Hypersensitivity (contd)

Type II Hypersensitivity (ADCC)

-- The **second class** of damaging reactions is caused by **specific antibody** binding to cells or tissue antigens. It is called **ADCC (Antibody dependent cellular cytotoxicity).**

-- The antibodies are of the **IgM** or **IgG** classes and cause cell destruction by **Fc dependent mechanisms** either **directly** or by recruiting **complement** via the classical pathway.

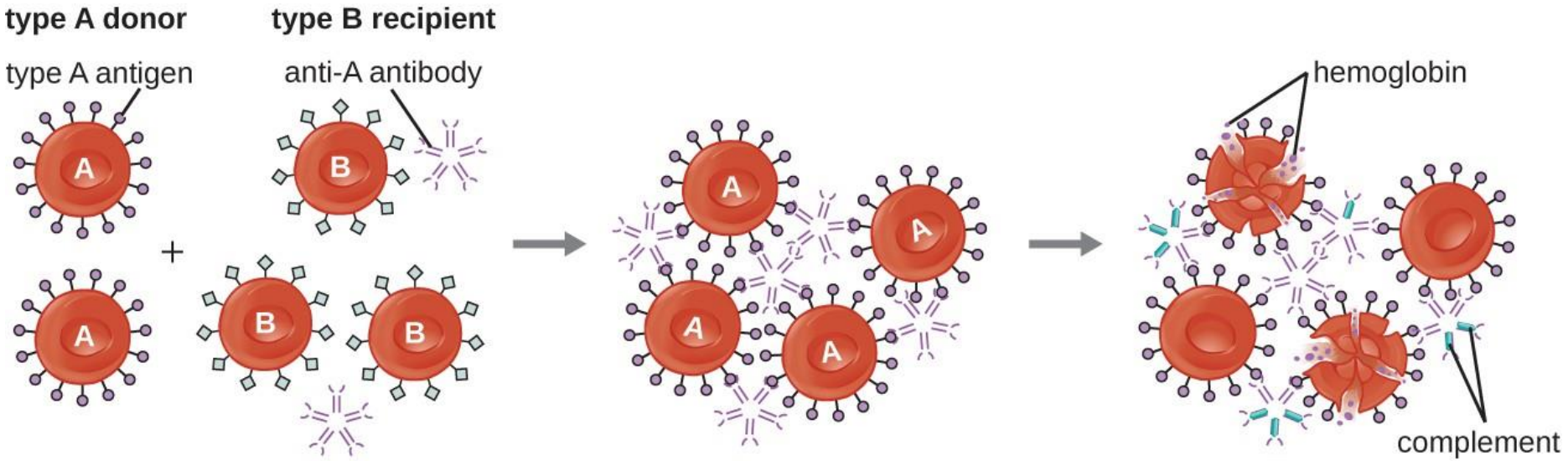
-- **Except** where the reaction is **autoimmune**, the target cells are **foreign** to the host.

Fc dependent mechanisms include phagocytosis and destruction of opsonized virus particles or the depletion of virus-infected cells via the mononuclear phagocytic system.

-- In practice, the **type II hypersensitivity** reactions are usually **only seen in blood transfusion** recipients and patients with certain **autoimmune diseases**.

-- The classic **ABO incompatibility** reaction is of **type II**, with **IgM antibodies** causing **complement lysis of erythrocytes**.

-- Because of **cross-matching**, transfusion reactions are now rare.



1 Donated type A blood with type A antigens enters bloodstream of type B recipient.

2 Anti-A antibodies in plasma of type B recipient bind to donated type A red blood cells.

3 Bound anti-A antibodies activate complement cascade, causing hemolysis and release of hemoglobin.

Type III Hypersensitivity

-- Type III hypersensitivity is mediated by **immune complexes** of **IgG** antibodies with soluble antigens.

-- It is now thought that this form of hypersensitivity has a lot in **common with type I**.

-- The major **difference** is that the antibody involved is **IgG,** not IgE**.**

Generalized or systemic Type III reactions

-- The presence of sufficient quantities of **soluble antigen** in circulation produce a condition of **antigen excess** which leads to the formation of **small antigen-antibody complexes** which are **soluble** and **poorly cleared**.

-- The major pathology is due to **complex deposition** on the surface of various tissues.

This process can be divided into **three** phases:

Phase 1:

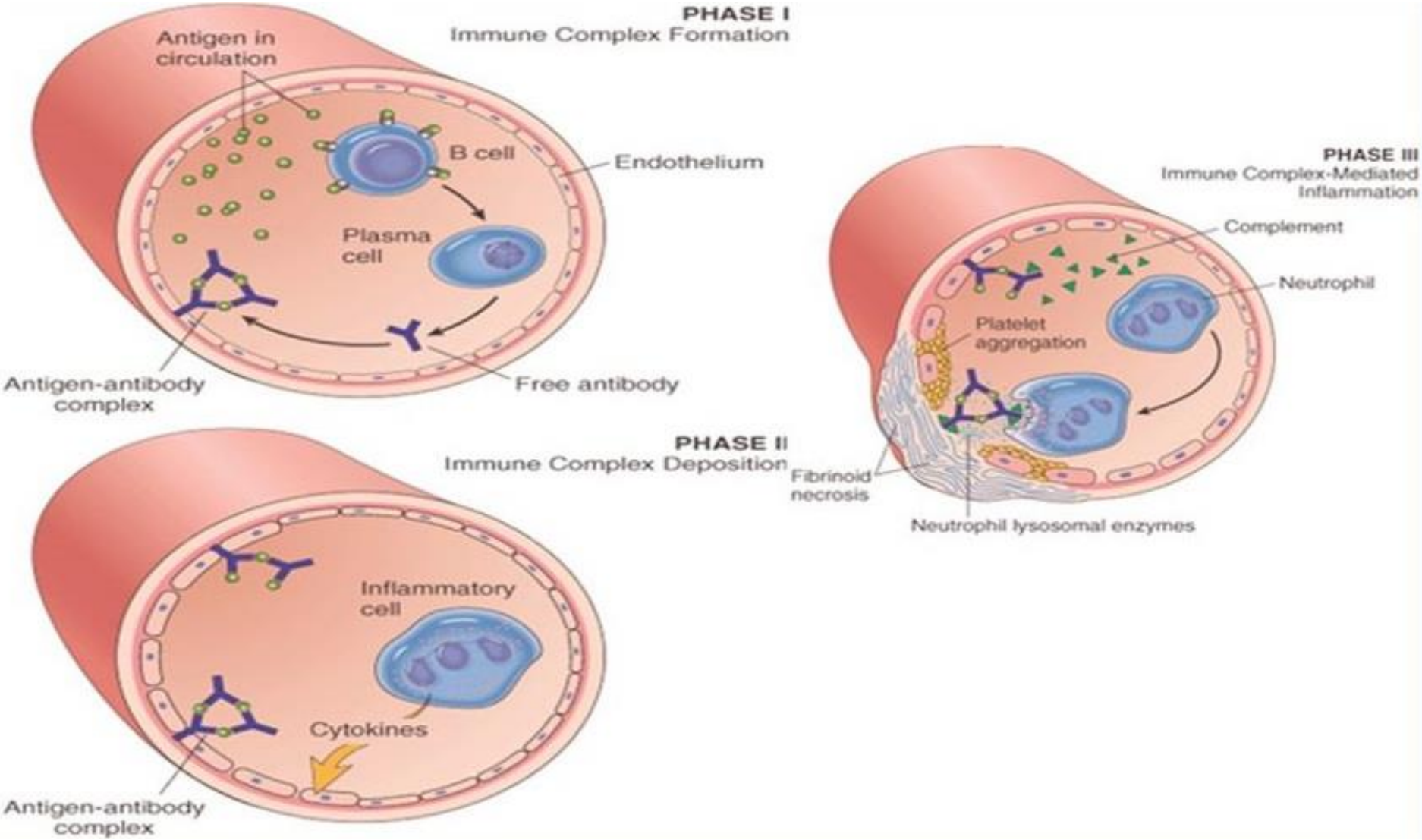
Formation of immune complexes and deposition on tissue surface.

Phase 2:

The deposited immune complexes attract phagocytes esp. **neutrophils,** which **release cytokines** and discharge their **granule contents** with consequent damage to the **surrounding endothelium** and **basement membranes**.

Phase 3:

This is followed by **complement activation** and **platelet aggregation** at the site of action.


PHASE I
Immune Complex Formation
Antigen in circulation
B cell
Endothelium
Plasma cell
Antigen-antibody complex
Free antibody
PHASE II
Immune Complex Deposition
Inflammatory cell
Cytokines
Antigen-antibody complex
PHASE III
Immune Complex-Mediated Inflammation
Complement
Neutrophil
Platelet aggregation
Fibrinoid necrosis
Neutrophil lysosomal enzymes

Serum sickness

-- Serum sickness is a **systemic inflammatory response** to the presence of **immune complexes** deposited in many areas of the body.

-- After injection of foreign serum or some drugs, the antigen is **excreted slowly over a period of time**.

-- During this time, **antibody production starts**.

-- The **simultaneous** presence of antigen and antibody leads to the formation of **immune complexes** which may circulate or get deposited at various sites.

-- Typical symptoms are fever, urticaria, arthralgia, lymphadenopathy, splenomegaly and eosinophilia after a **few days to 2 weeks.**

-- Serum sickness is classified as **immediate reaction** because symptoms appear **promptly** once immune complexes are formed.

-- Symptoms improve as immune system **removes** the antigen.

Other examples of generalised type III reactions

-- The complexes may be deposited in a variety of sites such as **skin, kidney** and **joints**.

-- Common examples of generalised type III reactions are **post-infection** complications such as **arthritis** and **glomerulonephritis.**

The Arthus reaction (local type III hypersensitivity reaction)

-- The Arthus reaction is the name given to a **local type III hypersensitivity reaction.** It occurs at the site of injection or insect bite.

-- It is comparable to Type 1 hypersensitivity reaction but it is **slow**, typically **maximal at 4-8 hrs**, and consequently more diffuse.

-- This is because the FcγRIII for IgG present on phagocytic and other cells is a **low affinity** receptor as compared with IgE receptor in case of Type I hypersensitivity reaction.

-- After attachment of immune complexes to cell receptors, **complement is activated** which leads to cell damage**.**

-- Consequently **neutrophils are also attracted** and their degranulation aggravates the situation.

Type IV Hypersensitivity (TDTH)

-- This is the **only** class of hypersensitive reactions to be triggered by **antigen-specific T cells**.

-- These cells are **TH1 cells** but they were originally termed **TDTH cells** after the alternative name for this reaction – **the delayed type hypersensitivity.**

-- Delayed type hypersensitivity results when an **APC** which has picked up antigen and presented it on surface is contacted by an **antigen specific memory TH1 cell** patrolling the tissue.

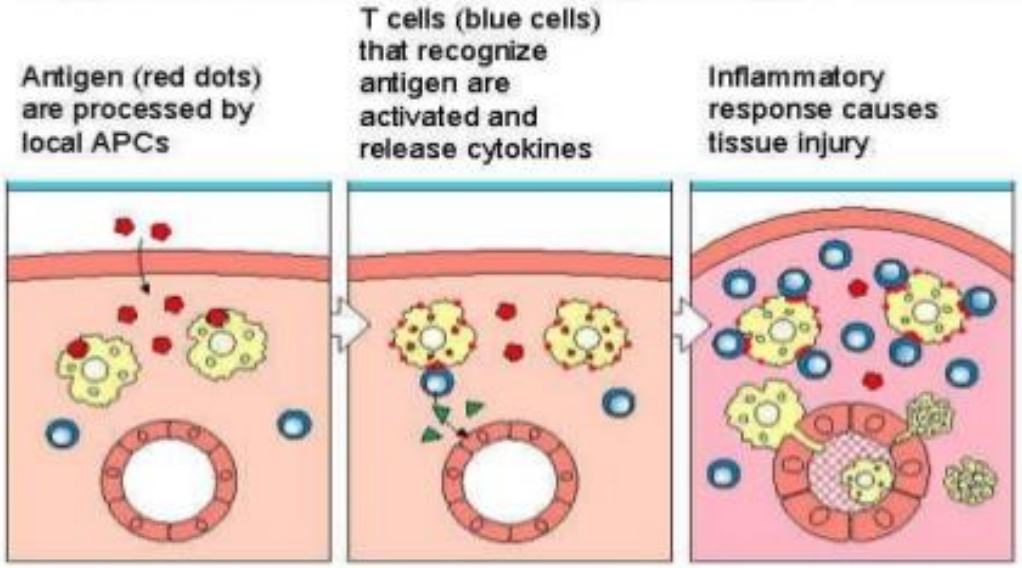
-- The resulting **activation** of the TH1 cell produces **cytokines** such as chemokines which activate **macrophages**, other T cells especially **T killer cells** and, to a lesser extent, **neutrophils** as well as TNFβ and IFNγ production.

-- The consequences are **direct attacks** on cells in that area and formation of a **cellular infiltrate** in which **mononuclear** cells (T cells and macrophages) tend to predominate.

-- It is usually maximal in **48-72 hours**.

introduction

Type IV hypersensitivity – delayed-type or contact



Antigen is presented by APCs to antigen-specific memory T cells that become activated and produce chemicals that cause inflammatory cells to move into the area, leading to tissue injury. Inflammation by 2-6 hours; peaks by 24-48 hours.

Tuberculin type hypersensitivity

-- **Delayed hypersensitivity** to microbial antigens, typified by **tuberculin** reaction has been used as an aid in diagnosis.

-- When a person with previous infection (or vaccination) by TB bacillus is injected with small amount of tuberculin **intradermally**, there is **little reaction in first few hours.**

-- But redness and induration gradually appears and **peaks at 48-72 hours.**

-- A reading of **10 mm or above** is generally considered **positive** result.

-- A positive test **does not confirm** current disease but **conversion** from negative to positive test does confirm it.

-- Test may be negative in persons with current infection if immune system is **suppressed** due to disease or drugs.

-- Similar tests are available for **leprosy** and many **fungal diseases.**

Skin diseases

-- Many skin diseases are caused by **cytotoxic T-cell** attacks on skin cells.

-- The most **common** triggers are herpes simplex virus-1, *Mycoplasma pneumonia* and drugs like sulfonamides and penicillins.

-- The symptoms are in the form of **lesions** often involving the **extremities** which can be very extensive and blistering as in case of **Stevens-Johnson syndrome** and **toxic epidermal necrolysis.**

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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