Allergy and Hypersensitivity
Introduction

- Allergy is an altered reactivity to antigenic stimulation.

- von Pirquet intended that the term refers to all forms of changed reactivity to antigenic stimulation (immunity or hypersensitivity).

- By contrast, the term allergy now is almost exclusively used, particularly in the clinical setting, to refer to a subset of potentially harmful immune responses.
• Common usage now primarily restricts the term allergic reactions, as encountered clinically, to responses to certain environmental antigens (allergens) such as components of food, drugs, pollen and so on.

• Coombs and Gell scheme of classification proposes four major types of hypersensitivity reactions or allergic reactions that may be deleterious to the tissues and harmful to the host (depending on the initiating mechanism).
<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Typical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-Mediated Hypersensitivity</td>
<td>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema</td>
</tr>
<tr>
<td>II</td>
<td>IgG-Mediated Cytotoxic Hypersensitivity</td>
<td>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia</td>
</tr>
<tr>
<td>III</td>
<td>Immune Complex-Mediated Hypersensitivity</td>
<td>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-Mediated Hypersensitivity</td>
<td>Typical manifestations include contact dermatitis, tubercular lesions and graft rejection</td>
</tr>
</tbody>
</table>

**Type I**: Allergen interacts with Fc receptor for IgE, resulting in degranulation of mast cells and basophils, releasing vasoactive mediators.

**Type II**: Antigen binds to cell surface antigens, activating cytotoxic cells through ADCC or complement activation.

**Type III**: Immune complexes activate complement, leading to neutrophil infiltration and tissue damage.

**Type IV**: Sensitized T<sub>H</sub>1 cells release cytokines activating macrophages or T<sub>C</sub> cells, mediating direct cellular damage.
Type 1 Hypersensitivity – Allergy

- **Immediate type** (IgE – Mediated): Asthma, Hay fever, Atopic dermatitis, and Allergic gastroenteritis

- Atopy: affects up to 40% of the population.
- Hygienic hypothesis.

**General Features**
- genetically determined
- continued production of IgE.
- target organ hyper-responsiveness.
Type 1 Hypersensitivity – Allergy

- Pathology is related to mast cell degranulation, and the reaction is driven by mast cell mediators.

- General features of IgE – associated allergies:
  - They are often associated with high levels of IgE production.
  - They are now known to be promoted by antigen-specific Th2 cells.
  - The tissue responses may be affected by genetic and diverse nongenetic factors.
  - They have two phases, sensitization and effector phases.
  - Clinically they have acute, late and chronic phases.
Allergens

- Allergens are antigens that can elicit specific IgE responses.
- The identification of a simple set of “general rules for allergenicity” has remained elusive.
- Certain generalizations about the properties of allergens (all of which have exceptions) have emerged:
  - Allergens typically are proteins (often glycoproteins) or chemicals (haptens) that can become bound to proteins.
  - Analysis of common allergens so far have not revealed why these substances induce a Th2 cell driven IgE associated response.
Allergens

- Many allergens are enzymes but many lack enzymatic activity.

- Food allergens can be derived from a long list of food items, but allergens derived from peanuts and other legumes, tree nuts, fish and shellfish, crustaceae and mollusks, cow milk, hen’s egg, and cereal grains account for a large fraction of clinically significant allergens.

- Insect venoms contain allergens, many of them enzymes, that can induce IgE – associated responses in both atopic and nonatopic individuals (anaphylaxis). Many drugs have been associated with anaphylactic responses.
Features of inhaled allergens that may promote the priming of TH2 cells that drive IgE responses

<table>
<thead>
<tr>
<th>Protein</th>
<th>Only proteins induce T-cell response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Protease</td>
</tr>
<tr>
<td>Low dose</td>
<td>Favors activation of IL-4- producing CD4 cells</td>
</tr>
<tr>
<td>Low molecular weight</td>
<td>Diffuses out of particles into mucus</td>
</tr>
<tr>
<td>High solubility</td>
<td>Readily eluted from particle</td>
</tr>
<tr>
<td>Stable</td>
<td>Allows survival in desiccated particle</td>
</tr>
<tr>
<td>Contains peptides that bind host MHC class II</td>
<td>Required for T-cell priming</td>
</tr>
</tbody>
</table>
Regulation of IgE Synthesis

- Binding of allergen by allergen – specific B cells via BCR.

- Allergen processing and presentation to Th2 cells as peptide fragments in association with MHC class II molecules.

- Activated T-cells provide B cells with two signals:
  1) IgE-Switching cytokine IL-4 and/or IL-13.
  2) Binding of CD40 ligand on Th2 to CD40 on B cells.
T cell help to B cells

IL-4 and IL-13

Antigen

CD40

CD40 Ligand
Receptors For IgE

- The high affinity receptor FcεR1
  - primarily expressed on mast cells and basophils
  - The activation of mast cells or basophils by FcεR1 aggregation initiates a coordinated sequence of biochemical and morphological events that result in:
    1) Exocytosis of secretory granules.
    2) Synthesis and secretion of newly formed mediators.
    3) Synthesis and secretion of cytokines
Mast Cells and the Allergic Response

Allergen (antigen) binds to IgE on the surface of the mast cell. This triggers the release of granules containing histamine and other inflammatory agents. Histamine and other inflammatory agents are then released, leading to an allergic response.
Receptors For IgE

• Mediators are responsible for symptoms.

• Serum IgE concentration and FcεR1 expression correlate.

• Levels of FcεR1 expression can be regulated by IgE.

• IgE-dependent upregulation of FcεR1 expression may be part of a positive feedback mechanism for inducing further production of IgE (mast cells and basophils produce IL-4).

Fc εR II / CD23 (binds IgE with a relatively low affinity)
Effector cells and Mediators

Mast Cells and Basophils

- Distributed strategically throughout normal connective tissues.

- Contain or elaborate on appropriate stimulation, a diverse array of potent biologically active mediators.

I- Major mediators stored in cytoplasmic granules:

A- Histamine

B- Others (heparin, proteases, acid hydrolases, cathepsin G, and Carboxypeptidases).
Effector cells and Mediators

II- Major lipid Mediators produced on appropriate activation (arachidonic acid metabolites)

A- Prostaglandin D2
B- Leukotriene C4 → D4 → E4 (SRS- A)
C- Platelet – activating factor (PAF)

III- Cytokines: IL-4, IL-5, IL-6, IL-8, IL-13, TNFα, and others.
### Compounds Released from Mast Cells

<table>
<thead>
<tr>
<th>Class of product</th>
<th>Examples</th>
<th>Biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>Tryptase, chymase, cathepsin G, carboxypeptidase</td>
<td>Remodel connective tissue matrix</td>
</tr>
<tr>
<td>Toxic mediator</td>
<td>Histamine, heparin</td>
<td>Toxic to parasites, increase vascular permeability, cause smooth muscle contraction</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IL-4, IL-13</td>
<td>Stimulate and amplify TH2 cell response</td>
</tr>
<tr>
<td></td>
<td>IL-3, IL-5, GM-CSF</td>
<td>Promote eosinophil production and activation</td>
</tr>
<tr>
<td></td>
<td>TNF-α (some stored preformed in granules)</td>
<td>Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium</td>
</tr>
<tr>
<td>Chemokine</td>
<td>MIP-1α</td>
<td>Attracts monocytes, macrophages, and neutrophils</td>
</tr>
<tr>
<td>Lipid mediator</td>
<td>Leukotrienes C4, D4, E4</td>
<td>Cause smooth muscle contraction, increase vascular permeability, stimulate mucus secretion</td>
</tr>
<tr>
<td></td>
<td>Platelet-activating factor</td>
<td>Attracts leukocytes, amplifies production of lipid mediators, activates neutrophils, eosinophils, and platelets</td>
</tr>
</tbody>
</table>

Pre-formed and in granules

Synthesized upon mast cell activation

7/21/2013
Eosinophils

- Granules contain Lysosomal hydrolases and cationic proteins.

- Crystalloid core of the granule is composed of the major basic protein (MBP).

- The non core matrix contains eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eosinophil peroxidase, lysosomal hydrolases and lysophospholipase (Charcot – Lyden crystals)
Eosinophils

- They also produce lipid mediators upon activation (Lt-C4, Lipoxins) and Cytokines (IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-16, GM-CSF, TNF-α ...).

- The potential for eosinophils to cause tissue injury is illustrated by the rare hypereosinophilic syndromes.
Eosinophils

- The clinical manifestations are damage to the endocardium and nerves leading to heart failure and neuropathy.
- Eosinophils accumulate in large numbers in local allergic reactions.
- Their continued presence is characteristic of chronic allergic inflammation.
- Eosinophils are thought to be the chief contributor to tissue damage that occurs.
## Compounds Released from Eosinophils

<table>
<thead>
<tr>
<th>Class of product</th>
<th>Examples</th>
<th>Biological effects</th>
</tr>
</thead>
</table>
| Enzyme           | Eosinophil peroxidase                   | Toxic to targets by catalyzing halogenation  
                |                                          | Triggers histamine release from mast cells |  
|                  | Eosinophil collagenase                  | Remodels connective tissue matrix                                                   |
| Toxic protein    | Major basic protein                     | Toxic to parasites and mammalian cells  
                |                                          | Triggers histamine release from mast cells |  
|                  | Eosinophil cationic protein             | Toxic to parasites  
                |                                          | Neurotoxin                               |  
|                  | Eosinophil-derived neurotoxin           | Neurotoxin                                                                         |
| Cytokine         | IL-3, IL-5, GM-CSF                      | Amplify eosinophil production by bone marrow  
                |                                          | Cause eosinophil activation              |  
| Chemokine        | IL-8                                    | Promotes influx of leukocytes                                                       |
| Lipid mediator   | Leukotrienes C4, D4, E4                | Cause smooth muscle contraction  
                |                                          | Increase vascular permeability         |  
|                  |                                        | Increase mucus secretion                                                            |
|                  | Platelet-activating factor             | Attracts leukocytes  
                |                                          | Amplifies production of lipid mediators |  
|                  |                                          | Activates neutrophils, eosinophils, and platelets                                  |
Mechanisms of IgE – Associated Allergic Inflammation

- **Acute Allergic Reaction**
  - Expressed seconds or minutes after exposure to allergen.
  - Multiple local effects are produced including:
    1. Enhanced local vascular permeability.
    2. Increased cutaneous blood flow with intravascular trapping of red cells.
    3. Other effects such as itching due to the stimulation of cutaneous sensory nerves by histamine.
Late – Phase Reaction

- It characteristically does not develop until several hours after initial allergen challenge, in many cases after the signs and symptoms related to the acute allergic reaction have greatly diminished or even disappeared.

- It is now clear that a large fraction of patients with allergic asthma (50% of adults and > 70% of children) express late phase reaction to inhaled allergens (second phase of bronchoconstriction which usually is maximal at 6-12 hours and resolves by 24 hours).
Several points about human LPR appear to be well established:

• The response can be elicited by appropriate allergen challenge.

• The reaction is almost always preceded by an acute allergic reaction.

• The signs and symptoms characteristic of LPR are associated with the recruitment of circulating leukocytes to the site of the reaction.
Mechanisms of IgE – Associated Allergic Inflammation

- **Chronic Allergic Inflammation**
  - It typically occurs at anatomic sites that have been repeatedly challenged with allergens over prolonged periods.
  - Sites contain effector cells that have been recruited from the circulation and also can be associated with striking, chronic changes in underlying tissues.
  - The inflammatory infiltrate at such sites typically include eosinophils and T – cells (esp. Th2) and the affected tissue exhibit significant alterations in their function.
Cellular culprits of allergy: T cells

- Eosinophil & mononuclear cells infiltrate the bronchi of asthmatics
- Activated T cells elevated in the peripheral blood of severe acute asthmatics
- Activated T cells in peripheral blood correlated with airway narrowing
- Bronchial CD4 lymphocyte numbers correlated with eosinophil numbers
- Elevated IL-5 expressing T cells in asthmatic bronchial mucosa and BAL
• T cells that release IL-5 co-localise with eosinophils

• Eosinophils cause airway hyperresponsiveness, inflammation, desquamative bronchitis, mucous hypersecretion and smooth muscle contraction

• IL-5 promotes differentiation and regulates the survival of eosinophils

• Steroid treatment is associated with a decrease in IL-5 producing cells
Anaphylaxis

• Refers to the occurrence of IgE - mediated reaction simultaneously in multiple organs.

• The usual causative allergen is a drug, insect venom or food. It can be evoked by minute amounts of an antigen.

• It lacks the genetic propensity of atopy and it has no predilection for the atopic individual.

• Urticaria (skin) and angioedema (subcutaneous tissue) are mild localized forms of anaphylaxis.
# IgE-Mediated Allergic Reactions

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Common allergens</th>
<th>Route of entry</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic anaphylaxis</td>
<td>Drugs, serum, venoms, peanuts</td>
<td>Intravenous (either directly or following rapid absorption)</td>
<td>Edema, increased vascular permeability. Tracheal occlusion. Circulatory collapse. Death</td>
</tr>
<tr>
<td>Wheal-and-flare</td>
<td>Insect bites</td>
<td>Subcutaneous</td>
<td>Local increase in blood flow and vascular permeability</td>
</tr>
<tr>
<td>Pollens (hay fever)</td>
<td>Pollens (ragweed, timothy, birch)</td>
<td>Inhaled</td>
<td>Edema of nasal mucosa. Irritation of nasal mucosa</td>
</tr>
<tr>
<td>Dust-mite feces</td>
<td>Dust-mite feces</td>
<td>Inhaled</td>
<td></td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>Pollens</td>
<td>Inhaled</td>
<td>Bronchial constriction. Increased mucus production. Airway inflammation</td>
</tr>
<tr>
<td>Food allergy</td>
<td>Shellfish, Milk, Eggs, Fish, Wheat</td>
<td>Oral</td>
<td>Vomiting, Diarrhea, Pruritis (itching), Urticaria (hives), Anaphylaxis (rarely)</td>
</tr>
</tbody>
</table>
Normal larynx

Laryngeal oedema
Diagnosis and Management of IgE – Mediated Allergy

Diagnosis

- RIST, RAST, Skin testing

Management

- Drug treatment
- Desensitization
- Vaccination by allergen peptides
- Anti IgE receptor
- Inhibitors of cytokines
- Blocking of mediator actions.
## Allergy treatments

<table>
<thead>
<tr>
<th>Target step</th>
<th>Mechanism of treatment</th>
<th>Specific approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_H2$ activation</td>
<td>Reverse $T_H2/T_H1$ balance</td>
<td>Injection of specific antigen or peptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration of cytokines, e.g., IFN-$\gamma$, IL-10, IL-12, TGF-$\beta$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of adjuvants such as CpG oligodeoxynucleotides to stimulate $T_H1$ response</td>
</tr>
<tr>
<td>Activation of B cell to produce IgE</td>
<td>Block co-stimulation Inhibit $T_H2$ cytokines</td>
<td>Inhibit CD40L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibit IL-4 or IL-13</td>
</tr>
<tr>
<td>Mast-cell activation</td>
<td>Inhibit effects of IgE binding to mast cell</td>
<td>Blockade of IgE receptor</td>
</tr>
<tr>
<td>Mediator action</td>
<td>Inhibit effects of mediators on specific receptors</td>
<td>Antihistamine drugs</td>
</tr>
<tr>
<td></td>
<td>Inhibit synthesis of specific mediators</td>
<td>Lipooxygenase inhibitors</td>
</tr>
<tr>
<td>Eosinophil-dependent inflammation</td>
<td>Block cytokine and chemokine receptors that mediate eosinophil recruitment and activation</td>
<td>Inhibit IL-5 Block CCR3</td>
</tr>
</tbody>
</table>
Type II (Cytotoxic Antibody) Hypersensitivity

• IgM and / or IgG to cell surface determinants whether self or foreign.

• Cell destruction may be brought about by complement – dependent or complement – independent mechanisms.

• Include transfusion reaction, HDN, ITP, Good Pasture syndrome, hyperacute graft rejection, pemphigus, and anti-receptor antibody (Graves, Diabetes).

• Anti-receptor antibody may block or enhance the function of the receptor (block recognition site, imitation of the natural ligand, damage of receptor, accelerated degradation and alteration of binding a affinity).
Type III (Immune complex) Hypersensitivity

- Soluble immune complexes at slight antigen excess.
- Deposition is related to hemodynamics.
- The prototype of the reaction is Arthus Reaction in rabbits.
- Serum sickness in humans.
- The pathology is marked by a neutrophil-rich infiltrate.
Soluble antigen → Body → Antibody

Immune complex

Small molecular soluble Immune complex → intermediate molecular soluble Immune complex → Large molecular insoluble Immune complex

Deposit on the basement of capillaries
Eliminate by phagocytosis

Combine and activate complement system

Basophils and mast cells

C3a, C5a, C3b → Platelets

Release of vasoactive amine → Phagocytose complex → Release the enzymes in lysosome → Tissue injury

Increase vascular permeability → Edema

Blood Clotting Mechanisms

Release of vasoactive amine → Aggregation of platelets → Thrombus → Increase vascular permeability → Edema

Tissue injury

Local or systemic immune complex diseases
Serum Sickness

• A systemic immune-complex complement dependent reaction to extrinsic antigens

• Severity is antigen-dose dependent

• Fever, skin rash, lymphadenopathy, and arthralgia

• C5 activates neutrophils to secrete protease that produce tissue damage
Serum Sickness (immune complexes in the blood)

- Foreign serum injection
- Foreign serum proteins
- Antigen:antibody complexes
- Antibody against foreign serum proteins
- Fever, vasculitis, arthritis, nephritis

Fig 12.20 © 2001 Garland Science
Immune Complex Mediated Hypersensitivity

1. Immune complexes are deposited in wall of blood vessel.

2. Presence of immune complexes activates complement and attracts inflammatory cells such as neutrophils.

3. Enzymes released from neutrophils cause damage to endothelial cells of basement membrane.
Type IV (Delayed Type) Hypersensitivity

• Refers to inflammation generated by the reaction of antigen with its corresponding (specific) T-cell.

• Characteristics:
  – delayed (48-72 hours).
  – Lack of tissue specificity.
  – Antibody – Independent.
  – Tendency towards mononuclear cell infiltration, often in a perivascular distribution. The hallmark is granuloma.
  – Refractoriness to antigen-specific desensitization.
  – Adoptive transfer of the hypersensitivity.

• Prototype is PPD.
Delayed-type hypersensitivity (DTH) (e.g., tuberculin skin test)

- Antigen is injected into subcutaneous tissue and processed by local antigen-presenting cells.
- A $T_H1$ effector cell recognizes antigen and releases cytokines which act on vascular endothelium.
- Recruitment of phagocytes and plasma to site of antigen injection causes visible lesion.

$T_H1$ from a previous immunization (memory)

Fig 12.22 © 2001 Garland Science
(a) Sensitization phase

Intracellular bacteria

APC

CD4+ T_H

T_H1 cells (generally)

Antigen-presenting cells: Macrophages, Langerhans cells

DTH-mediating cells: T_H1 cells generally CD8 cells occasionally
(b) Effector phase

Sensitized T\textsubscript{H}1

Membrane TNF-\beta

Secreted IFN-\gamma

Resting macrophage

Class II MHC

Activated macrophage

TNF receptor

\textbf{T\textsubscript{H}1 secretions:}

Cytokines: IFN-\gamma, TNF-\beta, IL-2, IL-3, GM-CSF

Chemokines: IL-8, MCAF, MIF

\textbf{Effects of macrophage activation:}

↑ Class II MHC molecules

↑ TNF receptors

↑ Oxygen radicals

↑ Nitric oxide
Chemical Mediators of DTH

Antigen is processed by tissue macrophages and stimulates $T_H^1$ cells

- Chemokines
- Cytokines
- Cytotoxins

$T_H^1$

**Chemokines**
- Recruit macrophages to site of antigen deposition

**IFN-γ**
- Induces expression of vascular adhesion molecules.
- Activates macrophages, increasing release of inflammatory mediators

**TNF-α and TNF-β**
- Cause local tissue destruction.
- Increase expression of adhesion molecules on local blood vesssels

**IL-3/GM-CSF**
- Stimulate monocyte production by bone marrow stem cells

Fig 12.23 © 2001 Garland Science
# Delayed-type hypersensitivity

Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Antigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-type hypersensitivity</td>
<td>Proteins: Insect venom, Mycobacterial proteins (tuberculin, lepromin)</td>
<td>Local skin swelling: Erythema, Induration, Cellular infiltrate, Dermatitis</td>
</tr>
<tr>
<td>Contact hypersensitivity</td>
<td>Haptens: Pentadecacatechol, DNFB, Small metal ions: Nickel, Chromate</td>
<td>Local epidermal reaction: Erythema, Cellular infiltrate, Vesicles, Intraepidermal abscesses</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy (celiac disease)</td>
<td>Gliadin</td>
<td>Villous atrophy in small bowel Malabsorption</td>
</tr>
</tbody>
</table>
Type IV (Delayed Type) Hypersensitivity

- **Allergic contact dermatitis**
  - Pentadecyl catechol (poison ivy and poison oak).
  - Organic chemicals (cosmetic, insecticides, disinfectants).
  - Metals (nickel, mercury, chromium, copper).
  - Synthetic products (rubber, leather).

- **Photoallergic contact Dermatitis**
  - Antigens require activation by UV light.
  - Affects sun exposed areas.
  - Associated with drugs or chemical constituents of topical products such as soap, cosmetics, and topical drugs.
Allergic Contact Dermatitis Response to Poison Ivy Hapten
Contact Dermatitis

Contact-sensitizing agent penetrates the skin and binds to self proteins, which are taken up by Langerhans' cells

Langerhans' cells present self peptides haptenated with the contact-sensitizing agent to T<sub>H1</sub> cells which secrete IFN-γ and other cytokines

Activated keratinocytes secrete cytokines such as IL-1 and TNF-α and chemokines such as IL-8, IP-9 and MIG

The products of keratinocytes and T<sub>H1</sub> cells activate macrophages to secrete mediators of inflammation
Allergic Bronchopulmonary Aspergillosis

- **Biphasic:** IgE to spore allergens (atopy) and IgG to mycelial antigen (serum sickness).

Hypersensitivity pneumonitis (extrinsic allergic alveolitis)

- It involoves antibodies, T cells or both but T – cell mechanisms predominate.
- Allergens are frequently components of biologic organisms or their products.
- It is an occupational disease (Bird handlers disease, birds fanciers lungs, pigeon breeder’s disease …)
Relevance of Th subsets in humans
Lepromatous and tuberculoid leprosy

Infection with *Mycobacterium leprae* shows two main clinical forms associated with Th1 and Th2 responses

**Tuberculoid leprosy**
- Low infectivity
- Localised infection
- Normal serum Ig
- Normal T cell response
- Poor growth of mycobacteria in macrophages

**Lepromatous leprosy**
- High infectivity
- Disseminated infection
- Hypergammaglobulinaemia
- Unresponsive
- Florid growth of mycobacteria in macrophages
Tuberculoid leprosy