Hypersensitivity Mechanisms: An Overview

Stephen Canfield, MD, PhD

Asst. Prof. Medicine

Pulmonary, Allergy, and Critical Care Medicine

Origins of Hypersensitivity

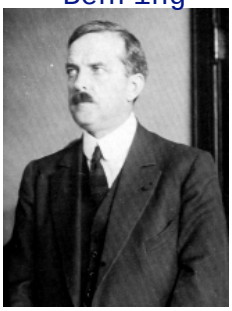
"Hypersensitivity" first used clinically in 1893:

- attempting to protect against diphtheria toxin
- test animals suffered *enhanced* responses, even death following second toxin exposure
- at miniscule doses not harmful to untreated animals

The term "Allergy" is coined in 1906:

- postulated to be the product of an "allergic" response
- from Greek *allos ergos* (altered reactivity)

Emil von Behring



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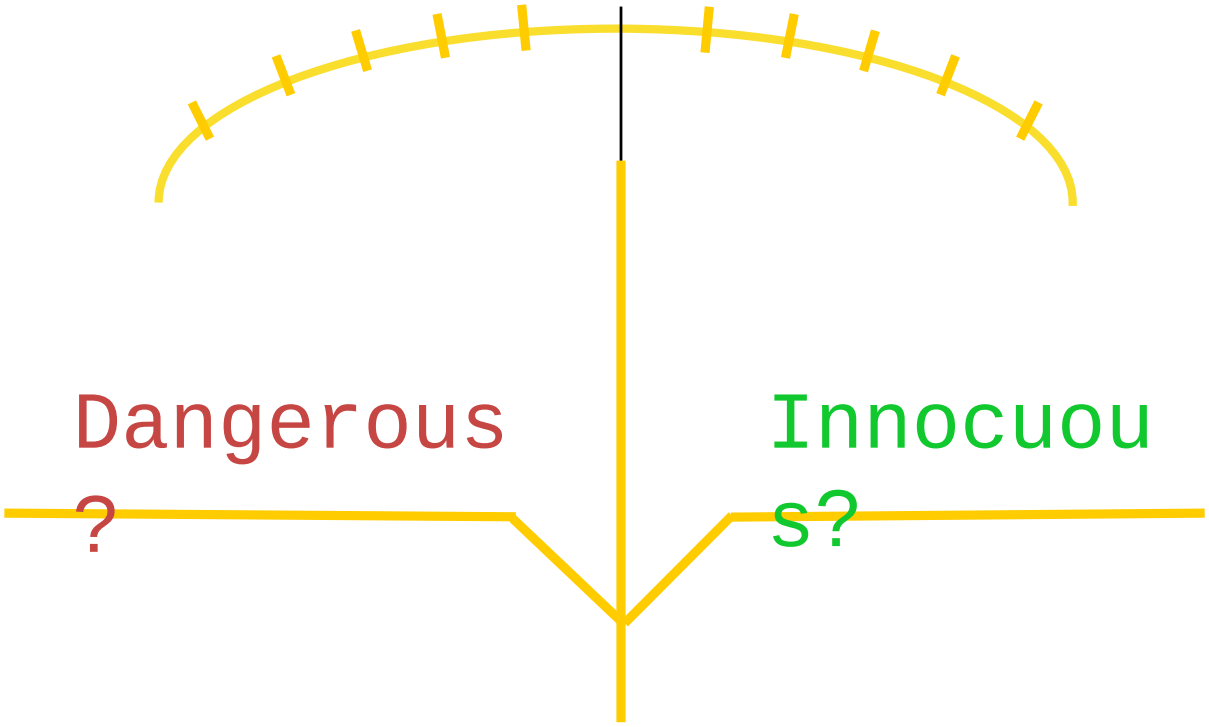
First Task of the Immune System



Modern Use

- Hypersensitivity:
  - Aberrant or excessive immune response to foreign antigens
  - Primary mediator is the adaptive immune system
    - T & B lymphocytes
  - Damage is mediated by the same attack mechanisms that mediate normal immune responses to pathogen

Mechanisms of Hypersensitivity

Gell & Coombs Classification

G&C Class	Common Term	Mediator	Example
Type I	Immediate Type	IgE monomers	Anaphylaxis
Type II	Cytotoxic Type	IgG/IgM monomers	Drug-induced hemolysis
Type III	Immune Complex Type	IgG/IgM multimers	Serum sickness
Type IV	Delayed Type	T cells	PPD rxn Contact Dermatitis

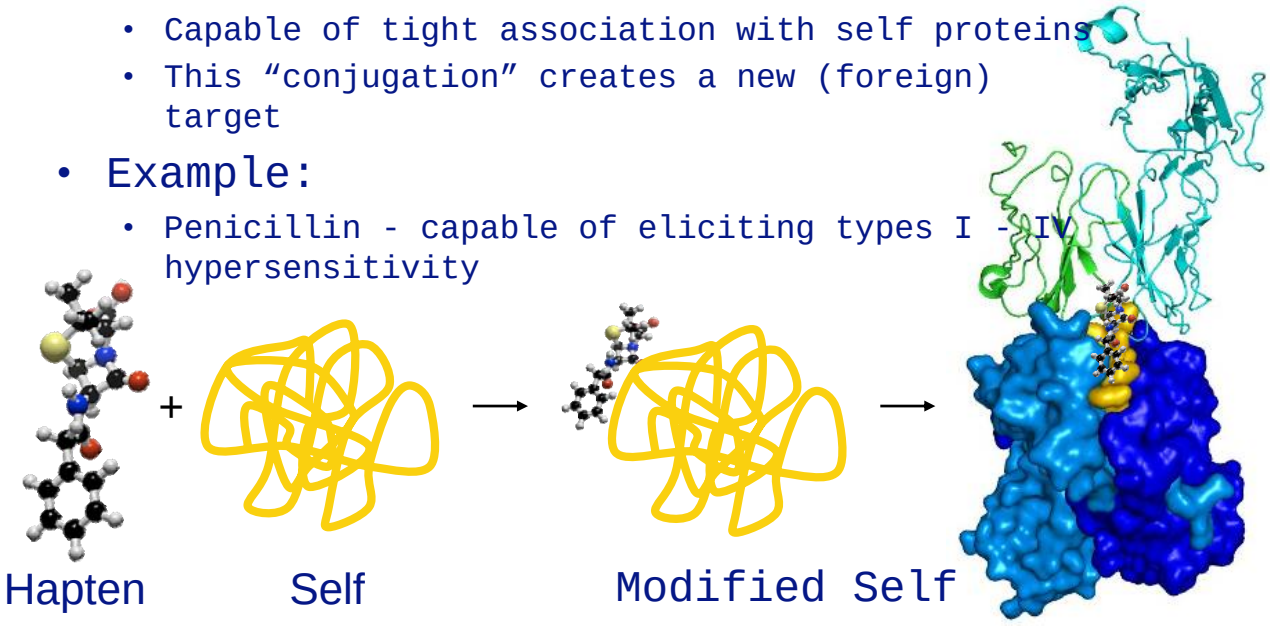
Common to All Types

Adaptive (T & B Cell) Immune Responses

- Reactions occur only in sensitized individuals
  - Generally at least one prior contact with the offending agent
- Sensitization can be long lived in the absence of re-exposure (>10 years) due to immunologic memory
- Antigen is a protein or is capable of complexing with protein (hapten)

Haptens

- Definition:
  - Chemical moiety too small to elicit a T cell response alone
  - Capable of tight association with self proteins
  - This “conjugation” creates a new (foreign) target
- Example:
  - Penicillin - capable of eliciting types I - IV hypersensitivity

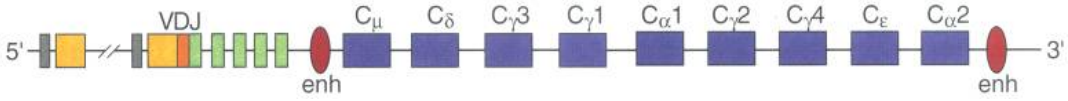


Type I (Immediate) Hypersensitivity

Type I Hypersensitivity

- Sensitization
  - Antigen contact, typically low-dose via mucous membranes (respiratory, GI) ⌫ IgE production
- Elicitation (Re-exposure)
  - Pre-formed IgE (allergen-specific) triggers mast cell activation ⌫ mediator release
- Reactions
  - Can occur within seconds-minutes of exposure
  - Severity ranges from irritating to fatal

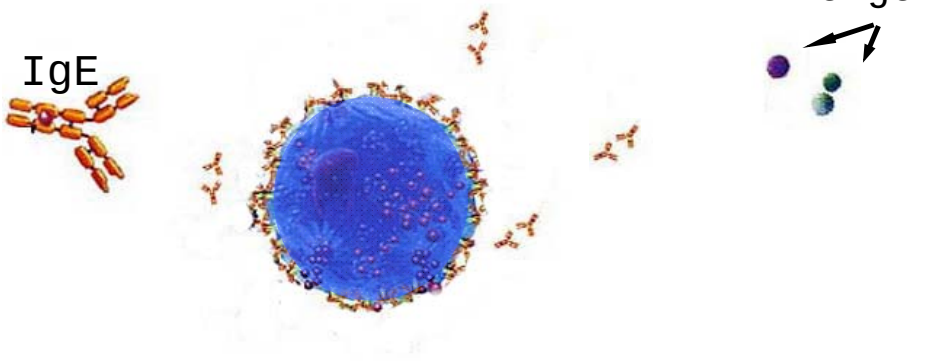
IgE Production



- Secondary immune response (multiple or persistent exposures)
- B cell class switch to IgE requires T cell help: CD40L and IL-4 or IL-13 (Th2 cytokines)
- The propensity to make an IgE response to environmental antigens varies among individuals
- ”Atopic” individuals are those with an inherited predisposition to form IgE responses

Sensitization ⌫ Response

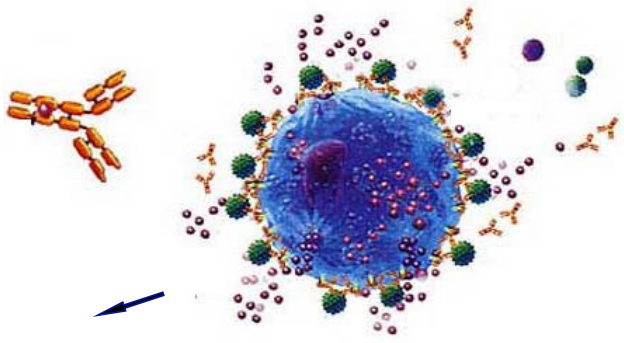
- IgE produced by plasma cells is rapidly taken up by $Fc_{\varepsilon}RI$ on tissue mast cells and circulating basophils (serum $\tau_{1/2}$~2 days; compare to IgG~21 days)



Sensitization ⌫ Response

Early Phase: IgE crosslinking by antigen ⌫ release of

preformed mediators



Immediate

Histamine (also tryptase, heparin)

⌫Smooth muscle constriction

⌫Vasodilatation; vascular leak

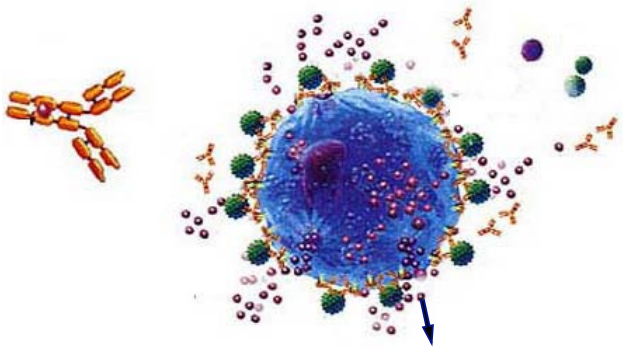
⌫G.I. motility (increased)

⌫Mucous Secretion

⌫Sensory nerve activation

Sensitization ⌫ Response

Early Phase: Followed by rapid production of arachadonic acid products



Minutes

Leukotrienes, prostaglandins

⌫Smooth muscle constriction

⌫Vasodilatation; vascular leak

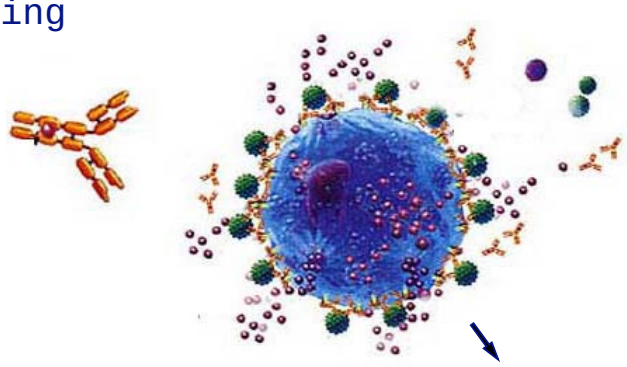
⌫Mucous Secretion

⌫Neutrophil chemotaxis

Sensitization ⌫ Response

Late Phase: Gene activation ⌫ new cytokine production

~6 hours after antigen triggering



Cytokines

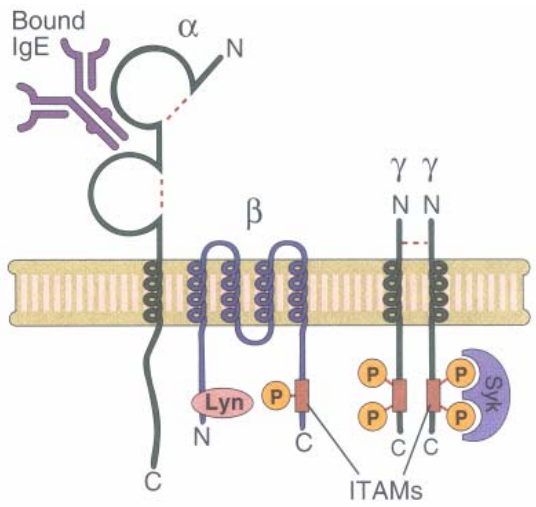
TNFα ⌫ recruit inflammatory cells

IL-3, IL-5, GM-CSF ⌫ eosinophil production

IL-4, IL-13 ⌫ propogate Th2 response

FcεRI Signaling

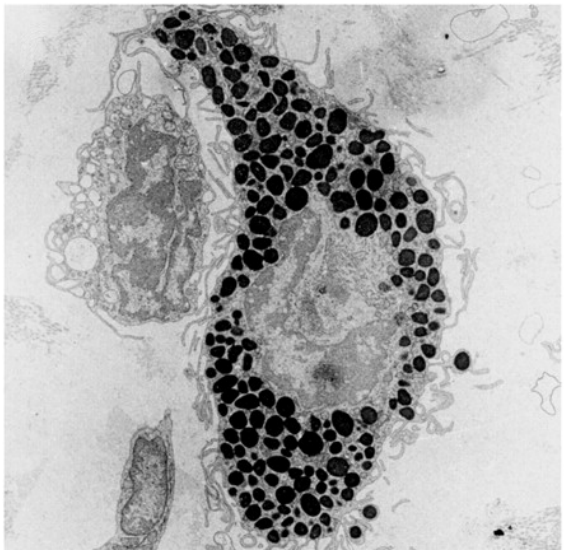
- Structure: $\alpha\beta\gamma_2$
  - α - binds IgE monomer
  - γ - shared by IgG FcR's I & III
- Receptor aggregation
  - Pre-bound IgE binds polyvalent Ag
  - Initiates ITAM phosphorylation
- ITAM's
  - Conserved tyrosine-containing sequence motifs within a variety of receptors (TCR, BCR, FcR's)



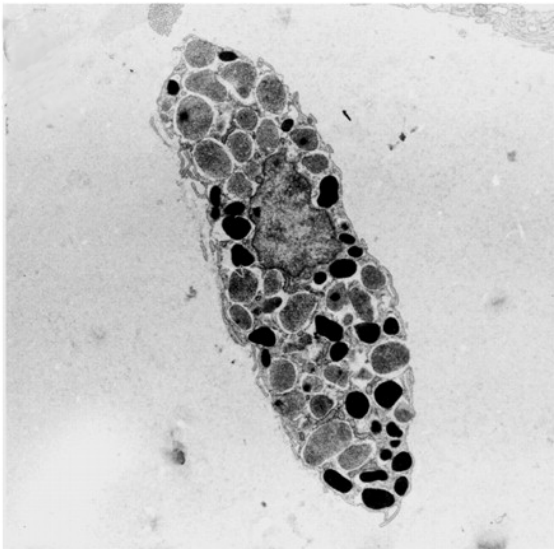
Immunoreceptor
Tyrosine-based
Activation
Motif

Mast Cell Degranulation

Before



After



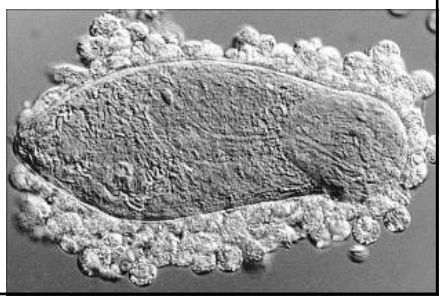
Eosinophils

- Innate responder cell in Type I hypersensitivity
- Production in bone marrow driven by:
  - IL-5 (Th2 cytokine); also IL-3 and GM-CSF
- Chemotaxis from blood to tissue sites utilizes:
  - IL-5
  - Eotaxins (CCL11, CCL24, and CCL26)
- Primed for activation by IL-5, eotaxins, C3a/C5a
  - ↑ Expression of FcR for IgG, IgA, IgE; also

Eosinophils (cont'd)

- Activation:
  - Most potent trigger is FcR-crosslinking (IgA>IgG>IgE)
  - Results in exocytosis of preformed toxic proteins
    - Major basic protein
    - Eosinophil cationic protein
    - Eosinophil-derived neurotoxin

} → Directly toxic to helmin
} → Collateral tissue damage

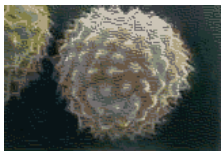


- Propogate the response:
  - Secrete IL-3, IL-5, GM-CSF
  - Secrete IL-8 (PMN attractant)

Evolutionary Role of Type I Response

- Mast cells line all subepithelial mucosa
  - Rapid recruitment of PMN, eosinophils, monocytes to sites of pathogen entry
  - ↑Lymph flow from peripheral sites to lymph node
  - ↑G.I. motility ➠ favors expulsion of G.I. pathogens
- Important role in parasite clearance
  - c-kit$^{-/-}$ mice have no mast cells ➠↑susceptibility to trichinella, strongyloides
  - Eosinophil depletion (Ab-mediated) ➠↑severity of schistosomal infection

Manifestations of Type I Hypersensitivity

Exposure	Syndrome	Common Allergens	Symptoms
Respiratory Mucosa	Allergic Rhinitis	 	Nasal Pruritis Rhinorrhea Congestion
	Asthma	 	Bronchospasm Chronic Airway Inflammation
G.I. Mucosa	Food Allergy	 	Cramping/Colic Vomit/Diarrhea Eczema
Skin	Contact Urticaria	 	Hives Pruritis
Circulation	Anaphylaxis	 	Hives Laryngeal Edema Hypotension

Anaphylaxis

- Response to systemic circulation of allergen
  - IgE cross-linking on mast cells in peri-vascular tissue
  - Circulating histamine, PG's/LT's ➠ vasodilatation, vascular leak
  - High-output shock: ↓↓BP despite ↑'ed cardiac output
  - Other symptoms: urticaria, wheeze, laryngeal edema with airway compromise, G.I. cramping, diarrhea, "feeling of dread"
- Symptoms progress rapidly (seconds)
- Treatment
  - Immediate: epinephrine 0.3 cc I.M., followed by antihistamines (H1 and H2 blockade) IM or IV ➠

Demonstrating Type I Hypersensitivity

- Skin testing for allergic sensitization
  - Allergen (airborne, food, venom, medication) is introduced by prick or intradermal injection
  - Sensitization is evident with 15 minutes as a wheal/flare at site of allergen introduction

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

Type II (Cytotoxic) Hypersensitivity

Type II Hypersensitivity

- Damage mediated by tissue-specific IgG or IgM
- Origins of tissue-specific antibody response
  - Hapten response
  - Molecular mimicry
  - Idiopathic - loss of self-tolerance (autoimmunity)

Hapten Response

- Mechanism of Sensitization
  - A foreign agent (typically drug) acts as a hapten
  - Conjugates self protein ⌫ modified self ⌫ T cell/B cell response ⌫ high-affinity anti-self IgG or IgM
- On re-exposure
  - Hapten conjugation to self ⌫ modified self protein
  - Binding of IgG or IgM to modified self tissue (platelet, RBC)
  - Activation of normal immunoglobulin effector

Molecular Mimicry

- Pathogen elicits appropriate inflammatory response
  - ⌫High-affinity anti-pathogen IgG
- Pathogen-specific antibody cross-reacts with self
- Long-lived anti-pathogen IgG ⌫ persistent tissue damage

Type II Hypersensitivity

Ab Function	Target	Result	Syndrome
Opsonization	Platelets	Splenic clearance	Drug-induced ↓platelets ➡bleeding
Complement Fixation	Erythrocytes	RBC destruction	Intravascular Hemolytic anemia
Antibody-Dependent Cellular Cytotoxicity	Cardiac myosin, perivascular connective tissue	Endocarditis, Myocarditis	Rheumatic Heart Disease
Neutralization	Acetylcholine Receptor	Muscle weakness	Myasthenia Gravis

Type III (Immune Complex) Hypersensitivity

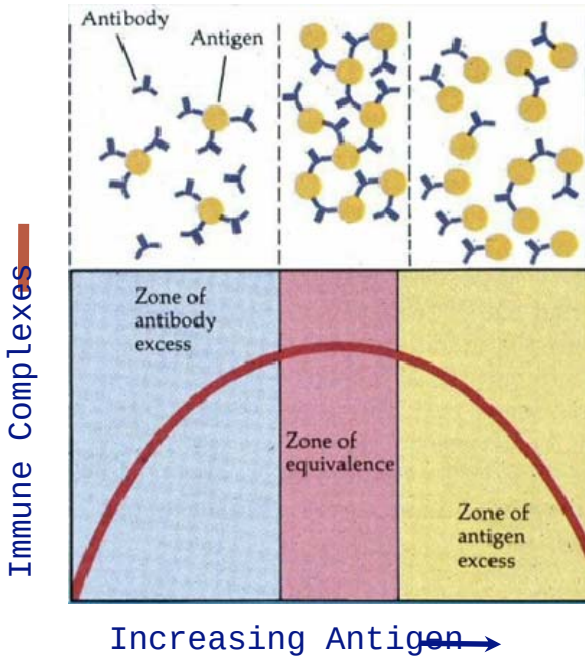
Type III Hypersensitivity

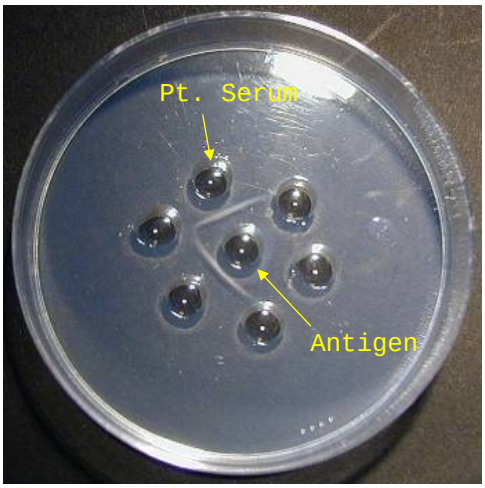
First Description: Arthus Reaction

- Another attempt at protection gone wrong:
  - IV infusion anti-toxin antiserum
  - Followed with SQ injection of small dose of toxin

  - Outcome: local (cutaneous) erythema, swelling, hemorrhage and necrosis within 8

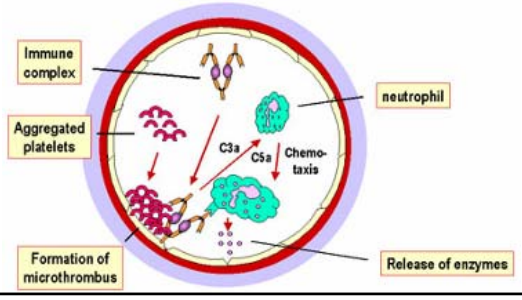
Immune Complex Formation





Mechanism of Damage

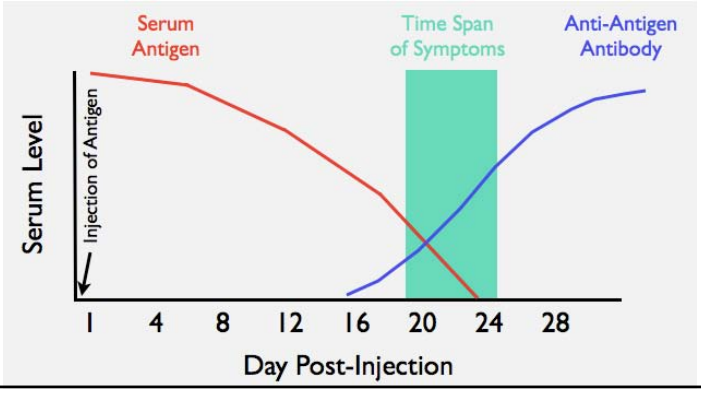
- Ag-Ab complexes deposit in local blood vessel walls
- Fix complement ⌫ generate C5a
  - Chemoattactant for neutrophils
  - Mast cell activator ⌫ histamine release ⌫ hives, tissue edema
- Bind Fc Receptors on:
  - Neutrophils ⌫ release of O_2 free radicals, proteases
  - Platelets ⌫ a necrosis



Clinical Type III Hypersensitivity

- Serum Sickness
  - Fever
  - Lymphadenopathy
  - Urticaria
  - Joint Pain
  - Proteinuria

} 2-3 weeks following infusion of antigen (classically an anti-serum of horse origin)



Type IV (Delayed) Hypersensitivity

Type IV (Delayed) Hypersensitivity

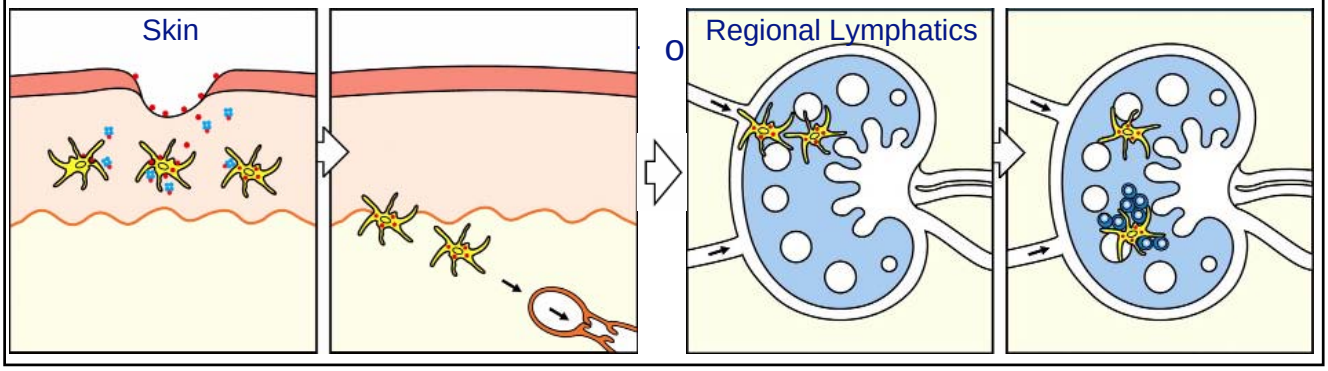
- Group of T cell mediated responses to antigen
  - Direct killing of target cells (by CD8+ T cells)
  - Indirect via activation of macrophages (CD4+ T cells)
- Sensitization is required
- On re-exposure - reactions occur over 1-3 days
- T cells are necessary and sufficient
  - Athymic subjects do not have Type IV reactions

Varieties of DTH Reactions

Type	Site	Clinical Appearance	Antigen
Tuberculin Test	Dermis	Local Induration (swelling)	Mycobacteria, Candida, Mumps
Contact Dermatitis	Epidermis	Erythematous Papular Scaling Blistering	Poison ivy, latex, organic mols., metals (Ni^{++})
Drug Rash	Circulation	“Measles-like” rash, ↑LFT’s	Almost any medication

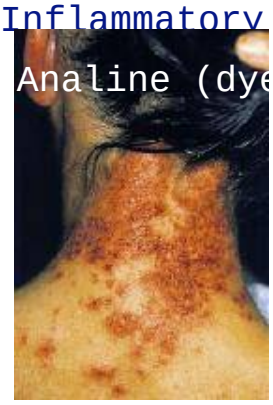
Contact Hypersensitivity: Sensitization

- Agent (antigen) crosses epidermis
  - If hapten, associates with epidermal cell proteins ⌫ self
- Langerhans cells process antigen proteins
  - Load antigen peptides into MHC I and MHC II
- LC migration ⌫ presentation to naïve T cells



Contact Hypersensitivity: Re-exposure

- If hapten modifies *extracellular* proteins, these will be taken up by cutaneous APC's → MHC II
- Effector CD4+ T cells respond:
  - Production interferon-γ, chemokines
  - Recruit macrophages ⌫ produce TNF-α
  - Inflammatory infiltration, local edema/erythema



Contact Hypersensitivity: Re-exposure

- If lipophilic, the hapten easily crosses the cell membrane, modifying *cytoplasmic* proteins →MHC I
- Effector CD8+ T cells respond:
  - Targeting of haptenylated keratinocytes for cytolysis
  - Keratinocyte d

Hypersensitivity: Overview

	Type I	Type II	Type III	Type IV	
Common Name	Immediate Hyper-sensitivity	Bystander Reaction	Immune Complex Disease	Delayed-type Hypersensitivity	
Example	Peanut Anaphylaxis	PCN-assoc. Hemolysis	Serum Sickness	Contact Dermatitis (Ni^+), PPD	Contact Dermatitis (poison ivy)
Mediator	IgE	IgG Monomer	IgG Multimers	CD4 T cell	CD8 T cell
Antigen	Soluble	Cell or Matrix Bound	Soluble	Soluble, extracellular	Lipophilic
Effector Mechanism	Mast Cell Activation	Complement, ADCC, Neutraliz., Opsonization	Complement, PMN, MΦ	Macrophage Activation	Cytotoxicity (perforin & granzyme)