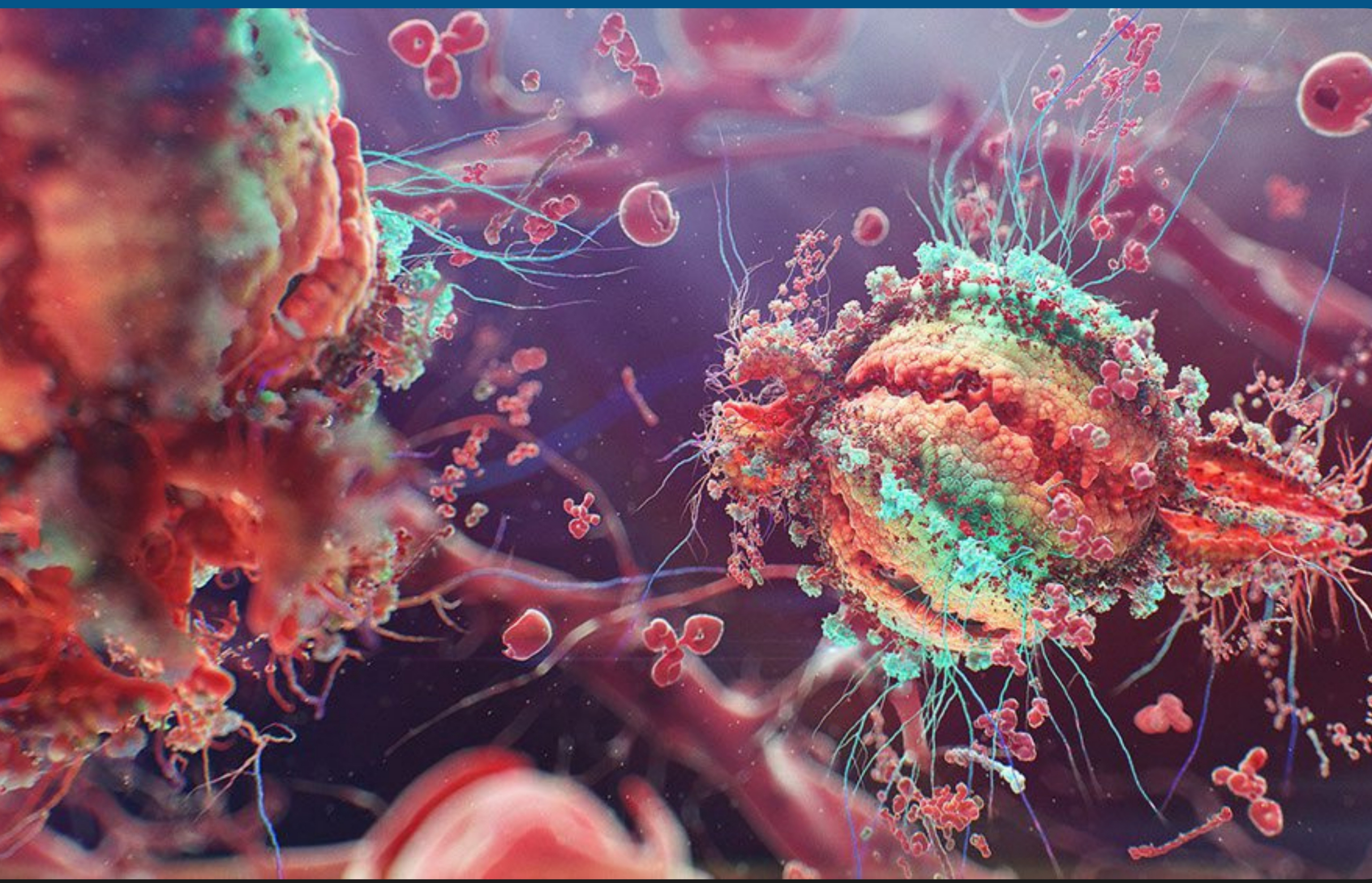
IMMUNOLOGY & RHEUMATOLOGY

TAILORED FOR MEDICAL STUDENTS, USMLE, PLAB, PA & NURSING



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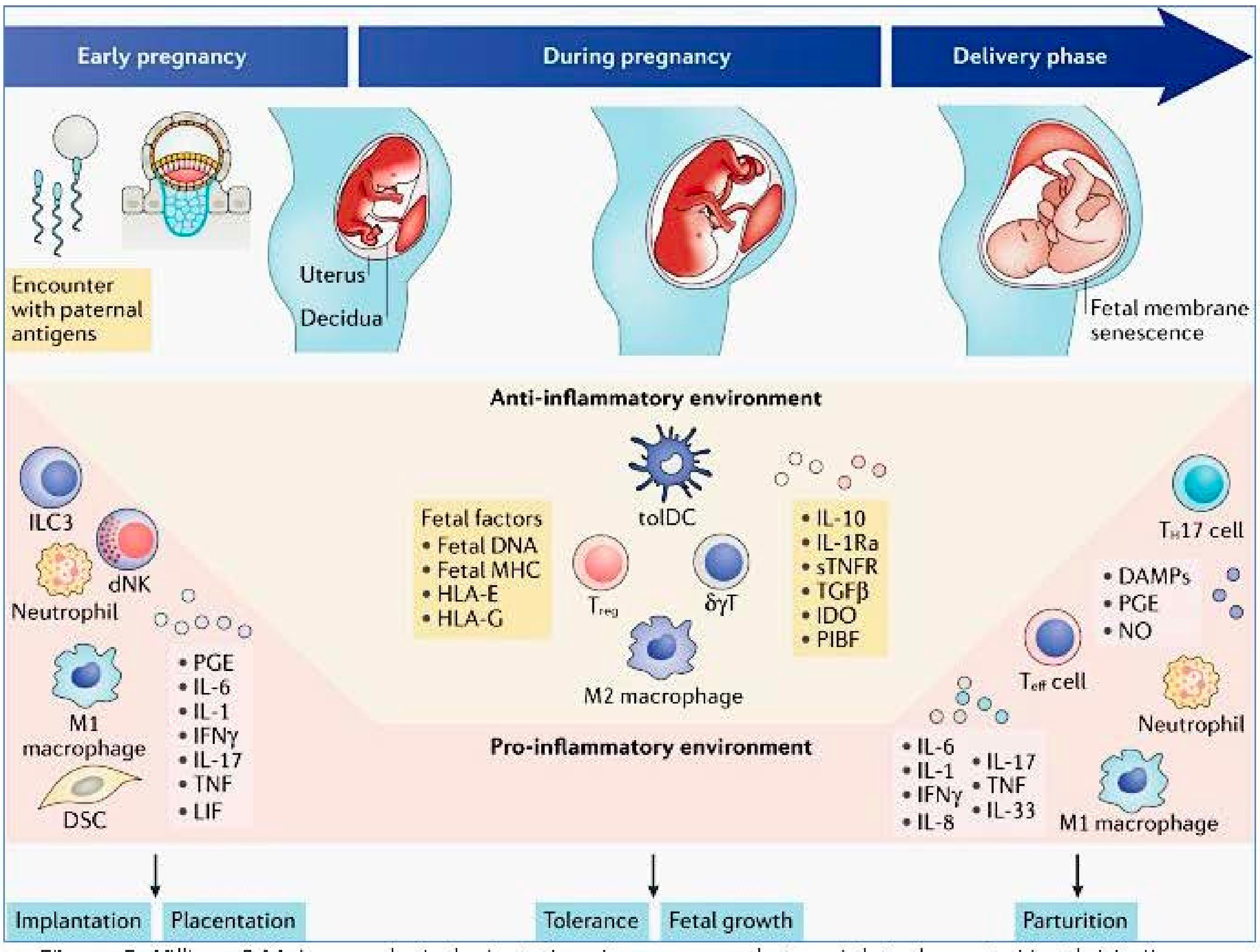
REJECTION IMMUNOLOGY

REJECTION IMMUNOLOGY

Placental Immunology: (How the Foetus Avoids Immune Rejection):

- **Foetuses are 50% Foreign to the Mother and would usually lead to Immune Rejection via T-Cells.**
- **However, the Foetus can Survive; But the Mechanisms behind this are still largely unknown:**
  - **Note:** Self-immunosuppression of the mother is pointless, as this would leave the mother & foetus vulnerable to infection.
- **Medawar's 3 Strategies for Foetal Survival:**
  - **1- Reduced/Modified MHC Antigen Expression on Trophoblasts:**
    - Foetal Trophoblasts DO NOT express Classical MHC-I molecules (Ie: Neither HLA-A or HLA-B).
      - They DO, however, express ***HLA-G*** (A NON-Polymorphic, NON-Classical MHC-I).
        - *HLA-G* is thought to prevent NK-Cell Attack
      - Also express ***HLA-C*** & ***HLA-E*** which aren't recognised as foreign.
        - *HLA-C* & *HLA-E* also bind to NK-Cells & prevents NK-Cell Attack.
    - → Lack of Antigen-Stimulation of Maternal Lymphocytes.
  - **2- Modulation of Maternal Immune System:**
    - Immune cell functions change during pregnancy.
      - Trophoblast Secretions → *Cytokines* that Suppress *Local* T-Cells (Local)
      - High Progesterone & HCG → Immunosuppressive (General)
  - **3- Placenta is a Physical Barrier which Can't be crossed by Lymphocytes:**
    - Although placenta is a Foetus-Derived tissue, its outer layer (Trophoblasts) is the only interface between Foetal & Maternal Tissues.
    - There is NO Vascular Continuity between Mother & Foetus.

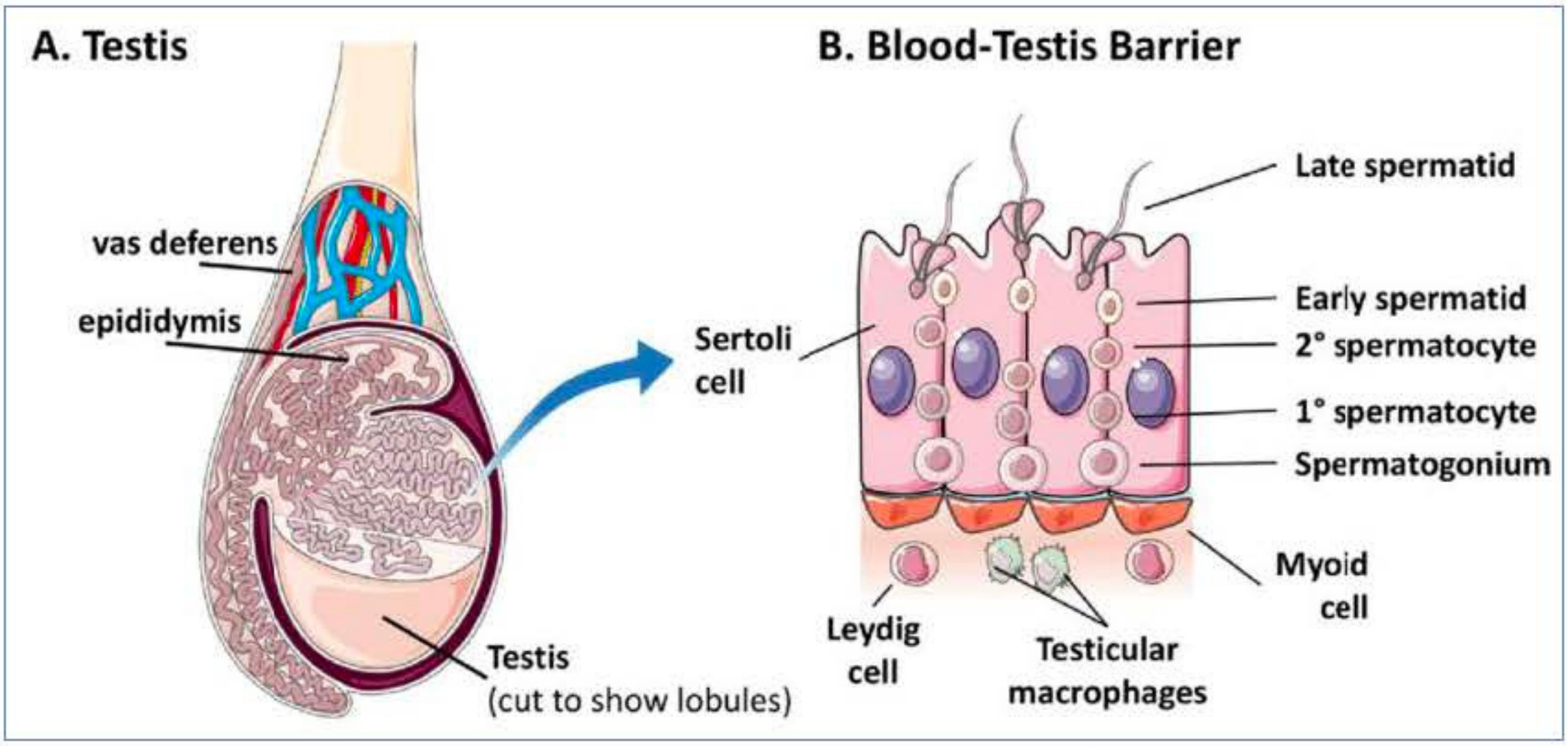


Förger, F., Villiger, P.M. Immunological adaptations in pregnancy that modulate rheumatoid arthritis disease activity. *Nat Rev Rheumatol* **16,** 113–122 (2020). https://doi.org/10.1038/s41584-019-0351-2

Testicular Immunology: **(How the Sperm Avoids Immune Attack):**

- **Sperm are highly Antigenic (since they are genetically unique).**
- **(In Males) – The *'Blood-Testes Barrier'* Protects the Sperm from the Immune System:**
  - Epithelial Barrier in Epididymis (joined by Tight Junctions) separate sperm from immune system.
  - **Abnormalities of the Blood-Testes Barrier can expose Sperm to the Immune System:**
    - (Eg: Malformation, Trauma, Infection, Obstruction)
    - → Production of Anti-Sperm Antibodies → Possibly Infertility

- **(In Females) – Sperm in Female Repro-Tract → Intense Inflammatory Response:**
  - Functions to remove excess sperm & microbes (≈24hrs post coitus)
  - However, can → Production of Anti-Sperm Antibodies → Possibly Infertility.



Persistence and Sexual Transmission of Filoviruses - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Localization-of-the-blood-testis-barrier-within-the-male-reproductive-tract-A_fig1_329384250

TRANSPLANT BASICS:

- **Terminology of Transplant:**

Types of Tissue and Organ Grafts and Their Complications		
Graft	**Procedure**	**Complications**
Autograft	From self to self	No rejection concerns
Isograft	From identical twin to twin	Little concern of rejection
Allograft	From relative or nonrelative to individual	Rejection possible
Xenograft	From animal to human	Rejection possible

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Principles of Transplant Immunology:

- **Alloantigens =** "Antigens that differ between members of the same species."
  - MHC is the most obvious Alloantigen & is the most potent trigger of rejection.
  - However, other alloantigens include Minor Histocompatibility Antigens, which are self-proteins which have been broken down into peptides & displayed on MHC-I Molecules.

- **"1st-Set" & "2nd-Set" Graft Rejection:**
  - **1st Set Rejection:**
    - Allogenic graft is given to Unsensitised Individual. (Without Immunosuppressants)
    - Graft is Rejected fairly rapidly once Host Sensitisation has occurred.
  - **2nd Set Rejection:**
    - Allogenic graft from the *Same Donor* is given to a *Pre*-Sensitised Individual (Without Immunosuppressants)
    - Graft Rejection is *Accelerated* → Rejection is much more rapid.
    - **(Note:2nd-Set Rejection is *Specific*** – Ie: It will only occur if the Recipient is *Pre*-Sensitised to *That Specific Donor*)
  - **Note: Transfer of "2nd-Set" Rejection by Lymphocyte Transfusion:**
    - Transfusion of Lymphocytes from a Pre-Sensitised Individual to a Naive Individual confers Instant Alloimmunity (2nd-Set Rejection).

- **Even Matching just the MHC 'Type', Doesn't Guarantee Graft Survival:**
  - (Ie: MHC genes may be the same, but other *Minor* Histocompatibility genes may be different.)
  - **Minor Histocompatibility Antigens** ('Minor H Antigens') are cell-proteins which have been broken down into peptides & displayed on MHC-I Molecules of all cells.
    - Minor H Antigens will be different between Graft & Host (unless genetically identical).
    - Note: Most minor H antigens are encoded by autosomal genes, & most are unknown.
  - **Matching MHC-Type @ the HLA Locus will Prolong Graft Survival, but NOT Guarantee Survival**

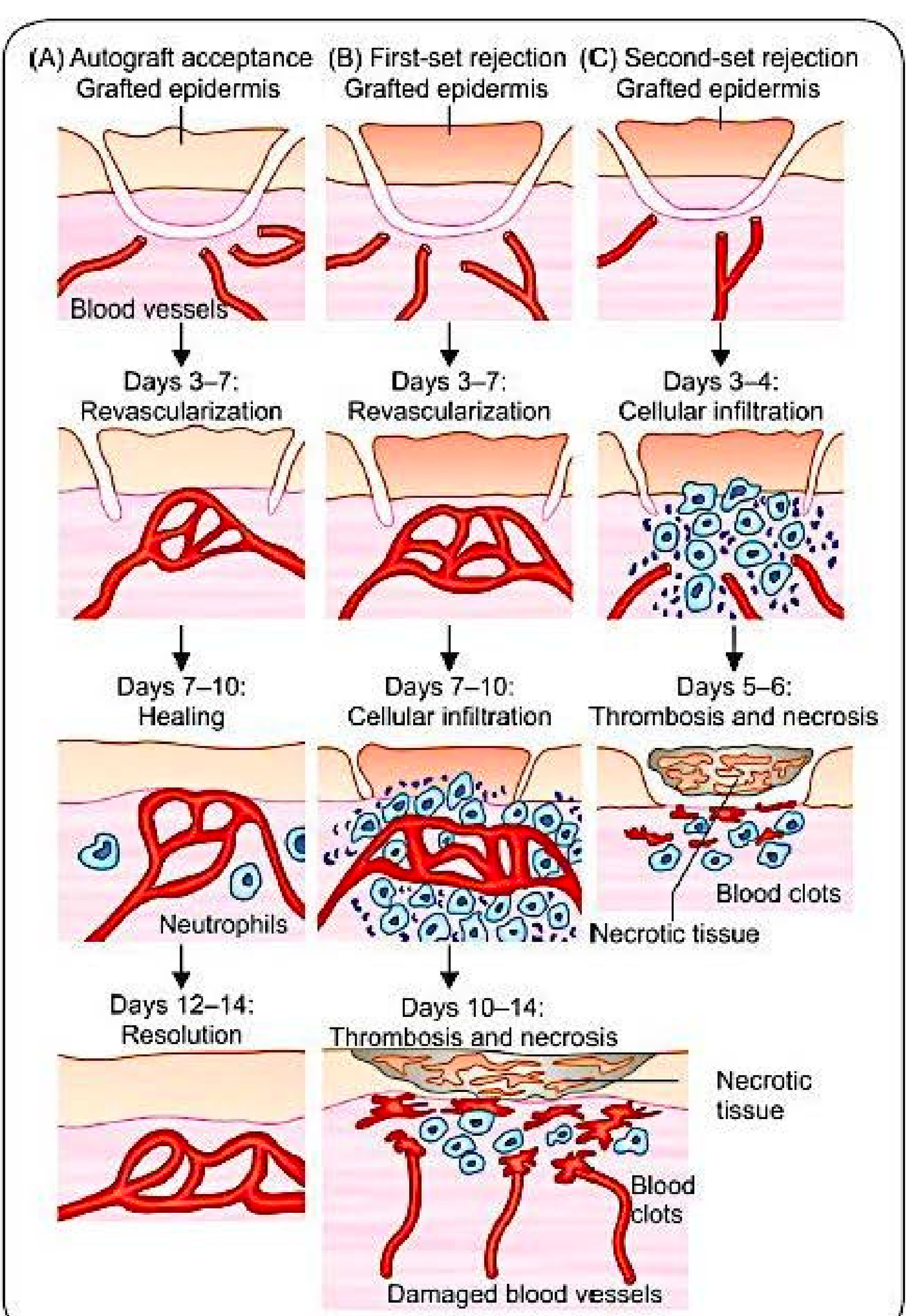
- **"The Alloimmune Response" → 2 Pathways to Rejection:**
  - **1- Direct Allorecognition (AKA. Direct Sensitisation):**
    - **Note:** Organ grafts contain APCs of *Donor Origin*.
    - These Donor Dendritic Cells migrate to Local Lymph Node via Lymph & expose their MHC or Minor-H-Antigen → Directly stimulates *Alloreactive* Host T-Cells.
      - (These T-Cells have TCRs specific for the allogenic MHC-I/II:Peptide Complexes)
    - Alloreactive Effector T-Cells are carried back to the graft → Attack the graft directly.
    - **Note:Direct Allorecognition is thought to be largely responsible for Acute Rejection**.
  - **2- Indirect Allorecognition (AKA. Indirect Sensitisation):**
    - Uptake & Processing of Allogenic Graft-Proteins by the Host's Dendritic Cells → Presents Peptide bound to self-MHC → Stimulates Ag-specific T.Cells.
    - Alloreactive Effector T-Cells are carried back to the graft → Attack the graft directly.
  - **(Note: During the Alloimmune Response, the Regional Lymph Nodes become enlarged due to masses of Proliferating Effector T-Cells.)**

Afferent & Efferent arms of Alloimmune Rejection:

- **Afferent** = Sensitization phase of the immune response (Direct/Indirect Allorecognition)
- **Efferent** = Lymphocytes differentiate into Effector Lymphocytes → Initiate an Immune Response.

The Central Role of T-Cells in Rejection:

- Direct Cytotoxic T Cell attack on graft cells occurs when the T Cells recognise the Graft MHC directly.
- If MHC Restriction occurs (ie: T Cells don't properly recognise graft MHC), the T Cells may still contribute to Graft Rejection by:
  - a) Activating Macrophages → Tissue Injury & Fibrosis
  - b) Activating B Cells to Produce Allo Antibodies → Ab/Compliment Mediated Graft Destruction.



Source: Transplant and Cancer Immunology, https://doi.org/10.5005/jp/books/12637_20

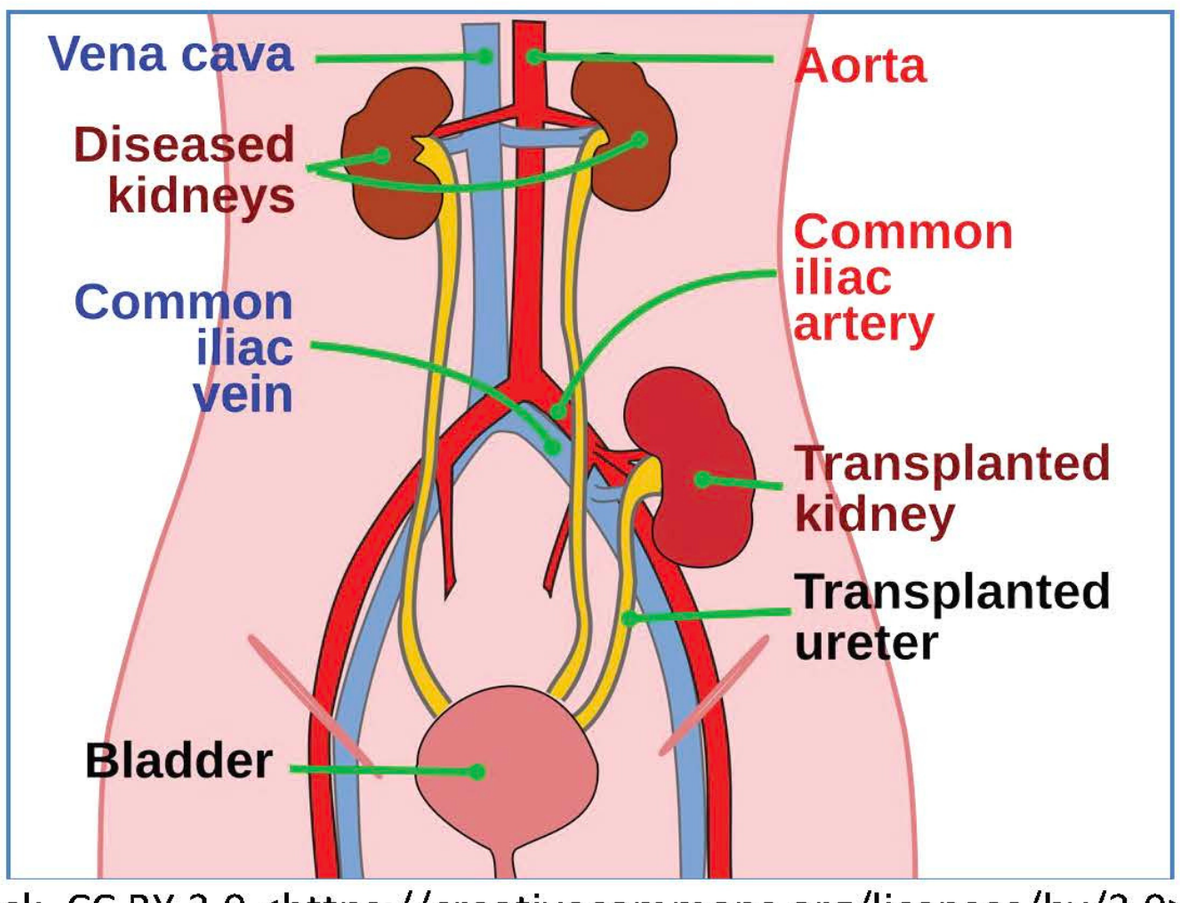
CLINICAL TRANSPLANTATION:

Ischaemic Times:

- **Cold Ischaemic Time:**
  - Begins when the organ is Clamped & Cooled during Removal.
  - Ends when the organ is Returned to Physiological Temperature.
- **Warm Ischaemic Time:**
  - Starts when the organ is Returned to Physiological Temperature.
  - Ends when Surgical Anastomoses are complete → Reperfusion.

Organ Transplant (Eg: Kidney):

- **Indication:**
  - Chronic Kidney Failure
- **Requirements:**
  - **Absolute Requirements:**
    - ABO blood group must be Identical OR Compatible.
    - Negative T-Cell Cross match (Ie: Incubate donor T-Cells with Recipient's Serum → No Reaction)
    - No Previous Antibodies against Donor HLA.
    - No shared incompatibilities with previous donors.
  - **Other Considerations:**
    - *Degree* of HLA Match
    - Viral Status
    - Previous blood transfusion?
- **Factors Affecting Graft Survival:**
  - *ABO blood group identity
  - *Negative Cross Match
  - *Degree of HLA match
  - **Immunosuppressive Therapy.
- **Complications of Kidney Transplants:**
  - Transplant Rejection (See below)
  - Infections (Due to Immunosuppressant drugs)
  - Post-Transplant Lymphoproliferative Disorder (Eg: Immune Suppressant Induced Lymphoma)
  - Electrolyte Imbalances (Ca/Ph) which can lead to ↓Bone Density.
  - Side Effects of Immunosuppressive Medications.
- **Signs of Kidney Rejection:**
  - **Histological (Ie: By Biopsy):**
    - Abundant Infiltration of Inflammatory Cells in Renal Tubules
  - **Functional:**
    - ↓EPO (Erythropoietin Release) → Anaemia & Hypoxia
    - ↑BP – Due to ↓GFR
    - ↑Uraemia



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Bone Marrow Transplant:

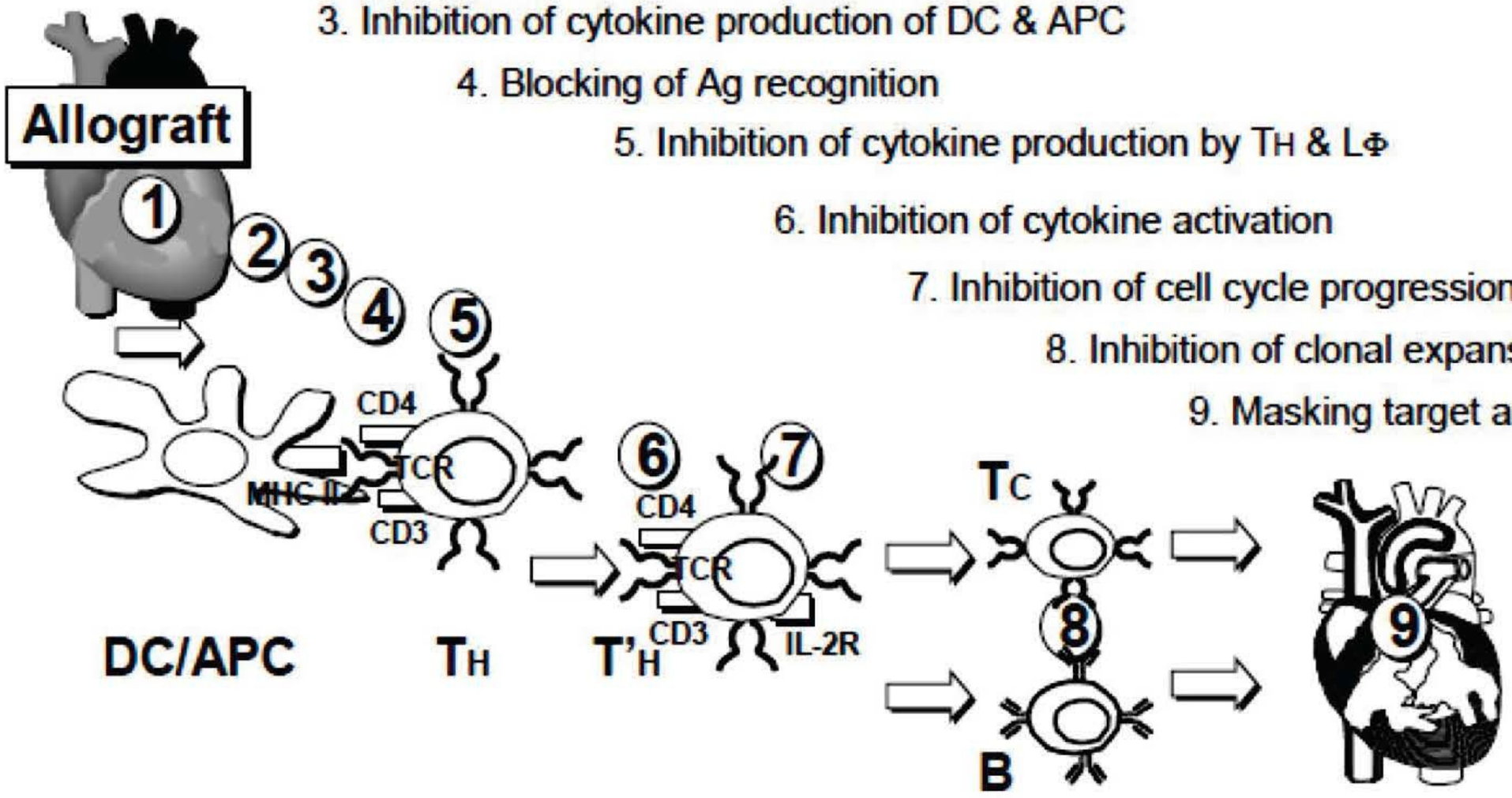
- **Note:BM Transplants are dangerous because they require the recipient's bone marrow to be destroyed.**
  - **Therefore, Assessment of Risk/Benefit Ratio is essential.**
- **Indications:**
  - **Any Abnormality of Bone-Marrow (Myeloid) Stem Cells:**
    - Ie: Malignancies (Leukaemia/Lymphomas)
    - Ie: Immunodeficiencies
    - Ie: Acquired Abnormalities (Eg: Thalassaemia/Sickle Cell Disease/Aplastic Anaemia)
- **Requirements:**
  - **HLA Matching:**
    - **MHC-I/II matching is Essential (To Prevent Graft Rejection or Graft Vs. Host Disease)
    - This is done by Genetic Techniques to match HLA Genes.
  - **Cross Matching:**
    - Incubate Donor Cells in Recipient Serum.
    - To Determine whether Antibodies in Recipient's Serum will *Cross-React* with Donor Cell Ags.
    - (To Avoid hyperacute rejection)
  - **Mixed Lymphocyte Culture (MLC):**
    - To detect level of reactivity between Donor & Recipient Lymphocytes
    - (Detects subtle differences in MHC-II that aren't detectable by standard techniques)
    - (To Avoid GVHD & Rejection)
- **Considerations:**
  - **Relating to the Disease:**
    - Is it *Curable* by Transplant?
    - Is there an *Alternative*?
  - **Relating to the Procedure:**
    - Recipient Age
    - General Health
    - Infection
    - Donor Availability.
- **(Note: Umbilical *'Cord Blood'* can be used as BM Transplants**, because ↑[Stem Cell] & Non-Invasive extraction procedure**)**
- **BMT Procedure:**
  - **1- Elimination of Recipient BM Stem Cells:**
    - By High-Dose Chemotherapy/Total-Body Irradiation.
    - Why? – To Eliminate the Pt's *Immune System* → ↓Risk of Graft-Rejection.
  - **2- BM Donation:**
    - 500-1200ml of BM is extracted from donor. (Usually 1st degree relatives)
      - BM Donation is treated with Anti-T-Cell-Antibodies to leave only Stem Cells.
    - OR Umbilical Cord Blood.
  - **3- BM Transplant:**
    - Transfusion of Donor Marrow into Recipient's Bone.
- **Complications of BMT:**
  - **Graft Failure:**
    - Rejection...OR
    - Insufficient # of BM Cells in Post-Transplant Period. (Treated by stimulatory Cytokines)
  - **Infection:**
    - High rates despite preventative measures.
  - **Graft Vs. Host Disease:**
    - Where the Immunologically-Mature Graft Cells *Attack the Host*! (Ie: Reverse Rejection)
      - Can occur even if donor & recipient are HLA-identical because the immune system can still recognise differences in Minor-H-Antigens.
      - Therefore, it is necessary to select donors with a *Similar Genotype* for Minor-H-Ags.
    - Occurs 7-10 days post-op.
    - Symptoms: - Skin Rash/Fever/Hepatosplenomegaly/Bloody Diarrhoea/Breathlessness.
    - *70% Mortality Rate*

IMMUNE INTERVENTION IN TRANSPLANTATION:

- **Types of Immune Intervention:**
  - **Immunosuppression of Recipient:**
    - Most Common
    - Currently drugs are *Non-Specific* → *General* Immunosuppression → Immunocompromise.
      - (However, more specific drugs are being developed)
    - **Note:** The *Strength* of Immunosuppressants is a fine balance between Rejection & Infection.
      - Too much immunosuppression → Infections / Cancer risk
      - Too little immunosuppression → Rejection
  - **Induction of Specific Tolerance:**
    - Impossible in humans
  - **Pre-treatment of Allograft Prior to Transplant:**
    - Ie: Removal of Donor APCs from graft tissue

- **Potential Sites for Immunomodulation:**
  - Drug development could target any one of the following processes.

1. Pretreatment of donor tissue & organs
2. Reduction of histo-incompatibility
3. Inhibition of cytokine production of DC & APC
4. Blocking of Ag recognition
5. Inhibition of cytokine production by TH & LΦ
6. Inhibition of cytokine activation
7. Inhibition of cell cycle progression
8. Inhibition of clonal expansion
9. Masking target antigens



IMMUNOSUPPRESSION:

- **Requirements of Immunosuppressive Agents:**
  - Induction must be at/before *Initial Exposure* to the Allograft.
  - Maintenance to prevent Allograft Rejection
  - Treatment of Rejection Episodes.
- **Current Immunosuppressive Agents:**
  - **Non-Specific:**
    - *Corticosteroids
    - *Cyclosporin
    - Irradiation
    - Cytotoxic Agents
    - Antibodies
  - **Specific:**
    - NONE.

- **Corticosteroids:**
  - **(Eg: Prednisone)**
  - **Mechanism of Action:**
    - **Anti-Inflammatory Effects:**
      - ↓- Oedema/Cap.Dilation/Angiogenesis/Diapedesis/Phagocytosis/Fibrosis.
    - ***Immunosuppressive Effect:**
      - Inhibit gene transcription for the Inflammatory Cytokines (IL-1 to IL-8), Particularly IL-1 & IL-2 → (↓Antigen-Induced B & T Lymphocyte Proliferation)
      - →↓Circulating Lymphocytes & Monocytes (Macrophages)
      - →↓Antigen Presentation
  - **Side Effects:**
    - ↑Risk of Infection
    - Growth Suppression in Children
    - Diabetes
    - Gastric Ulcer
    - Hypertension
    - Cushings Syndrome (Hyper-cortisolism)

- **Cytotoxic Agents (AKA. Cytostatics):**
  - **(Primarily used in Chemotherapy for Cancer)**
  - **Mechanism of Action:**
    - Blocks DNA Synthesis (S-Phase) → Inhibits Cell Division →Kills Rapidly Dividing Cells.
    - Note: Since Lymphocytes rapidly divide, they are susceptible → Bone Marrow Suppression.

- **Cyclosporin & Tacrolimus:**
  - **(A Fungal Metabolite)**
  - **Mechanism of Action:**
    - Inhibits IL-2 Receptors → (↓Antigen-Induced Lymphocyte Proliferation)
    - Inhibition of Cytokine Production by Lymphocytes
  - **Side Effects:**
    - Renal Toxicity

- **Antibodies as Immunosuppressants:**
  - **Mechanism of Action:**
    - The aim is to *Inhibit Lymphocyte Function* by giving Abs directed against Lymphocytes.
    - Eg: IL-2-Receptor Antibodies → Inhibit the function of IL-2 Receptors.
  - **Problems:**
    - Selection of Relevant Antigens specific to Lymphocytes.
    - Avoiding Antibodies against blood products.
  - **Monoclonal Antibodies:**
    - Specific Antibodies manufactured to bind to Specific Antigens.

HYPERSENSITIVITY & ALLERGY

HYPERSENSITIVITY & ALLERGY.

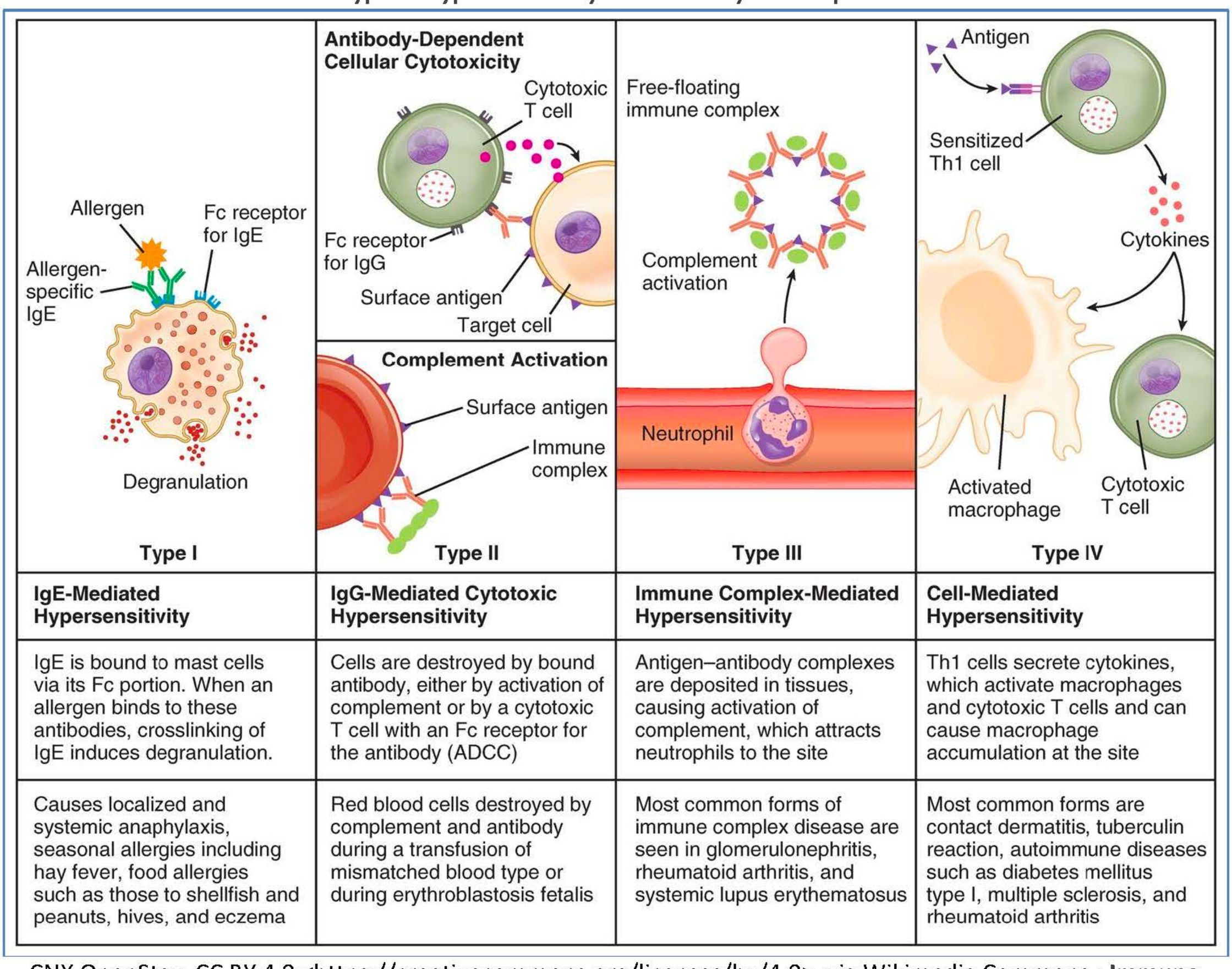
Hypersensitivity:

- **= an *Abnormal state of Immune Reactivity* with *Deleterious Effects* on the Host.**
- (Note: Often the immune response is to an otherwise innocuous antigen.
- **(Atopy = "Tendency to produce Immediate Hypersensitivity Reactions (usually IgE-Mediated) against Innocuous Substances)**

There are 4 Types of Hypersensitivity:

- **I - Anaphylactic**
- **II – Antibody Dependent Cytotoxicity**
- **III – Immune Complex**
- **IV – Cell Mediated Disease**

Components of the immune system cause four types of hypersensitivity. Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

CNX OpenStax, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons : **Immune Hypersensitivity** Components of the immune system cause four types of hypersensitivity. Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.

	Hypersensitivity Types and Their Mechanisms			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
Mechanism of activation	Allergen-specific IgE antibodies bind to mast cells via their Fc receptor. When the specific allergen binds to the IgE, cross-linking of IgE induces degranulation of mast cells.	IgG or IgM antibody binds to cellular antigen, leading to complement activation and cell lysis. IgG can also mediate ADCC with cytotoxic T cells, natural killer cells, macrophages, and neutrophils.	Antigen-antibody complexes are deposited in tissues. Complement activation provides inflammatory mediators and recruits neutrophils. Enzymes released from neutrophils damage tissue.	T_H1 cells secrete cytokines, which activate macrophages and cytotoxic T cells.
Examples of hypersensitivity reactions	Local and systemic anaphylaxis, seasonal hay fever, food allergies, and drug allergies	Red blood cell destruction after transfusion with mismatched blood types or during hemolytic disease of the newborn.	Post-streptococcal glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Contact dermatitis, type I diabetes mellitus, and multiple sclerosis

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TYPE-I HYPERSENSITIVITY:

- ***(Anaphylaxis/Allergy)*** ***- IMMEDIATE***
- **– A Function of Th2-Cells, IgE-Antibodies & Mast Cells**
- **Common Type-I Hypersensitivities:**

Type I Hypersensitivities		
Common Name	**Cause**	**Signs and Symptoms**
Allergy-induced asthma	Inhalation of allergens	Constriction of bronchi, labored breathing, coughing, chills, body aches
Anaphylaxis	Systemic reaction to allergens	Hives, itching, swelling of tongue and throat, nausea, vomiting, low blood pressure, shock
Hay fever	Inhalation of mold or pollen	Runny nose, watery eyes, sneezing
Hives (urticaria)	Food or drug allergens, insect stings	Raised, bumpy skin rash with itching; bumps may converge into large raised areas

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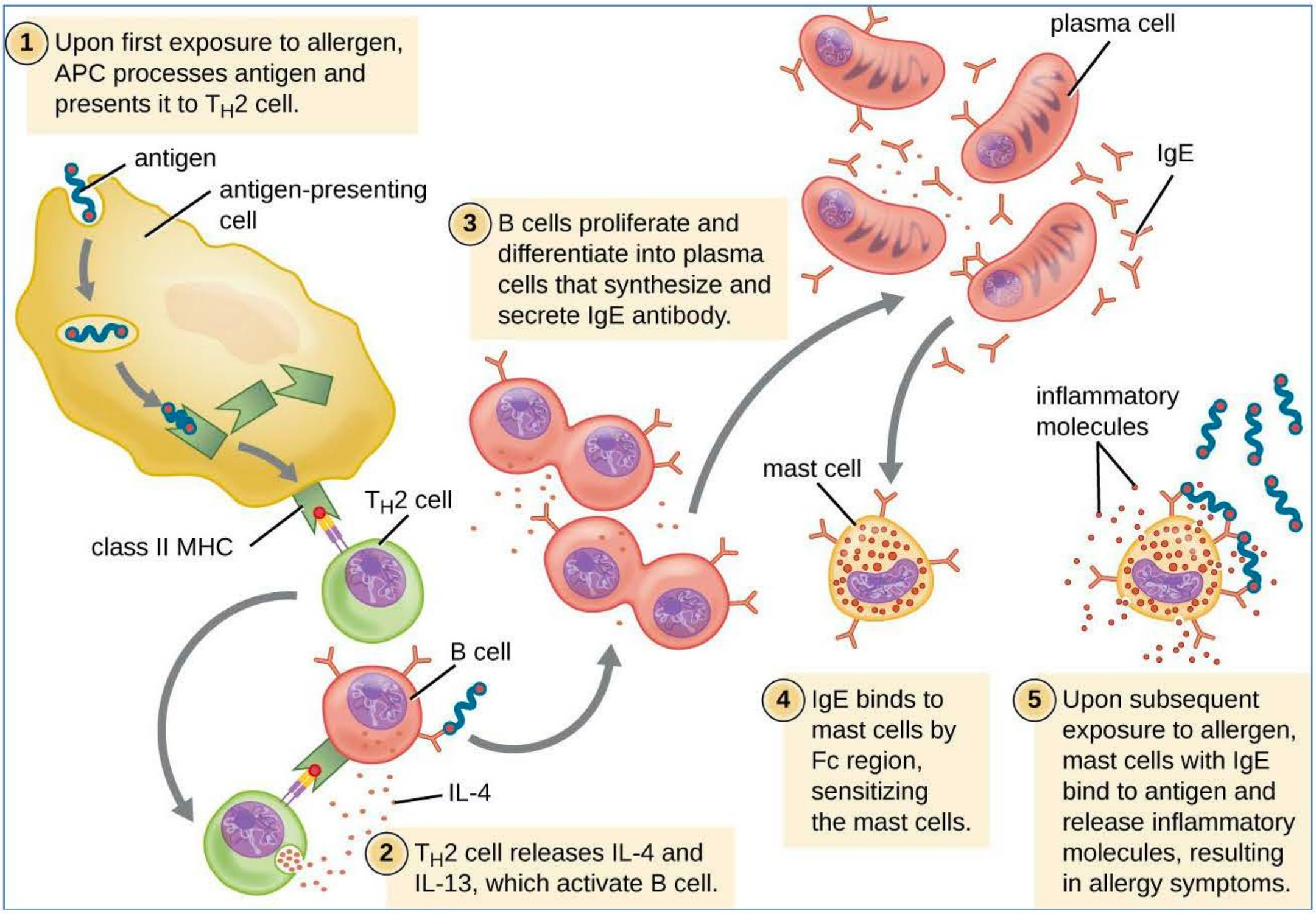
- **Mechanism:**
  - **Rapid immune reaction to a Previously-Sensitised Antigen**
  - **- Antigen is Re-Exposed to a sensitized Mast-Cell/Basophil →*Degranulates* IgE-Bound 'Mast Cells':**
    - → Releasing Inflammatory Mediators of Type-1-Hypersensitivity Reactions.
  - **Sensitization:**
    - 1- Allergen enters the body.
    - 2- APCs Presents the Allergen to Ag-Specific Th2-Cells
      - (Note: Allergens preferentially stimulate a Th2-Cell response → Drives IgE production)
    - 3- Th2-Cells → Activate Ag-Specific B-Cells to secrete IgE (**Via IL-4, IL-13 + Co-Stimulation**)
      - (Remember that Ig-Switching from IgM to IgE is Mediated by IL-4 from Th2-Cells.)
    - 4- B-Cells Produce **IgE**-Antibodies against the Allergen.
    - 5- Fc-Portion of IgE-Antibodies attach to *High-Affinity*-Fc-Receptors on Mast-Cells.
      - (Ie: Mast cells effectively become primed against the specific allergen.)
  - **Re-Exposure:**
    - 6- Re-Exposure of Antigen →Antigen binds Antibody on Mast-Cell → Mast-Cell Degranulates:
      - →Releases Inflammatory Mediators → Vasodilation & Smooth Muscle Contraction.
        - Mediators Include:
          - Histamine
          - Leukotrienes
          - Prostaglandins

          } →Cause Symptoms of Allergic Reaction.
      - →Releases IL-4 → Potentiates & Amplifies IgE Production by Plasma Cells.

(↑ IgE = ↑ Mast cell Activation = ↑ Inflammatory Mediators & Inflammatory cells = ↑ IgE)



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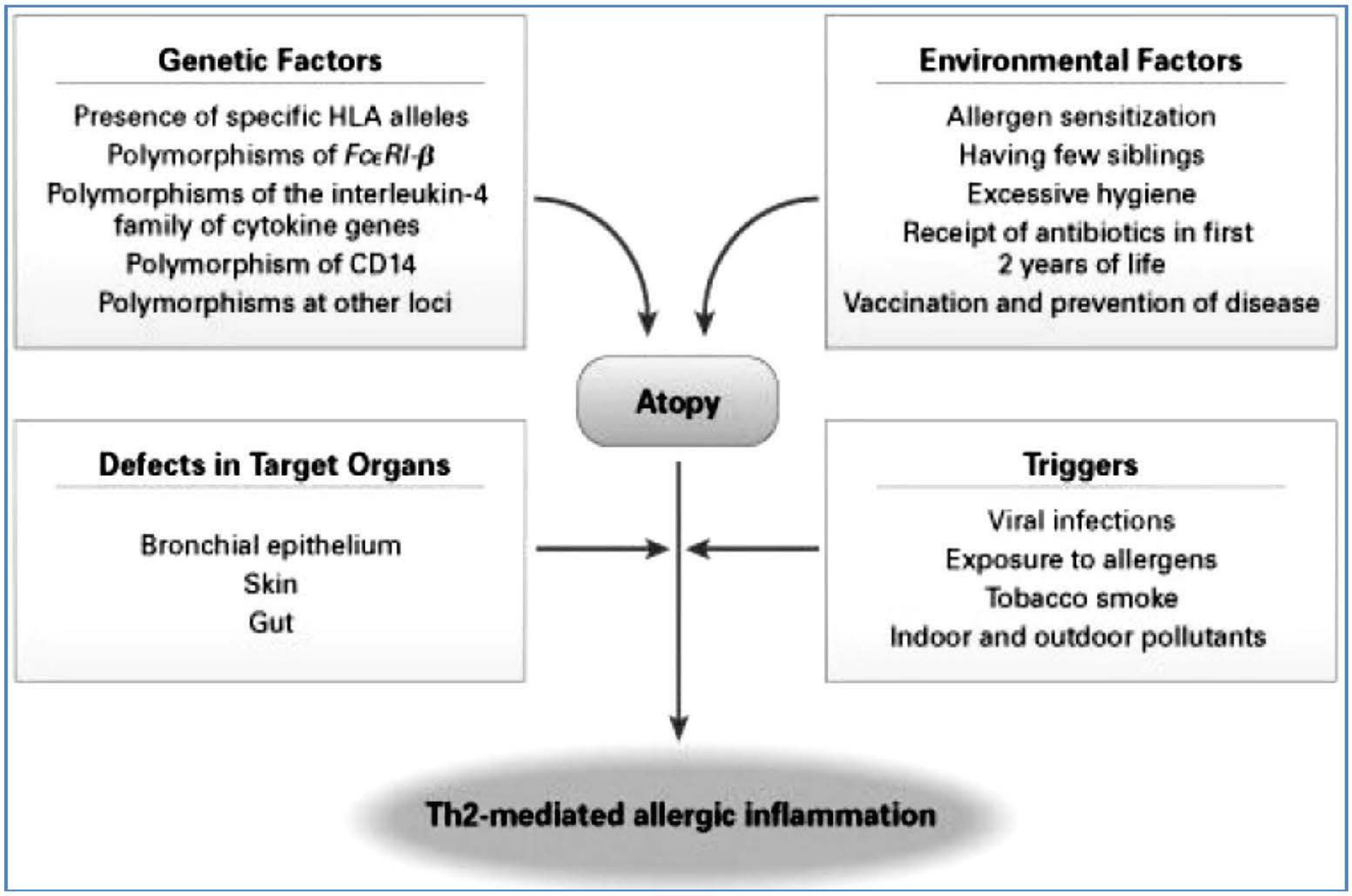
- **<u>Mast Cells in Type-I Hypersensitivity:</u>**
  - **Mast Cells line *Body Surfaces*** → Alert the immune system to local infection.
  - **Have *High-Affinity* Fc-Receptors** → Allow mast cells to bind Ag-Specific IgE Antibodies.
  - **Binding of Ag to IgE:FcRs →Degranulation** of basophilic granules.
  - **<u>Molecules Released in Degranulation:</u>**
    - ****Histamine:**
      - Vasodilation
      - ↑Vascular Permeability
      - Bronchial Smooth Muscle Contraction.
    - ****IL-4:**
      - Stimulates & Amplifies Th2-Cell Response.
    - ***Prostaglandins & Leukotrienes → Trigger further Histamine Release →:**
      - Vasodilation
      - ↑Vascular Permeability
      - Bronchial Smooth Muscle Contraction
      - ↑Mucus Secretion.
    - **TNFα:**
      - Proinflammatory Effects
      - Activates Endothelium.
    - **CCL3 Chemokine:**
      - Attracts Phagocytes (Monocytes, Macrophages & Neutrophil).

- **<u>Allergic Responses are *'Bi-Phasic'* – (Immediate- & Late- Phase Responses in Allergy):</u>**
  - **Immediate Phase Response:**
    - Occurs within seconds of Exposure.
    - Due to *Release of Preformed* Mediators by Mast-Cells. (Ie: Histamine, Prostaglandins)
  - **Late Phase Response:**
    - Occurs 8-12hrs after Exposure → Oedema.
    - Due to *Synthesis* of Mediators by Mast-Cells. (Ie: Cytokines, Leukotrienes & Chemokines)

- **Clinical Effects of Mast Cell Degranulation:**
  - **Effects Depend On:**
    - **1-** Specific Allergen
    - **2-** Dose of Allergen
    - **3- Route of Entry (Antigen Location)**
      - **Blood Stream** → Systemic anaphylaxis → Anaphylactic shock
      - **Airborne** → Allergic conjunctivitis/ rhinitis/ asthma
      - **Skin** → Wheel and flare reaction/ urticaria/ atopic dermatitis (eczema)
      - **Food** → GIT transepithelial fluid loss → Diarrhoea/ bloating/ etc.

- **Determinants of Allergic Diseases (Incl: Asthma):**
  - **Genetic Susceptibility:**
    - 'Atopy' has a strong familial basis.
    - Ethnic differences in susceptibility for Atopy.
    - There are distinct *Susceptibility Genes* for Allergic Diseases.
  - **Environmental:**
    - **'The Hygiene Hypothesis' – A decrease in exposure to microbes in early childhood** is a possible cause of the increase in allergies in high SES populations & Developed Countries.
      - Proposes that *Less Hygienic* Environments & Minor Infections during early childhood are protective against Atopy & Asthma.
      - Implies that Th2 (atopic) responses in early childhood are *Reprogrammed* to Th1 (non-atopic) responses by cytokines from early infections.
      - (Remember that Ig-Switching from IgM to IgE is Mediated by IL-4 from Th2-Cells.)
    - Allergen Levels
    - Environmental Pollution
    - Dietary Changes (Eg: food allergies)

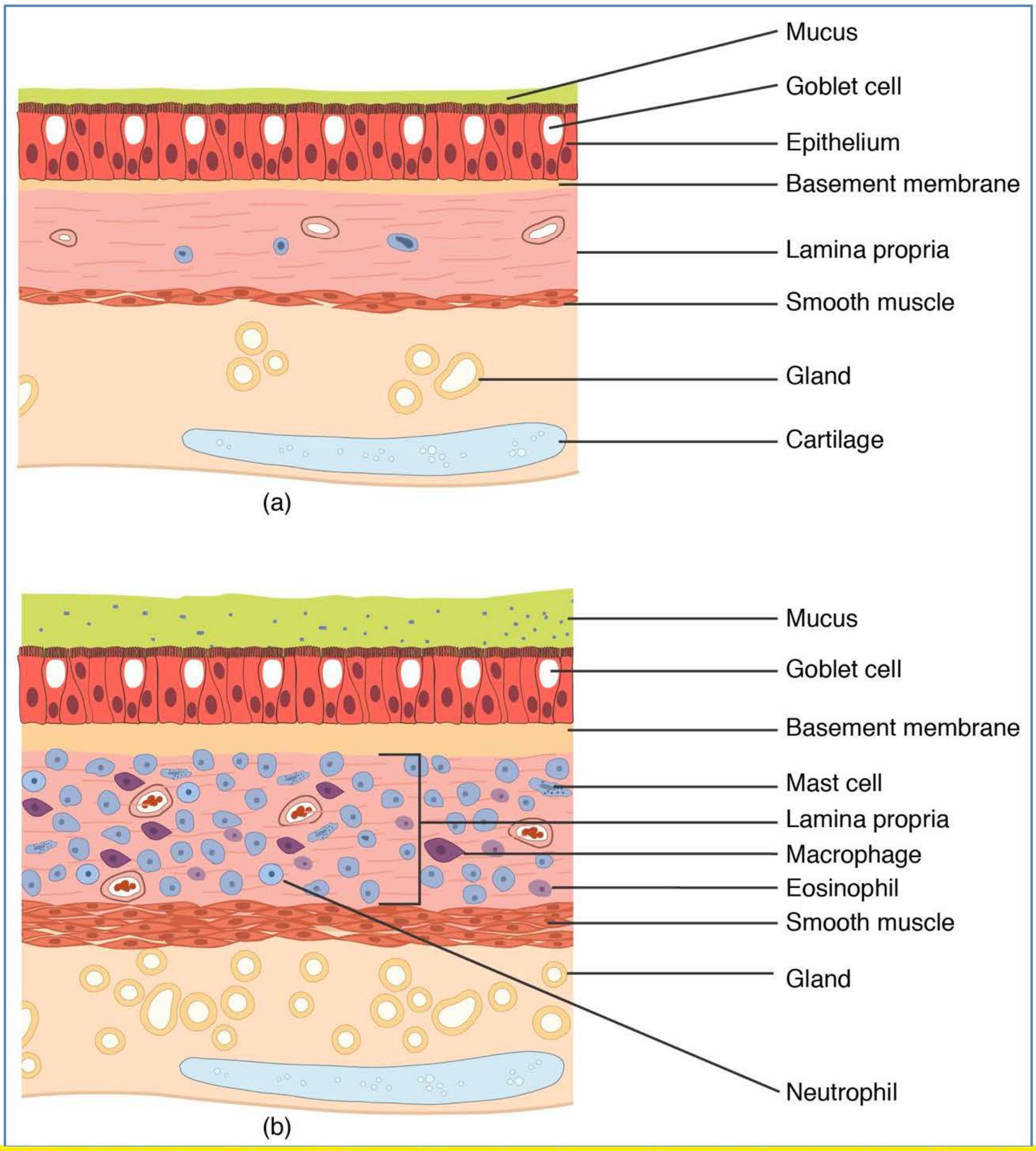


- **Question – *What is the Immunological Basis for Hypo-Sensitisation?*:**
  - (AKA: Allergen Immunotherapy)
  - = Involves giving *Gradually-Increasing* quantities of specific allergens to people with IgE-Mediated (Type-I Hypersensitivity) Conditions. The *Aim* is to divert the Th2-Cell (IgE) Response to a Th1-Cell Response → Decrease in IgE Production.

EXAMPLES OF COMMON TYPE-I HYPERSENSITIVITY DISEASES:

****Eg: Allergic (Atopic) Asthma:**

- **Exposure of Respiratory Sub-Mucosa to Allergen → Local Mast Cell Degranulation:**
  - →Local Histamine, Prostaglandin & Leukotriene Release
  - →Airway Vasodilation, ↑Vascular Permeability & **Constriction of Airway Smooth Muscle. (Bronchoconstriction)**
    - →Life-Threatening *Airway Obstruction*.
- **Triggers:**
  - Exposure to Allergens
  - Viral Infections
  - Tobacco Smoke
  - Pollutants
  - Exercise
  - Cold Air
  - Drugs – (β-Blockers, Aspirin, NSAIDs)
- **Biphasic Response:**
  - **Immediate Phase Response – The "Attack":**
    - Occurs within seconds of Exposure.
    - Due to *Release of Preformed* Mediators by Mast-Cells:
      - (Ie: Histamine, Prostaglandins)
  - **Late Phase Response:**
    - Occurs 8-12hrs after Exposure → Oedema, SM Contraction, SM Hyperplasia, SM Hypertrophy.
    - Due to *Synthesis* of Mediators by Mast-Cells:
      - (Ie: Cytokines, Leukotrienes & Chemokines)
- **Pathophysiological Features:**
  - Airflow limitations → Wheezing & Hyperinflated Chest.
  - Over-distended lungs.
  - Airway hyper-reactivity – (Exaggerated broncho-constriction to non-specific stimuli)
  - Remodelling of Airway due to Inflammation:
    - ↑Inflammatory Cells
    - Oedema
    - SM Hypertrophy
    - ↑Mucous
  - (Often associated with Eczema, Urticaria/hives, Rhinitis, or Nasal Polyps)
- **Diagnosis:**
  - *Obstructive Spirometry – (Responsive to Bronchodilators)
  - IgE Levels – (Measurement of Allergic Status)
- **Treatment:**
  - **Symptomatic –** Bronchodilators (β-Agonists. Eg: Salbutamol)
  - **Immunosuppressants –** Inhaled Cortico-Steroids (ICS)
- **(*Note:Other Types of Asthma*):**
  - **Episodic Asthma:**
    - Pt is often asymptomatic but suffers attacks of asthma during URTI or after exposure to certain aeroallergens.
      - Common in older patients.
  - **Occupational Asthma:**
    - Variable airway obstruction caused by workplace exposures - (Fumes/Gases/Chemicals/Dust)
    - Due to hypersensitivity reaction to a substance at work.
      - Eg: Heavy exposure to Gas/Fumes/Vapour.



Normal and Bronchial Asthma Tissues (a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

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Eg: Allergic Bronchopulmonary Aspergillosis (ABPA):

- **What is it?**
  - An Allergic (Type-I Hypersensitivity) Reaction to Aspergillus Fungus.
- **Mechanism – Same as Asthma:**
  - **Exposure of Respiratory Sub-Mucosa to Aspergillus → Anti-Aspergillus IgE Antibodies → Bind to Mast Cells.**
  - **Re-Exposure → Local Mast Cell Degranulation:**
    - →Local Histamine, Prostaglandin & Leukotriene Release
    - →Airway Vasodilation, ↑Vascular Permeability & Bronchoconstriction.
      - → Intense Bronchial Inflammation with high IgE & Eosinophilia.
- **Diagnostic Features:**
  - Asthma (majority of cases)
  - Mucus Plugging
  - Proximal Bronchiectasis
  - Positive Skin-test to an extract of Aspergillus Fungus.
  - Elevated serum IgE – (Specific to Aspergillus)
  - Shadows on Chest XR.
  - Presence of Aspergillus in Sputum Microscopy.
- **Treatment:**
  - Prednisolone (Oral Corticosteroid) → Immunosuppressant avoids further tissue damage.
  - High dose *Inhaled* Corticosteroid → (As above)

Eg: Allergic Rhinitis:

- **What is it?**
  - Characterised by Episodes of Sneezing/Itching/Rhinorrhoea/Nasal Obstructions.
- **Treatment:**
  - Allergen Avoidance
  - Anti-Allergic Meds
  - Immunotherapy for specific allergens.

****Eg: Anaphylaxis (& Anaphylactic Shock):**

- **Blood-Borne Antigen → Systemic Mast-Cell Degranulation:**
  - →Systemic Histamine, Prostaglandin & Leukotriene Release
  - →Systemic Vasodilation & ↑Vascular Permeability
    - →Life-Threatening *Fluid Shifts*, *Oedema* & *Hypotension* →Anaphylactic Shock:
- **Features of Shock – (The result of Hypoperfusion of Vital Organs):**
  - Low Blood Pressure
  - Cool Extremities
  - ↓Cerebral Perfusion → Altered Mental Status
  - ↓Renal Perfusion → ↓Urine Output
  - ↓Coronary Perfusion → Ischaemic Chest Pain
  - ↓General Tissue Perfusion → Lactic-Acidosis
- **Treatment:**
  - *Adrenaline – (A Vasoconstrictor, Antihistamine, Bronchodilator & Cardiostimulator)
  - Remove Causative Agent
  - Volume Replacement
- **Q: How does Penicillin Cause Anaphylaxis?**
  - **- Penicillin forms Conjugates with Self-Proteins → Essentially *Modifying* them:**
  - →APCs can take up Penicillin-Modified Self-Peptides → Present them to Th2-Cells:
    - →Th2-Cells Activate Penicillin-Binding B-Cells → IgE against Penicillin.
      - →IgE binds to High Affinity Fc-Receptors on Mast-Cells
  - **– Binding of Penicillin to IgE-Bound Mast-Cells → Degranulation → Anaphylaxis:**
    - →Systemic Histamine, Prostaglandin & Leukotriene Release
    - →Systemic Vasodilation & ↑Vascular Permeability
    - →→Causes Life-Threatening *Fluid Shifts*, *Oedema* & ↓*BP* →Shock.

Anaphylaxis: *Pathogenesis*

Authors:
Matt Piaseczny
Christina Schweitzer
Reviewers:
Taylor Sheppard
Luis Murguia-Favela*
** MD at time of publication*

Note: Anaphylaxis is a Type I hypersensitivity reaction, see *Type I Hypersensitivity* slide

Drugs (e.g. penicillin, NSAIDs, ACEi, radiocontrast dye)

Foods
Insect stings/bites
Latex

Immunologic (IgE dependent)

Initial exposure to Ag (*sensitization*)

APCs present Ag to T_H cells

Individual may be genetically predisposed to this reaction

T_H cells stimulate B-cells to differentiate into plasma cells & produce IgE against Ag

IgE binds to FcεRI receptors on mast cells, sensitizing them to the Ag

On **re-exposure,** Ag causes cross-linkage of IgE/FcεRI on mast cells

Ag-Ab complexes (indirect complement activation)
Direct complement activation

Immunologic (IgE independent)

Generation of anaphylatoxins (complement peptides C3a, C4a, C5a)

Exercise
Environment (heat/cold, sunlight)

Non-immunologic (physical stimuli)

Note: While the primary mechanism of anaphylaxis is mast cell activation, basophils and eosinophils may also play a role

Inappropriate mast cell activation

Immediate Phase
(seconds-minutes)

Mast cell **degranulation** → release of preformed mediators

Histamine
Lipid mediators (e.g. prostaglandins, leukotrienes)
Other mediators (e.g. PAF, tryptase, TNF)

Late Phase
(minutes-hours)

Additional production of inflammatory mediators (e.g. cytokines, chemokines)

Inflammatory mediators cause:

Vasodilation
↑ vascular permeability
Smooth muscle contraction in airways
↑ mucus secretion
Recruitment of inflammatory cells
ANS activation

Anaphylaxis: *A systemic life-threatening allergic hypersensitivity response*

Abbreviations:
- **Ab** – Antibody (immunoglobulin)
- **Ag** – Antigen (allergen)
- **IgE** – Immunoglobulin E
- **APC** – Antigen presenting cell
- **ANS** – Autonomic nervous system
- **PAF** – Platelet activating factor
- **TNF** – Tumor necrosis factor

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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Type-II Hypersensitivity:

- **(*Autoimmune Diseases & Drug Allergies*) - *DELAYED***
- **– Antibody-Mediated Attack against *Altered* Cell-Surface Antigens:**
  - **Eg: Drug-Induced Haemolytic Anaemia** (Drugs bind to surface antigens of RBCs)
  - **Eg: Autoimmune Thrombocytopenia** (Drugs bind to surface antigens of Platelets)
  - **Eg: Rheumatic Heart Disease.** (Anti-*M-Protein*-Abs cross react with Cardiac Myosin)
  - **Eg: Blood Transfusion Reactions**

Common Type II Hypersensitivities		
Common Name	**Cause**	**Signs and Symptoms**
Hemolytic disease of the newborn (HDN)	IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction	Anemia, edema, enlarged liver or spleen, hydrops (fluid in body cavity), leading to death of newborn in severe cases
Hemolytic transfusion reactions (HTR)	IgG and IgM bind to antigens on transfused RBCs, targeting donor RBCs for destruction	Fever, jaundice, hypotension, disseminated intravascular coagulation, possibly leading to kidney failure and death

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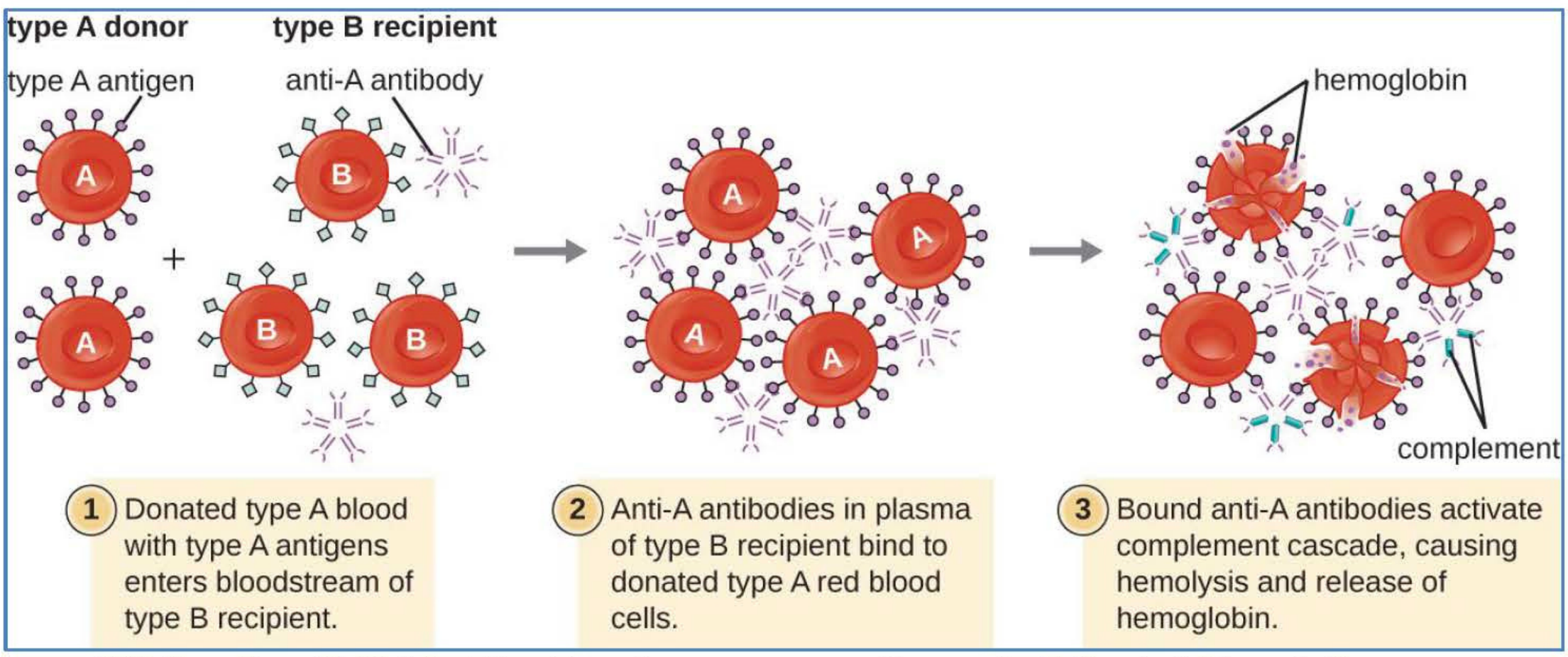

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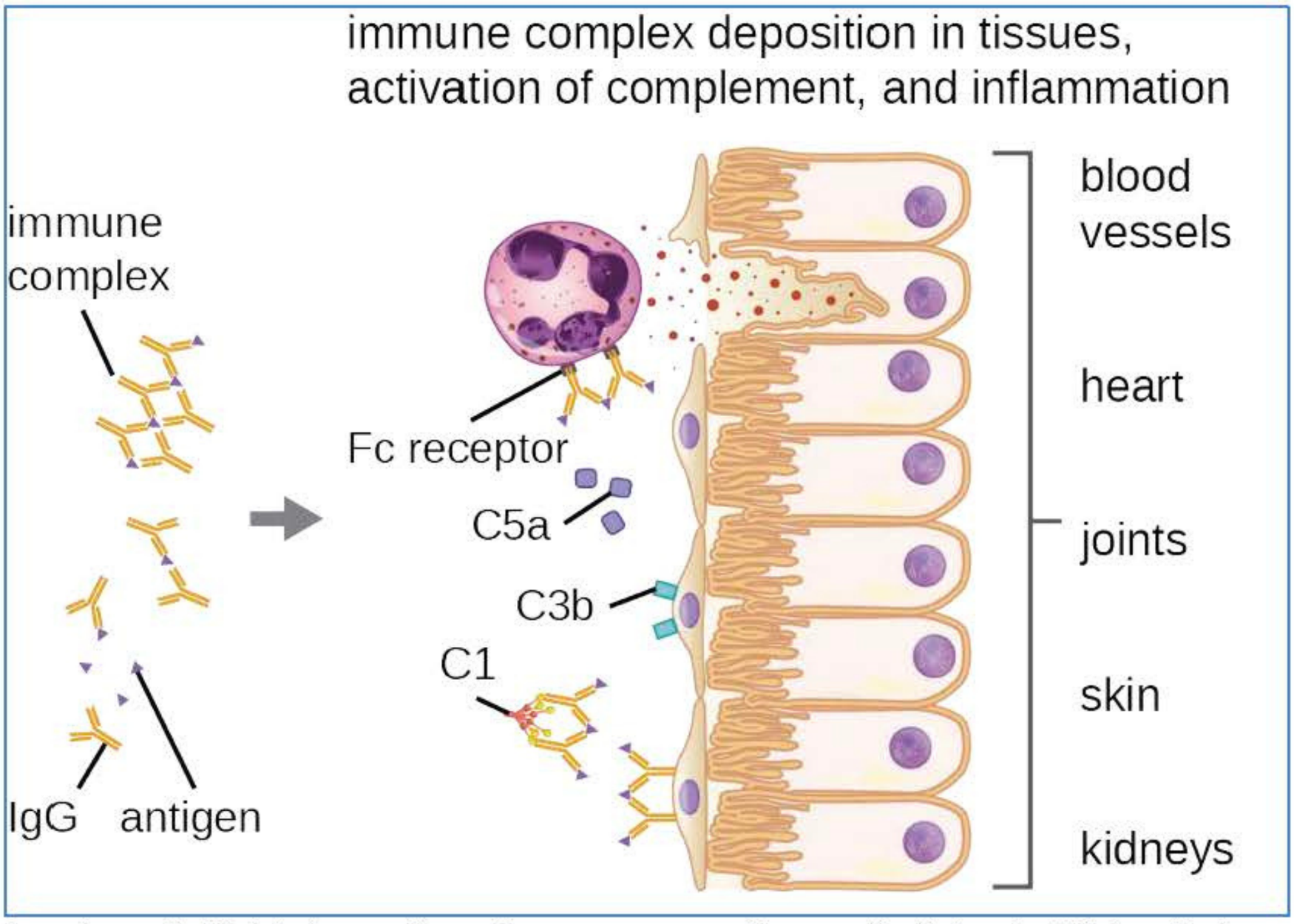
- **Mechanism:**
  - **IgG Antibodies against specific Host Cell-Antigens bind to Cells & Opsonise them for Phagocytosis:**
    - → Altered Blood-Borne cells targeted are cleared by Macrophages in the Spleen.
      - (Eg: Drug-Induced Haemolytic Anaemia)
      - (Eg: Autoimmune Thrombocytopenia)
    - → Tissue-Cells targeted are destroyed by *Resident* Macrophages in that tissue.
      - (Eg: Rheumatic Heart Disease)
  - **Note: Drug-Induced Haemolytic Anaemia/Thrombocytopenia:**
    - Specific Drugs bind to the Surface of RBCs/Platelets → Are Targeted by Anti-Drug IgG.
    - → Anti-Drug IgG binding to RBCs/Platelets → Opsonises them for Phagocytosis in Spleen.

Type-III Hypersensitivity:

- ***('Arthrus Reaction', 'Serum Sickness' & Some Autoimmune Diseases)*** **- *DELAYED***
- **– Immune-Complex (Ag:Ab) Deposition → Activate Fc-Receptor^{+} & Complement :**
  - **Eg: 'Arthrus Reaction' → Vasculitis.**
  - **Eg: 'Serum Sickness'**
  - **Eg: Rheumatoid Arthritis**

- **Mechanism:**
  - **Deposition of *Small* Immune-Complexes (Ag:IgG) in Vessel Walls:**
    - → IgG binds to Fc-Receptor on **Mast Cells** → Degranulation.
      - → Local Inflammation → Vasodilation, ↑Vascular Permeability.
      - → Local Oedema → Vessel Occlusion.
    - → Activation of **Complement** & Recruitment of Granulocytes.
    - →→**Vasculitis**.



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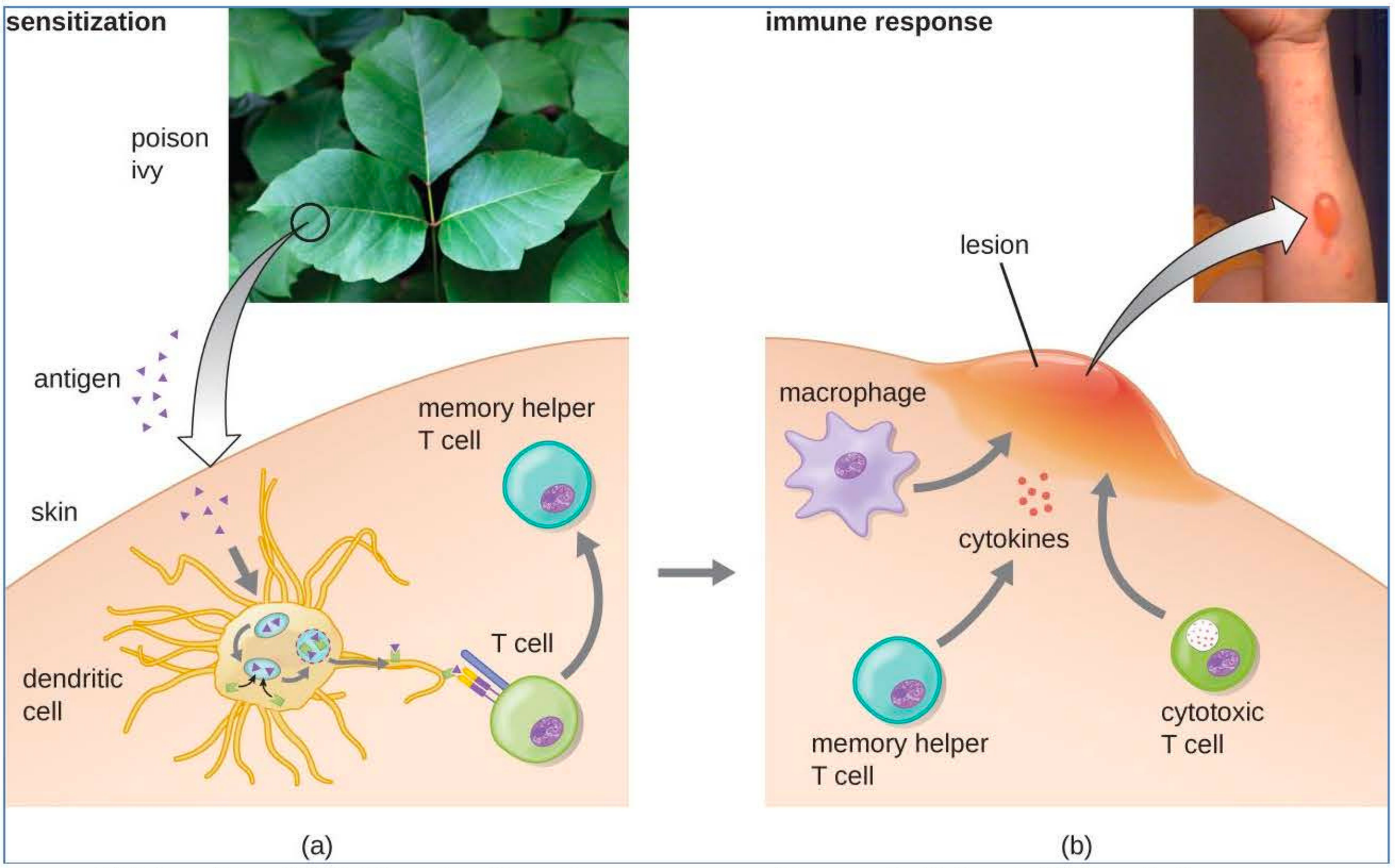
  - **Eg: 'Arthrus Reaction' → Vasculitis:**
    - Intradermal Injection of Antigen → In Situ formation of Ag:IgG Complexes:
      - Local Deposition of Ag:IgG in dermal Blood Vessels →Manifests as local Vasculitis.
  - **Eg: 'Serum Sickness' → Vasculitis/Glomerulonephritis/Arthritis.**
    - IV Injection of Foreign Antigen (Eg: Tetanus Antiserum) → formation of Ag:IgG Complexes:
      - Systemic Deposition of Ag:IgG in Blood Vessels:
        - →Manifests as Vasculitis/Glomerulonephritis/Arthritis. (Self-Limiting)

(Note: Rarely seen anymore due to advent of *Monoclonal* Antibodies.)

Type-IV Hypersensitivity:

- **(*Autoimmune Diseases*) - *DELAYED***
- **– Function of Th1, Th2 & Cytotoxic T-Cells:**
  - ***Th1 – Eg: Contact Dermatitis, Tuberculin Reaction (Mantoux Test) – *OUR FOCUS!***
  - **Th2 – Eg: Chronic Asthma, Chronic Rhinitis.**
  - **CTL – Eg: Type-1-Diabetes Mellitus**
  - **Eg: Multiple Sclerosis**
  - **Eg: Coeliac Disease**

- **Mechanism:**
  - **Pre-Primed Ag-Specific Th-1-Cells *Recognise and Bind* Macrophages displaying Ag:MHC-II →*Activates* Macrophages → Secretion of Cytokines, Chemokines & Cytotoxins:**
    - IFNγ & TNFβ → Activates Endothelium & ↑Vessel Permeability → inflammation.
      - →Visible Swelling
    - →→Tissue Damage → ***Granulomas***



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