Hyper sensitivity reactions

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- Adaptive immunity serves the important function of host defense against microbial infections,
- but exaggerated immune responses, inadequately controlled, inappropriately targeted to host tissues (type , 2, 3 and 4 hypersensitivity), or environmental antigens that are usually harmless (allergy or type 1 hypersensitivity)); are also capable of causing tissue injury and disease.

TABLE 19-1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: type I	IgE antibody, T_H2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody–mediated: type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: type IV	1. $CD4^+$ T cells (T_H1 and T_H17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation

Table 5 - Comparison of Different Types of hypersensitivity				
characteristics	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	exogenous	cell surface	soluble	tissues & organs
response time	minutes30-15 hrs 2-	minutes-hours	hours 12-3	hours 72-48
appearance	weal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma

Types of hypersensitivity reactions

- **Type I reactions (i.e., immediate hypersensitivity reactions, allergy, atopy) :**Involves immunoglobulin E (IgE)–mediated release of histamine and other mediators from mast cells and basophils against foreign environmental proteins (pollens, animal danders - وبر – and house mites).

- **Type II reactions (i.e., antibody- mediated hypersensitivity reactions) :**
  Involves IgG or IgM antibodies bound to surface antigens on own cells of the body (autoimmune) or to foreign antigen, with subsequent opsonization and phagocytosis, complement- mediated lysis (autoimmune hemolytic anemia) and abnormality in cellular funcion**. RBC lysis or autoimmune disease**

- **Type III reactions (i.e., immune-complex reactions) :**
  Involves circulating antigen-antibody immune complexes that deposit, with subsequent attraction of polymorphs causing local inflammation and tissue damage (SLE, chronic glomerulonephritis, serum sickness). **erythema and edema, Autoimmune disease**

- **Type IV reactions (i.e., delayed hypersensitivity reactions (DTH), cell-mediated immunity) :**
  They are mediated by memory TH1 cells following 2nd contact to same Ag which secrete inflammatory cytokines that attract macrophages which release inflammatory mediators. Or by memory TH2 cell activate eosinophils infiltration in chronic asthma.or CTL mediated self cell damage. **erythema and induration, autoimmune disease and granuloma**

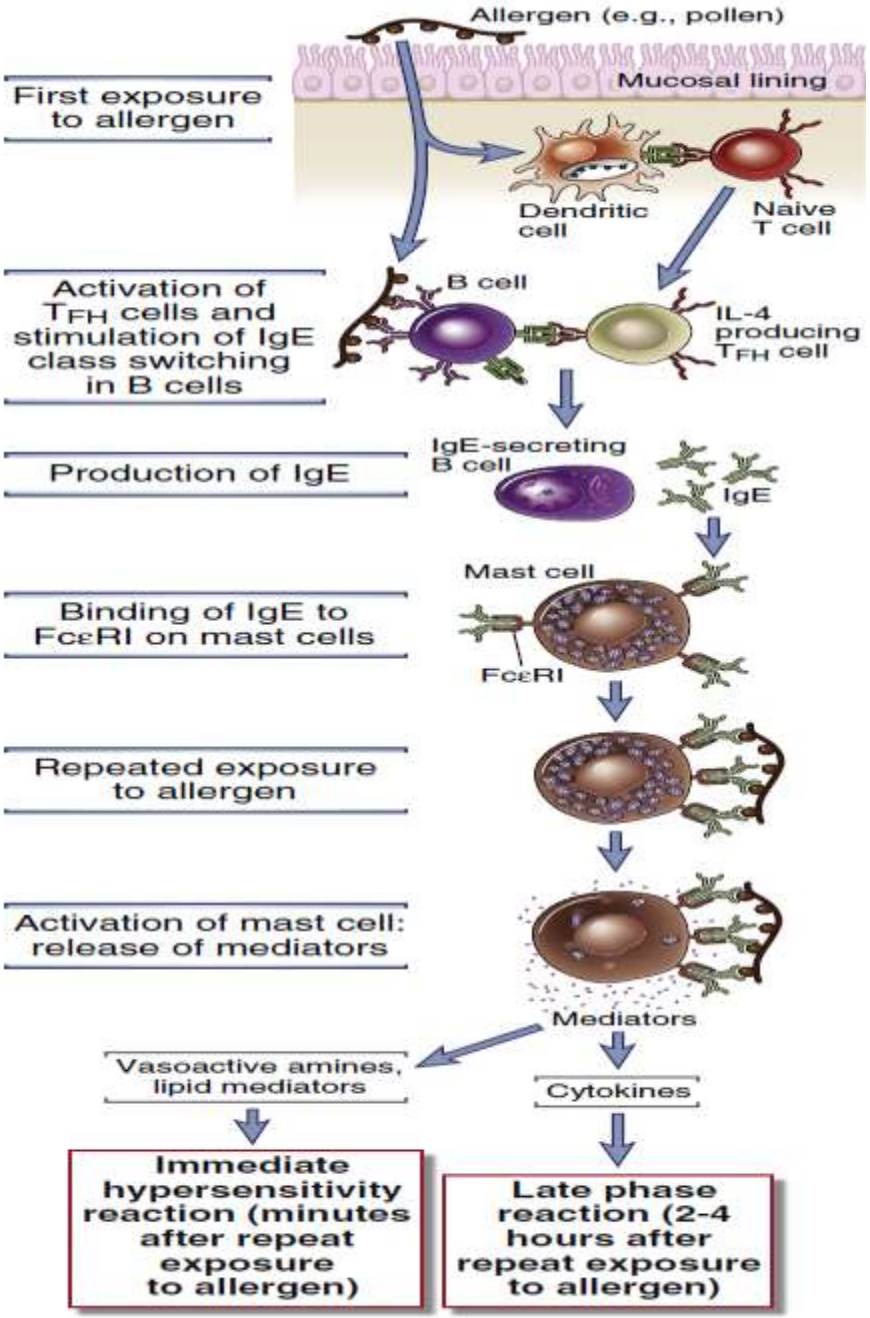
Type 1 hypersensitivity reaction
Allergy or atopy

- The allergic reaction first requires sensitization to the specific allergen and occurs in geneto-environmental factors predisposed individuals (those having certain MHC haplotype).
  The allergen is either inhaled contact skin or ingested or inected and is then processed by the dendritic cell
  The antigen-presenting cells then migrate to lymph nodes, where they prime naive TH cells to be TH2.

- These primed TH2 cells then bind activated B cells by same allergen, and TH2 release more IL-4, IL-5 and IL-13. then B cells to promote production of antigen-specific IgE antibodies.
- **IgE** antibodies can then bind to high-affinity receptors (FcεR1) located on the surfaces of mast cells and basophils(sensitization phase).

→ → → →

- Reexposure to the antigen can then result in the antigen binding to and cross-linking the bound IgE antibodies on the mast cells and basophils (effector or symptomatic phase). Cross linking is the binding of 2 IGE with one allergen
- This causes the release and formation of chemical mediators from these cells. These mediators include preformed mediators, newly synthesized mediators,


Allergen (e.g., pollen)
Mucosal lining
First exposure to allergen
Dendritic cell
Naive T cell
Activation of T_{FH} cells and stimulation of IgE class switching in B cells
B cell
IL-4 producing T_{FH} cell
Production of IgE
IgE-secreting B cell
IgE
Mast cell
Binding of IgE to FcεRI on mast cells
FcεRI
Repeated exposure to allergen
Activation of mast cell: release of mediators
Mediators
Vasoactive amines, lipid mediators
Cytokines
Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)
Late phase reaction (2-4 hours after repeat exposure to allergen)

The major mediators released from mast cells and their functions are described as follows

Preformed mediators (important for early phase reaction with in 5 min.):

- **Histamine (vasoactive amines)** : biogenic amines, short acting, This mediator acts on histamine 1 (H1) and histamine 2 (H2) receptors to cause contraction of smooth muscles of the airway and GI tract, increased vasopermeability and vasodilation, enhanced mucus production, pruritus (itching) , cutaneous vasodilation, and gastric acid secretion. H1 receptor antagonists (commonly called antihistamines) can inhibit the allergy response, H2 antagonist inhibit gastric secretions
- **Tryptase** : its exact role is uncertain,
- **Proteoglycans** : Proteoglycans include heparin.

Newly formed mediators

- **Mast cell activation results in the rapid de novo synthesis and release of lipid mediators that have a variety of effects on blood vessels, bronchial smooth muscle, and leukocytes.**
- **Lipid metabolites**
  - **Leukotrienes** cause prolonged bronchoconstriction
  - **Platelet-activating factor (PAF**): **Adenosine**: **Bradykinin (all function as histamine)** It increases vascular permeability, causes bronchoconstriction,
  - **prostaglandin D2** (PGD2). Released PGD2 binds to receptors on smooth muscle cells and acts as a vasodilator and a bronchoconstrictor

late phase reaction (cytokines)

- The immediate wheal-and-flare reaction is followed 2 to

4 hours later by a late-phase reaction consisting of the

accumulation of inflammatory leukocytes, including neutrophils,eosinophils, basophils, and helper T cells

- Cytokines produced by TH2 cells promote the activation

of eosinophils and their recruitment to late-phase reaction

inflammatory sites

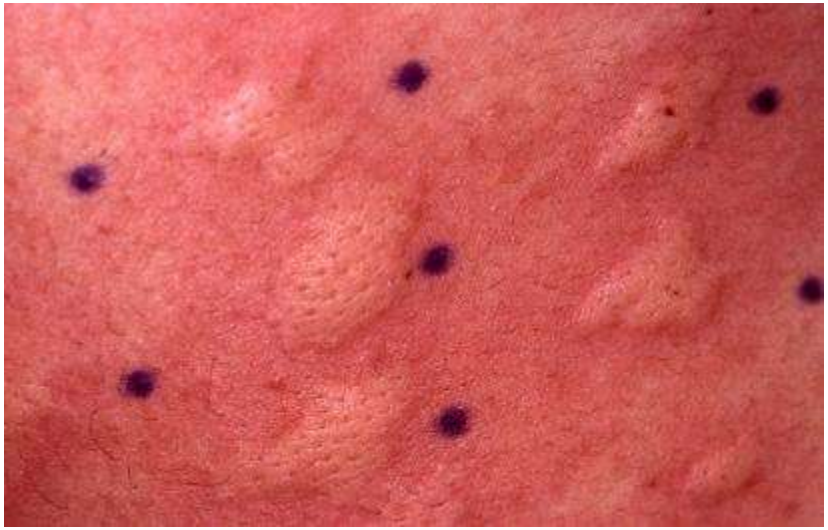
- **IL-4:**
  Stimulates and maintains TH2 cell proliferation and switches B cells to IgE synthesis.
- **IL-5:**
  This cytokine is key in the maturation, chemotaxis, activation, and survival of eosinophils.

- **IL-6: promotes mucus production.**
- **IL-13: This cytokine has many of the same effects as IL-4.**
- **Tumor necrosis factor-alpha: This activates neutrophils, increases monocyte chemotaxis,**

Clinical pictures

- **Urticaria (Eczema. Atopic dermatitis) and wheals formation:** Release of the above mediators in the superficial layers of the skin can cause pruritic wheals (suface swelling in the skin) with surrounding erythema. If deeper layers of the dermis and subcutaneous tissues are involved, angioedema results.
- **Allergic rhinitis (**nasal inflammation, called hay fever,**):** Sneezing, itching, nasal congestion, rhinorrhea, and itchy or watery eyes.
- **Allergic conjunctivitis** with itchy eyes
- **Anaphylaxis**: Systemic release of the above mediators affects more than one system and is known as anaphylaxis. systemic vasodilation and vasopermeability can result in significant hypotension and edema and is referred to as anaphylactic shock. Anaphylactic shock is one of the two most common causes for death in anaphylaxis; the other is throat swelling and asphyxiation (suffocation) .
- **The GI system** : Food allergy; It can also be affected with nausea, abdominal cramping (stomach ache) , bloating (swelling of abdomen), and diarrhea

wheals



Allergen

- They are proteins of low molecular wt.
- Examples :
- Pollens, house dust mite (most common allergen), cat or dog hair flakes
- Some are ingested like, egg, milk, peanuts and fish
- Drugs like penicillin and cephalosporin

Diagnostic tests for allergy

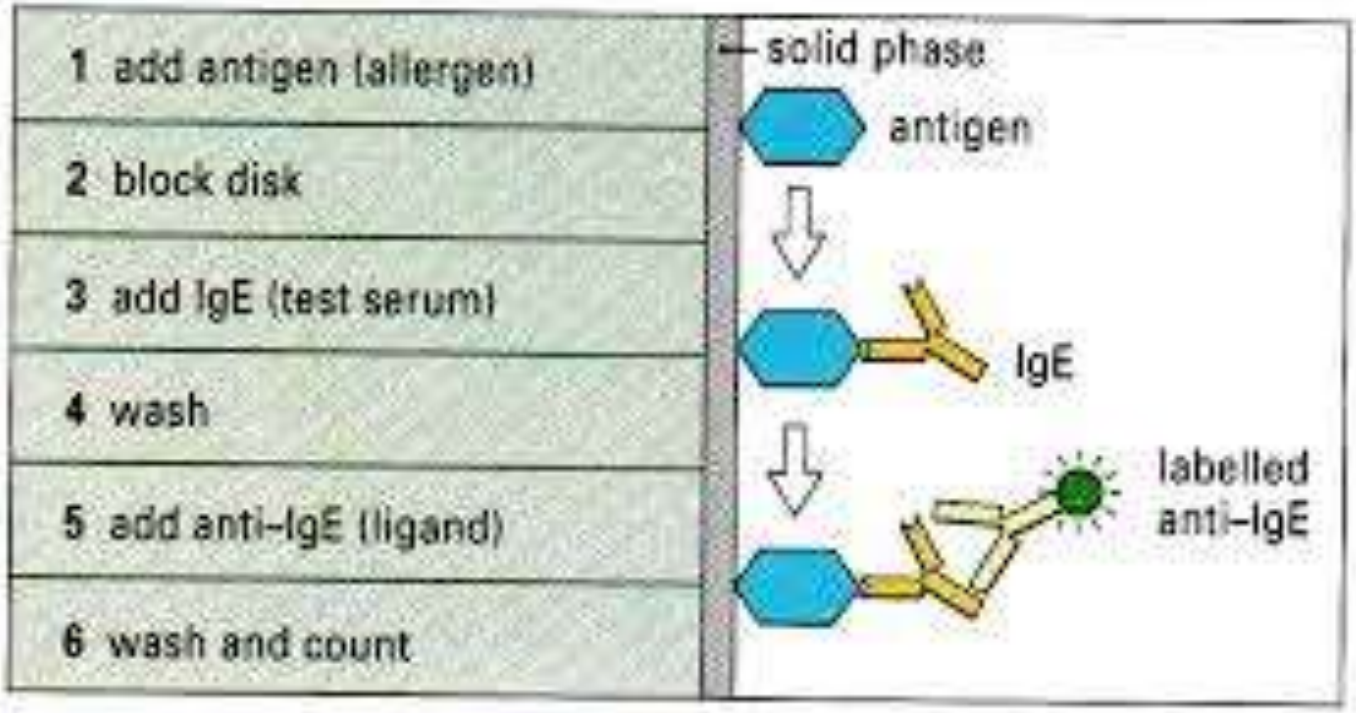
-**Skin test** (prick and intradermal). Induction of very low amount of extract allergen and see the reaction in 15 mins.
Extracavation of serum, pruritis and erythema (wheal and flare ; itchy flaming sweling of skin).

-**Skin patch test; allergen patch** followed by biopsy of the skin 24 or 48hrs after putting the patch, eczema, spongiosis (formation of sponge-like layer in the skin) of the epidermis and cell infiltrate are checked for.

--**Serum assay** of IgE antibodies RAST

The RAST test is a radioimmunoassay test to detect specific IgE antibodies in patient serum to suspected or known allergens (ready made). By mixing both then add Radiolabeled anti-human IgE antibody. The amount of radioactivity is proportional to the patient serum IgE for the allergen.

The radioallergosorbent test (RAST)



Treatment by drugs

- Anti-histamine, leukotrienes antagonists, corticosteroids
- **For anaphylactic shock**; IM adrenaline, IV anti-histamine and corticosteroids.
- Humanized monoclonal Anti-IgE

Proposed treatment; shifting the immune response from TH2 to TH1

-IL12

- Anti IL-4
- Anti-IL-5 (mainly in asthma)

Treatment by immunotherapy

- Its based on regular injections or sublingual treatment with increasing doses of allergen over months (induces tolerance).
- Exposure to microbes during early childhood may reduce the risk for developing allergies
- TH2 modified response happen in people who are raised in a house with frequent exposure to insect venom, cat and rat allergen and food antigen
- TH2 produce more and increase the IgG4 that decrease IgE production from B cells

- Used for seasonal hay fever from house dust mite and anaphylactic sensitivity to venom of bees and wasps -دبور–.

Asthma

- Release of the above mediators in the lower respiratory tract can cause bronchoconstriction, mucus production, and inflammation of the airways, resulting in chest tightness, shortness of breath, and wheezing
- Asthma is **an inflammatory disease** caused mostly (70%) by repeated immediate-type 1 hypersensitivity the remaining is non-atopic asthma
- the clinicopathologic triad of
  - intermittent and reversible airway obstruction,
  - chronic bronchial inflammation with eosinophils, mast cells? TH1 and TH17 cells, Leukotriene and cytokines, Type 4 reaction

Asthma therapy

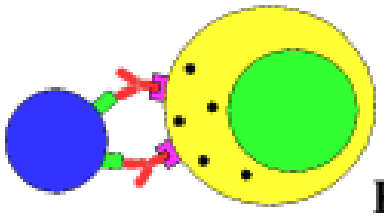
- Current therapy for asthma has two major targets:
  - prevention and reversal of inflammation by Inhaled corticosteroids block the production of inflammatory cytokines
  - and relaxation of airway smooth muscle by inhaled long acting β2-agonists.
- Leukotriene inhibitors block the binding of broncho-constricting leukotrienes to airway smooth muscle cells.
- Humanized monoclonal anti-IgE antibody is an approved therapy that effectively reduces serum IgE levels in atopic patients

Type 2 hypersensitivity reaction

- Antibody mediated sensitivity, Ab bind **antigens present on the cell surface** (self or foreign; like RBCs) or tissue surface ,
  - Activation of the complement pathway.lysis
  - Antibody dependent cellular cytotoxicity → lysis
  - Opsonization and phagocytosis, Erythrocytes coated by auto Ab are bound by macrophages, and they are phagocytosed and destructed there
- Antibody bind receptors lead to abnormalities in cellular functions, e.g., hormone receptor signaling, neurotransmitter receptor blockade
  - Antibodies specific for thyroid stimulating hormone receptor or the nicotinic acetylcholine receptor cause functional abnormalities that lead to Graves' disease and myasthenia gravis, respectively

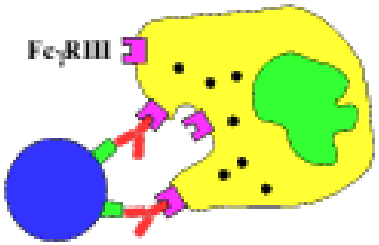
Way of destruction

Type II Hypersensitivity



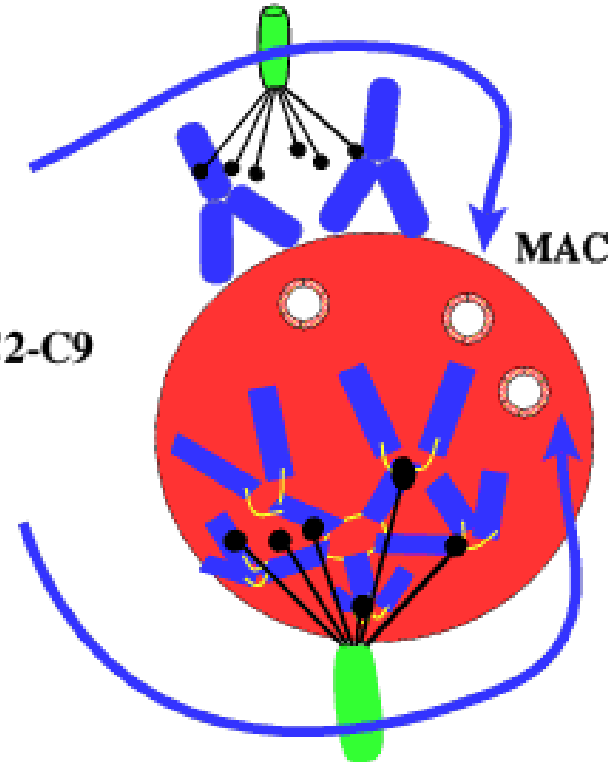
K cell

Antibody dependent cell cytotoxicity



macrophage

classical pathway complement activation



- Antibodies that cause cell- or tissue-specific diseases are usually autoantibodies produced as part of an autoimmune reaction, but sometimes the antibodies are specific for microbes.
- The antibody may target RBCs as in:

1-Transfusion rejection and hyper acute graft rejection. (incompatible ABO system antigen)

Pre-formed IgM Ab in recipient attack the RBC of donor lead to intravascular hemolysis, No need to pre-exposure.

how?? Such natural antibodies are believed to arise in response to carbohydrate antigens expressed by bacteria that normally colonize the intestine, and happen to cross-react with various auto antigens.

2-Hemolytic anemia of newborn (RH system antigen) IgG Ab against RH+ (formed in RH- mother after first RH+ baby) attack baby RBC+ lead to hemolysis in baby, need pre-exposure.

3-Autoimmune hemolytic anemia, which can be either spontaneous or drug induced :

1-Warm reactive auto-Ab (IGG) unknown cause, destruction in spleen

2- Cold reactive auto-Ab (against certain carbohydrates on the RBCs , mainly IgM) destruction intravascular

3- Auto-Ab caused by allergy to drugs (penicillin ,methyldopa, quinine)

The drug –Ab is adsorbed on the erythrocytes surface → type 2 hypersensitvity

Other autoimmune diseases

- The target may be neutrophils (DNA, cytoplasm protein and mitochondria) expressed on the surface of the cells in SLE then bound to auto-Ab,
- platelet in ITP (idiopathic thrombocytopenic purpura)

- Good pasture,: renal and lung basement membrane (IgG)
- Myasthenia gravis: Acetylcholine receptors in muscle (IgG),muscle weakness
- Pemphigus: adhesion molecules in skin, HLA-dr4 related (IgG4)
- Antibodies specific for thyroid stimulating hormone receptor in graves' disease. hyperthyroidism, Ab attacks the thyroid and causes it to make more thyroid hormone than your body needs

Testing ; coombs test

- Direct coombs (test for diagnosing the RBC for the presence of attached AB) to detect the presence of Ab on surface of cell(sensitized RBC)

✓ autoimmune hemolytic anemia

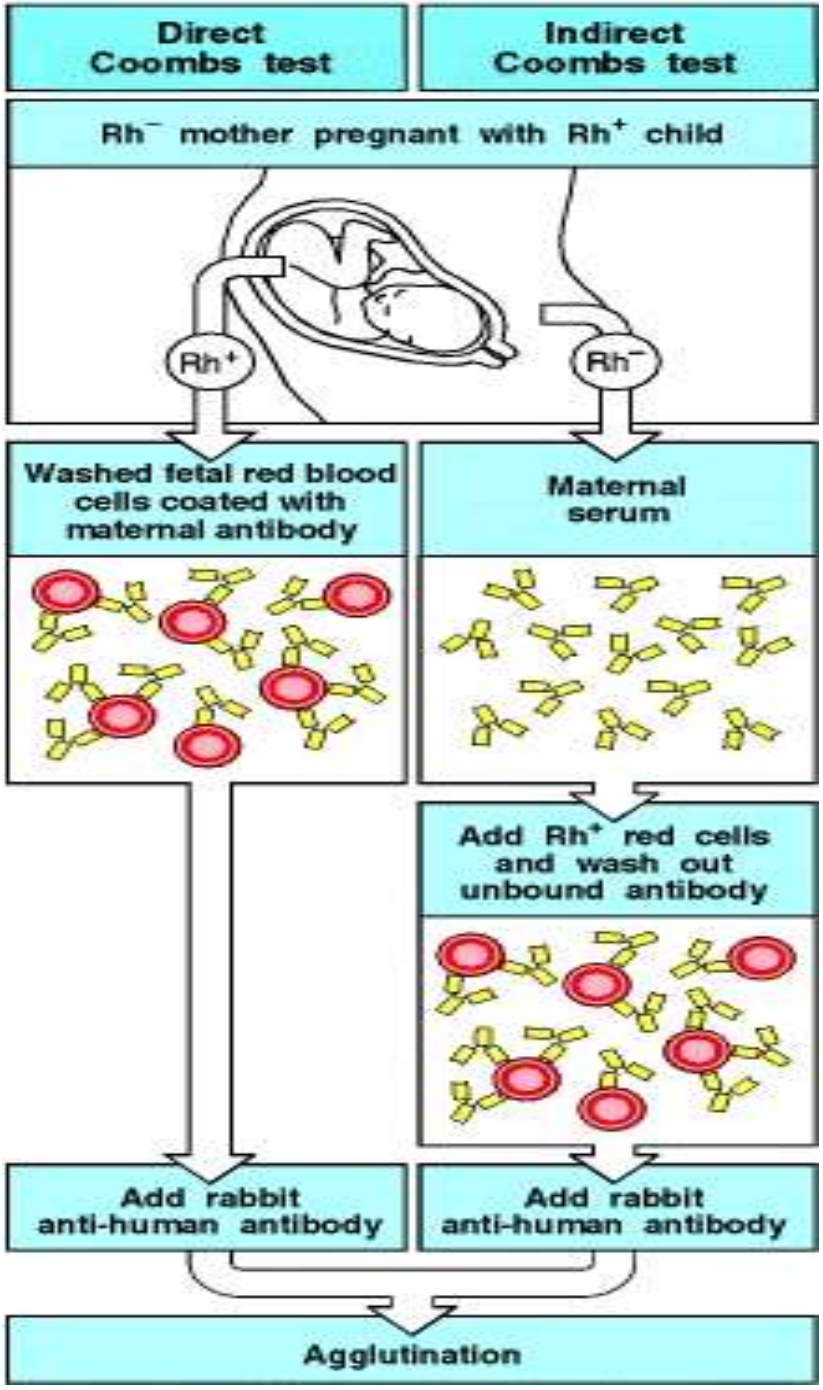
✓ hemolytic disease of the newborn

✓ sensitization of red blood cells caused by the presence of drugs, or a transfusion reaction

- Indirect coombs test (indirect agglutination test) for looking for specific antibodies in serum
  - Of recipient for presence of Ab against donor blood in Preparation for blood transfusion
  - screening mothers who are susceptible to have baby with hemolytic anemia of newborn.

- Direct Coombs' test
- The key component of the test is antibody to human Ab (rabbit anti-human antibody)that is made in animals or by means of hybridoma techniques (Coombs reagent).
- Such antibody will react with the FC portion of the human antibody attached to red blood cells (if present mean positive).
- Agglutination takes place because the antihuman globulin is able to agglutinate the sensitized cells.

- The ***indirect coombs test*** is used to determine the presence of a particular antibody in a patient.
- This is a two-step process.
- washed red blood cells (from donor in transfusion or RH+ RBC in from RH+ baby) and antibody from patient are allowed to combine , and the cells are then carefully washed again to remove any unbound antibody.
- When antihuman globulin is added, a visible reaction occurs where antibody has been specifically bound.
- is used In antenatal care, to screen pregnant women for antibodies that may cause hemolytic disease of the newborn , Pregnant serum + RH+ RBC
- and to screen for antibodies in the preparation of blood for blood transfusion (Cross match). Recipient serum + donor RBC


Direct Coombs test
Indirect Coombs test
Rh⁻ mother pregnant with Rh⁺ child
Rh⁺
Rh⁻
Washed fetal red blood cells coated with maternal antibody
Maternal serum
Add Rh⁺ red cells and wash out unbound antibody
Add rabbit anti-human antibody
Add rabbit anti-human antibody
Agglutination

Other tests and treatment

- Diagnostic tests if damage on tissues
  - (biopsy) by immunofluorescence; the presence of antibody and complement in the lesion. The staining pattern is normally smooth and linear, such as that seen in Goodpasture's nephritis (renal and lung basement membrane) and pemphigus (skin intercellular protein, desmosome).
  - The lesion contains antibody, complement and phagocytes.

- Treatment involves anti-inflammatory and immunosuppressive agents

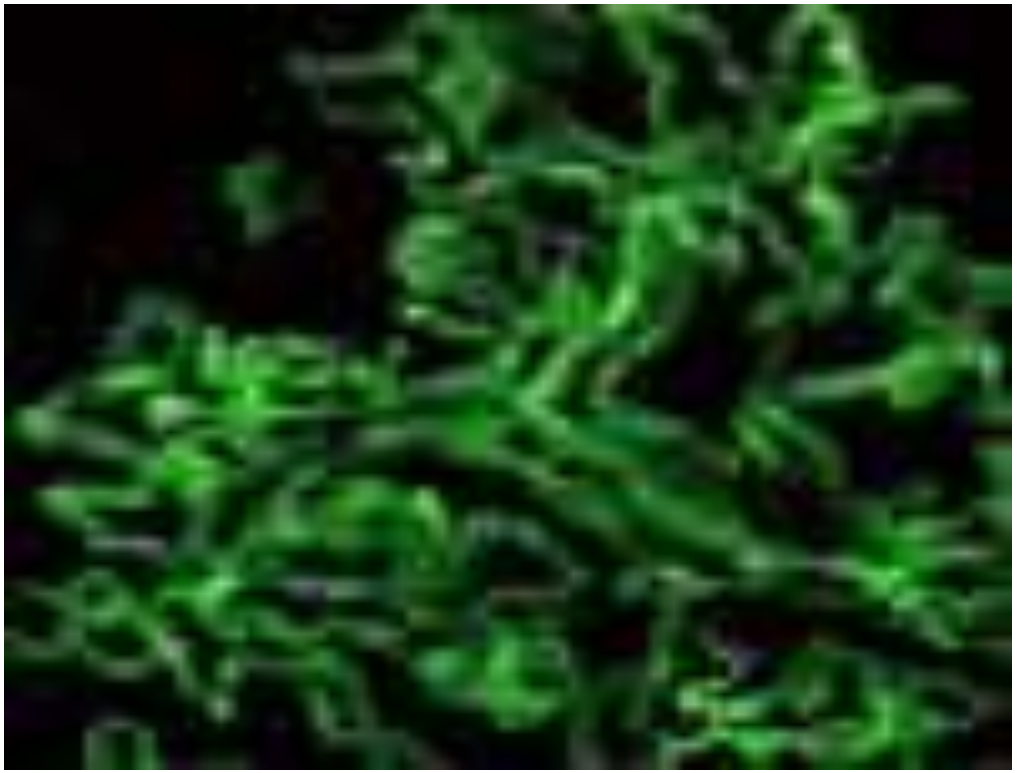
Type 2 hypersesitivity therapeutic importance

- Monoclonal Ab binding to surface of cells and cause its damage is used as treatment for tumors

Anti-CD20 Ab in B cell lymphoma

Anti-CD52 Ab in B, T cell leukemia

Good pasture disease



Type 3 hypersensitivity reaction

It involves soluble antigens that are not bound to cell surfaces (as opposed to those in type II hypersensitivity). When these antigens bind antibodies, immune complexes of different sizes form

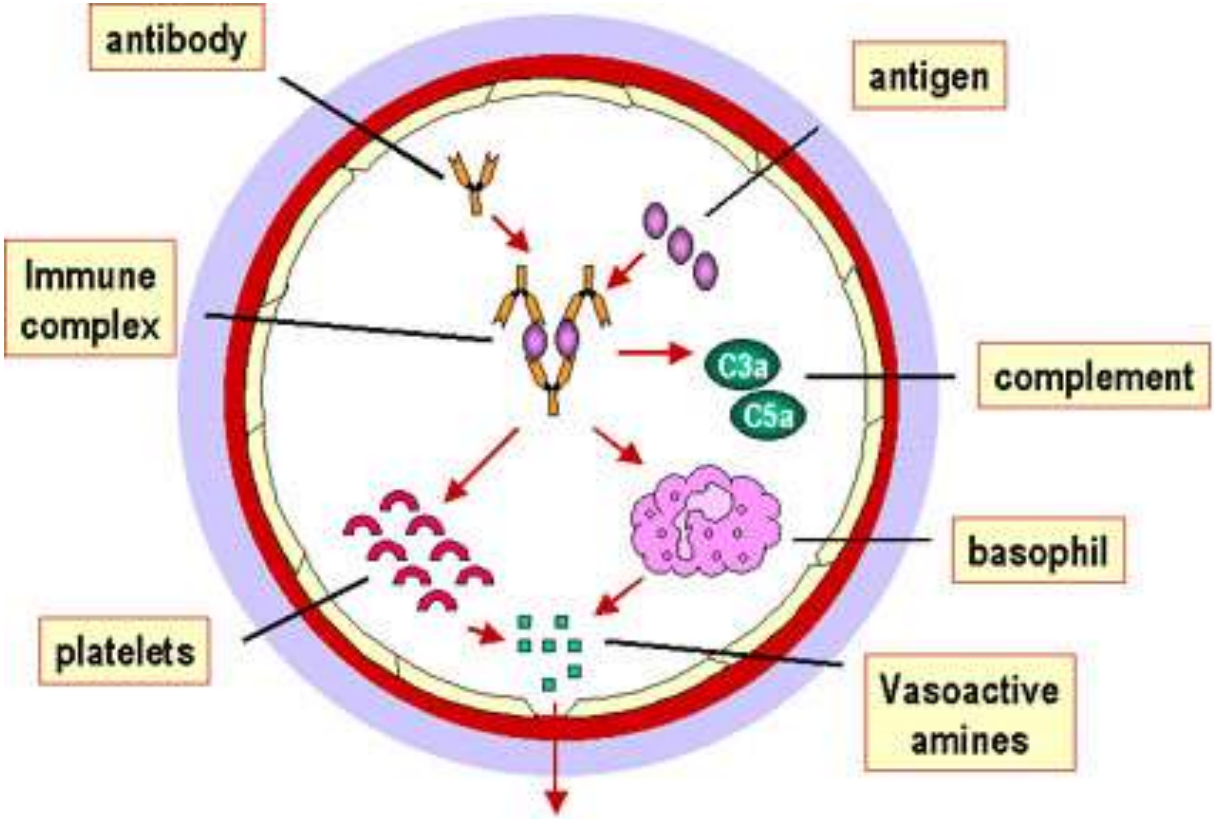
Circulating Immune complex deposition, it is generally due to high quantity of **soluble antigens and/or antibody**:

- **Persistent infection**: strep. Viral hepatitis
- **Autoimmune disease**: SLE, Rheumatoid arthritis
- **Frequent inhalation of antigen** : extrinsic allergic alveolitis (IgG)
- **Injection of large quantity of Ag** (injection of high quantity of penicillin or antitoxins for long period called serum sickness)
- **Impaired clearance of the immune complex as in SLE**

Pathophysiology.

- complexes can be cleared normally by macrophages or transferred by erythrocytes (have CR1) to spleen
- but for some reasons as decrease complement level or increase complex formation rate
- they have difficulty in the disposal of immune complexes. These immune complexes insert themselves into small blood vessels, joints, and glomeruli, causing symptoms and diseases.
- The tissue damage results from
  - Complement and Ab mediated recruitment of leukocytes causing platelet and basophils aggregation or release their mediators that increase vascular permeability
  - Increase anaphylatoxins (C3a, C5a)
  - Neutrophils and macrophages are attracted by C5a and react with complex because high immune complex size, they release mediators out side lead to inflammation and tissue damage. Activate macrophage release IL-1 and TNF alpha

Mechanism of damage in immune complex



RCH

models of Type 3 hypersensitivity

- At the time, diphtheria infections were treated with serum from horses that had been immunized with the diphtheria toxin, which is an example of passive immunization against the toxin by the transfer of serum containing antitoxin antibodies. Von Pirquet noted that joint inflammation (arthritis), fever developed in patients (serum sickness), skin eruptions (mainly consisting of urticaria), and lymphadenopathy
- Identifying serum sickness was a landmark observation in understanding immune complex diseases.) type 3 hypersensitivity reaction →immuncomplex deposition in the kidney & joints (glomerulunephritis , arthritis)

arthus reaction

- **The Arthus reaction involves the local formation of antigen/antibody complexes after the intradermal injection of an antigen**
- **If the patient was stimulated in a second time(has circulating antibody) with the same antigen, an Arthus reaction occurs and manifests as local vasculitis due to deposition of immune complexes in dermal blood vessels.**
- **(** large and less identified erythema after 5-12 hrs)

examples

- Systemic lupus erythromatosus (SLE), high anti-DNA and anti-nuclear proteins antibody, immune complex in kidney, skin joints
- Post strept-glumerolonephritis, high ab against strep Ag- immune complex on joints
- Poly arteritis nodosa; chronic infection of viral hepatitis, high ab, immune complex on vessels

Testing

- Symptoms depending on site of precipitation
- Tissue biopsy and staining by Immunofluorescence (granular appearance)
- Assay for circulating immune complexes using patient serum (C1q binding assay)
- Low levels of C3 and C4 as in SLE; high immune complex formation (active disease) lead to high consumption of C3 and C4 and results in decrease solubility of immune complexes
- Treatment; Anti-inflammatory drugs as cortisone

Type 4 hypersensitivity reaction or Delayed hypersensitivity

- In second immune response to the same antigen, mediated by CD4 cytokines; memory TH1 and TH17 cells secrete cytokines (IFN gamma and IL-17) that recruit and activate monocytes and neutrophils (cytokine mediated)
  - Autoimmune; As in rheumatoid arthritis (RA), multiple sclerosis, type 1 diabetes, psoriasis, psoriasis and inflammatory bowel disease
  - non autoimmune is contact dermatitis (poison ivy , chemicals, heavy metals, etc.) and in TB test, the lesions are more papular.
- Mediated by cells;
  - CTLs may contribute to type 4 reaction as in type 1 diabetes (cell mediated) after viral hepatitis
  - lymphocytes and macrophages over activation is involved in the granulomas formation after intracellular infection result from.(leprosy, histoplasmosis, toxoplasmosis, leishmaniasis, etc.)

- is called delayed because it typically develops 24 to 48 hours after antigen challenge in second exposure, in contrast to immediate hypersensitivity (allergic) reactions, which Develop within minutes

Table 3 - Delayed hypersensitivity reactions				
Type	Reaction time	Clinical appearance	Histology	Antigen and site
contact	hr 72-48	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, ,heavy metals (*.etc*
tuberculin	hr 72-48	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, (*.etc* ,lepromin
granuloma	days 28-21	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, (*.etc* ,leprosy

Contact dermatitis after 72hr

- Local eczema ; mostly from nickle or rubber ; the Ag is very small & lipophilic (hapten).
  These chemicals are haptens then react with self proteins, creating hapten-peptide complexes,
- **Two phases :**

  1- Sensitization after first exposure ; takes10-14days .
  cutaneous Langerhans' cells take up and process **antigen** , and then migrate to regional lymph nodes, where they **activateTc and TH cells toward TH1**, and TH17 with the consequent production of **memory T cells**, which end up in the dermis.

  2- In the elicitation (activation) phase in second exposure (gives the symptoms), further exposure to the sensitizing chemical leads to **antigen** presentation to memory **T cells** in the dermis, with release of T-cell cytokines such as **IFN**-γ and **IL**-17.
  This stimulates the keratinocytes of the epidermis to release cytokines such as **IL**-1, **IL**-6, **TNF**-α .
  These cytokines and chemokines enhance the inflammatory response by inducing the migration of macrophages (Giant cells), T cell accumulation with macrophages (granuloma)
- Cessation of reaction is as a result of : Removing the Ag , more IL-10 (from TH2 cells), TGF beta (from keratinocytes) & PGE (from macrophages)

Tuberculin test (PPD test or mantoux test) (after 72hr)

Tuberculin test :

patients who have been exposed to the bacteria, after second exposure to tuberculin Ag develop a delayed hypersensitivity reaction manifested by inflammation and hardening in the dermis (from TB) → skin hardening and fever.

Mediated by memory Th1 and macrophages (IL-1, TNF and IFN gamma).

Most people with a positive TB skin test means they probably have TB germs in their body, latent TB infection or TB disease? should be confirmed by more tests. chest x-ray.

Used as for :

-general measure of the efficacy of cell mediated immunity by using injection with common antigens as candid albicans.

-Test for TB.

- A false positive result may be caused by nontuberculous mycobacteria or previous administration of BCG vaccine
- A false negative in Those who are immunologically compromised, especially those with HIV and low CD4 T cell counts

Granulomatous

-Results from aggregation of macrophages and lymphocytes (after 21-28 days)

-Granuloma formation is a strategy that has evolved to deal with those intracellular pathogens that have learned to evade the host immune system by various means like resisting phagocytosis and killing within the macrophages. Granulomas try to wall off these organisms and prevent their further growth and spread.

Causes :

1- immune granuloma as in

- .TB, Leprosy, leishmania
- . Immune mediated crohns and sarcoidosis (Ag is unknown)

2- Inorganic Antigen as talc and silica (non immune-granuloma, no T lymphocytes involvement)

Histology :

1- Epithelioid cells are activated macrophages resembling epithelial cells

2- giant cells from fusion and aggregation of epithelioid cells

3-granuloma

diagnosis

- Generally is biopsy; it will show infiltration by lymphocytes and monocytes, increased fluid between the fibrous structures, granuloma and some cell death

Cytokine treatment in type 4

- The first success with this class of biologic agents came with a soluble form of the TNF receptor and anti-TNF antibodies, which bind to and neutralize TNF. In rheumatoid arthritis (RA), Crohn's disease, and the skin disease psoriasis.
- Antibodies to the IL-6 receptor have been successfully used in trials for adult rheumatoid arthritis (RA).