Hypersensitivity

Teaching Objectives:

1. **Understand the classification of hypersensitivity reactions**
2. **Know the diseases associated with hypersensitivity reactions**
3. **Understand the mechanisms of damage in hypersensitivity reactions**
4. **Know the methods for diagnosing conditions due to hypersensitivity & know the modes of treating disease**

Hypersensitivity describes an abnormal or pathologic immune reaction that is caused by an immune response **to repeated exposure to an antigen** (Allergens). Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction.

Type I Allergy (immediate) **Hypersensitivity**	Atopy Anaphylaxis Asthma	IgE	Fast response occurs in minutes, rather than multiple hours or days. Free antigens cross link the IgE on mast cells and basophils which causes a release of vasoactive biomolecules. **Testing can be done by skin (prick and intradermal) test and measurement of specific IgE and total IgE by ELISA.**
Type II Cytotoxic, antibody-dependent	Autoimmune hemolytic anemia Thrombocytopenia Rheumatic heart disease	IgM or IgG Complement MAC (membrane attack complex)	Antibody (IgM or IgG) binds to antigen on a target cell, which is actually a host cell that is perceived by the immune system as foreign, leading to cellular destruction via the MAC. **Testing includes both the direct and indirect Coombs test**
Type III Immune complex disease	Serum sickness **Arthus reaction** **RA and** Post streptococcal glomerulonephritis **Lupus nephritis** **SLE**	IgG Complement Neutrophils	Antibody (IgG) binds to soluble antigen, forming a circulating immune complex. This is often deposited in the vessel walls of the joints and kidney, initiating a local inflammatory reaction
Type **IV** **Delayed-type hypersensitivity,** or cell-mediated immune memory response, antibody-independent	Contact dermatitis Mantoux test Chronic transplant rejection	**T-helper (TH1) cells**	Helper T cells (specifically Th1 helper t cells) are activated by an antigen presenting cell. When the antigen is presented again in the future, the memory Th1 cells will activate macrophages and cause an inflammatory response. This ultimately can lead to tissue damage

Hypersensitivity – Type I

Production of IgE in genetically predisposed, it occurs in response to repeated low-dose exposure to inhaled allergens such as **dust mite, or grass** pollen.

Allergens: the antigens that give ف rise to immediate hypersensitivity.

IgE antibodies bind to specific receptor, FcεRI, on mast cells and basophils. When **bound IgE** is cross-linked by specific allergen, **mediators including histamine, leukotrienes and cytokines are released.**

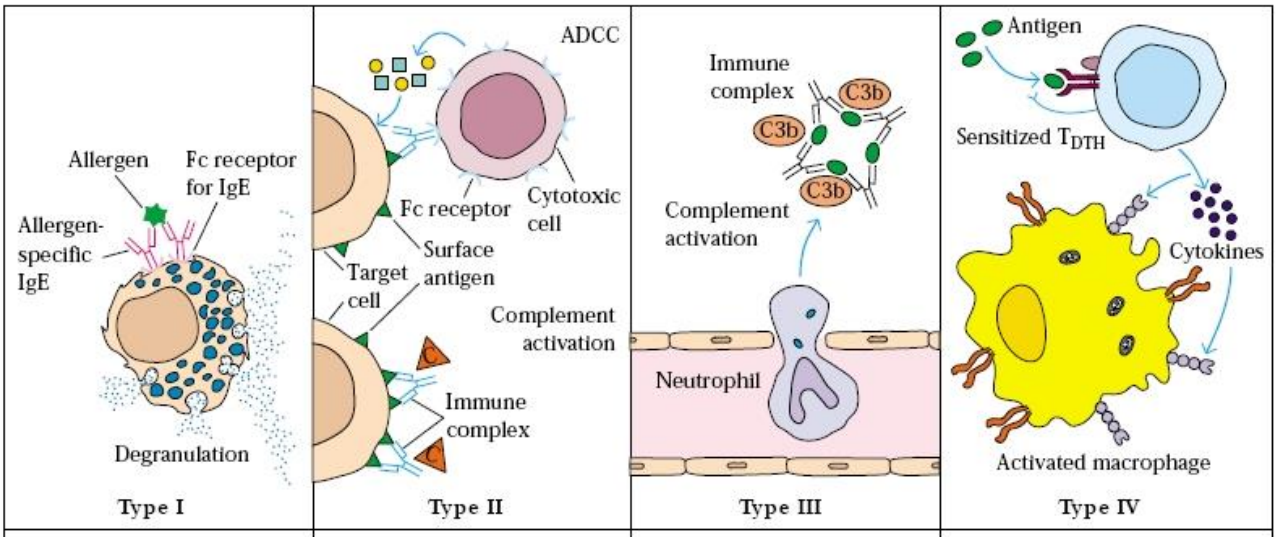
Allergic diseases include **anaphylaxis, seasonal hayfever, atopic dermatitis and allergic asthma.** Therapy includes antihistamines, adrenaline, bronchodilators, corticosteroids, reducing exposure to allergens and specific allergen immunotherapy. **The severity of symptoms depends on IgE antibodies, the quantity of allergen**,

Type II It is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. The antigensف are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. Drug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time is minutes to hours. Itis primarily mediated by antibodies of IgM or IgG class and complement Phagocytes andNKcells may also play a role (ADCC).occur when antibodies, either of the IgG or IgM isotypes are produced against surface antigens present on cells of the body.

Type III or immune complex disease occurs when excess complexes are formed in the circulation that cannot be cleared by macrophages or other cells . The reaction may be general (*e.g.*, serum sickness) or may involve individual organs including **skin** (*e.g.*, systemic lupus erythematosus, Arthus reaction), **kidneys** (*e.g.*, lupus nephritis), lungs (*e.g.*, aspergillosis), blood vessels (*e.g.*, polyarteritis), joints (*e.g.*, rheumatoid arthritis). The reaction may take 3-10 hours after exposure to the antigen (as in Arthus reaction). It is mediated by soluble immune complexes. They are mostly of **IgG class**, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous *e.g.*, systemic lupus eythematosus, SLE). Primary components are soluble immune complexes and complement (C3a, 4a and 5a). The damage is caused by **platelets and neutrophils.**

Type IV or cell-mediated reactions:

The classical example of this hypersensitivity is **tuberculin** (**Montoux**) reaction which peaks **48 -72 hours** after the injection of antigen (tuberculin). The lesion is characterized by **induration and erythema.** Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper **T (TH1) cells** secrete cytokines which activate cytotoxic Tcells and recruit and activate monocytes and macrophages, which cause the bulk of the damage . simples examples contact sensitivity (e.g. to nickel or poison ivy) and graft rejection. Type IV is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis.



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

Table 5. Comparison of Different Types of hypersensitivity

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