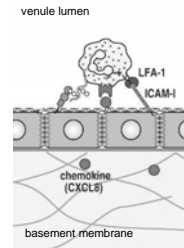


Science is like looking through a keyhole: The closer you get to the keyhole, the more you see of the room on the other side.

-George Wald
1967 Nobel Laureate in Medicine

Firm Adhesion is Triggered by Chemokine Activation of Leukocyte Integrins

QuickTime™ and a Sorenson Video decompressor are needed to see this picture.

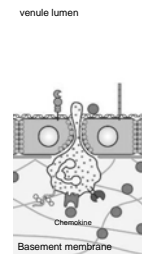


Movie, courtesy T. Springer

A Day in the Life of a Phagocytic Leukocyte

Diapedesis: Crawling Through Endothelial Junctions and Into the Tissue

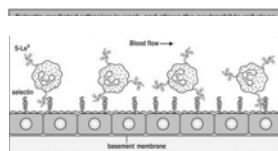
QuickTime™ and a Sorenson Video decompressor are needed to see this picture.



Movie, courtesy T. Springer

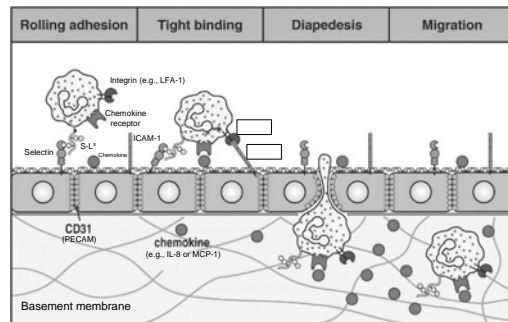
Selectin-mediated Adhesion is Weak and Promotes "Rolling" of Leukocyte Along Endothelia

QuickTime™ and a Sorenson Video decompressor are needed to see this picture.



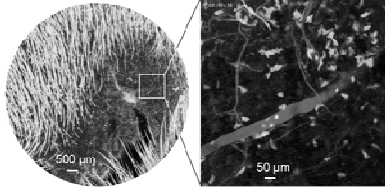
Movie, courtesy T. Springer

Leukocyte Migration, Start to Finish



Modified from: Parham, *The Immune System*, 2nd ed. (Garland: New York), 2005

Intravital Imaging of a Subset of Mouse Monocytes in Dermal Blood Vessels



CX₂CR1-expressing cells express GFP in reporter mice, and dermal blood vessels are labeled with rhodamine-conjugated dextran.

From: Auffray et al., *Science* 317:666, 2007

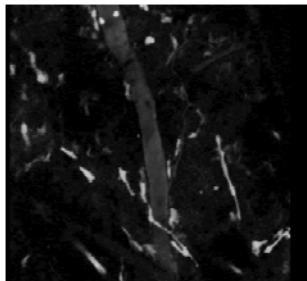
Relative Risk of Death Associated With Death of a Biological Parent Before the Age of 50

Cause of Death	Relative Risk
All causes	1.7
"Natural causes"	2.0
Infectious	5.8
Cardiovascular	4.5
Cancer	1.2

Conclusion: Genes that determine responses to infectious agents have a disproportionate effect on mortality

Source: Sorensen et al., *New Engl. J. Med.*, 318:727, 1988

A Subset of Monocytes "Patrol" the Vasculature, Primed for Diapedesis



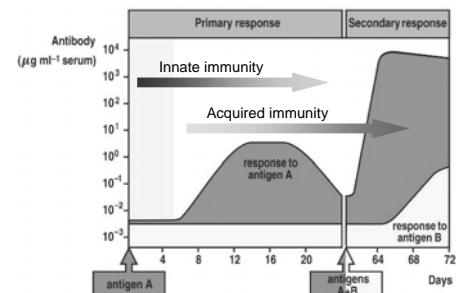
From: Auffray et al., *Science* 317:666, 2007

Distinctions Between Innate and Adaptive Immunity

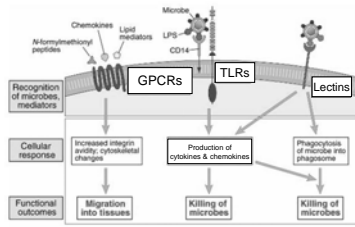
	Innate immune system	Adaptive immune system
Receptors	Germline-encoded	Somatically engineered
Distribution	Non-clonal	Clonal
Kinetics	Rapid	Slow (requires clonal expansion)
Specificity	Recognizes non-self "pattern recognition"	Recognizes "altered self" Primary structure (TCR) Higher order structure (Immunoglobulin; BCR)
Effector Cells	All	Primarily lymphocytes, DCs, Mφ

The Innate Immune Response to Bacterial and Fungal Infections

What Really Happens During the Lag Period Before the Acquired Immune Response?

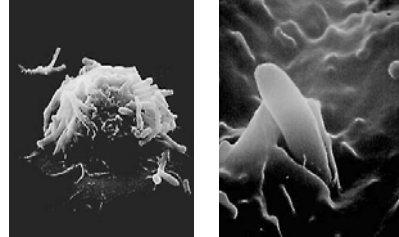


Receptors Important in Innate Immunity

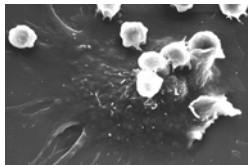


GPCR = G protein-coupled receptors
 TLRs = Toll-like receptors
 Lectin: A molecule that binds carbohydrates

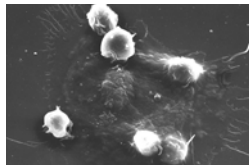
Mast Cells Can Phagocytose Too!



Phagocytosis of IgG-coated Targets by Macrophages

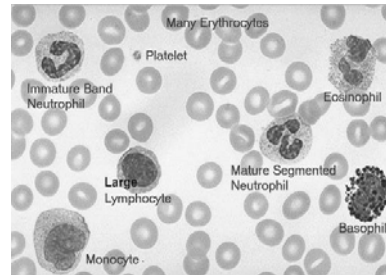


3 min

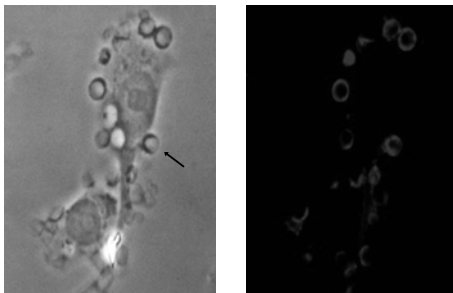


10 min

Most, but not all Leukocytes Can Perform Phagocytosis



Extension of an F-actin-rich "Phagocytic Cup" Around Phagocytic Targets



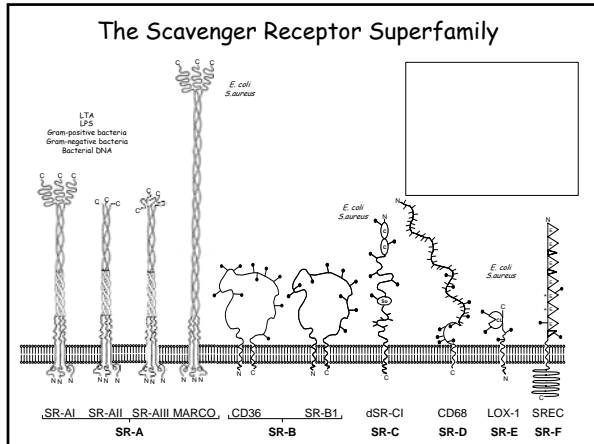
Opsonic vs Non-opsonic Phagocytosis

- Non-opsonic phagocytosis is typically mediated by cell surface receptors on leukocytes that recognize repeating carbohydrate subunits (comprising "molecular patterns") on microbes.
- Opsonic phagocytosis is typically mediated by deposition of proteins (e.g., antibodies) on microbes that target them for recognition by specific phagocytic receptors on leukocytes.

(<Latin *opsonare*, to buy provisions<Greek *opsonēin*, condiment

"Opsonin is what you butter the disease germs with to make your white blood corpuscles eat them."

-G.B. Shaw, *The Doctor's Dilemma*



Opsonic Phagocytosis

Y IgG

- Complement

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Non-opsonic Phagocytosis

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

What is complement?

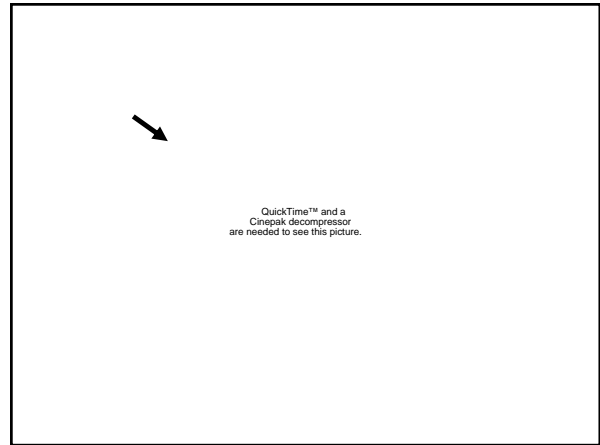
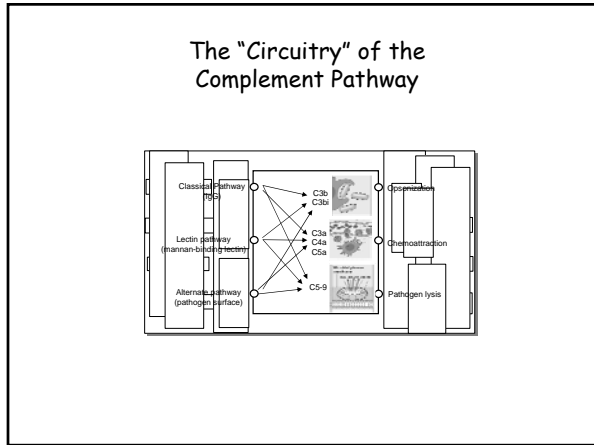
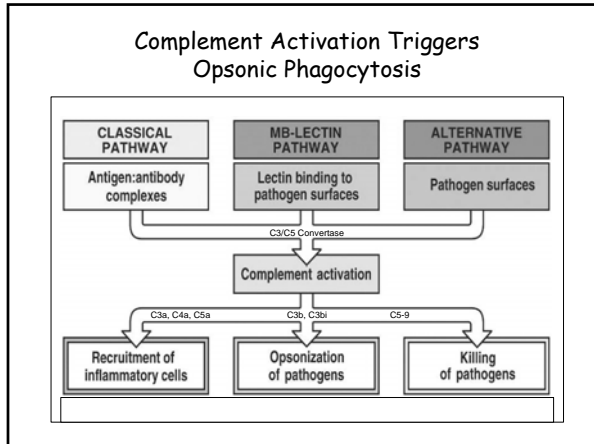
Opsonic Phagocytosis

Y IgG

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Complement Proteins Deposit on Pathogen Surfaces, Triggering Phagocytosis, Inflammation, and Pathogen Lysis

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.



Metchnikoff is the First to Describe a Role for Phagocytosis in Immunity

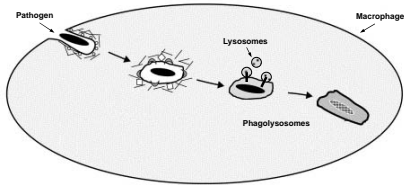
Elie Metchnikoff, 1845-1916

FIG. 34.—Microphage of guinea-pig filled with cholera vibrios, the majority of which are transformed into granules.

Phagosome-Lysosome Fusion?

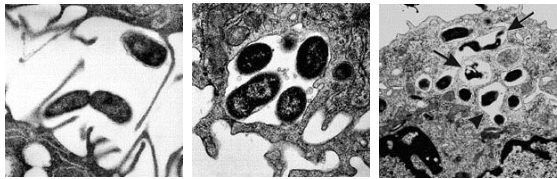


Post-phagocytic Events: Phagosome-Lysosome Fusion



Oxidant-dependent Killing of Bacteria and Fungi

Phagocytosis of Bacteria is Followed by Phagosome-Lysosome Fusion



0-3 min

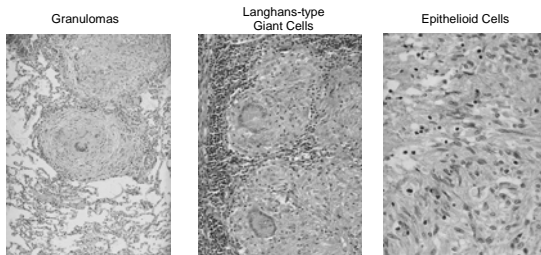
1-5 min

30 min-hrs

From: Allen et al., *J. Exp. Med.* 191:115, 2000

QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

The Granuloma: a Delayed Response to Indigestible Pathogens and Particles in Macrophages

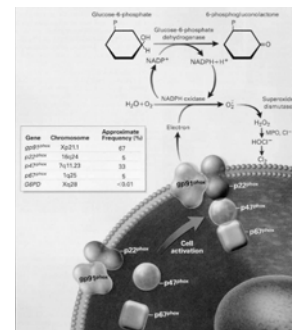


Granulomatous inflammation consists of epithelioid macrophages, giant cells, lymphocytes, plasma cells, and fibroblasts.

Langhans-type giant cells represent fused macrophages. The nuclei are lined up around the periphery of the cell.

Epithelioid cells accumulate around the center of a granuloma. They get their name from the fact that they have pink cytoplasm similar to squamous epithelia.

Chronic Granulomatous Disease (CGD), an Inherited Defect of the NADPH Oxidase Complex

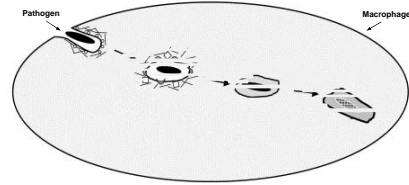


From: Lekstrom-Himes and Gallin, *N Engl J Med.* 343:1703, 2000

Chronic Granulomatous Disease: Clinical Manifestations

- 1/250,000 live births in the US
- Characterized by recurrent infections with catalase-positive organisms, such as *Staphylococcus*, *Burkholderia cepacia*, *Nocardia*, *Mycobacteria*, *Serratia*, *Klebsiella*, *Pseudomonas* species, and fungi, especially *Aspergillus* species and *Candida*.
- Recurrent bacterial and fungal infections result in lymphadenitis, abscesses, and granuloma formation, with most patients presenting within the first 2 years of life.

Post-phagocytic Events



Chronic Granulomatous Disease: Clinical Manifestations

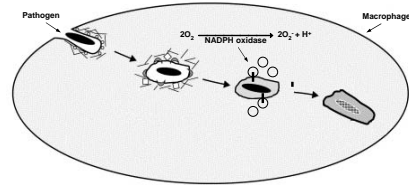
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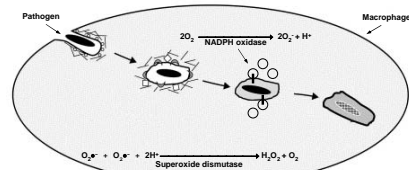
From: Khanna et al., *Radiographics* 25:1183, 2005

Post-phagocytic Events: "Phagosome-Oxidase Fusion"

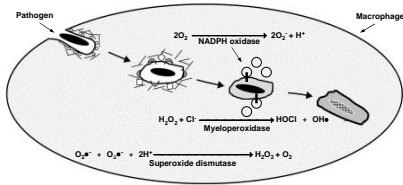


What happens following pathogen ingestion?

Post-phagocytic Events: Generation of H₂O₂



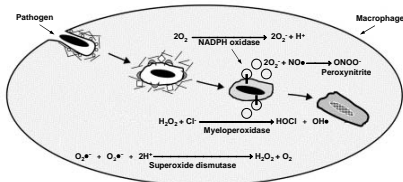
Post-phagocytic Events: Myeloperoxidase Activity



Reactive oxygen species: $O_2^{\bullet-}$, HOCl, H_2O_2 , O_3

No QuickTime™ Killing Mechanisms
TIFF (Uncompressed) decompressor
are needed to see this picture.

Post-phagocytic Events: Peroxynitrite Production



Reactive oxygen species: $O_2^{\bullet-}$, HOCl, H_2O_2 , O_3

Reactive nitrogen species: ONOO⁻

Non-oxidative Killing Mechanisms of Phagocytes

- Principally proteins within granules that are released upon cell stimulation
- These proteins include lysozyme, lactoferrin, proteases, defensins and other cationic proteins

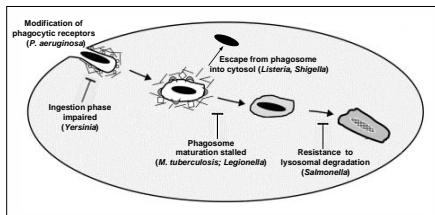
QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Lysozyme
Disrupts peptidoglycan

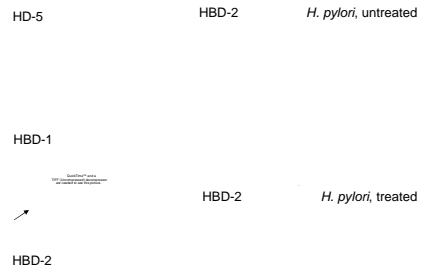
HBD1 HBD2 HBD3
Permeabilizes membranes

■ + charge
■ - charge

Bacterial Virulence Factors Subvert Host Defenses



Epithelial Cells Express Defensins, Too



From: Wehkamp et al., J. Clin. Path. 56:352, 2003; Hamanka et al., Gut 49:481, 2001

Phagocytosis: Not Just for Bugs

- ### Summary
1. Innate immunity represents the first-line of host defense. Its receptors are germline-encoded and recognize pathogen-associated "molecular patterns."
 2. Phagocytosis is a component of innate and acquired immunity. It is the principal means of destroying pathogenic bacteria and fungi. Phagocytosis initiates the process of antigen presentation.
 3. Many phagocytic receptors recognize a diverse array of microbial pathogens. Some pathogens (e.g., *S. pneumoniae*) require opsonization by antibodies and complement for their clearance. However, bugs fight back.
 4. Phagocytic leukocytes employ oxidative and non-oxidative means of killing. The NADPH oxidase generates reactive oxidants, such as superoxide anion and hypochlorous acid (bleach).
 5. Innate immunity ushers in acquired immunity: innate immune activation of APCs results in up-regulation of co-stimulatory molecules and enhances the effectiveness of antigen presentation.
 6. Phagocytosis is an essential component of development and tissue remodelling. Ingestion of apoptotic bodies is immunologically "silent" and is normally accompanied by a suppression of inflammation. Failure of this mechanism may result in autoimmunity.

Phagocytosis is the Principal Mechanism of Disposal of Apoptotic Corpses

Macrophage
Apoptotic Thymocyte

- Phagocytosis is the means of disposal of apoptotic corpses, and occurs continuously during the lifetime of an individual.
- In this setting, phagocytosis is not accompanied by inflammation, but rather leads to an "anti-inflammatory" signal (the production of TGF- β).
- As apoptotic corpses contain many potential self antigens, the lack of an appropriate anti-inflammatory signal has the potential to trigger autoimmunity.

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

From: Jennings et al., *Am. J. Resp. Cell Mol. Biol.* 32:108, 2005

