BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024,
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Programme: M.Sc., Biomedical Science

Course Code: BM35C6
Course Title: Immunology

Unit-IV

Immune response to infectious agents & Hypersensitivity reactions

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Unit IV:

Immune response to infectious agents & hypersensitivity reactions. Overview on immunity to intracellular and extracellular pathogens-Bystander damage caused by the immune response to infection- evasion of immune responses by various infectious agents. Overview on hypersensitivity reactions – Gell and Coombs classification, IgE-mediated (Type I), antibody- mediated (Type II), immune complex- mediated (Type III) (Glomerulonephritis, extrinsic allergic alveolitis, serum sickness) and TDTH-mediated (Type IV) hypersensitivity

PRESENTATION: 2

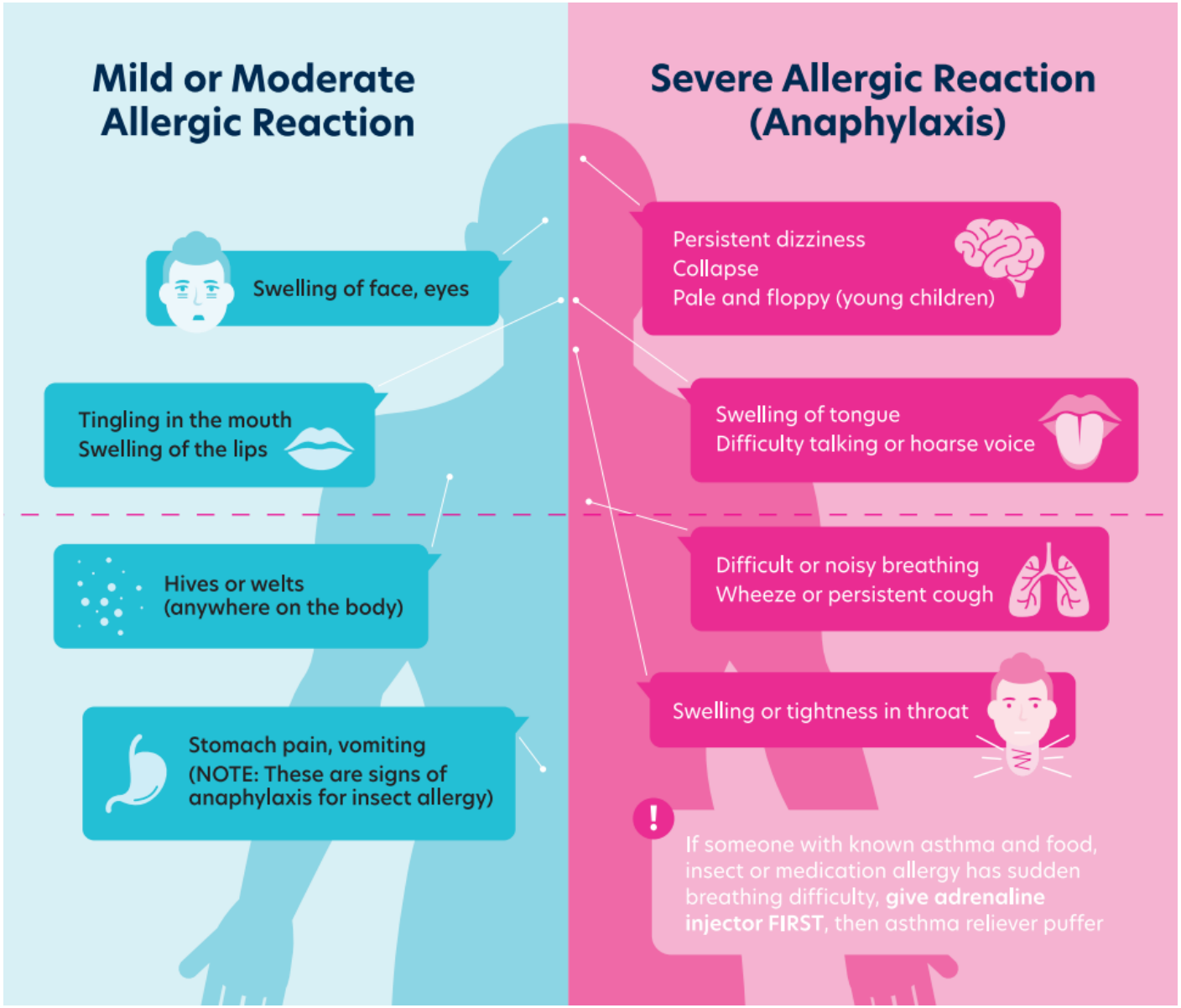
Hypersensitivity Reactions

- **Hypersensitivity reactions** are exaggerated immune responses to an antigen, or allergen, that can cause undesirable effects.
- They can lead to immune diseases such as allergies and autoimmunity.
- It is caused by many types of particles and substances from the external environment or from within the body that are recognized by the immune cells as antigens.
- The immune reactions are usually referred to as an over-reaction of the immune system and they are often damaging and uncomfortable.

Symptoms of Hypersensitivity reactions

- Symptoms can include redness, swelling, nasal discharge, airway narrowing, sneezing, coughing, and wheezing.
- Symptoms can appear in people who have had a previous exposure to the allergen.

Symptoms of Hypersensitivity reactions



Causes of hypersensitivity reactions

- Drugs, such as penicillin, can cause allergic reactions.
- Continuous or repeated exposure to an allergen can lead to chronic allergic inflammation.

Factors causing hypersensitivity

- Factors causing hypersensitivity – allergens
- In clinical terms ,hypersensitivity is called allergy
- Extrinsic factors & intrinsic factors

  Drugs – Penicillin, Aspirin, Sulphamide

  Airborne particles – Pollen grains, spores, animal dander's

  Food stuffs – Shell fish, vegetables, peanut

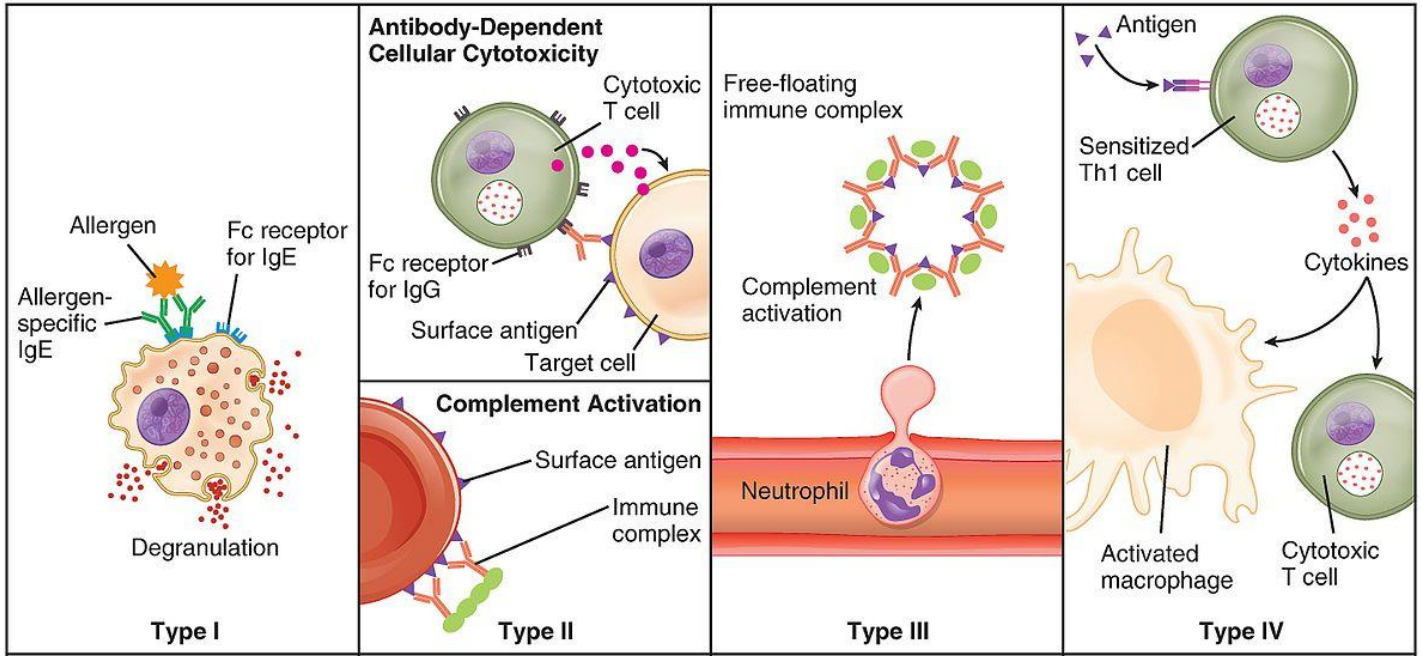
  Blood transfusion of mismatched blood

  Infectious organisms – bacteria, viruses, fungi, parasite

- In 1963, Philip George Houthem Gell and Robin Coombs introduced a systematic classification of the different types of hypersensitivity based on the types of antigens and immune responses involved.
- According to this system, known as the Gell and Coombs classification or Gell-Coombs's classification, there are four types of hypersensitivity, namely: type I, which is an Immunoglobulin E (IgE) mediated immediate reaction; type II, an antibody-mediated reaction mainly involving IgG or IgM; type III, an immune complex-mediated reaction involving IgG, complement system and phagocytes; and type IV, a cytotoxic, cell-mediated, delayed hypersensitivity reaction involving T cells.

- The first three types are considered immediate hypersensitivity reactions because they occur within 24 hours.
- The fourth type is considered a delayed hypersensitivity reaction because it usually occurs more than 12 hours after exposure to the allergen, with a maximal reaction time between 48 and 72 hours.
- Hypersensitivity is a common occurrence: it is estimated that about 15% of humans have at least one type during their lives, and has increased since the latter half of the 20th century.

Gell and Coombs classification of hypersensitivity



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

Overview of Hypersensitivity

Type I

IgE antibodies

- inflammation
- smooth muscle spasms

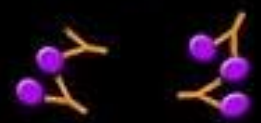
Type II

IgG/IgM antibodies

- *cytotoxic*: kill cells by complement, phagocytosis
- interfere with cell functions

Type III

IgG/IgM antibodies



immune complexes

- inflammation

Type IV

T-cells - mediated

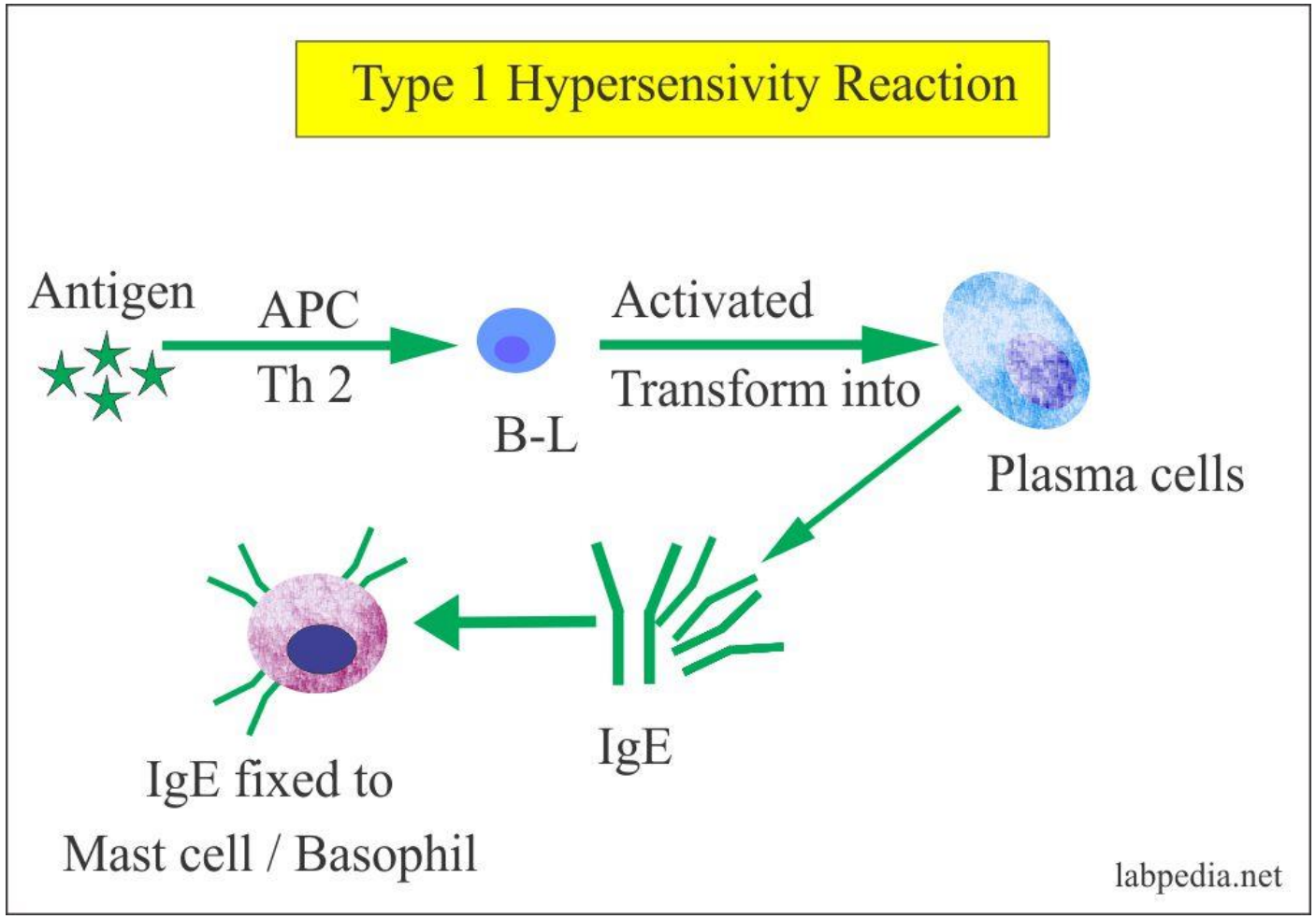
- inflammation

Alila
MEDICAL MEDIA

1. Type I Hypersensitivity (Immediate):

- **Mediated by:** IgE antibodies.
- **Mechanism:** Upon re-exposure to an allergen, IgE binds to mast cells and basophils, triggering the release of histamine and other mediators.
- **Types of antigens involved**
- Food: nuts, eggs, soy, wheat, shellfish, etc.
- Animal source: bees, wasp, cats, insects, rats, etc.
- Environmental factors: dust mites, latex, pollen, mold, flowers smell, etc.
- Atopic diseases: allergic asthma, allergic rhinitis, conjunctivitis, dermatitis, etc.
- Medication-induced reactions: antibiotics
- **Examples:** Allergic rhinitis, asthma, anaphylaxis.

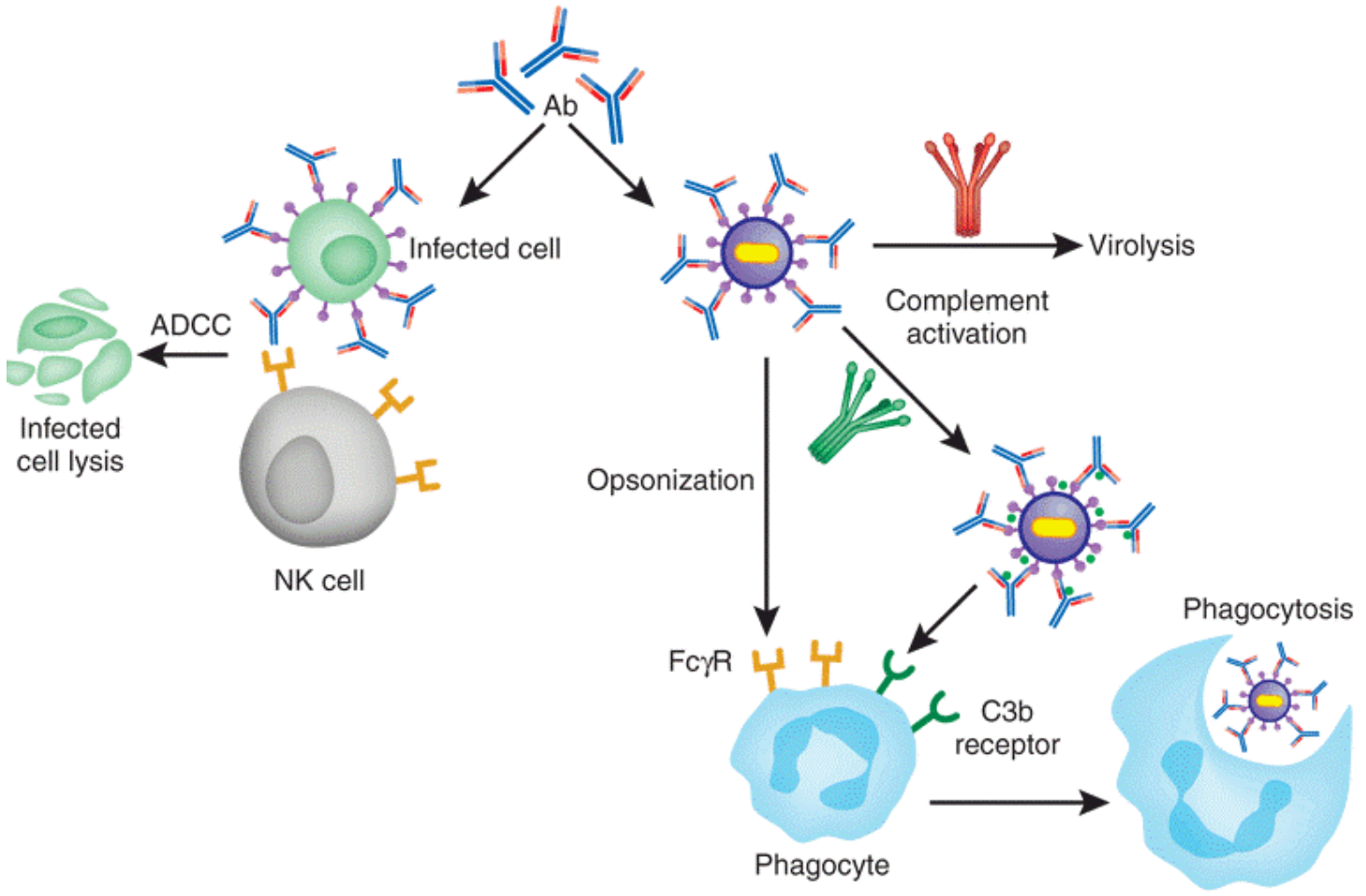
Type I Hypersensitivity



2. Type II Hypersensitivity (Cytotoxic):

- **Mediated by:** IgG or IgM antibodies against cell surface or matrix antigens.
- **Mechanism**:
- Antibody binding to cell surface receptors and altering its activity
- Activation of the complement pathway.
- Antibody-dependent cellular cytotoxicity.
- **Pathophysiology:**
- Cell depletion or destruction without inflammation
- Inflammation mediated by complement or Fc receptor
- Cellular dysfunction by antibodies
- The process involves a series of immune-mediated events that might take different forms.
- **Examples:** Hemolytic anemia, Goodpasture's syndrome.

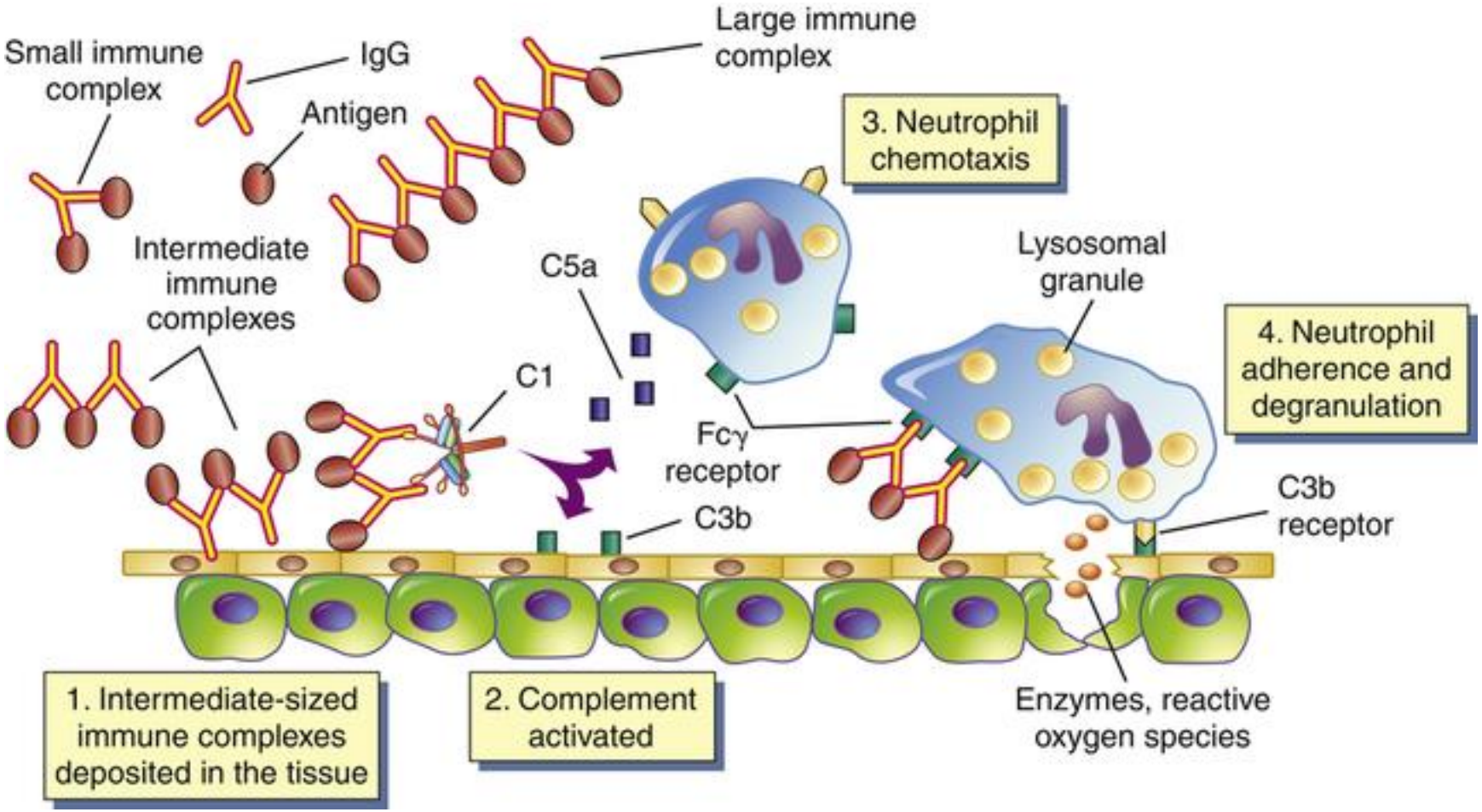
Type II Hypersensitivity



3. Type III Hypersensitivity (Immune Complex):

- **Mediated by:** Immune complexes (antigen-antibody complexes).
- **Mechanism:** Immune complexes deposit in tissues, activating complement and causing inflammation.
- **Examples:** Systemic lupus erythematosus (SLE), post-streptococcal glomerulonephritis.

Type III Hypersensitivity



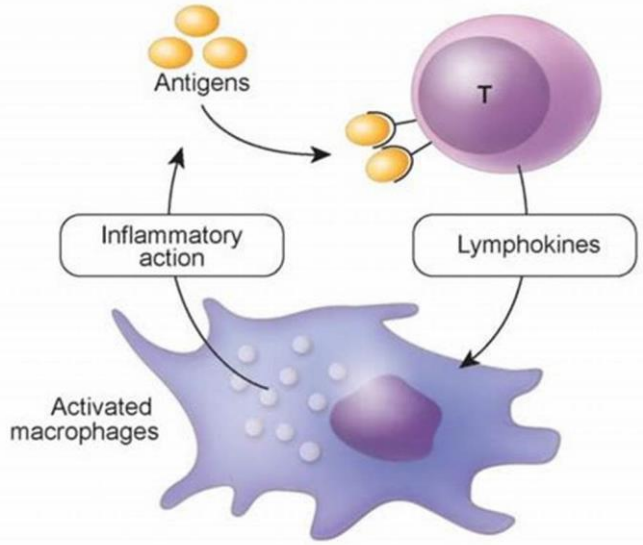
4. Type IV Hypersensitivity (Delayed-Type):

- **Mediated by:** T cells (mainly CD4+ T cells).
- **Mechanism:** Sensitized T cells release cytokines upon antigen re-exposure, leading to macrophage activation and tissue damage.
- **Examples:** Contact dermatitis, tuberculosis skin test (Mantoux test)

Type IV Hypersensitivity

Type IV Hypersensitivity Reaction

= Delayed or cell mediated HSR



Mechanism

- CD8+ T cell mediated: destructs virus-infected, neoplastic, or donor graft cells
- CD4+ T cell mediated: effector CD4+ T cells recognize antigen and release cytokines

Examples

- Granulomas (eg, TB, Histoplasma, Coccidioides)
- PPD skin test (for TB)
- Graft-versus-host disease (GVHD)
- Contact dermatitis and patch test
- Multiple sclerosis
- Guillain-Barré syndrome
- Type 1 DM
- Chronic asthma
- Candida skin test (rash = intact cell mediated immunity)

Don't be tricked:

- Type IV HSR is a type of **cell mediated immunity**
- Type IV HSR is the only type of HSRs which is **not mediated by antibodies** (ie, not transferable by serum)

Treatment

Immediate hypersensitivity reactions:

- The treatment of immediate hypersensitivity reactions includes the management of anaphylaxis with intramuscular adrenaline (epinephrine), oxygen, intravenous (IV) antihistamine, support blood pressure with IV fluids, avoid latex gloves and equipment in patients who are allergic, and surgical procedures such as tracheotomy if there is severe laryngeal edema.

1. Allergic bronchial asthma can be treated with any of the following: inhaled short- and long-acting bronchodilators (anticholinergics) along with inhaled corticosteroids, leukotriene antagonists, use of disodium cromoglycate, and environmental control. Experimentally, a low dose of methotrexate or cyclosporin and omalizumab (a monoclonal anti-IgE antibody) has been used.

2. Treatment of autoimmune disorders (e.g., SLE) include one or a combination of NSAIDs and hydroxychloroquine, azathioprine, methotrexate, mycophenolate, cyclophosphamide, low dose IL-2, intravenous immunoglobulins, and belimumab.

3. Omalizumab is a monoclonal antibody that interacts with the binding site of the high-affinity IgE receptor on mast cells. It is an engineered, humanized recombinant immunoglobulin. Moderate to severe allergic bronchial asthma can improve with omalizumab.

Delayed hypersensitivity reactions:

- Treatment of type 4 HR involves the treatment of the eliciting cause.

1. The most common drugs to treat tuberculosis include isoniazid, rifampin, ethambutol, and pyrazinamide. For drug-resistant TB, a combination of antibiotics such as amikacin, kanamycin, or capreomycin should be used.
2. The most common drugs to treat leprosy include rifampicin and clofazimine in combination with dapsone for multibacillary leprosy. A single dose of antimicrobial combination to cure single lesion paucibacillary leprosy comprises ofloxacin, rifampicin, and minocycline.
3. Praziquantel can be useful for treating infections caused by all *Schistosoma* species.
4. Hydroxychloroquine and chloroquine can use in the therapy of sarcoidosis involving the skin, lungs, and the nervous system.
5. The use of anti-TNF monoclonal antibodies such as adalimumab and certolizumab have been approved for Crohn disease.

Evasion of Immune Responses by Various Infectious Agents

- Pathogens have evolved numerous strategies to evade the immune system, ensuring their survival and proliferation within the host.

1. Antigenic Variation:

- **Viruses (e.g., Influenza, HIV):** Frequently change surface proteins to escape antibody detection.
- **Protozoa (e.g., *Trypanosoma brucei*):** Periodically switch their surface glycoproteins to avoid immune recognition.

2. Inhibition of Antigen Presentation:

- **Viruses (e.g., Herpes simplex virus, Cytomegalovirus):** Downregulate MHC class I expression, preventing CTL-mediated killing.
- **3. Inhibition of Phagocytosis:**
- **Bacteria (e.g., *Streptococcus pneumoniae*):** Produce a polysaccharide capsule that prevents phagocytosis.
- **Protozoa (e.g., *Leishmania*):** Inhibit phagolysosome fusion, surviving within macrophages.

4. Modulation of Host Immune Response:

- **Helminths:** Secrete molecules that skew the immune response towards a non-protective Th2 response.
- **Viruses (e.g., HIV):** Infect and deplete CD4+ T cells, crippling the immune system.

5. Latency:

- **Viruses (e.g., Herpesviruses, Varicella-zoster virus):** Enter a latent state within host cells, evading immune detection until reactivation.
- **6. Resistance to Antimicrobial Peptides:**
- **Bacteria (e.g., *Staphylococcus aureus*):** Modify their surface to resist antimicrobial peptides produced by the host.

ACKNOWLEDGEMENT

- The presentation is being used for educational and non-commercial purposes.
- Thanks are due to all the original contributors and entities whose pictures were used to create this presentation.