MIRACLE
Academy

قال تعالى (يَرْفَعِ اللَّهَ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

تفريغ المناعة
زميلتكم جنين الخطيب

لجان الدُّفعات

Hypersensitivity Reactions

هو تفاعلات الحساسية بتصير كتير معنا بحياتنا ، ممكن الإنسان يتحسس من أي اشي سواء أكل متل الفستق أو السمك ، أو من مواد معينة متل البنسلين ، أو حتى ممكن من فرو أو شعر الحيوانات ، أو من نوع قماش معين أو من الlabel اللي على الملابس ، وطبعا الإنسان بس يعرف إنه عنده حساسية من اشي معين بيصير كل حياته يتجنب التعرض لهاد الاشي لحتى يحمي نفسه

Objectives

- Difference between hypersensitivity and protective immunity
- Overview of the four major classifications of human hypersensitivity.

1. Type I hypersensitivity –
2. Type 2, 3, 4 hypersensitivities – Mechanisms and clinical consequences

Introduction

المواد اللي بتسبب حساسية هي مواد غير مضرة موجودة بالطبيعة لكن بس الناس اللي بيتحسسو منها رح تعمل عندهم تفاعلات الحساسية

- Hypersensitivity reactions – 'over reaction' of the immune system to harmless environmental antigens
- Hypersensitivity refers to undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.
- Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
- Allergen: the antigens that give rise to hypersensitivity

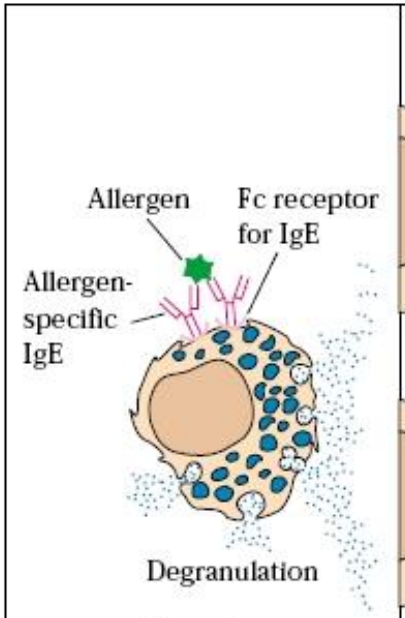
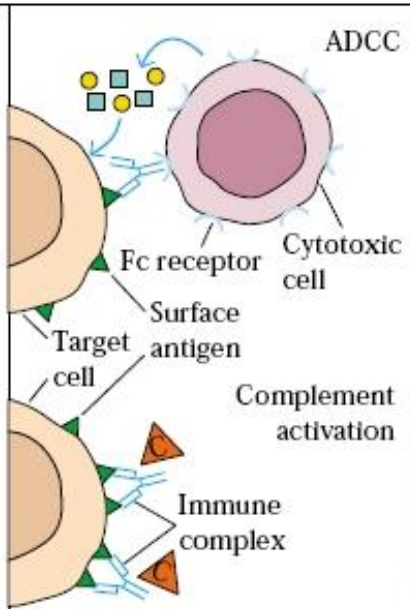
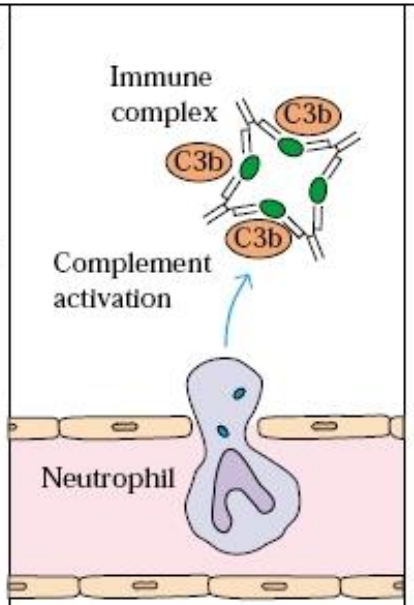
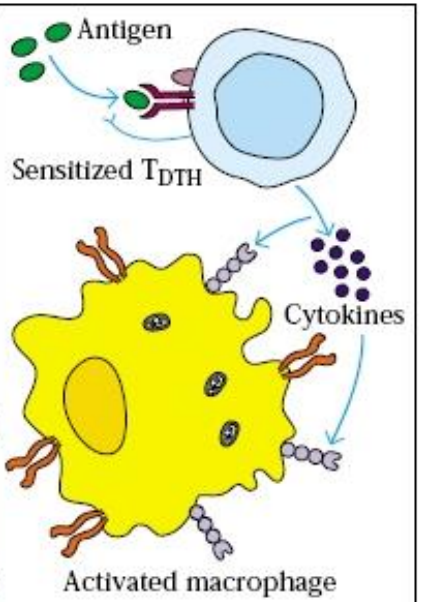
ممكن أحيانا تؤدي هي التفاعلات إلى الوفاة اذا تعرض الإنسان لكمية كبيرة من الantigen وما تم إسعافه بسرعه ، وطبعا هاد بيصير بسبب ال anaphylactic shock ، اللي بيصير فيها sudden decrease in BP وبعدين بيصير respiratory distress و syanosis و ahrticaria و broncospasm فالمريض بتوقف عنده التنفس وبيموت

Types of Hypersensitivity Reactions

- There are 4 types of hypersensitivity reactions

1. Type I: classical immediate hypersensitivity
2. Type II: cytotoxic hypersensitivity
3. Type III: immune-complex mediated hypersensitivity
4. Type IV: cell mediated or delayed hypersensitivity

- Types I, II and III are antibody mediated
- Type IV is cell mediated

 Type I	 Type II	 Type III	 Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators شرحها بالسلايد اللي بعد	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC antibody dependent cellular cytotoxicity	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia لما ننقل دم وتكون زمرة الدم غير متطابقة هاد تفاعل حساسية بيصير لما تكون زمرة دم الأم مختلفة عن زمرة دم الطفل بنظام Rh يعني مثلا كانت الأم موجب والطفل سالب وعند الولادة اختلط دم الأم مع دم الطفل	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Type 1

لما يتعرض المريض أول مرة للallergen بيكون الجهاز المناعي كميات كبيرة من الIgE وبيصير الها fixation على سطح الmast cells أو الbasophiles، هسا لما يتعرض الواحد للallergen مرة تانية بييجي هاد الantigen وبيعمل crosslinking للIgE الموجودة على سطح الmast cells , وهاد راح يعمل activation للmast cells وبعدين رح تعمل release لmediators وبعدها بتبدأ الconsequences of hypersensitivity reactions

Type I: Immediate hypersensitivity

- An antigen reacts with cell fixed antibody (IgE) leading to release of soluble molecules
  - An antigen (allergen)
  - soluble molecules (mediators)
- Soluble molecules cause the manifestation of disease
- Local atopic allergies; bronchial asthma, hay fever and food allergies
- Systemic life threatening; anaphylactic shock

أول أعراض ممكن تظهر على المريض لما يكون تفاعل الحساسية في بدايته هي ضيق النفس والكحة ، وبرضه بيصير فيه عنده حكة واحمرار في وجهه، وبالعادة عند الأطفال بتطلع حبوب خفيفة في منطقة الصدر أو الظهر أو الفخذ أو خلف الأذن
طبعا اذا ظهرت هي الأعراض اللي تعتبر أعراض بسيطة على حدا بالبيت عطول بنعطيه أي antihistamine drug موجود

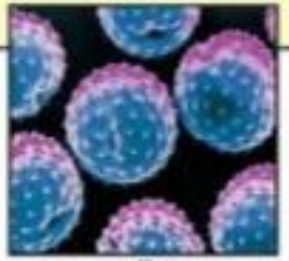
لكن إذا كانت الأعراض قوية لازم بأسرع ما يمكن ناخد المريض عالمستشفى لحتى نتجنب انه يصير عنده anaphylactic shock

plant pollens
اللي هي حساسية الربيع ،بتصير بسبب حبوب اللقاح من النبات ، بتصيب كتير ناس وبتكون الأعراض كتير واضحة عليهم من سيلان وكحة وعيونهم حمر ومنفخين ، في منهم بيمشو على inhalers ، وفي منهم بياخدو ابرة deposit اللي هي بتكون عبارة عن cortisone لمدة أربع شهور لحتى تخفف من أعراض الحساسية المفرطة خلال فصل الربيع

Common sources of allergens

Inhaled materials

- Plant pollens
- Dander of domesticated animals
- Mold spores
- Feces of very small animals
  - e.g., house dust mites


pollen


house dust mite

Injected materials

- Insect venoms
- Vaccines
- Drugs biologic drugs
- Therapeutic proteins


wasp


drugs

Ingested materials

- Food
- Orally administered drugs


peanuts


shellfish

Contacted materials

- Plant leaves
- Industrial products made from plants
- Synthetic chemicals in industrial products
- Metals

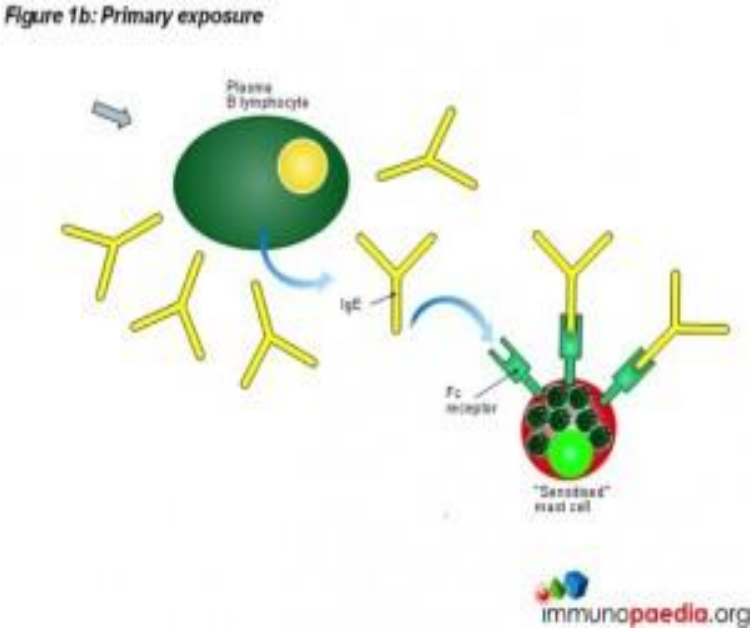

poison ivy


nickel coin

Pathophysiology

- First exposure to allergen: Allergen stimulates formation of antibody (IgE type). Ig E fixes, by its Fc portion to mast cells and basophiles

- Second exposure to the same allergen: It bridges between IgE molecules fixed to mast cells leading to activation and degranulation of mast cells and release of mediators



- Three classes of mediators derived from mast cells:
  1. Preformed mediators stored in granules (histamine)
  2. Newly sensitized mediators: leukotrienes, prostaglandins, platelets activating factor, Cytokines produced by activated mast cells, basophils e.g. TNF, IL3, IL-4, IL-5, IL-13, chemokines
- These mediators cause:
  1. smooth muscle contraction
  2. mucous secretion and bronchial spasm
  3. vasodilatation increse blood supply to the sensitized area
  4. vascular permeability and edema cause swelling and redness

Anaphylaxis

- Systemic form of Type I hypersensitivity
- Exposure to allergen to which a person is previously sensitized
- Allergens:
  1. Drugs: penicillin
  2. Serum injection : anti-diphtheritic or anti-tetanic serum
  3. Anesthesia or insect venom
- Clinical picture: Shock due to sudden decrease of blood pressure, respiratory distress due to bronchospasm, cyanosis, edema, urticaria
- Treatment: corticosteroids injection, epinephrine, antihistamines

very effective because of it's immunosuppressant and antiinflammatory effect

to raise the BP

at first , we give IV injection and then continue with oral antihistamine

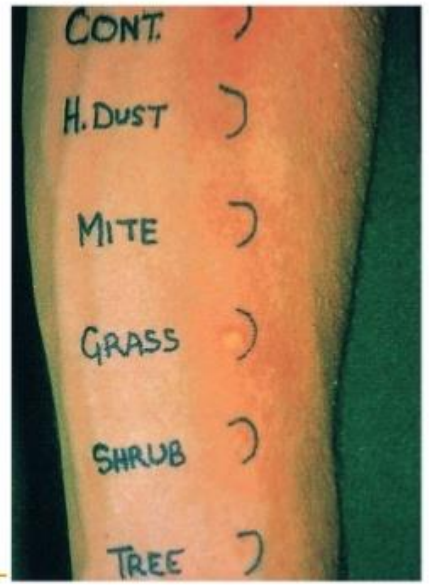
Atopy

- Local form of type I hypersensitivity
- Exposure to certain allergens that induce production of specific IgE
- Allergens :
  1. Inhalants: dust mite faeces, tree or pollens, mould spor.
  2. Ingestants: milk, egg, fish, chocolate
  3. Contactants: wool, nylon, animal fur
  4. Drugs: penicillin, salicylates, anesthesia insect venom
- There is a strong familial predisposition to atopic allergy
- The predisposition is genetically determined
- Allergic rhinitis, allergic asthma, atopic dermatitis are the most common manifestation of atopy. Allergic gastroenteropathy is rare. These manifestation may coexist in the same patients at different times. Atopy can be asymptomatic.

Diagnosis

1. History taking for determining the allergen involved
2. Skin tests: Intradermal injection of battery of different allergens. A wheal and flare (erythema) develop at the site of allergen to which the person is allergic متل اللي بالصورة واضح بعد الtest ما انعمل اله انه عنده حساسية من الgrass
3. Determination of total serum IgE level
4. Determination of specific IgE levels

to the different allergens



Management

1. Avoidance of specific allergen responsible for condition
2. Hyposensitization: Injection of gradually increasing doses of extract of allergen

اني أعمل injection للantigen على فترات ، أول اشي بيكون تركيزه قليل وبصير مع الوقت بزيد شوي شوي لحتى الجسم يبطل يعمل حساسية تجاه هاد الantigen

   - production of IgG blocking antibody which binds allergen and prevent combination with IgE
   - It may induce T cell tolerance
3. Drug Therapy: corticosteroids injection, epinephrine, antihistamines
4. Humanized anti-IgE monoclonal antibodies that neutralize IgE antibodies and prevent them from binding to FcεRI on mast and basophile cells

Type II: Cytotoxic or Cytolytic Reactions

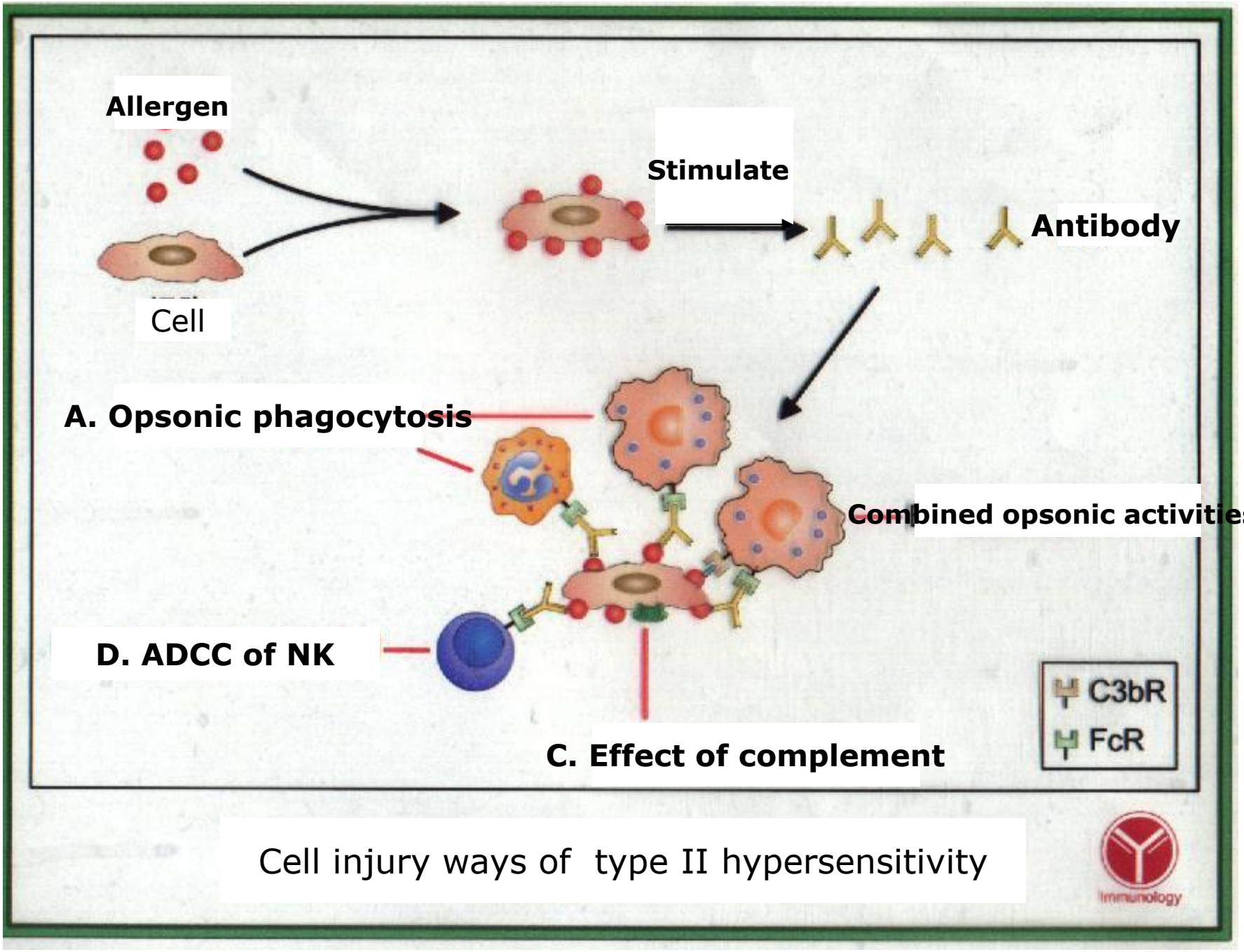
في هاد النوع بيكون في عندي antigen رابط على سطح الخلية ، بعدين بييجي الantibody بيرتبط بالantigen وبعد الارتباط بيصير عندي تحفيز لعدة actions

- Antibodies destruction of cells
- Tissue specific (antibodies destruction of cells but it is **systematic**)
- An antibody (IgG or IgM) reacts with antigen on the cell surface

- Antigen:
  - Intrinsic: normally made by host
  - Extrinsic : infection, medication attached to host

Mechanism of Cytolysis

1. Neutrophils cytotoxicity neutrophiles release reactive oxygen species and lysosoms , so both of them will cause destruction of cells
2. Complement fixation to antigen antibody complex on cell surface. The activated complement will lead to cell lysis
3. Opsonization and Phagocytosis is enhanced by the antibody (osponin) bound to cell antigen leading to opsonization of the target cell
4. Antibody depended cellular cytotoxicity (ADCC). Apoptotic response by NK perforin (cell lyses), Granzyme (apoptosis)



Cell injury ways of type II hypersensitivity

Clinical Conditions

1. Transfusion reaction due to ABO incompatibility
2. Rh-incompatability (Haemolytic disease of the newborn)
3. Autoimmune diseases: The mechanism of tissue damage is cytotoxic reactions e.g., autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, myasthenia gravis, Hashimoto's thyroiditis
4. A non-cytotoxic Type II hypersensitivity is Graves's disease

5- Graft rejection cytotoxic reactions: In hyperacute rejection the recipient already has performed antibody against the graft

6- Drug reaction (type II):

- Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to haemolysis
- Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura

Type III: Immune Complex Mediated Reaction

- In type III hypersensitivity reaction, an abnormal immune response is mediated by the formation of **antigen-antibody aggregates** called "**immune complexes**." They can precipitate in various tissues such as skin, joints, vessels, or glomeruli, and trigger the classical complement pathway.
- When antibodies (IgG or IgM) and **soluble** antigen coexist immune complexes are formed
- Immune complexes are removed by reticuloendoth. syst.
- Some immune complexes escape phagocytosis
- Immune complexes deposited in tissues on the basement membrane of blood vessels and cause tissue injury and inflammation (vasculitis)
- Most commonly kidney, joint
- **In type 2: antibodies attached to antigen attached to cell surfaces**

هون بيوضحلك الفرق بين ال type2 وال type3 انه ال type2 بيكون ال antigen رابط على سطح الخلية ،بينما type3 بيكون ال antigen soluble وبعدين بيكون complex مع ال antibody وبعدين بيصير الهم disposition على اماكن مختلفة بالجسم

Mechanism of Tissue Injury

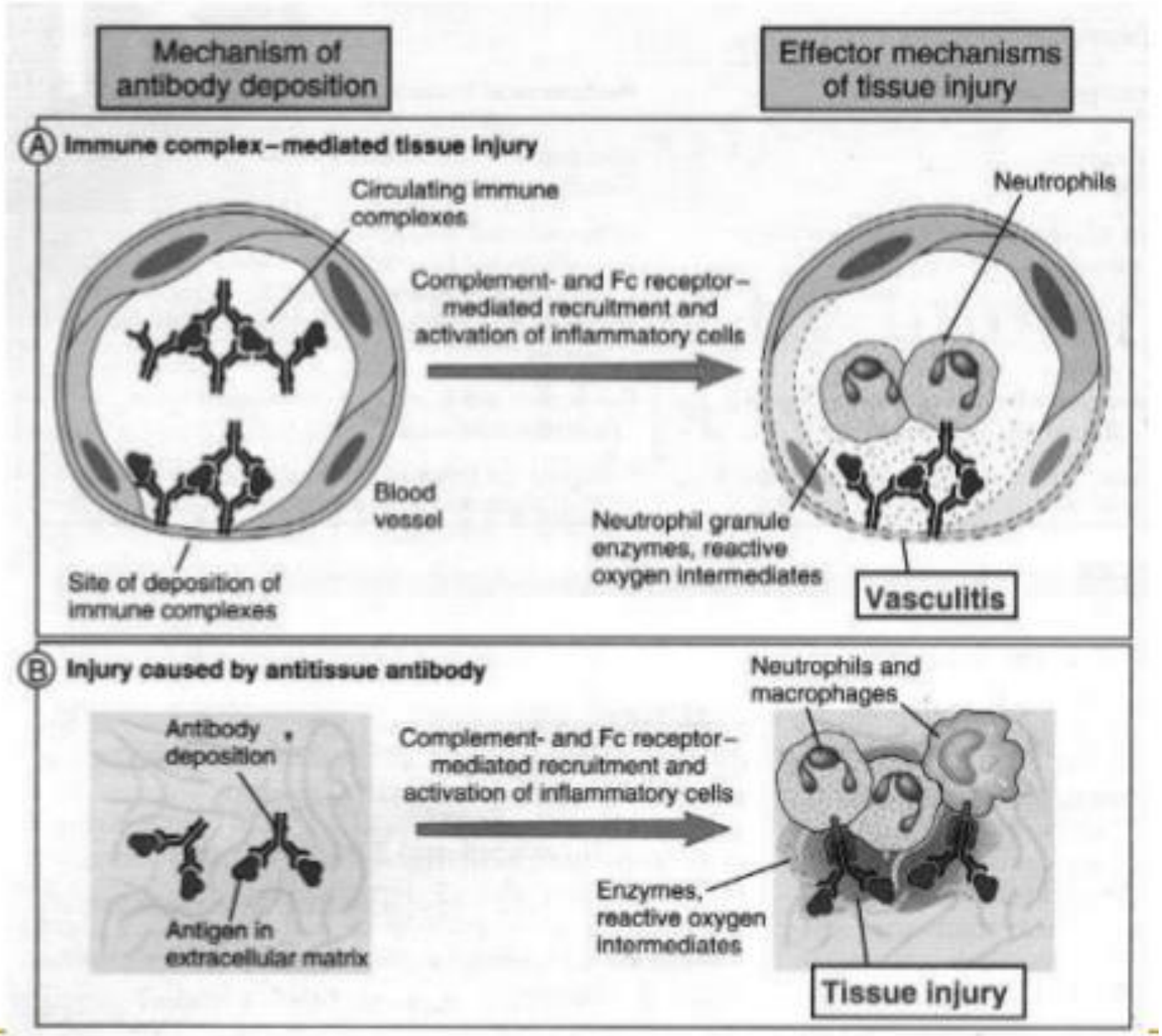
- Immune complexes trigger inflammatory processes:

1. Immune complexes ----activate the complement------release anaphylatoxins C3a, C5a----- stimulate degranulation of basophiles and mast cells-------release histamine -----Histamine increase vascular permeability and help deposition of immune complexes
2. Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammatory process
3. Platelets are aggregated with two consequences

a- release of histamine

b- form of microthrombi which lead to ischemia

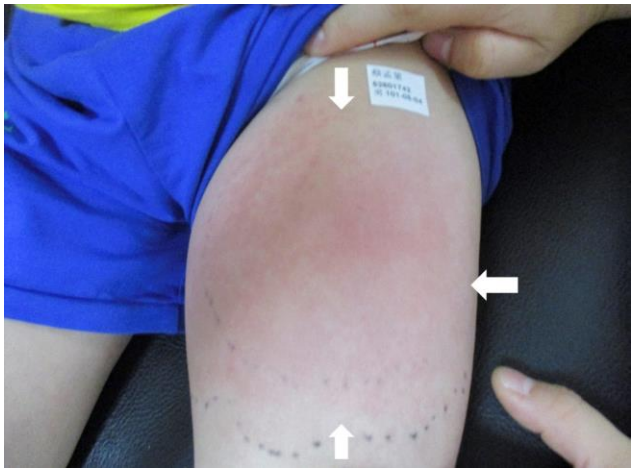
هي الصورة مش مطلوبة وهي أصلا نفس الحكي اللي فوق بس بتوضحها بطريقة أخرى



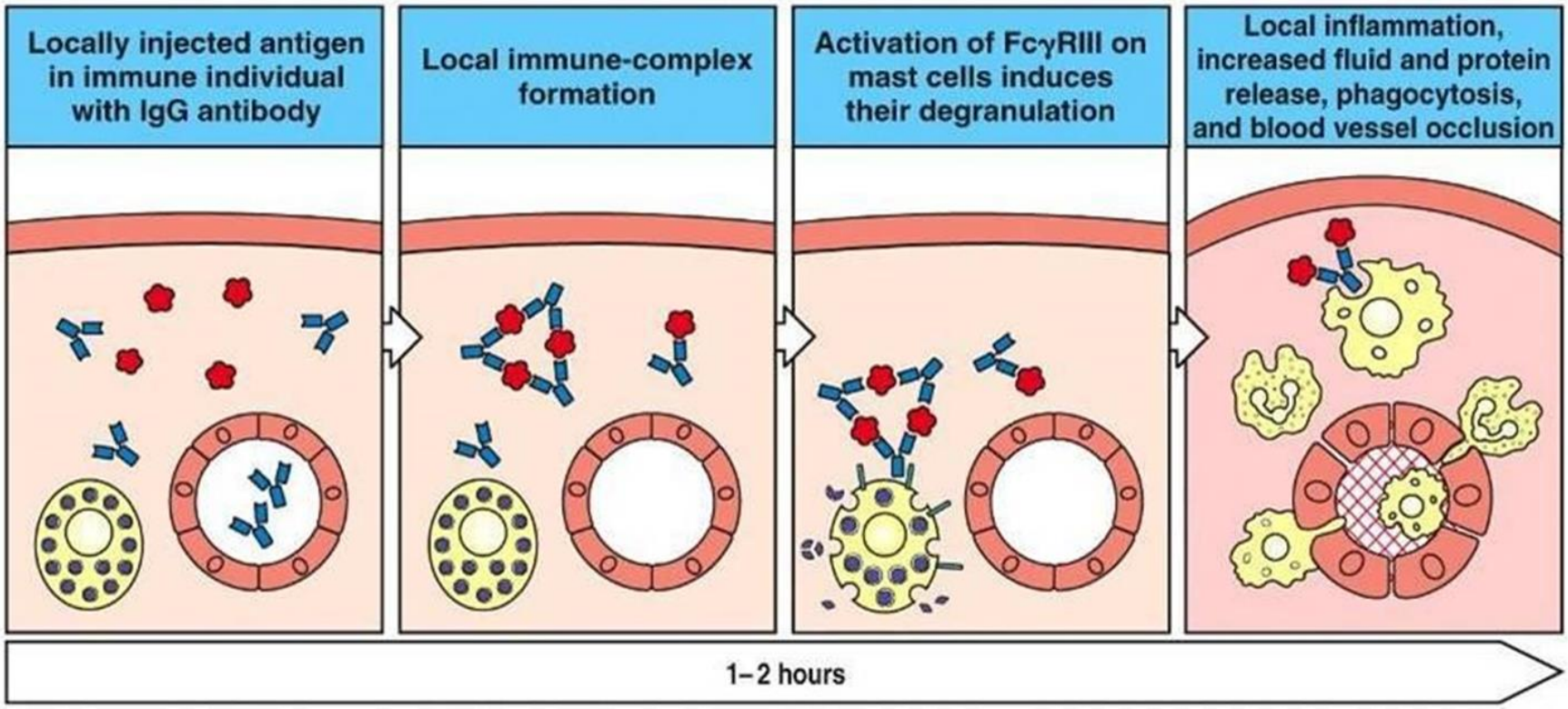
1- Arthus Reaction

- This is a local immune complex deposition phenomenon e.g. diabetic patients receiving insulin subcutaneously

1. Local reactions in the form of edema erythema necrosis
2. Immune complexes deposited in small blood vessels Leading to:
   - vasculitis
   - microthrombi formation
   - vascular occlusion
   - necrosis



وهي صورة بتوضح الcasecade اللي بيصير بالمرض اللي حكينا عنه فوق

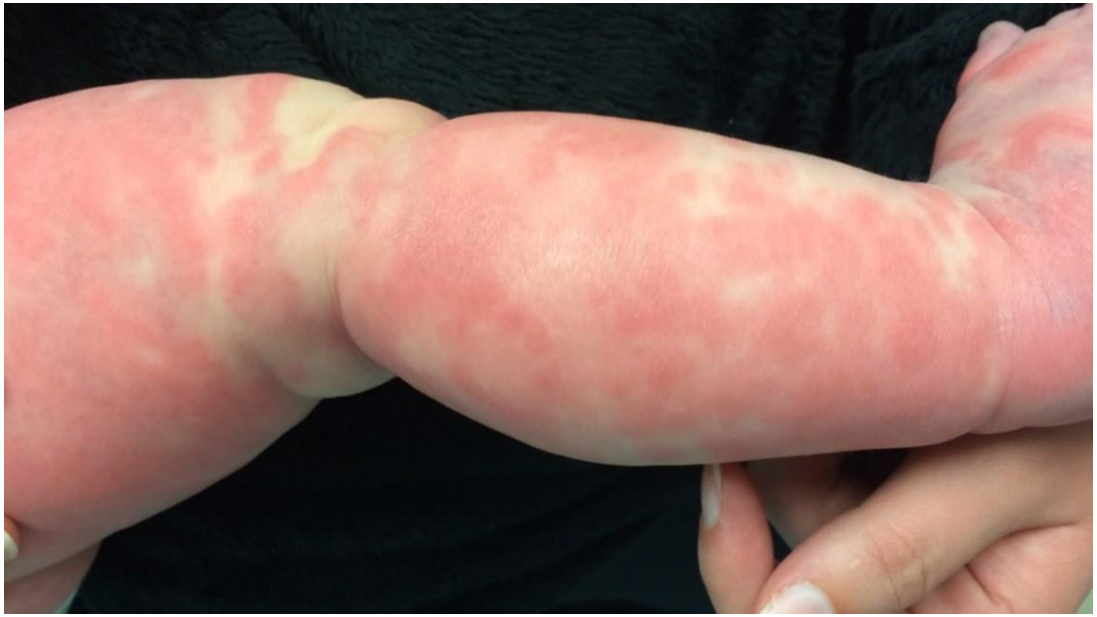


2- Serum Sickness

- A systemic immune complex phenomenon
- Injection of large doses of foreign serum متل قرصة حية أو عقرب
- Antigen is slowly cleared from circulation
- Immune complexes are deposited in various sites
- e.g. treatment with
  - antidiphtheritic serum
  - penicillin
  - sulphonamides

هي أدوية ممكن تسبب المرض

- 10 days after injection
  - fever
  - urticaria
  - arthralgia
  - lymphadenopathy
  - spleenomegaly
  - glomerulonephritis



3- Post-streptococcal glomerulonephritis: glomerulitis associated with infective endocarditis

4- Hypersensitive pneumonitis (farmer lung) immune complexes deposition in lung after repeated inhalation of dust, mould spores

5- Endogenous antigen antibody complexes involved in autoimmune diseases e.g. SLE, rheumatoid arthritis

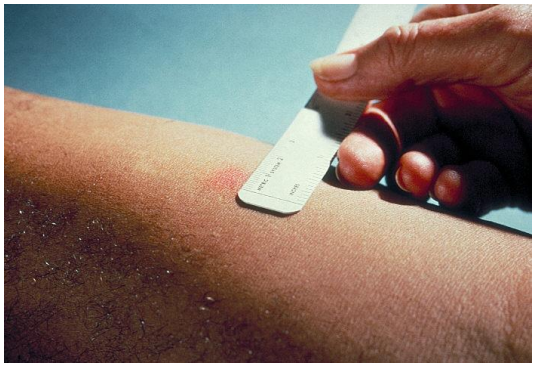
Type IV: Cell Mediated Delayed Type Hypersensitivity (DTH)

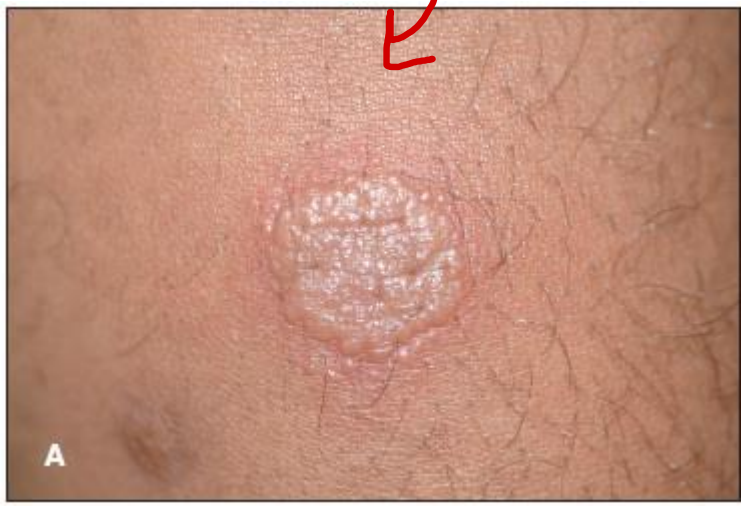
- Type IV hypersensitivity, also called delayed-type hypersensitivity (DTH), involves T cell-antigen interactions that cause activation and cytokine secretion.
- This type of hypersensitivity requires sensitized lymphocytes that respond 24–48 h after exposure to soluble antigens

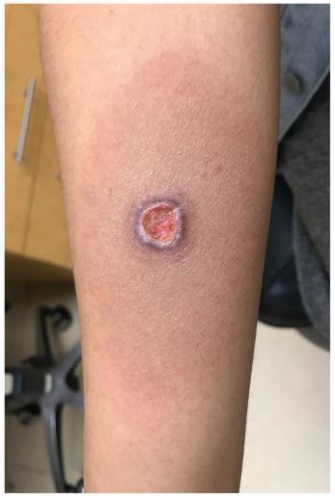
- T-cells cause tissue injury by directly killing target cells by CD8 cytotoxic T cell or by triggering DTH reactions by TH1

- TH1 secrete cytokines (IFN-γ and TNF)
  - Cytokines
    - attract lymphocytes
    - activate macrophages
    - induce inflammation
- Tissue damage results from products of activated macrophages

- Caused by products of antigen-specific effector T cells
- T cells undergo cellular division → production of reactive cells
- The classical example of this hypersensitivity is **tuberculin test** which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.



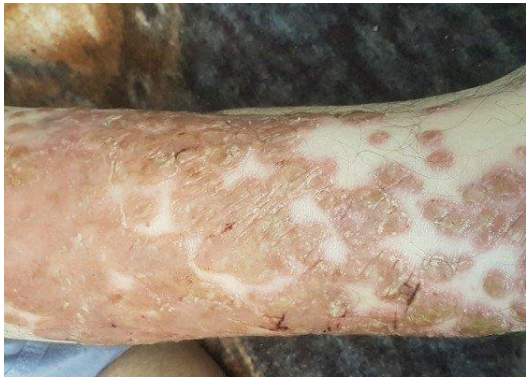


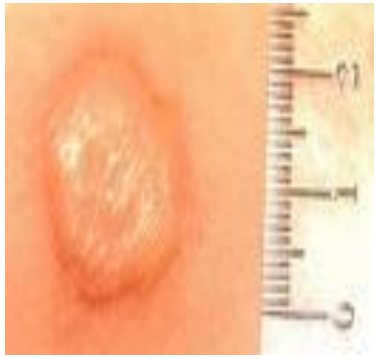


مثال على فحوصات الحساسية اللي بتعمل هو فحص السل ،اللي بيحقنو فيه كمية قليلة من الantigen
وبعد48 ساعة بيشوفو اذا تكونindurated area وبيقيسو الdiameter الها

1. Tuberculin –Type Hypersensitivity

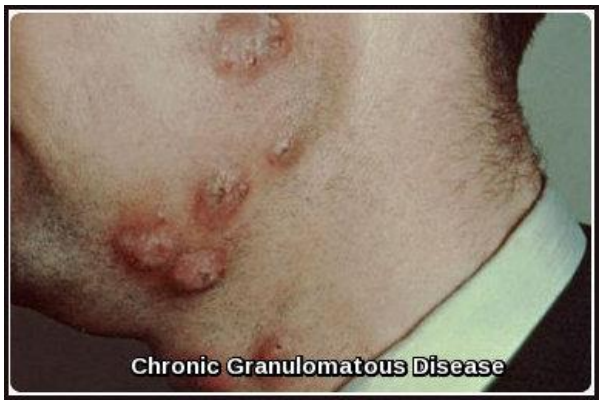
- When PPD is injected intradermally in sensitized person
- Local indurated area appears at injection site (48-72 hs)
- Indurations due to accumulation of macrophages and lymphocytes
- Similar reactions observed in diseases e.g. brucellosis, lepromin test in leprosy

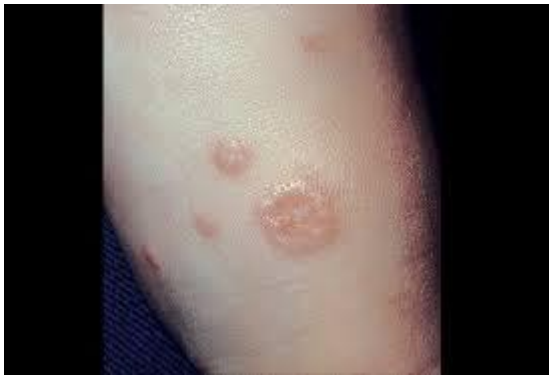




2. Granulomatous lesions

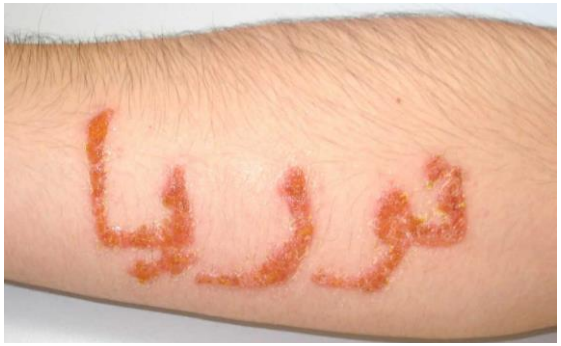
- In chronic diseases : TB, Leprosy, schistosomiasis نوع من أنواع الparacite
- Intracellular organisms resist destruction by macrophage.
- Persistent antigen in tissues stimulate local DTH reaction
- Continuous release of cytokines leads to accumulation of macrophages which give rise to epitheloidal and giant cell granuloma

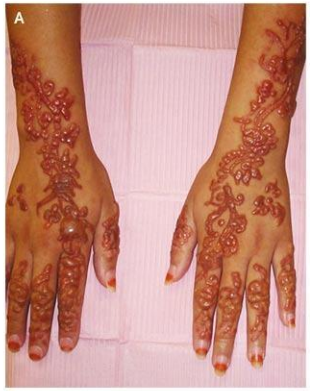


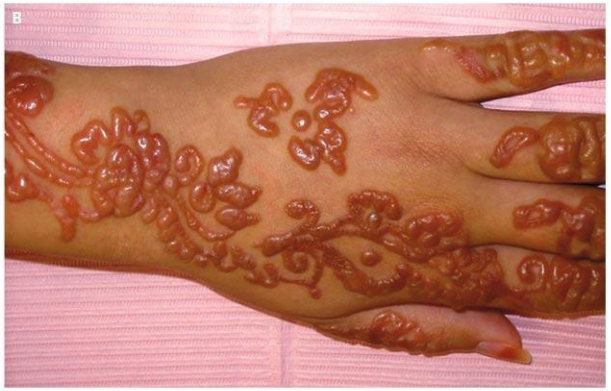


3. Contact Dermatitis

- Contact of skin with chemical substances or drugs e.g. poison, hair dyes, cosmetics, soaps, neomycin
- These substances enter skin in small molecules
- They are haptens that attached to body proteins, form immunogenic substances
- DTH reaction to these immunogenic subst. lead to: inflammatory reaction of skin in
  - eczema
  - rash
  - vesicular eruption







4- Auto immune diseases and graft rejection are due to in part to delayed hypersensitivity reactions

- Multiple sclerosis, IBD :Th1

Inflammatory bowel disease

5- Insulin dependant diabetes mellitus: T-cells invade the pancreatic islets and specifically destroy insulin secreting beta cells (Tc cell)

6- Hashimoto's thyroiditis

مطلوب كامل

Type I:	Type II	Type III	Type IV
1. Anaphylaxis 2. Atopy 3. Allergic rhinitis, 4. allergic asthma, 5. atopic dermatitis 6. Allergic gastroenteropathy	1. Transfusion reaction due to ABO incompatibility 2. Rh-incompatability (Haemolytic disease of the newborn) 3. autoimmune haemolytic anaemia, 4. idiopathic thrombocytopenic purpura, 5. myasthenia gravis, 6. Hashimoto's thyroiditis 7. Graves's disease 8. Graft rejection cytotoxic reactions: In hyperacute rejection 9. Drug reaction (type II): 10. Penicillin induce haemolytic anaemia 11. Quinine induce thrombocytopenic purpura	1. Arthus Reaction 2. Serum Sickness 3. Post-streptococcal glomerulonephritis: 4. 4- Hypersensitive pneumonitis (farmer lung) 5. SLE, 6. rheumatoid arthritis	1. Tuberculin 2. 2Granulomatous lesions 3. Contact Dermatitis 4. graft rejection 5. Multiple sclerosis, 6. IBD :Th1 7. 5- Insulin dependant diabetes mellitus: