HYPERSENSITIVITY

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INTRODUCTION

- **Hypersensitivity can be defined as a state of altered immune response against an antigen characterized by hyper reactivity leading to immunopathology**
- Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
- There are two categories of adaptive hypersensitivities:
  - Immediate hypersensitivities refer to humoral immunity (antigen/antibody reactions)
  - Delayed hypersensitivities refer to cell-mediated immunity(cytotoxic T-lymphocytes, macrophages, and cytokines)

CLASSIFICATION OF HYPERSENSITIVITY

Coomb and Gell in 1963 classified hypersensitivity reactions into the following four types based on the mechanism involved and time taken for the reaction.

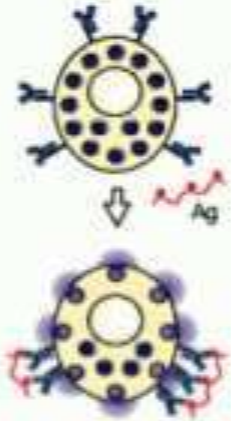
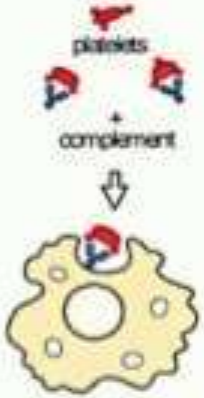
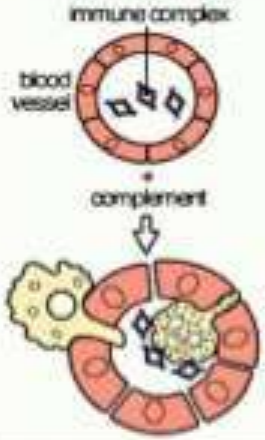
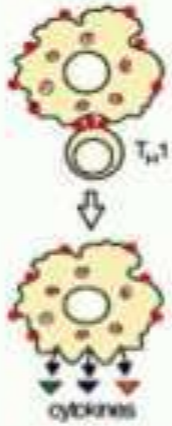
Table 2. Gell And Coombs Classification Of Hypersensitivity Reactions

Classification	Mechanism	Clinical Manifestations	Timing of Reaction
Type I (IgE-mediated)	Allergen IgE binds to mast cells with inflammatory mediators released	Anaphylaxis, urticaria, angio-edema	Immediate; minutes to hours
Type II (cytotoxic)	IgG and IgM bind to allergen on target cell; complement mediated	Neutropenia, thrombocytopenia, hemolytic anemia	Variable
Type III (immune complex)	Tissue deposition of IgG, bound to allergen; activated by complement	Serum sickness, vasculitis, glomerulonephritis	1-3 weeks postexposure
Type IV (delayed, cell-mediated)	T-lymphocytes, macrophages	Contact dermatitis	48-72 hours

Abbreviations: IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M.

Adapted from "Allergies And Anaphylaxis: Analyzing The Spectrum Of Clinical Manifestations," by Jonathan E Davis, MD, *Emergency Medicine Practice*, Vol. 7(10), 2005, Table 2, page 3, Copyright EB Medicine.

Coombs and Gell's Classification of Hypersensitivity

	Type I	Type II	Type III	Type IV	
Immune reactant	IgE antibody, T_H2 cells	IgG antibody	IgG antibody	T cells	
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR cells (phagocytes, NK cells)	Complement, Phagocytes	Macrophage activation	Cytotoxicity
					
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg penicillin)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Contact dermatitis

Type I Hypersensitivity

(IgE mediated anaphylactic hypersensitivity)

Characteristics of Type-I hypersensitivity

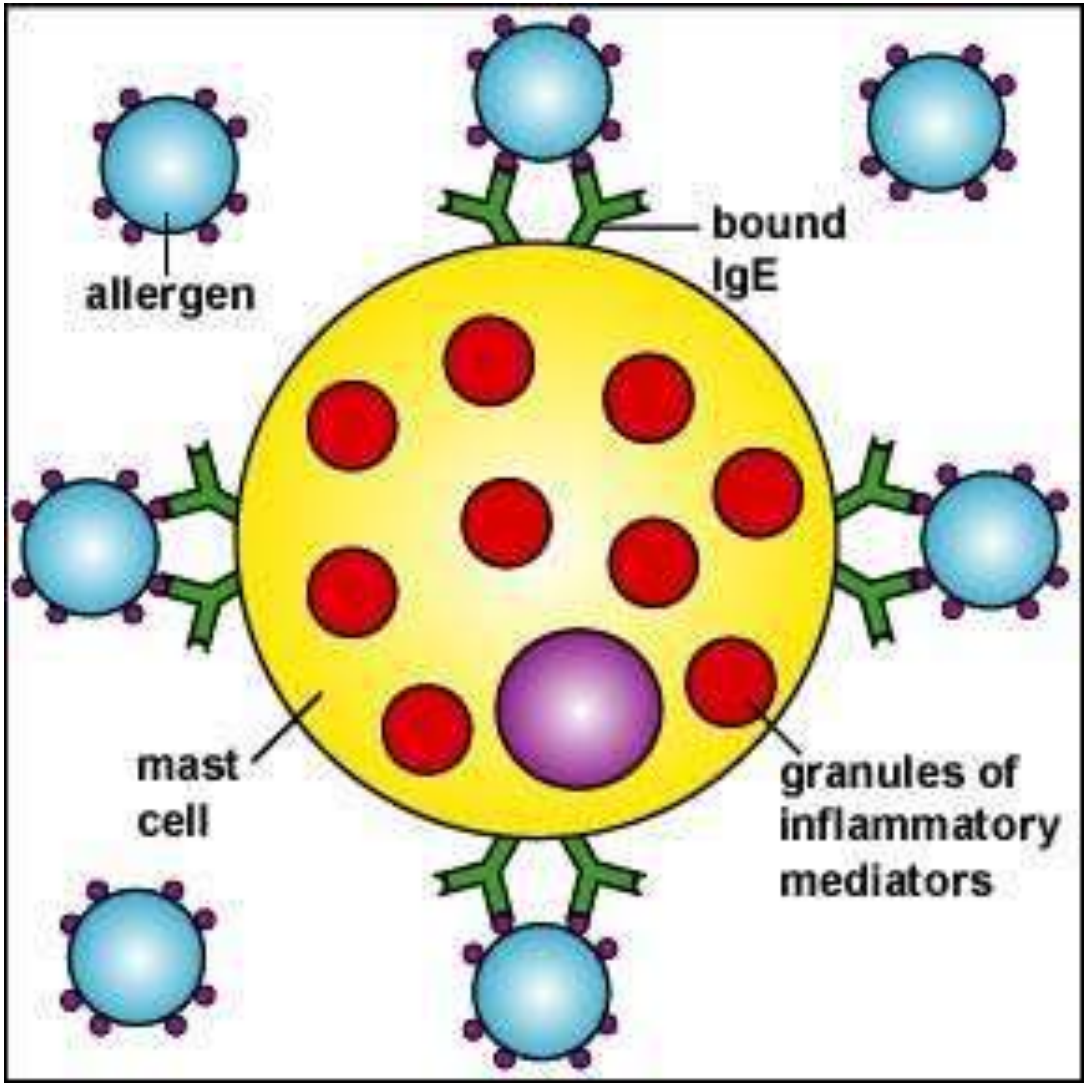
- It is also known as immediate or anaphylactic hypersensitivity and is mediated by IgE.
- The reaction occurs on exposure to allergen second time. The first exposure (sensitizing dose) results in sensitization of host to allergen and subsequent exposure (s) (shocking dose) will cause reaction
- **Anaphylactic shock** occurs in sensitized animals within seconds to minutes (15-30after exposure to the allergen) after exposure to the antigen, now called as an **allergen.** Sometimes the reaction may have a delayed onset (10-12 hours).
- In type I hypersensitivity reactions, the allergens are proteins with a molecular weight ranging from 10 to 40 kDa.
- Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests resulting in **wheal and flare reaction**, measurement of total IgE and specific IgE antibodies against the suspected allergens by ELISA, Radioallergosorbent test (RAST)

Mechanism of Type-I hypersensitivity

- The mechanism of reaction involves preferential production of IgE, in response to certain antigens (allergens).
- Individuals prone to type-I hypersensitivity preferentially produce **IL-4 and IL-13 that favor IgE** class switch.
- IgE has very high affinity for its receptor (FcεIII; CD23) expressed on surface of mast cells and basophils; the Fc portion of IgE binds to these receptors.
- A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances by a process called as **'degranulation'; mast cell degranulation is preceded by increased Ca*++* influx, which is a crucial process.**
- These agents cause the early phase of allergic reactions that appears within minutes after exposure to the antigen.

Cross-linking of IgE Fc-receptor is important in mast cell triggering

Cross linking of IgE by allergen triggers mast cell degranulation



Mechanism of Type-I hypersensitivity

- Degranulation of cells result in the synthesis and secretion of inflammatory mediators such as platelet-activating factor, leukotreins, bradykinins, prostaglandins, and cytokines that contribute to inflammation.
- The reaction is amplified by PAF (platelet activation factor) that causes platelet aggregation and release of histamine, heparin and vasoactive amines. Eosinophil chemotactic factor of anaphylaxis (ECF-A) and neutrophil chemotactic factors attract eosinophils and neutrophils, respectively, which release various hydrolytic enzymes that cause necrosis
- These agents cause the early phase of allergic reactions that appears within minutes after exposure to the antigen.
- Late phase allergic reactions may begin several hours after exposure to antigen.
- Cell-bound IgE on the surface of basophils of sensitive individuals binds a substance called histamine releasing factor (possibly produced by macrophages and B-lymphocytes) causing further histamine release

Induction and effecter mechanisms in Type-I Hypersensitivity

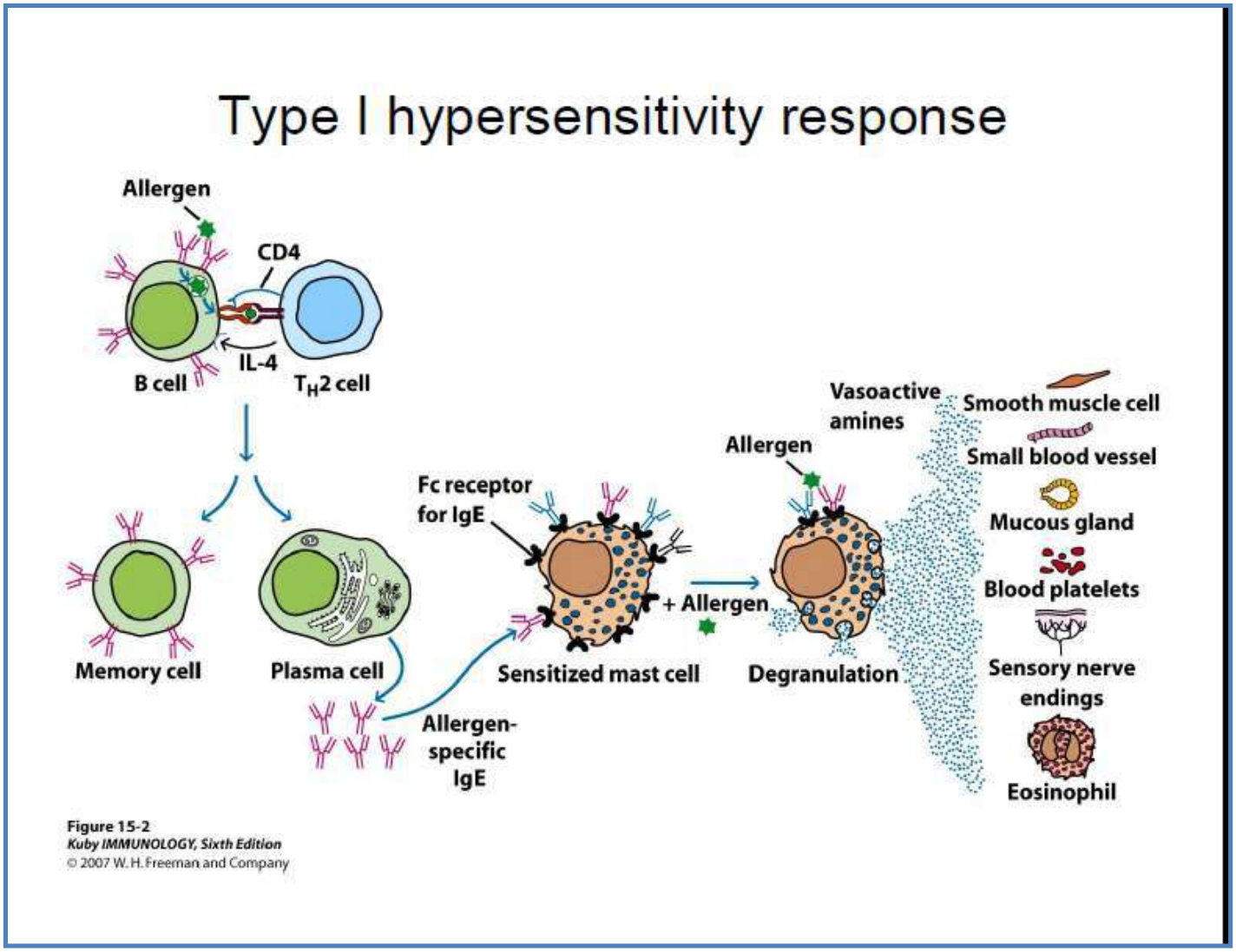


Figure 15-2
Kuby IMMUNOLOGY, Sixth Edition

Effects of Type-I Hypersensitivity

- The inflammatory agents released or produced cause the following:
  - dilation of blood vessels, which causes local redness (erythema) at the site of allergen delivery. If dilation is widespread, this can contribute to decreased vascular resistance, a drop in blood pressure, and shock.
  - increased capillary permeability, which causes swelling of local tissues (edema). If widespread, it can contribute to decreased blood volume and shock.
  - constriction of bronchial airways, which leads to wheezing and difficulty in breathing.
  - stimulation of mucous secretion, which leads to congestion of airways.
  - stimulation of nerve endings, which leads to itching and pain in the skin.

Pathology of Type-I hypersensitivity

- The primary cellular component in Type-I is mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.
- The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause from minor inconvenience to death.
- In most domestic species, the lungs are the primary target organs, and the portal-mesenteric vasculature is a secondary target; this is reversed in dogs.
- In dogs, the major organ affected by anaphylactic shock is the liver, and signs are associated with constriction of hepatic veins, resulting in portal hypertension and visceral pooling of blood. GI signs rather than respiratory signs are more apt to be seen in dogs.

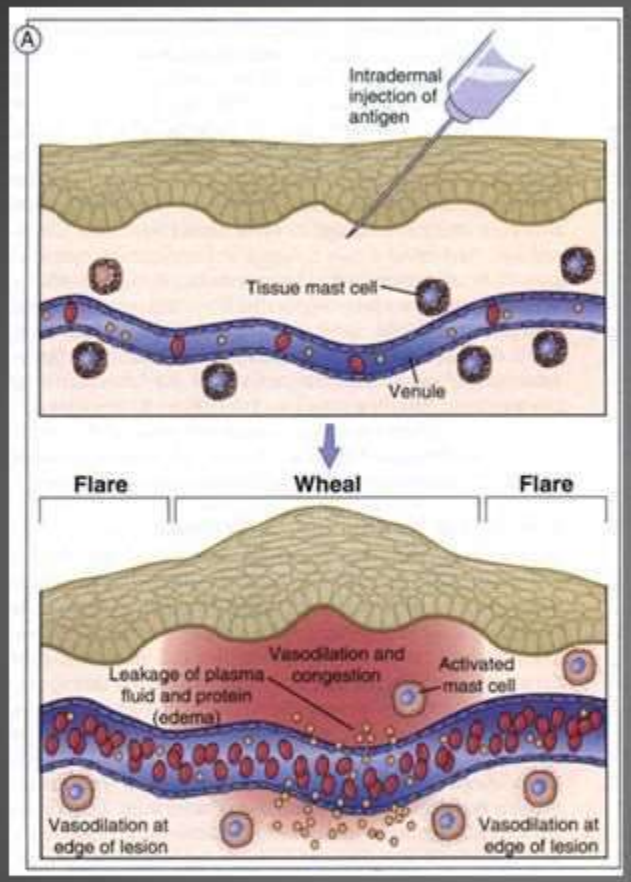
Pathology of Type-I hypersensitivity

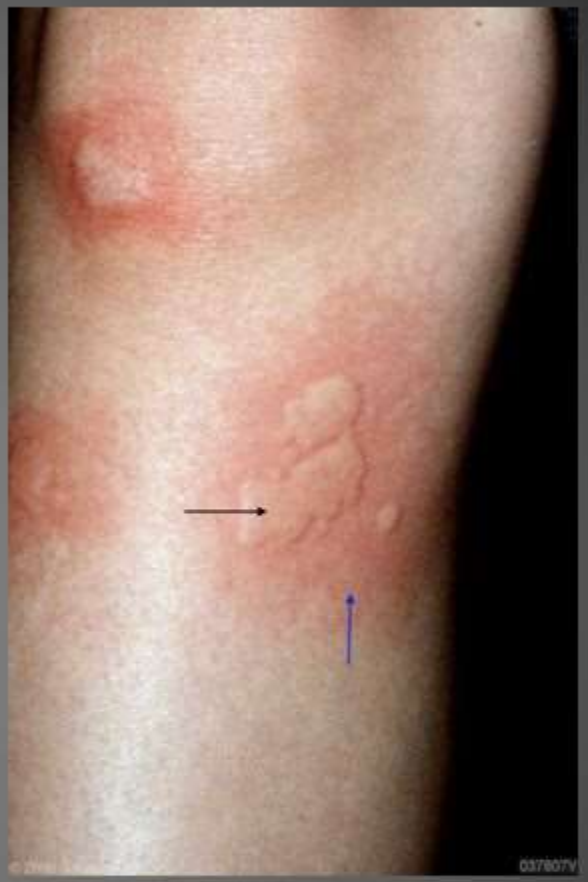
- The IgE mediated diseases in humans include systemic anaphylactic shock, asthma, Hay fever (allergic rhinitis), tropical pulmonary eosionophila, allergic conjunctivitis, skin reactions (urticaria, eczema), food allergies.
- The IgE mediated diseases in animals include systemic anaphylactic shock, urticarial reactions (hives), atopic dermatitis, food allergies, allergic enteritis, atypical interstitial pneumonia in cattle, chronic allergic bronchitis and pulmonary infiltration with eosinophilia in dogs, allergic bronchiolitis and asthma in cats.

Wheal and Flare reaction

- **Wheal and flare reaction** is the characteristic local cutaneous reaction, developing within 10 to 15 minutes of injecting an allergen into the skin.
- It consists of an elevated, blanched “wheal” surrounded by a spreading by a spreading “flare” of erythema caused by release of histamine from mast cells.
- Wheal is a raised, itchy (pruritic) area of skin. It reflect circumscribed dermal edema (fluid collection in the layer of skin below the surface). A wheal is also sometimes called a welt and often a hive.
- Flare is an area of redness surrounding wheal
- The larger the **wheal and flare**, the greater the sensitivity.

Urticaria: "Wheal and flare" reaction



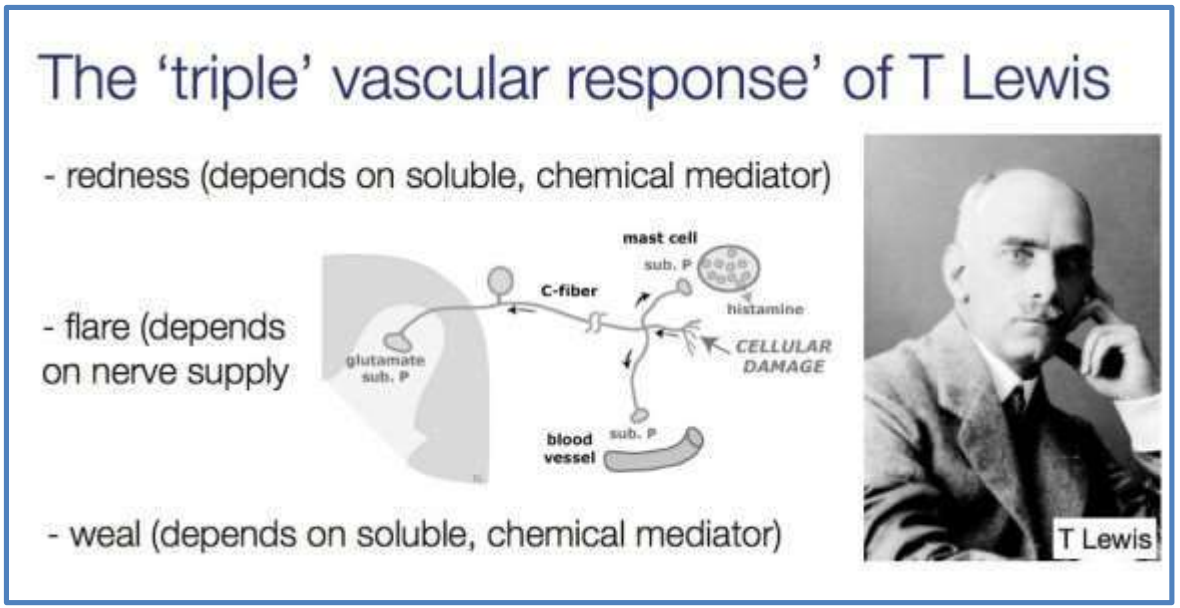


- Distinctive response utilized in allergy testing
- In response to release of mast cell mediators, local blood vessels dilated and become leaky
- Produces redness and local swelling (wheal) – black arrow
- Subsequent dilation of vessels at edge of swelling appears like a red rim (flare) – blue arrow

Mechanism of Wheal and Flare reaction

The mechanism of wheal and flare reaction is expressed by Triple response of Lewis:

- Red spot: due to capillary dilatation
- Flare: redness in the surrounding area due to arteriolar dilatation mediated by axon reflex.
- Wheal: due to exudation of fluid from capillaries and venules



Type II Hypersensitivity

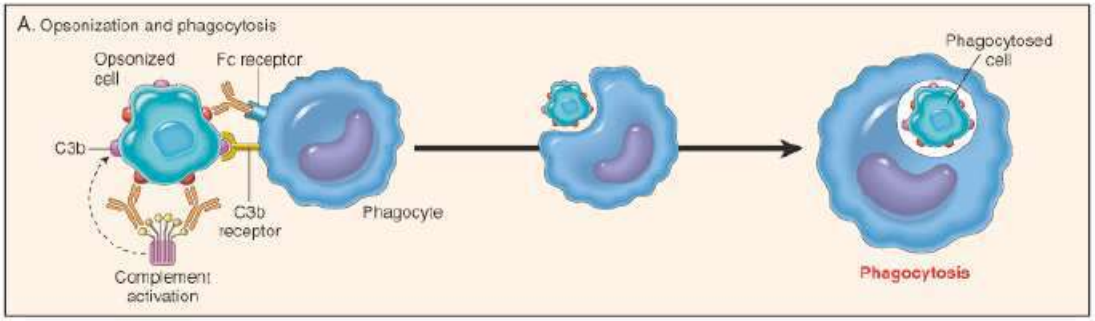
(Antibody-mediated cytotoxic hypersensitivity)

Characteristics of Type II Hypersensitivity

- Type II hypersensitivity are antibody mediated cytotoxic reactions occurring when an antibody binds to antigens located on the surface of cells (usually RBCs). The reaction time is minutes to hours.
- It is mediated, primarily, by antibodies of IgM or IgG class.
- The bound antibody can cause cell lysis by activating the classical complement pathway, promoting phagocytosis (opsonization) or through ADCC.
- Many different antigens may trigger this cell destruction, but an infection in a genetically predisposed animal appears to be a major triggering pathway.
- Antigens are normally endogenous, although exogenous chemicals (haptens, such as ivy or drugs) that can attach to cell membranes can also induce type II reactions.
- Autoimmune haemolytic anaemia, Blood transfusion reactions, *Erythroblastosis fetalis,* *d*rug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are examples.

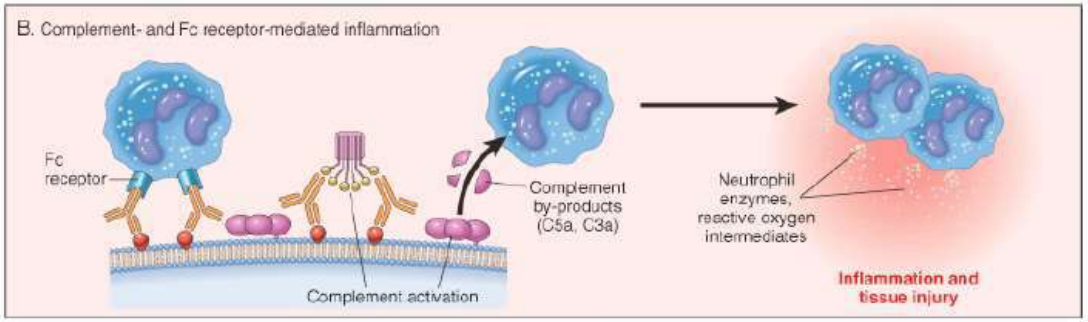
Mechanism of Type II Hypersensitivity

- IgM or IgG antibodies are made against self antigens either as a result of failure of immune tolerance or cross-reactive antibodies can develop during infections, which may bind to normal tissue antigens and trigger antibody-mediated cytotoxicity.
- Subsequent binding of these antibodies to the surface of host cells leads to:
  - **Opsonization** of the host cells whereby phagocytes stick to host cells by way of IgG, C3b, or C4b and discharge their lysosomes.
  - Activation of the classical **complement pathway** causing MAC induced lysis.
  - **ADCC** mediated destruction of the host cells whereby NK cells attach to the Fc portion of the antibodies.



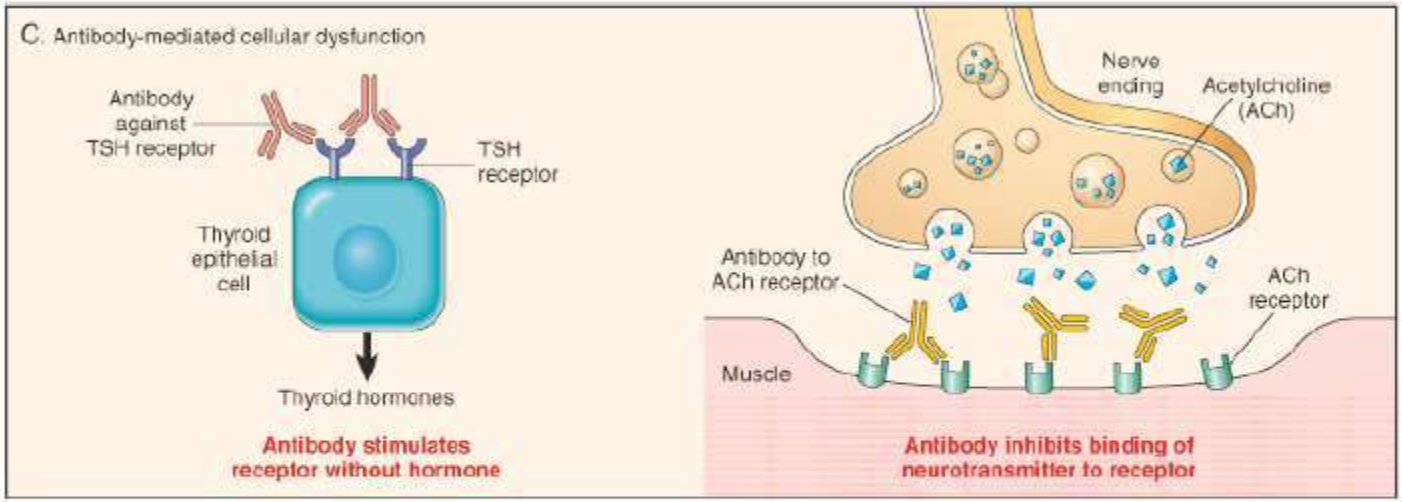
Examples: autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura

Kumar et al. Robbins and Cotran Pathologic Basis of Disease



Examples: pemphigus vulgaris, Goodpasture syndrome

Kumar et al. Robbins and Cotran Pathologic Basis of Disease



Examples: Graves disease (hyperthyroidism), myasthenia gravis

Kumar et al. Robbins and Cotran Pathologic Basis of Disease

Pathology of Type II Hypersensitivity

- Mediated by Abs directed towards antigens present on cell surfaces or the extracellular matrix (type IIA) or abs with agonistic/antagonistic properties (type IIB).

- The most common cells involved are blood cells. The outcome may be:
  - hemolytic anemia if RBCs are involved,
  - leukopenia involving WBCs, or
  - thrombocytopenia involving platelets.

- Under some circumstances, a cytotoxic attack on vascular epithelial cells will cause a vasculitis with local vascular leakage.

- The lesion contains antibody, complement and neutrophils

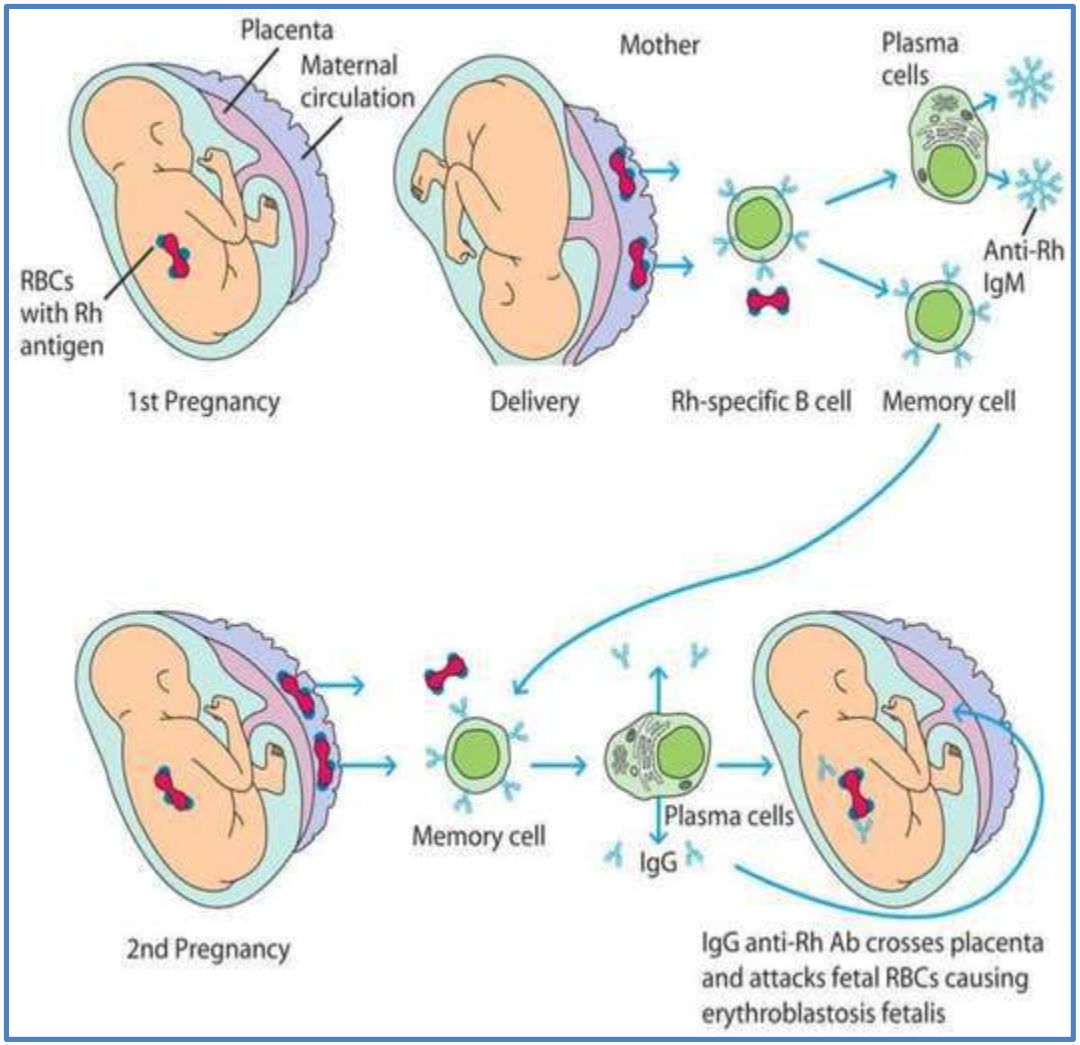
Examples of Type II Hypersensitivity

- AB and Rh blood group reactions (blood transfusion reactions, erythroblastosis foetalis)
- Autoimmune diseases:
  - Rheumatic fever where antibodies result in joint and heart valve damage;
  - Idiopathic thrombocytopenia purpura where antibodies result in the destruction of platelets;
  - myasthenia gravis where antibodies bind to the acetylcholine receptors on muscle cells causing faulty enervation of muscles;
  - Goodpasture's syndrome where antibodies lead to destruction of cells in the kidney;

Examples of Type II Hypersensitivity

- Autoimmune diseases:
  - Graves' disease where antibodies are made against thyroid-stimulating hormone receptors of thyroid cells leading to faulty thyroid function;
  - Multiple sclerosis where antibodies are made against the oligodendroglial cells that make myelin, the protein that forms the myelin sheath that insulates the nerve fiber of neurons in the brain and spinal cord;
- Some drug reactions, e.g. penicillin
- Bovine Neonatal Pancytopenia

Erythroblastosis Foetalis



TYPE – III HYPERSENSITIVITY

(Immune complex mediated hypersensitivity)

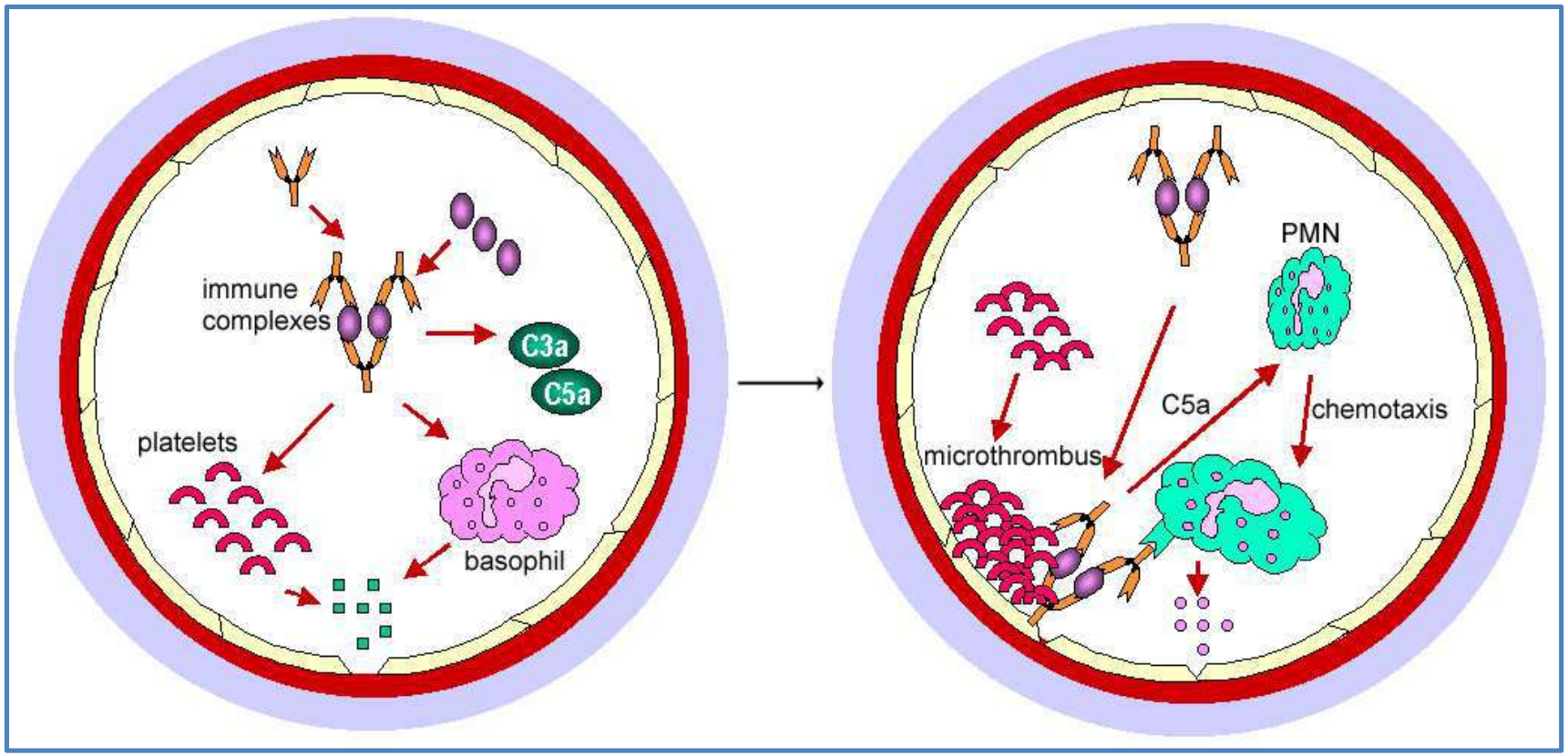
Characteristics of Type III Hypersensitivity

- In type III hypersensitivity, soluble immune complexes are formed in blood and are deposited in various tissues (typically the skin, kidney and joints), activate classical complement pathway and cause inflammatory damage.
- It is mediated by soluble immune complexes. They are mostly of IgG class, although IgM may also be involved.
- The reaction takes hours to days (3-10 hours) to develop.
- The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: *e.g., Systemic Lupus Erythematosus-SLE).*
- The antigen is soluble and not attached to the organ involved.
- The prerequisite for the development of immune-complex disease is the persistent presence of soluble antigen and antibody.

Mechanism of Type III Hypersensitivity

- Soluble antigen-antibody (IgG or IgM) complexes are normally removed by macrophages in the spleen and liver.
- On formation of excessive amount or large immune complexes these gets lodged in capillaries, pass between endothelial cells of blood vessels – specially those in the skin, joints, and kidneys - and become trapped on the surrounding basement membrane beneath these cells.
- The Ag-Ab complexes then activate the classical complement pathway; the damage being caused by platelets and neutrophils :
  - massive inflammation, due to complement protein C5a;
  - influx of neutrophils, due to complement protein C5a , resulting in neutrophils discharging their lysosomes and causing tissue destruction and further inflammation;
  - MAC induced lysis of surrounding tissue cells; and
  - aggregation of platelets, resulting in more inflammation and the formation of microthrombi that block capillaries.

TYPE – III HYPERSENSITIVITY



Pathology of Type III Hypersensitivity

- The affinity of antibody and size of immune complexes are important in production of disease and determining the tissue involved.
- The lesion contains primarily neutrophils and deposits of immune complexes and complement.
- Macrophages infiltrating in later stages may be involved in the healing process.
- The location of the immune complexes is largely determined by the route by which antigen enters the body:
  - Inhaled antigens give rise to a pneumonitis,
  - antigens that enter through the skin cause local skin lesions, and
  - antigens that access the bloodstream form immune complexes that are deposited in renal glomeruli or joints.
- **Clinical signs** are therefore variable but may include fever, cutaneous signs, polyarthritis, ataxia, behavior change, or nonspecific signs such as vomiting, diarrhea, or abdominal pain.

Examples of Type II Hypersensitivity

- Examples in human beings are: serum sickness, Arthus reaction, polyarteritis, rheumatoid arthritis, Glomerulonephritis, SLE, allergies to penicillin and sulfonamides, poststreptococcal glomerulonephritis, meningitis, hepatitis, mononucleosis.
- Examples in animals include:
  - Membranoproliferative Glomerulonephritis in dogs
  - Hypersensitivity Pneumonitis in large animals (Extrinsic allergic alveolitis, Farmer's lung disease)
  - Vasculitis
  - Periarteritis Nodosa (Polyarteritis Nodosa, Necrotizing Polyarteritis)
  - Canine Rheumatoid Arthritis
  - Plasmacytic-Lymphocytic Synovitis

Examples of Type II Hypersensitivity

- Examples in animals include:
  - **Purpura hemorrhagica** of horses is a severe non-thrombocytopenic purpura occurring as a sequelae to a *Streptococcus equi* infection; it occurs when immune complexes of antibody and streptococcal antigen are deposited in vascular basement membranes.
  - **Blue-eye disease** in dogs is an immune complex–mediated reaction that frequently occurs in the recovery stage of infectious canine hepatitis. It is haracterized by anterior uveitis and results from the reaction of serum antibodies with uveal endothelial cells infected with canine adenovirus 1.
  - **Equine recurrent uveitis** is associated with immunologic reactions to *Leptospira* or *Onchocerca* spp.

Arthus Reaction

- An **Arthus reaction** is a localized type III hypersensitivity reaction characterized by immune complex–mediated small-vessel vasculitis associated with deposition of immune complexes and activation of complement, and consequent organ damage
- Immune complexes form following high local concentration of vaccine antigens and high circulating antibody concentration.
- It was first observed by Arthus in 1903 following repeated injections of horse serum into rabbits.
- The formation of immune complexes initiates complement activation and an influx of inflammatory cells, followed by thrombus formation and hemorrhagic infarction in the areas of most intense inflammation; the types of mediators involved in Arthus reaction determines the pathological outcome of disease.

Arthus Reaction

- Arthus reaction is characterized by pain, swelling, induration, and edema beginning several hours after immunization and usually reaching a peak 12 to 36 hours after immunization.

- It is self-limiting, resolving over the course of a few days.

- The frequency and severity can be lessened by spacing immunizations more widely, as has been recommended for tetanus-diphtheria toxoid booster injections.

Arthus reaction

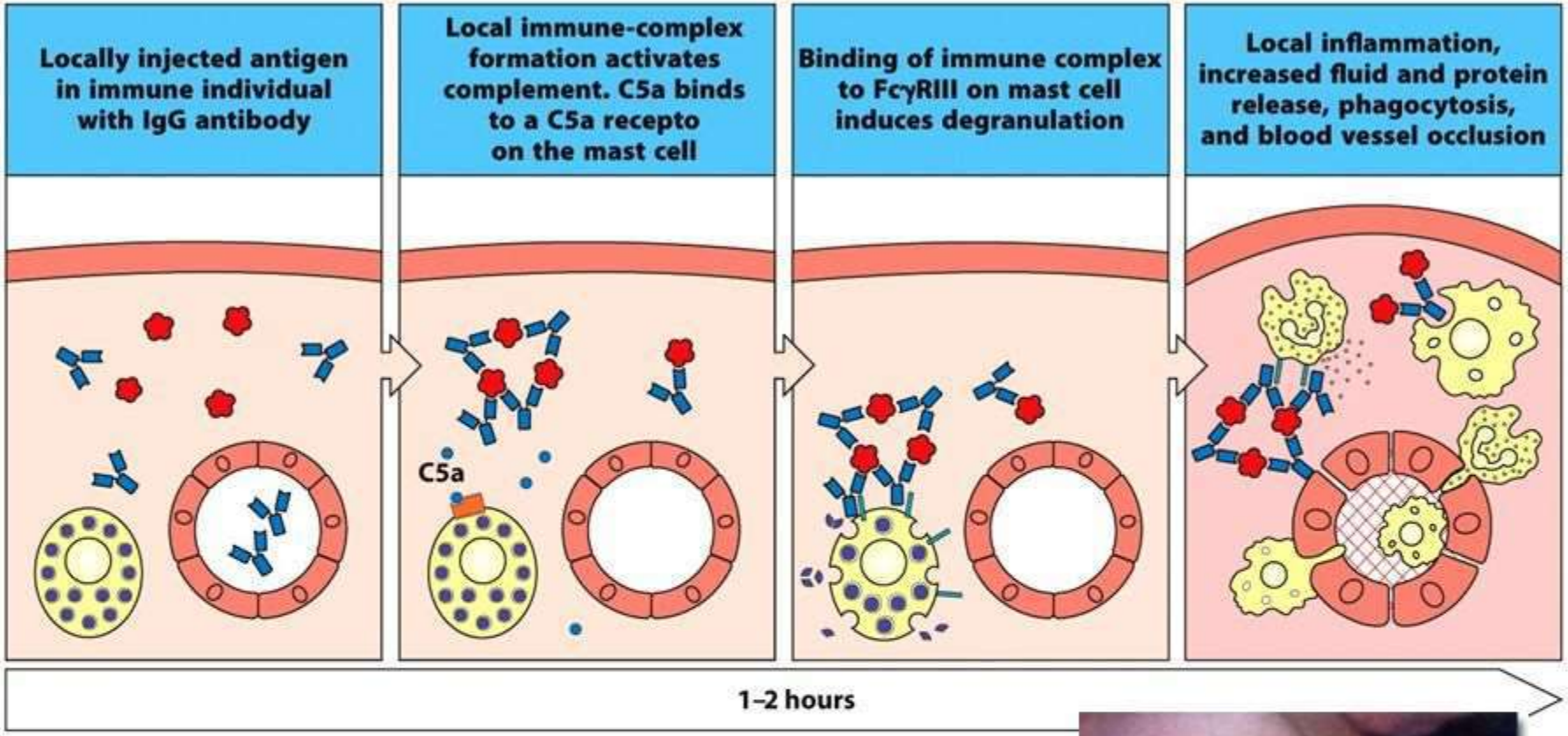
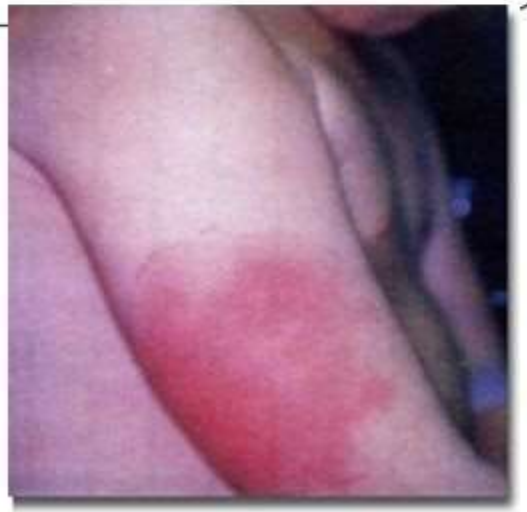


Figure 12.32 The Immune System, 3ed. (© Garland Science 2009)

hard swelling, erythema



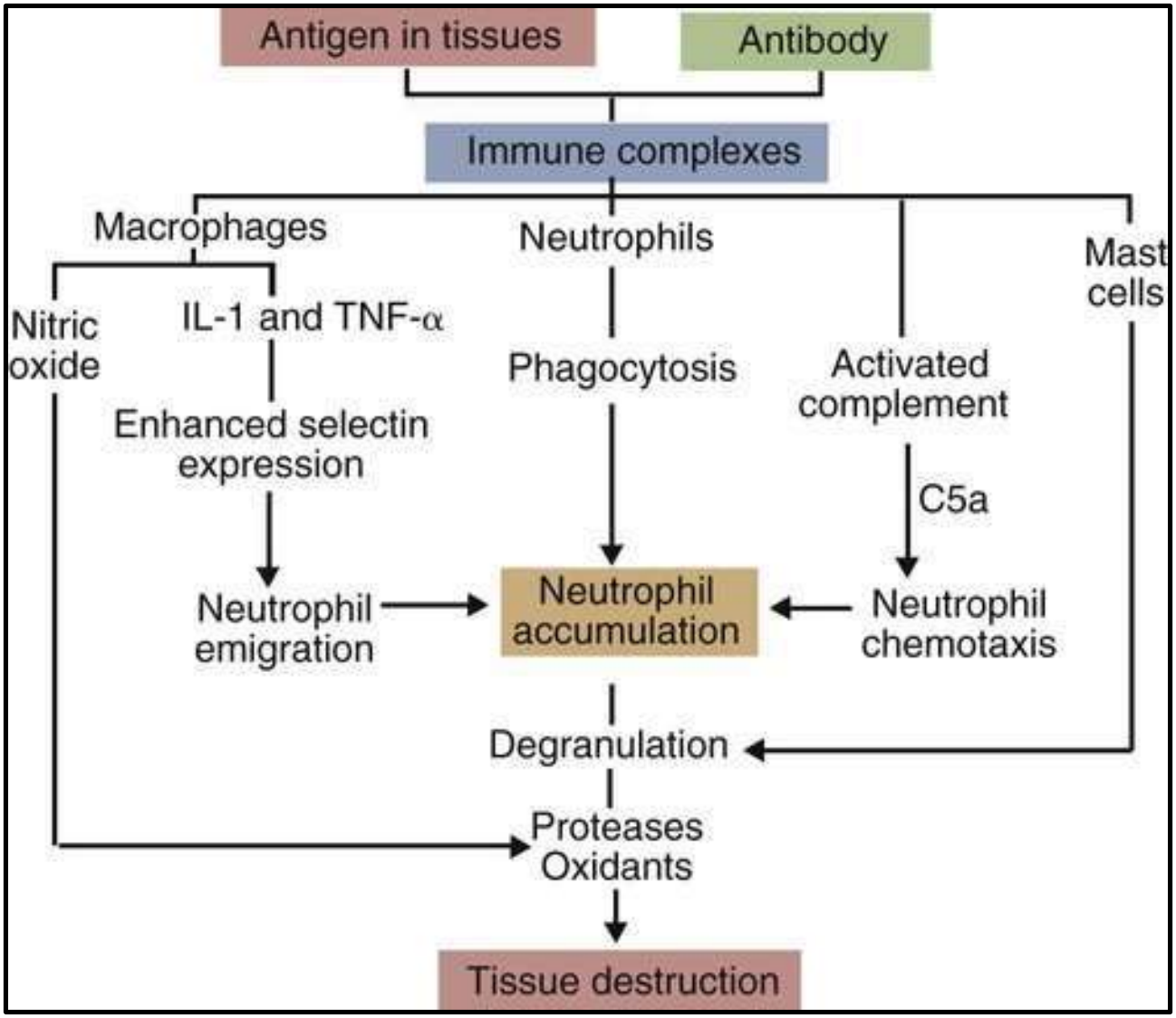
Serum Sickness

- Serum sickness is a systemic type III hypersensitivity reaction that results from the injection of heterologous or foreign protein or serum.
- Von Pirquet and Schick first described the syndrome in 1905, in regions draining the site of injection after patients were given antitoxin in the form of horse serum, hence the name
- Certain medications (eg, penicillin, nonsteroidal anti-inflammatory drugs [NSAIDs]) have also been associated with serum sickness–like reactions.
- These reactions typically occur 1 to 3 weeks after exposure to the drug, but may occur as early as 1 to 24 hours afterward.
- Clinical manifestations include general malaise, fever, urticaria, artheralgia, eosinophilia, splenomegaly and lymphadenopathy.

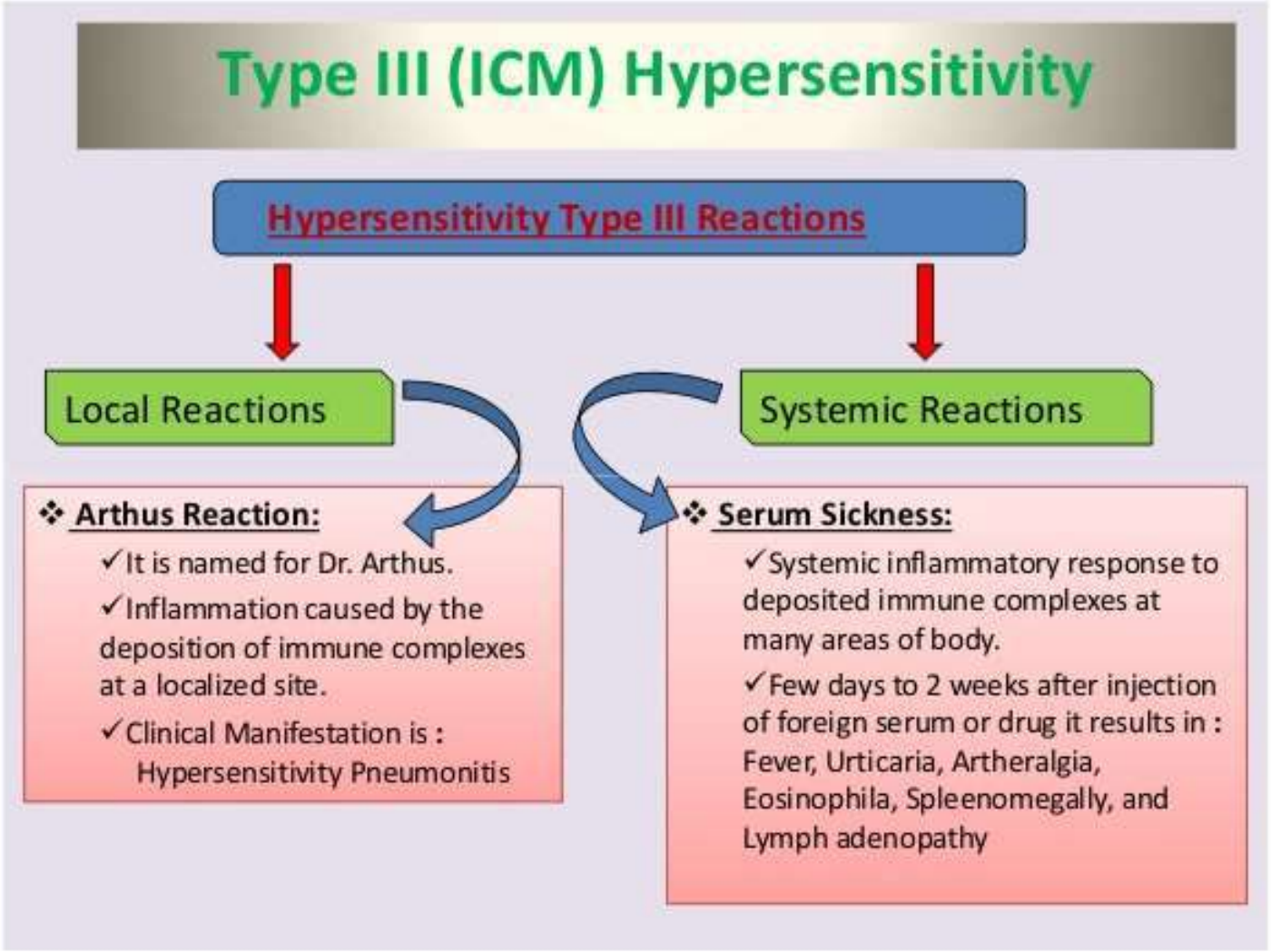
Serum Sickness

- On exposure to a foreign serum protein, 6-10 days later antibodies and form antigen-antibody complexes.
- If the macrophage activating system is not functioning properly, these complexes will become saturated in the circulation, leading to immune complex deposition, most commonly in parenchymal tissues and synovial joint fluid.
- The deposition of immune complexes may activate the classical complement pathway, which will trigger histamine release and increase vascular permeability, which leads to an inflammatory response in the tissues and joints.
- The mediation of injury in serum sickness appears to involve several mechanisms, such as vasoactive amines, infiltration of neutrophils, and cytokines, in particular TNFα) and IL-1

Pathogenesis of Serum Sickness



Arthus reaction *versus* Serum Sickness



TYPE – IV HYPERSENSITIVITY

(Cell mediated hypersensitivity)

(Delayed type hypersensitivity)

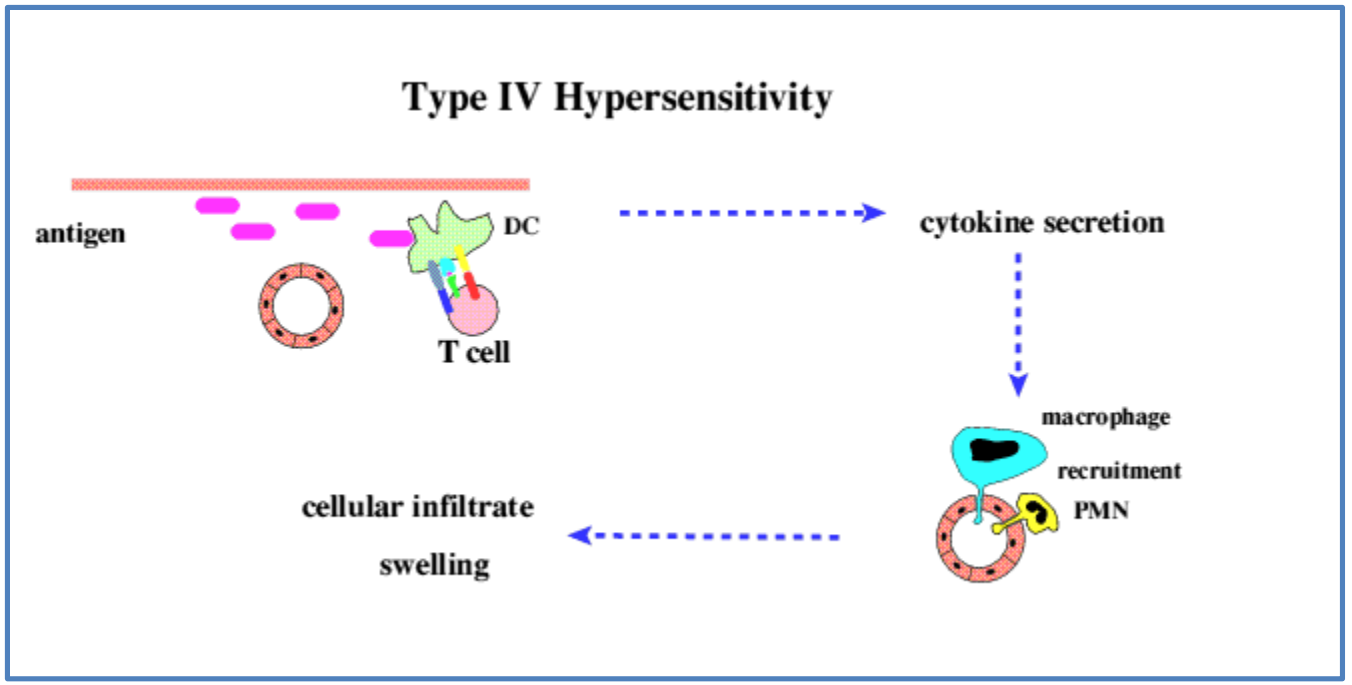
Characteristics of Type IV Hypersensitivity

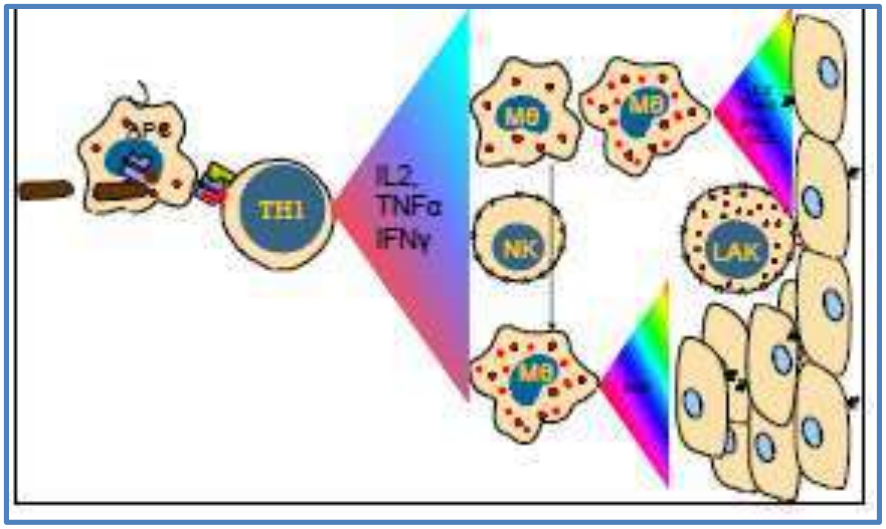
- Type IV hypersensitivity is often called delayed type hypersensitivity as the reaction takes more than 12 hours to develop. Typically the maximal reaction time occurs between 48 to 72 hours
- It is mediated by cells that cause an inflammatory reaction to either exogenous or autoantigens
- The major cells involved are T lymphocytes and monocytes/macrophages.
- This reaction to exogenous antigens involves T cells and also antigen-presenting cells (APC), all produce cytokines that stimulate a local inflammatory response in a sensitized individual.
- DHR cannot be transferred from an animal to another by means of antibodies or serum. However, it can be transferred by T cells, particularly CD4 Th1 cells.

Mechanism of Type IV Hypersensitivity

- CD8 cytotoxic T cells and CD4 helper T cells recognize antigen in a complex with either type I or II MHC antigens
- The antigen-presenting cells in this case are macrophages and they release interleukin 1, which further stimulates the proliferation of CD4 cells.
- These cells release IL-2 and IFN-λ, which together regulate the immune reaction; other lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, TNF α *etc.*
- Cytokines produced by keratinocytes, APC, and T cells recruit antigen-nonspecific T cells and macrophages to participate in a local inflammatory reaction.
- Activated CD8 cells destroy target cells on contact, while activated macrophages produce hydrolytic enzymes and, transform into multinucleated giant cells.

Mechanism of Type IV Hypersensitivity



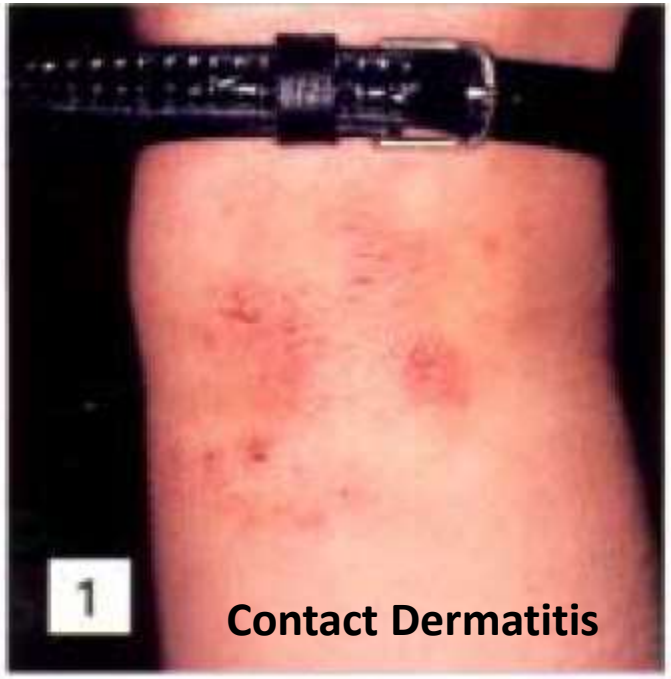


Pathology of Type IV Hypersensitivity

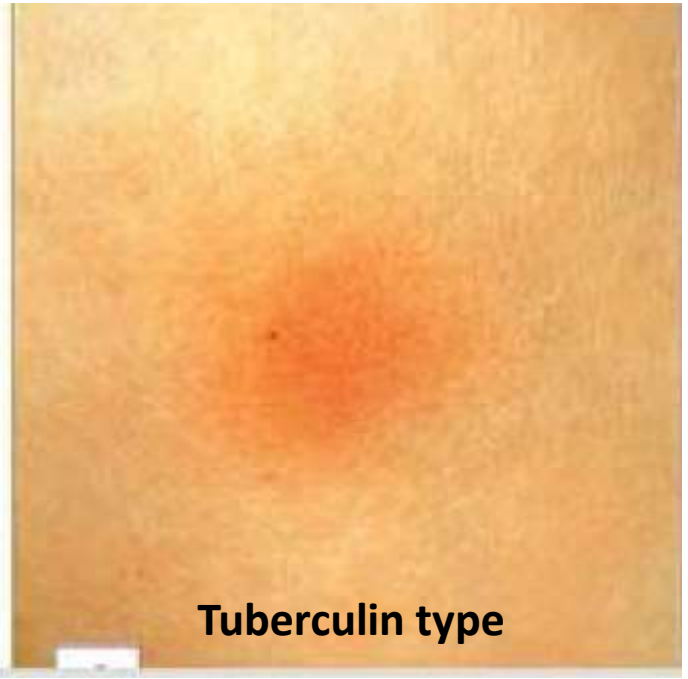
- Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, *etc.*) and granulomas due to infections and foreign antigens.
- There are three variants of delayed hypersensitivity as listed below and their maximal reaction time appears in brackets:
  - Contact (48 to 72 hours)
  - Tuberculin (48 to 72 hours)
  - Granulomatous (21 to 28 days)
- The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.
  - Contact: mononuclear cells infiltrates present in both dermis and epidermis.
  - Tuberculin: dermal infiltrate of leukocytes
  - Granulomatous: typical epithelioid-cell granuloma and giant cells in the center of the lesion surrounded by a cuff of lymphocytes.

Delayed Hypersensitivity Reactions

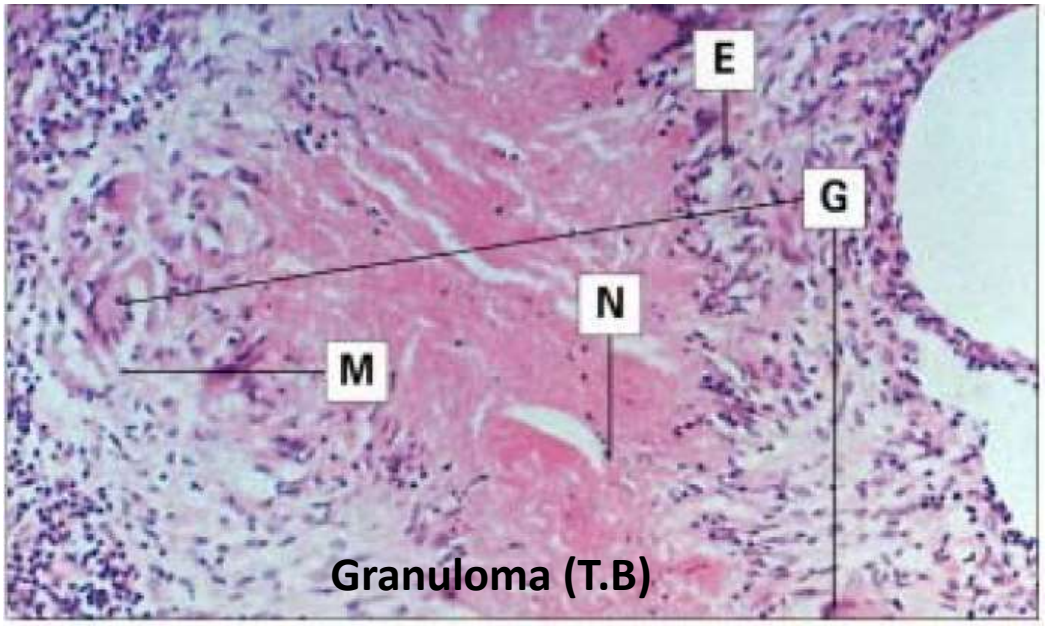
type	reaction time	clinical appearance	histology	antigen and site
contact	48-72 hr	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, heavy metals, *etc.*)
tuberculin	48-72 hr	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, lepromin, *etc.*)
granuloma	21-28 days	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, leprosy, *etc.*)



Contact Dermatitis



Tuberculin type

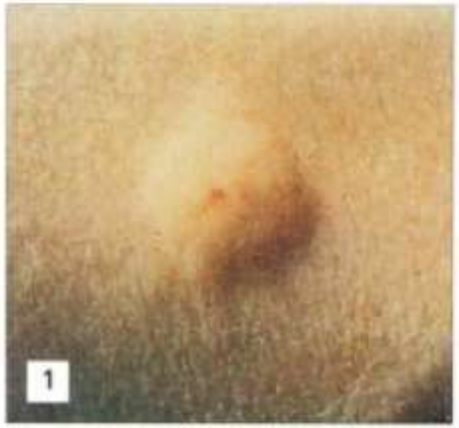


Granuloma (T.B)

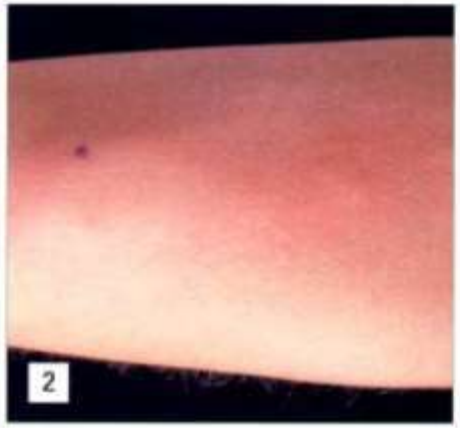
Roitt 24.23

Skin Reactions

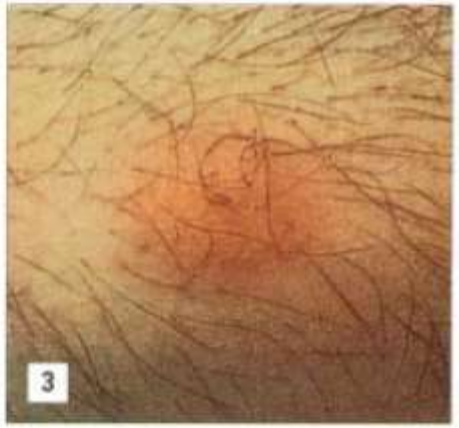
Immediate



Arthus

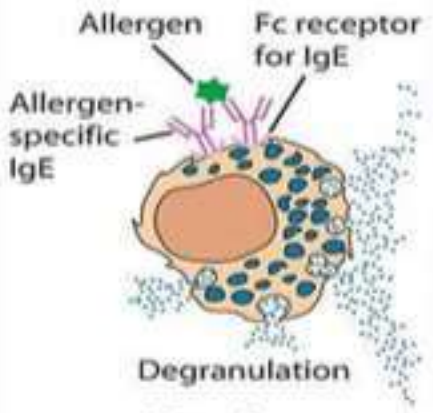
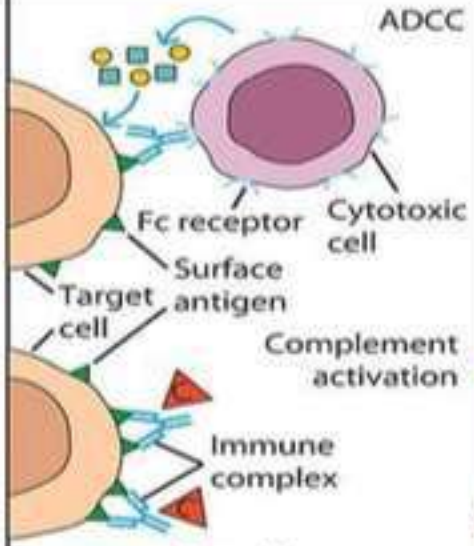
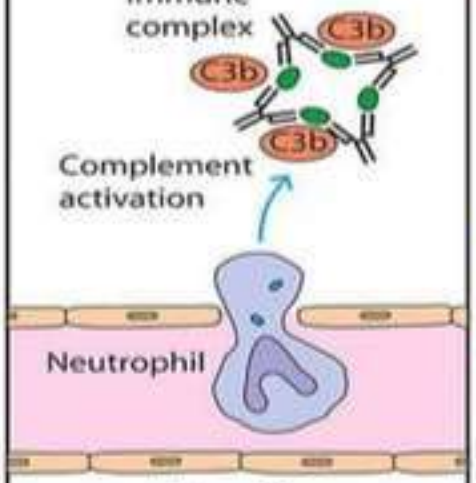
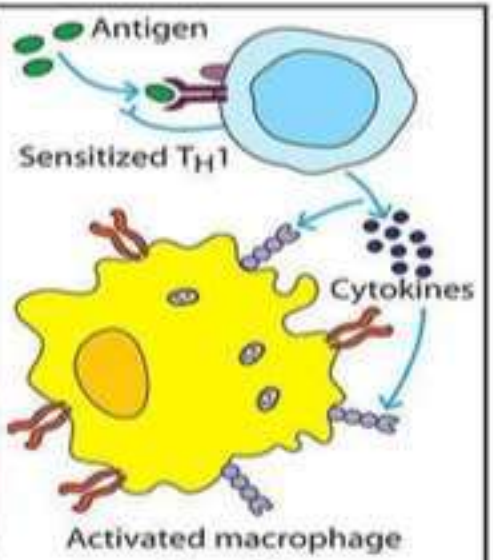


DTH



Roitt 23.9

Comparison of Types of Hypersensitivity

 **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	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	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	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

Comparisons of Type I-IV Hypersensitivity Reactions

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	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
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