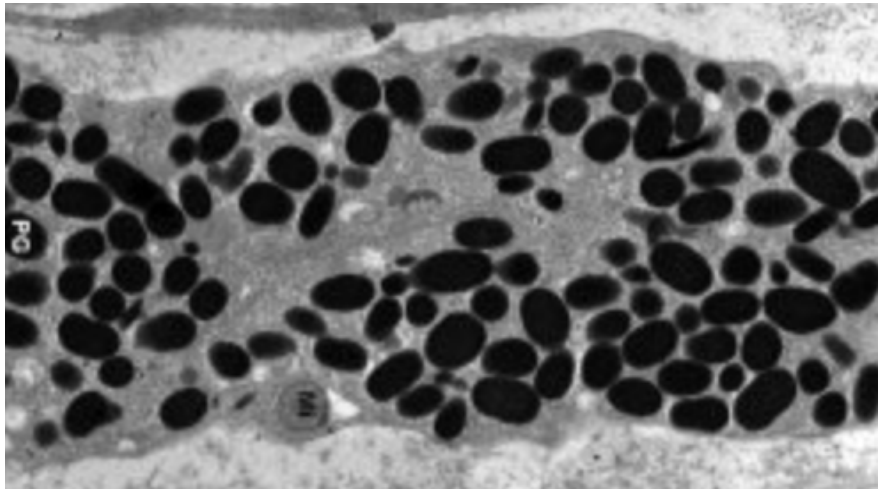
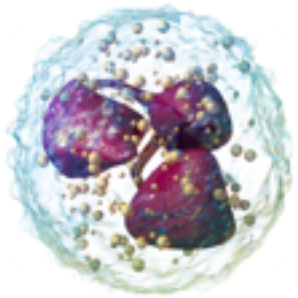


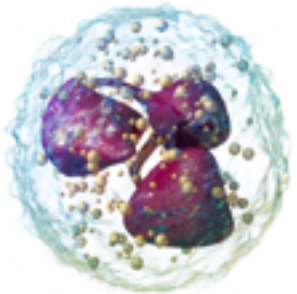
Leukocyte Adhesion Defect

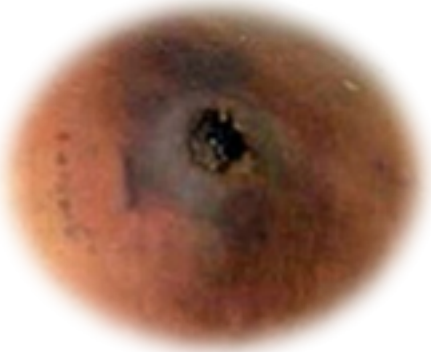
- Background:
  - Neutrophil, Failure of Migration. 'Can't get there from here'
- Pathogenesis
  - Defective leukocyte adhesion due to mutations in beta chain of CD 11/18 integrins.
- Distinguishing Clinical Features [skin (bacterial infections), mucosa, respiratory]
  - Poor Wound Healing: failure of umblical cord separation (omphalitis)
  - Hallmark: Absence of pus formation at sites of infection
  - Neutrophilia: they are present, just can't get there from here.

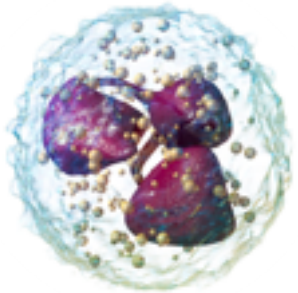
Omphalitis



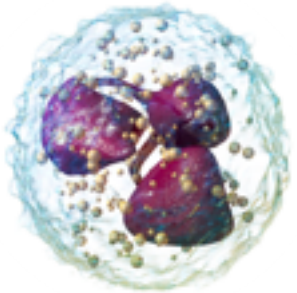
Infection

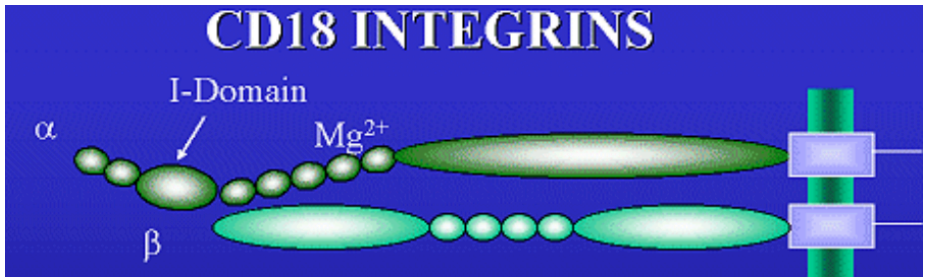






No pus





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