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## IMMUNOPATHOLOGY COURSE

# CHAPTER 1:

# HYPERSENSITIVITIES

Intended for students in: **3rd year Doctor of** Veterinary Medicine

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# CHAPTER 1: HYPERSENSITIVITIES

## 1. OBJECTIVES

Upon completion of this chapter, the student will be able to:

- Distinguishing between the different states of hypersensitivity
- Identify the cellular and molecular effectors involved in the lesioning processes
- Link clinical manifestations to immunopathological processes
- Define the decision tree that will allow him to make the immunological diagnosis for each type of hypersensitivity

## 2. DEFINITION

A reaction to an antigen is classified as immune if it does not cause pathological changes in the tissues.

The term "hypersensitivity" is reserved for an exaggerated or inappropriate immune response secondary to the introduction of various antigens (**allergens)** capable of producing changes either at the tissue level or in a generalized way.

## 3. ALLERGENS

Allergens are antigens introduced into the body through various routes:

### 3.1 INHALATION

Aeroallergens are allergens that enter the body through the airways. These mainly include: pollen, dust, animal products (hair, feathers, etc.), tobacco, and chemicals (chlorine, air fresheners, essential oils).

### 3.2 DIGESTIVE

The foods most often implicated in allergology are proteins (eggs, milk, nuts/peanuts, almonds, crustaceans and seafood) or food additives.

### 3.3 INJECTABLE

This is the case with insect bites (fleas in carnivores or diptera in horses), venoms (from bees or wasps), and medications (penicillins, anesthesia, and vaccines).

### 3.4 CUTANEOUS

Chemicals (cosmetics) and animal products cause a skin allergy known as contact allergy

### 3.5 OTHER WAYS

Allergens can be introduced into the body through other routes such as the ocular or genital mucous membranes…

# 4. CLASSIFICATION

Based on the cells and mediators involved, Coombs and Gell described four types of hypersensitivity (allergies) designated I, II, III and IV:

- Type I: immediate or anaphylactic : 15 to 30 min (IgE)
- Type II: cytotoxic : 1 to 3 hours (IgG, IgM)
- Type III: sub-acute : 3 to 6 hours (immune complexes)
- Type IV: delayed : 48 to 72 hours (cell-mediated)

The first three types involve **antibodies (humoral response)** while the last is due to macrophages **and** T **cells (cellular response)**.

## 4.1 HYPERSENSITIVITY TYPE I: IMMEDIATE ALLERGY

It is a rapid, abnormal and excessive immune and inflammatory reaction in some genetically predisposed (or atopic) individuals to allergens.

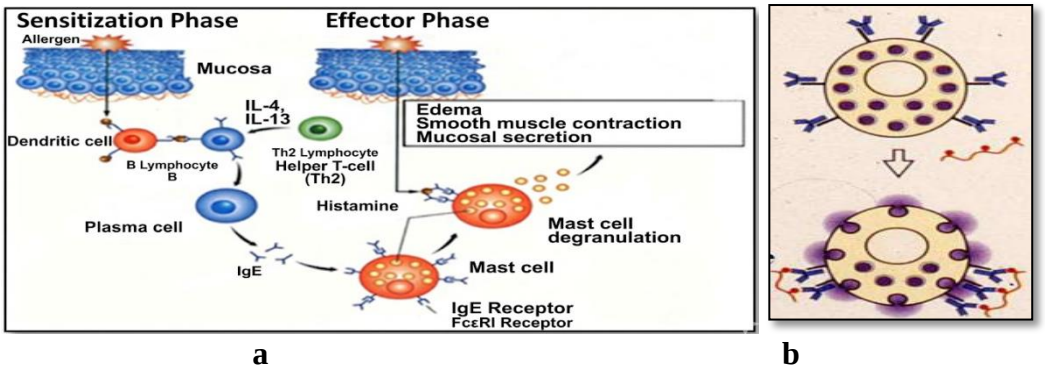
The symptoms are very rapid (a few minutes) after contact with the allergen.

### 4.1.1 Pathogenesis

There are two immunological phases in immediate hypersensitivity:

✓An initial sensitization (immunization) phase leads to the synthesis of specific IgE. It is clinically silent (asymptomatic).

✓A second phase, known as the "revelation" or "effector" phase, is clinically symptomatic, linked to the immediate activation by the allergen of cells (mainly mast cells and basophils) carrying IgE on their surface **(figure 1 a)**




**a** **b**

**Figure 1**: Type I hypersensitivity reaction ( Roitt et al, 1997)

(**A:** Immunological phases, **B:** IgE bridging phenomenon by the allergen)

### A. Sensitization phase

It occurs after the first contact with the allergen. It corresponds to a classic immune reaction:

- penetration of the allergen through the epithelial barriers
- handling of the allergen by dendritic cells (APCs: Antigen-presenting cells)
- maturation and migration of dendritic cells to the lymph nodes
- activation (by dendritic cells) of corresponding specificity T lymphocytes (CD4+ T cells) and orientation in allergy which will differentiate into Th2 cells ( T-cells or helper cells)
- Th2 lymphocytes release cytokines such as IL-4, IL-5, and IL-13, which are responsible for the proliferation of allergen-specific B lymphocytes that triggered the immune response and their transformation into plasma cells that exclusively synthesize IgE
- Cooperation between Th2 lymphocytes and B lymphocytes (switch signal)
- Thus, IL-5 stimulates the proliferation of eosinophils and their passage into the blood with hypereosinophilia and also their activation
- binding of IgE to their high-affinity receptors (Fc εRI : receptor I of the FC portion of IgE) present on mast cells and basophils

The awareness phase can last from a few weeks to a few years.

**B. Effector phase**

It is triggered upon the **second (and subsequent) contact** with the same allergen (Ag). The latter binds to at least two IgE molecules attached to the mast cell membrane (cross-linking of IgE carried by FcεRI), and induces **mast cell degranulation (Figure 1b)** with the release of inflammatory reaction mediators responsible for the clinical signs of allergy. The main mediators are:

- Primary "preformed" molecules, secreted during the immediate phase; such as vasoactive amines (**mainly histamine)**, proteoglycans, polypeptides, chemokines and cytokines
- Secondary "newly formed", secreted late which are the lipid and protein mediators newly synthesized from membrane phospholipids under the action of phospholipase A2, such as arachidonic acid derivatives (prostaglandins, leukotrienes) and platelet-activating factor (PAF) .

Degranulation is therefore a finely regulated process controlled by proteins specialized in the fusion of plasma membranes and organelles. Mast cell exocytosis is a rapid phenomenon, reaching its peak approximately 15 minutes after aggregation by the allergen, hence the name immediate hypersensitivity. The IgE- FcεRI complex, already present on the cell surface, thus prepares the cell for degranulation upon contact with the allergen.

### 4.1.2 Clinical manifestations

During the exocytosis of the granular contents, histamine diffuses through the tissues to bind to its receptors (mainly H1 and H2), causing local and systemic reactions:

- **Vasodilation** and **increased capillary permeability** => clinical consequences: urticaria, deep tissue edema, circulatory failure leading to shock
- **Contraction of smooth muscles** (branches and intestine) with bronchospasm (consequence: asthma attack) and an increase in intestinal peristalsis (diarrhea, vomiting).
- **Increased secretions from bronchial mucus glands**
- **Increased acid secretion in the stomach**

The term anaphylaxis refers to the set of symptoms linked to the activation of mast cells and basophils. It is often classified according to the severity of the symptoms: from **local reaction** (local signs) or grade I anaphylaxis (localized itching, erythema and edema), to moderate **systemic reactions** or grade II anaphylaxis (urticaria, angioedema, vomiting, diarrhea, moderate abdominal pain), to severe systemic reactions or grade III anaphylaxis (cyanosis, dyspnea, bronchospasm, drop in blood pressure), anaphylactic shock or grade IV anaphylaxis (shock, cardiorespiratory arrest).

### 4.1.3 Diagnosis

- **Medical history:** circumstances of onset, clinical signs, season
- Exploration of atopic terrain
- ***In vivo* tests :**
  - **Immediate reading skin tests (15-20 min):**
    - **Prick test (most commonly used):** Drops of the allergen + prick through the drop with the needle => reading after 15 to 20 minutes => Positive reaction: induration, erythema, diameter >15 mm
    - **Scratch test (less commonly used):** Skin abrasion + application of allergen to the skin => reading after 15 to 20 minutes => Positive reaction: wheal, erythema, diameter >15 mm
  - **Delayed reading skin tests (24-48 h):** In dogs, the flea extract IDR is always read at 15 min and at 48h.
  - **Total IgE levels:** non-specific (also elevated during parasitic infection)
- ***in vitro* tests**

The main serological or cellular tests are: ELISA, radioimmunoassay, and fluorescence (or HPLC).

### 4.1.4 Treatment and prevention

- **Avoidance** (elimination) of the allergen
- **Desensitization:** administration of increasing doses of the allergen
- **Pharmacological management: Antihistamines** (H1 antihistamines are more specific; H2 antihistamines can be used in combination), **Corticosteroids** (usually prednisolone)
- **Innovative drug** : Anti-IgE antibodies, e.g., Omalizumab (very expensive, a last resort)

## 4.2 TYPE II HYPERSENSITIVITY (HSII): CYTOTOXIC

Also known as "cytotoxic hypersensitivity," it can affect a variety of organs and tissues, causing significant damage and impaired function. The reaction time ranges from a few minutes to a few hours.

-This type of hypersensitivity is characterized by the involvement of two other classes of immunoglobulin: IgG and IgM, the complement system, phagocytic cells, and NK cells.

-The antigen is membrane-bound or intracellular

-Blood cells (red blood cells, white blood cells and platelets) can be a target of reactions of this type of hypersensitivity

### 4.2.1 Injury Mechanisms

The effector is an IgG-type antibody primarily capable of (Figure 2):

- Activating complement via the classical pathway, resulting in direct lysis => this is complement- dependent cellular cytotoxicity (CDCC).
- Opsonizing the target cell activates cells expressing an FcR (receptor for the FC portion of Ig), such as macrophages, polymorphonuclear leukocytes, or NK cells => this is phagocytosis (ADCP: Antibody-Dependent Cellular Phagocytosis) or ADCC (Antibody-Dependent Cellular Cytotoxicity) for NK cells
- It may be possible to simply stimulate a receptor on the target cell (hormone receptors, neurotransmitters, etc.) where Ig acts as a ligand (agonist or antagonist) without lysis of the target cell.

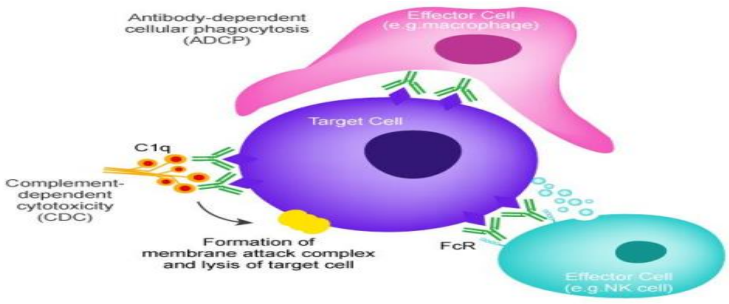



**Figure 2:** Mechanisms involved in type II hypersensitivity (Mebirouk, 2023)

****Noticed :**

IgM antibodies do not interact with effector cells, which lack the receptor, but being pentameric, they very easily activate the complement cascade and can agglutinate cells that carry the antigens.

### 4.2.2 Examples of diseases related to type II hypersensitivity

- **Autoimmune diseases**

The course of autoimmunity is frequently accompanied by the production of IgG or IgM autoantibodies, some of which cause cellular or tissue damage by participating in type II hypersensitivity reactions such as:

- **Myasthenia gravis** (human, dog and cat), **Hyperthyroidism or Graves' disease** (human, canine), **Severe glomerulonephritis** or "good pasture syndrome" (human, horse), **Anemias and cytopenias** : these can be of drug origin (penicillin, quinidine, aminosalicylic acid, phenylbutazone, sulfonamide) , infectious ( equine infectious anemia "retroviral disease", anaplasmosis, lipopolysaccharides of *Salmonella sp* .), parasitic (babesiosis), or toxi**c**

- **Transfusion reactions**

Transfusion of blood to a recipient who has circulating antibodies directed against the donor's erythrocytes can precipitate the onset of an immediate transfusion reaction (less frequent in animals during a first transfusion) and often severe in humans which results from intravascular lysis of the donor's cells and reflects a type II hypersensitivity reaction.

- **Hemolytic disease of the newborn**

It occurs in the newborn when maternal IgG class antibodies directed against fetal erythrocyte (red blood cell) antigens (antigens inherited from the father and foreign to the mother) cross the placenta and destroy the fetal erythrocytes.

This is the case with RhD disease in humans. The risk exists when an Rh-negative mother carries an Rh-positive child. Immunization most often occurs after childbirth, when fetal red blood cells enter the maternal circulation. This explains why the first child is generally unaffected. The risk appears in the second child and increases progressively in subsequent children.

Maternal antibodies can occasionally enter the newborn's bloodstream in certain animal species (primarily Thoroughbred foals) via colostrum. There, they cause hemolytic anemia (with

progressive weakness, pallor, jaundice, and hemoglobinuria), which is usually severe and sometimes fatal. Treatment involves changing the source of milk for 72 hours.

### 4.2.3 Diagnosis

The diagnosis of type II hypersensitivity is based on the detection of circulating, tissue or complement antibodies (in biopsy); example direct or indirect Coombs test.

### 4.2.4 Processing

Currently, the treatment of autoimmune diseases consists of correcting clinical disorders and using immunosuppressive drugs to control abnormal immune responses.

Transfusion accidents and hemolytic disease of the newborn can be prevented by appropriate donor and recipient selection.

## 4.3 TYPE III HYPERSENSITIVITY (HSIII): Sub-acute

### 4.3.1 Characteristics

- ✓ Hypersensitivity mediated by the deposition of immune complexes (IC) in the vascular bed, within tissues, or in organs ➔ (immune complex hypersensitivity).
- ✓ In their normal state, these immune complexes are not pathogenic, but when they persist in the circulation or in tissues, they can cause an abnormal (harmful) inflammatory reaction.

In normal cases, the elimination of ICs by the immune system involves (Figure 3):

1. **Complement system:** allows the solubilization of CI via the C3b fragment
2. **Red blood cells:** presence of complement receptors CR1 (Complement Receptor1) allowing the transport of ICs to the organs of elimination (liver, spleen)
3. **Hepatic and splenic macrophages:** Phagocytosis and elimination after capture of ICs via FcγRII and CR2 (Complement Receptor 2) receptors present on phagocytic cells

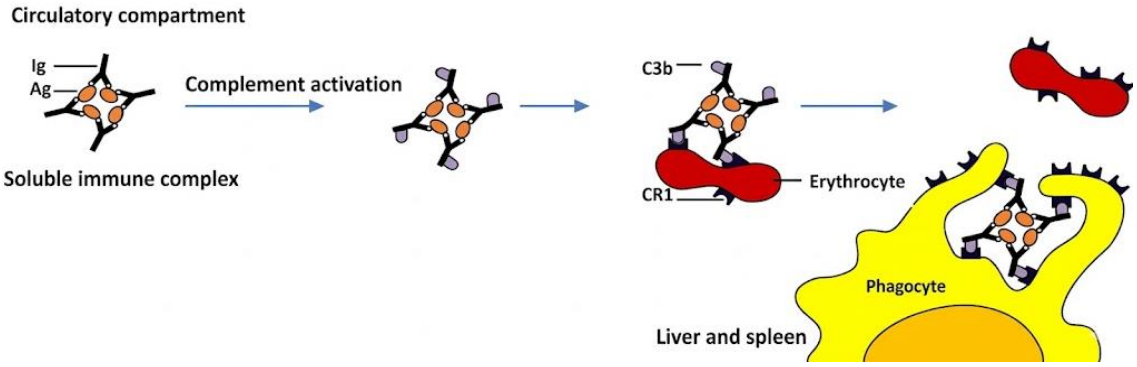



**Figure 3:** Elimination of ICs by the immune system (Zemouli, 2022)

### 4.3.2 Factors determining the persistence of immune complexes

**A. Size of immune complexes (IC)**

The size of the ICs depends on the concentration of the Ag or the Ab and on interactions with other plasma constituents:

- Thus, large ICs, formed in the equivalence zone or in the zone of excess antibodies with multivalent antigens, are rapidly eliminated.
- Small or intermediate-sized interferons that form in areas of antigen excess are the most pathogenic because they are eliminated more slowly and tend to accumulate in tissues and organs.

**B. Ig class**

- IgG binds to red blood cells and is gradually eliminated
- IgA binds poorly to red blood cells and is rapidly cleared from circulation to be deposited in the basement membranes of tissues

**C. Capacity for clearance of ICs by the hepatosplenic phagocytic system**

- Complement system and/or phagocytosis deficiency
- CR1 deficiency in red blood cells
- System saturation

**D. Hemodynamic factors:**

• **Increased blood pressure and turbulence**: ICs are more easily deposited in areas of turbulence and high blood pressure (glomerulus+++, synovial capillaries, choroid plexus of the eye).

• **Increased vascular permeability**: is probably the most important factor in the deposition of ICs in tissues following the release of vasoactive amines and anaphylactoxins (histamine, serotonin, C3a, C5a,…)

**E. Electrical charge of ICs**

Positively charged Ag will deposit more easily on negatively charged basement membranes.

### 4.3.3 Injury mechanisms

The antigens (Ag) that trigger a type III hypersensitivity reaction can be environmental (exogenous), infectious (chronic infection) or endogenous (self-Ag or modified self-Ag in autoimmune diseases).

These Ag induce the formation of IgG or IgM antibodies (Ab) which form with them Ag-Ab complexes or immune complexes (IC) which can trigger acute inflammatory reactions by various mechanisms.

The complexes can initially stimulate macrophages via their Fcγ receptors , thereby inducing the release of pro-inflammatory cytokines, particularly IL-1 and TNF. Macrophages often have difficulty digesting the insoluble complexes they have phagocytosed, which therefore constitute a persistent activating stimulus.

In the event of complement fixation, anaphylatoxins C3a and C5a cause the release of mediators by mast cells, basophils and platelets and thus the increase in vascular permeability , which promotes the deposition of immune complexes in the vessel wall .

Thus, chemotactic factors (C5a) will trigger an influx of neutrophils, which cannot phagocytose the deposited ICs and release their lysosomal enzymes and toxic radicals into neighboring tissues, causing various types of damage (arteriolar lesions with thrombosis, hemorrhage, and necrosis of capillary walls). Consequently, platelets aggregated in contact with the collagen of the vascular basement membrane form microthrombi (thrombosis).

### 4.3.4 Types

Type III hypersensitivity states can be divided into **systemic and local reactions:**

- In **systemic forms, circulating soluble** immune complexes form at a distance from where they will induce lesions, corresponding to the experimental model of serum sickness.
- In **local forms, insoluble** immune complexes cause tissue damage at the point of antigen penetration into the body, a phenomenon corresponding to the experimental model of the Arthus phenomenon.

### 4.3.5 Pathologies associated with type III hypersensitivity

The elimination of ICs is therefore more or less rapid by the phagocytic cells of the reticuloendothelial system, but these ICs can escape the phagocytes and will be deposited locally on blood vessels, or in organs (kidney, lungs, eye and joint) causing the following diseases:

**a. Arteritis**

Observed during equine viral arteritis and polyarteritis nodosa in carnivores.

**b. Glomerulonephritis**

It is often the result of type III hypersensitivity involving the deposition of soluble interferons on the glomerular basement membrane (as in systemic lupus erythematosus with

autoantibodies) or of insoluble intravascular interferons. These deposits impair glomerular filtration and trigger an inflammatory reaction leading to proteinuria and even hematuria. Glomerulonephritis is not uncommon in humans and has been described in all domestic animal species.

**c. Pneumonia and pulmonary alveolitis**

Allergic reactions occur in humans, horses, and cattle following repeated inhalation of antigens (spores of *Micropolyspora faeni,* various Actinomyces species, etc.) contained in moldy hay. The antibodies produced form immune complexes with the corresponding antigens and cause the appearance of a fairly characteristic respiratory symptomatology (extrinsic allergic alveolitis). Other pneumonias with a similar mechanism are occupational in humans (farmer's lung, bird fancier's lung, and pigeon fancier's lung).

**d. Uveitis**

Uveitis in animals is a fairly common consequence of the formation of circulating intraocular antibodies (IOA). It occurs primarily after vaccination or infection with canine adenovirus type 1 (canine infectious hepatitis), but also in other chronic diseases such as toxoplasmosis, leptospirosis, and fungal infections. The inflammation of the eye will damage the cornea, causing it to become opaque.

**e. Arthritis**

Among the many forms of arthritis, rheumatoid arthritis is a chronic inflammatory polyarticular condition in which anti-IgG antibodies, for example IgM or IgA (called rheumatoid factor), are deposited in the synovium and circulate in the blood.

**4.3.6 Diagnosis**

- **Precipitation of CIs** with **PEG (polyethylene glycol) or RAJI** cells (a lymphoblast-like cell line created from a lymphoma) on serum
- **Detection of ICs by immunohistochemistry** Immune complex deposits in lesions are visualized on tissue sections obtained from biopsies using immunofluorescence. This method is more sensitive and specific for identifying immune complexes within lesions, thus offering real diagnostic value, but it does present technical challenges **.**

**4.3.6 Processing**

- The avoidance of inhaled exogenous antigens is obvious
- Elimination of microorganisms associated with IC disease through the use of antibiotics
- Heparin and salicylates are often used to stabilize platelets and reduce inflammation.

- Corticosteroids are particularly potent inhibitors of inflammation and are immunosuppressants.

## 4.4 TYPE IV HYPERSENSITIVITY (HSIV): DELAYED

### 4.4.1 Characteristics

Delayed hypersensitivity (DHS) differs from other types of hypersensitivity in two ways:

➢ Injection of the antigen into a sensitized individual triggers a local reaction that manifests between 24, 48 , and 72 hours. This HSR is always localized to a tissue.

➢ Passive transfer from a sensitized animal to a naïve animal occurs only via T cells and not via serum. This is a cell-mediated HS.

The HSR is involved in:

- Autoimmune diseases (contact dermatitis, type 1 diabetes, thyroiditis)
- Responses to certain infections or foreign bodies: granuloma
- Control of certain infectious diseases: tuberculous granuloma
- Acute and subacute graft rejection

### 4.4. 2 Types

Three types of type IV HS are currently recognized**: contact**, **tuberculin**, and **granulomatous** . They are distinguished by the nature of the reaction produced and the duration of their onset. The first two types manifest 48 to 72 hours after further stimulation by the antigen. In contrast, the third type extends over a period of 21 to 28 days.

The situation can be complicated by the fact that these three forms of HSR can either overlap or occur sequentially following a new antigenic stimulation. Therefore, the HSR reactions observed in practice do not fall into a single category.

❖ **Contact hypersensitivity**

Clinically, it is characterized by the appearance of an eczematous lesion at the site of contact with the allergen 48 hours later; these are pruritic lesions with the appearance of small vesicles (edema).

The agents involved (allergens) are haptens such as nickel, mercury, chromium salt (cement) or certain low molecular weight chemical compounds (<1000Da) such as products used in the composition of gums, rubber, glues, paints, pesticides, cosmetics or certain drugs (anti-inflammatories).

Contact HS is primarily epidermal, and is determined by two phases: sensitization and triggering (figure 4):

**A. Awareness (or induction) phase**

The first contact with the allergen leads to the generation of T lymphocyte clones and their differentiation into Th1 memory cells.

The hapten, which is too small (lipophilic), binds to a normal skin protein called a carrier protein. This complex is then processed by epidermal Langerhans cells (APCs). These APCs are dendritic cells that express the CD1 antigen of cortical thymocytes and MHC class II antigens. Langerhans cells leave the epidermis and migrate, via efferent lymphatic vessels as veiled cells, to the paracortical zone of the regional lymph node where they differentiate into interdigitating cells. The hapten-protein complex is processed and presented, in association with MHC-II molecules, to CD4+ lymphocytes, resulting in a population of memory CD4+ cells.

However, in some models of contact dermatitis, transfer is ensured by CD8+ T cells that interact with MHC class I Ag.

Dermal and epidermal infiltrates intensify, reaching a maximum between 48 and 72 hours.

**B. Triggering (or provocation) phase**

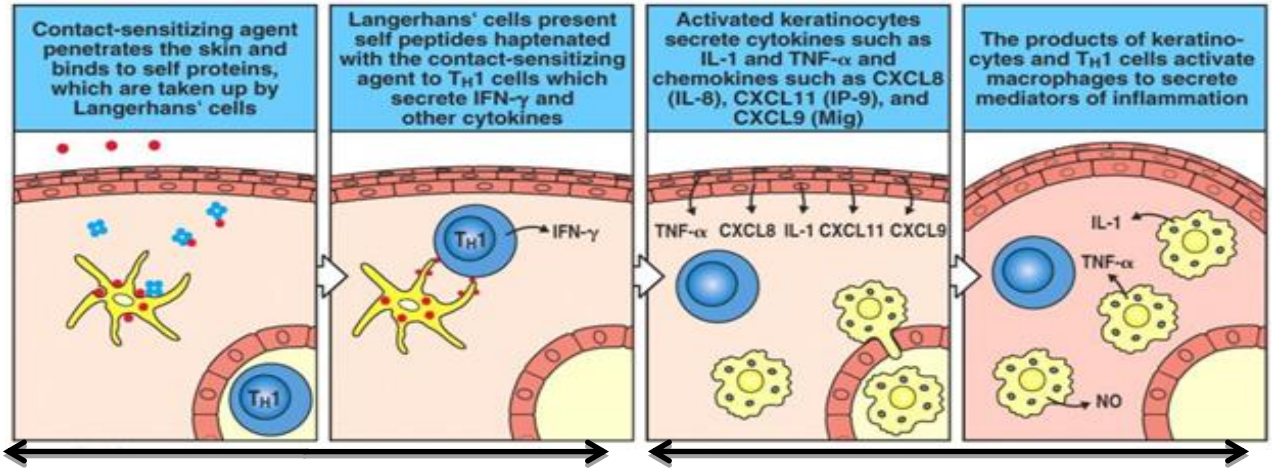
This phase leads to dermatitis, which occurs upon reintroduction of the allergen. Memory Th1 lymphocytes, brought to the skin by the bloodstream, encounter the antigen (hapten + protein) presented by the Langerhans cell or other antigen-presenting cell of the epidermis.

Local activation of memory lymphocytes initiates local inflammatory phenomena with dermal and epidermal infiltrates made up of CD4+ and CD8+ lymphocytes, mononuclear cells and macrophages.

Activated T cells will synthesize cytokines including IL-2 and IFN γand will simultaneously express the IL-2 receptor which, by interacting with the cytokine, induces the proliferation of T lymphocytes and the stimulation of keratinocytes (CPA) to the synthesis of IL1 and TNF α.

Furthermore, the IFN γand TNF αproduced induce the expression of the adhesion molecules ICAM-1 and MHC II on the surface of endothelial cells of dermal capillaries and on the surface of keratinocytes, 24 to 48 hours after application of the Ag.

Beyond 72 hours, macrophages intervene, which after recruitment will attenuate the inflammatory reaction by synthesizing, among other things, prostaglandin PGE2 which inhibits the production of IL-2 and IL-1. These attracted macrophages are retained at the site of the inflammatory reaction thanks to the MIF produced by the activated T cells.




**A:** Awareness phase **B:** Triggering phase

**Figure 4:** Delayed contact hypersensitivity ( Roitt et al, 1997)

❖ **Tuberculin-type hypersensitivity**

This form of hypersensitivity was originally described by Koch, who observed that subcutaneous injection of tuberculin, a lipoprotein antigen extracted from the tubercle bacillus, caused a febrile reaction and general malaise in tuberculosis patients. This reaction was accompanied by an area of induration and swelling at the injection site, along with central necrosis if the reaction was very severe. It only manifests 24 hours after the injection, reaching its peak after 48 to 72 hours.

Soluble antigens obtained from a large number of microorganisms, such as *Mycobacterium tuberculosis* and *Leishmania tropica,* induce similar reactions in sensitized subjects.

Skin reactions are frequently used as a test to screen patients who have been exposed to these microorganisms. This form of hypersensitivity can also be induced by non-microbial antigens such as beryllium and zirconium.

The recruited memory lymphocytes align with the Th1 profile and produce cytokines (including IFN γand TNF α). Monocytes and macrophages are activated by Th1 cytokines and produce inflammatory cytokines (TNF and IL1).

A biopsy would show, from the 12th hour onwards, an infiltration of the dermis by mononuclear cells (lymphocytes, lymphoblasts and macrophages) without polymorphonuclear leukocytes (except for a brief influx)

The tuberculin lesion normally disappears in 5 to 7 days. The progression to a granulomatous reaction depends on the persistence of the antigen.

❖ **Granulomatous hypersensitivity**

It is considered the main clinical form of delayed hypersensitivity (the most severe form). It results from the persistent presence in the body, and more specifically in macrophages, of the antigen (intracellular microorganisms, particles or immune complexes) that the cell is unable to destroy.

Histologically, granulomatous HS is characterized by:

- ✓ Epithelioid cells (large flattened cells, derived from macrophages that are active for a prolonged period by TNF cytokines).
- ✓ Giant multinucleated cells (Langhans cells), resulting from the fusion of epithelioid cells. They would represent a terminal stage of the monocyte/macrophage lineage.
- ✓ Macrophages

The granuloma, which is the central area of the reaction, can become a necrotic focus that will be invaded by fibrosis.

*** Examples of pathologies accompanied by granulomatous-type HSR: tuberculosis, listeriosis, leishmaniasis, sarcoidosis, Crohn's disease and certain deep mycoses…

### 4.4.2 Diagnosis

- ***In vivo* tests** => skin tests: patch test, intradermal test, biopsy
- ***In vitro* tests** => testing of lymphoblastic transformation or measurement of lymphokine production (MIF, IL-2, IFN $\gamma$) after stimulation by a specific antigen