Type IV hypersensitivity / Cell mediated (delayed) H.S.

- Inflammatory reaction occurs as a result of interaction between actively sensitized T-Lymphocytes & specific Ag.

- The reaction is mediated by:
  
  a. **Lymphokines** (CD4⁺ → Th1 → T_{DTH})
     
     The effector cells that are responsible for delayed-type hypersensitivity reaction are CD4⁺ Th1(T_{DTH}). The Lymphokines secreted by these cells recruit & activate macrophages and cause tissue damage.

  b. **Cytotoxicity** (CD8⁺ → CTLs)
     
     The effector cells that are responsible for cell mediated cytotoxic reaction are CD8⁺ CTLs.

  c. **Both reactions**.

- It is a delayed type reaction because it takes 24-72 hours to develop.

- The complement & antibodies play no role in this reaction.

- Delayed type H.S. is a major immune response to intracellular microbes, including:
  
  a. Bacteria → Mycobacterium T.B., Mycobacterium Leprae
  
  b. Viruses → Measles, chicken pox, herpes
  
  c. Parasite → Leishmania species
  
Mechanism of delayed type H.S.:
Antigens that induce type IV H.S. tend to activate Th lymphocytes of Th1 subset, which are often referred to as $T_{DTh}$ cells.
The activated Th1 cells secret a number of Lymphokines including:
1. Migration-inhibition factor (MIF) → inhibit migration of lymphocytes
2. Macrophage-activation factors (MAF) such as IFN-$\gamma$, granulocyte – macrophage- colony stimulating factor (GM-CSF), and TNF-$\alpha$ enhance the microbicidal and cytolytic activity of macrophages.
3. Leukocyte inhibition factor inhibits random migration of neutrophils.
4. Macrophage chemotactic factor
5. IL2 stimulates the growth of activated T cells & activates cytotoxic T lymphocytes.
6. TNF-$\beta$ (lymphotoxin)
These cytokines lead to the recruitment of large number of monocytes from the blood & to their activation when they become macrophages in the tissues.
The activated macrophages phagocytose the Ag & release active $O_2$ metabolites, proteases & other lysosomal enzymes, some of which leak out of the cells & damage the surrounding tissue.
**Mechanism of CTLs mediated cytotoxicity:**

Plays a critical role in the host-cell mediated immune response against viral infection, graft rejection ...etc

The CTLs recognize target cell following interaction between its TCR & MHC class I antigens on surface of target cell. The CTLs kill their target by delivery of toxic granule contents that induce the apoptosis of the cell to which they attach. This process occurs in four phases:

1. **Attachment** to target
2. **Activation** (Concentrate granules against attached target)
3. **Exocytosis** of granule contents (perforin & granzymes)
4. **Detachment** from the target
Clinical examples on delayed type H.S.:

*Tuberculin skin test (TT):*
- Positive TT indicates the presence of specifically sensitized T-lymph.
- Principles:
  - The antigen is PPD (purified protein derivatives) of tuberculosis bacillus → Standardized to Tu (Todd units)
  - 5-250 Tu of PPD are injected intradermally
  - The reaction appears slowly after 48-72 hours.
  - In positive reaction, there is erythema & induration of > 10 mm in diameter.
- **Negative TT indicates:**
  1- No T.B. infection
  2- Presence of Anergy (state of unresponsiveness) due to:
    ** Overwhelming infection
    ** Immunosuppressive illness
    e.g. sarcoidosis, AIDS, Hodgkin's disease.

*Positive tuberculin (Mantoux) test indicates:*
1- Active T.B. infection
2- An unapparent (sub clinical) infection
3- Past history of the disease
4- Previous immunization

**Allergic contact dermatitis:**
- Due to contact with sensitizing substances or Ag including:
  - Topically applied drugs (neomycin)
  - Cosmetics, nickel & chromate (costume jewelers)
  - Dyes, rubber compounds, preservatives ...etc.
Most of these substances are small molecules that can complex with skin proteins & serve as haptens. This complex is internalized by APC in
the skin (Langerhans cells), then processed & presented together with MHC class II mol. causing activation of sensitized T<sub>DTH</sub> cells.

**Immunological features:**
- T-cell mediated eczematous disease
- Characterized by 48hrs delayed eczematous response to the epicutaneous application of Ag.

**Clinical features:**
- Eczematous reaction.
- Acute form → erythema, oedema, vesiculation
- Chronic form → scaling

**The site of lesion is a clue for diagnosis:**
- Ear lobes → earring
- Around neck → neck lacer
- Wrist → watch, bracelets, bands

**Diagnosis:**
- History
- Distribution of lesion
- In vivo diagnosis
- * patch test

**Patch test:**
A low dose of suspected Ag is placed on a patch of the patient's skin. Eczema may develop 48-72 hrs later, indicative of type IV H.S.
**NOTE:** Penicillin can induce HS reaction by 4 mechanisms.

**Penicillin-induced H.S. reactions:**

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Ab or lymphocyte induced</th>
<th>Clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE</td>
<td>- Urticaria&lt;br&gt;- Syst. Anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>IgM IgG</td>
<td>- Haemolytic anemia</td>
</tr>
<tr>
<td>III</td>
<td>IgG</td>
<td>- Serum sickness&lt;br&gt;- G.N.</td>
</tr>
<tr>
<td>IV</td>
<td>TDTH cells</td>
<td>- Contact dermatitis</td>
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**The 4 types of hypersensitivity reactions:**