DEFINING HYPERSENSITIVITY
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**Type I hypersensitivity**

Anaphylaxis: Prior sensitization has resulted in an immune response initially mediated by CD4 lymphocytes (of the Th2 variety) that promote mast cell proliferation and plasma cell production of IgE. The IgE becomes bound to mast cells in places such as respiratory tract mucosa. Encountering the allergen again leads to mast cell degranulation with release of primary mediators (such as histamine, serotonin) which cause vasodilation, bronchoconstriction, etc. and release of secondary mediators (such as leukotrienes, prostaglandin) which lead to inflammatory cell infiltrates. There are two forms of anaphylaxis:

- Systemic anaphylaxis: In some individuals, a severe reaction occurs within minutes, leading to symptomatology such as acute asthma, laryngeal edema, diarrhea, urticaria, and shock. Classic examples are penicillin allergy and bee sting allergy.
- Local anaphylaxis (atopy): About 10% of people have "atopy" and are easily sensitized to allergens that cause a localized reaction when inhaled or ingested. This can produce hay fever, hives, asthma, etc. Classic examples are food allergies and hay fever to ragweed pollen.

Laboratory Findings

- Type 1 hypersensitivity reactions may be accompanied by an increase in eosinophils, as noted with differential count of peripheral white blood cells.
- The serum tryptase may be increased in the hour following mast cell activation.
- Measurement of serum IgE levels and levels specific for certain antigens may be undertaken when allergy therapies are planned.

**Type II Hypersensitivity**

Complement dependent reactions: Antibody is directed against antigen on cells (such as circulating red blood cells) or extracellular materials (basement membrane). The resulting Ag-Ab complexes activate complement (via the classic pathway), leading to cell lysis or extracellular tissue damage.

Diseases in this complement dependent category include:

- Transfusion reactions: incompatible RBC's or serum is transfused.
- Autoimmune hemolytic anemia: antibody is made against one's own RBC's.
- Erythroblastosis fetalis: maternal IgG crosses the placenta and attaches to fetal RBC's.
- Goodpasture's syndrome: glomerular basement membrane antibody is present.

Antibody-dependent cell-mediated cytotoxicity (ADCC): Low concentrations of IgG or IgE (in the case of parasites) coat target cells. Inflammatory cells such as NK (natural killer) cells, monocytes, and granulocytes then bind to the immunoglobulin Fc receptors and lyse, but do not phagocytize, the target cells.

A macrophage with Fc receptors on its surface is able to recognize a target cell coated with antibody via the Fc receptor portion of the attached antibody. The macrophage can then demolish the targeted cell by elaboration of proteases.

Examples of ADCC include:

- Transplant rejection
- Immune reactions against neoplasms
- Immune reactions against parasites

Antireceptor antibodies: IgG antibody is directed against receptors in target cells, resulting in complement-mediated destruction of the receptors.

Diseases caused by this mechanism include:

- Myasthenia gravis: acetylcholine receptor antibody.
- Grave's disease (thyrotoxicosis): anti-TSH receptor antibody
- Pernicious anemia: anti-parietal cell antibody.

**Type III Hypersensitivity**

*Immune (Ag-Ab) complexes* promote tissue damage primarily through complement activation (alternate pathway). C3b as an opsonin attracts neutrophils, which then release lysosomal enzymes. C5a as a chemoattractant brings in neutrophils. Serum complement is reduced as it is used up in this process.

Antigen-antibody complexes are circulating and becoming trapped beneath the basement membrane of a small blood vessel, setting off the complement cascade and generating components that attract PMN's to generate an ongoing inflammatory response.

Immune complexes can be deposited systemically or locally.
Systemic immune complex disease: Ag-Ab complexes form in the circulatory system and are deposited in tissues, typically near basement membranes in places such as blood vessels, glomeruli, skin, joints, pleura, and pericardium. Larger immune complexes are quickly phagocytized by macrophages and removed, but small to intermediate complexes formed with antigen excess may escape removal leading to:

- Glomerulonephritis
- Serum sickness
- Vasculitis

Local immune complex disease: Also called an "Arthus" reaction, it occurs with local injection of the antigen and leads to focal vasculitis. This kind of immune reaction also plays a role in the development of hypersensitivity pneumonitis (so-called "farmer's lung").

**TYPE IV- Delayed hypersensitivity**

*CD4 T Lymphocytes* which process antigens with class II HLA molecules and release lymphokines.

Hypersensitivity reactions with this mode of action include:

- Granulomatous diseases (mycobacteria, fungi)
- Tuberculin skin reactions
- Transplant rejection
- Contact dermatitis

*Cytotoxic T lymphocyte (CTL) mediated responses*: CD8+ T cells are generated and lyse specific cells. Class I HLA molecules play a role. Reactions with this mode include:

- Neoplastic cell lysis
- Transplant rejection
- Virus-infected cell lysis
- Anti-double stranded DNA (native DNA antibody): SLE
- Anti-Smith: SLE
- anti-histone: drug-induced SLE
- anti SS-A and anti SS-B: Sjogren's syndrome
- anti DNA-topoisomerase I (Scl-70): PSS
- anti-histidyl-tRNA synthetase (Jo-1): polymyositis
- anti-RNP (ribonucleoprotein): MCTD
- anti-phospholipid antibody (anti-cardiolipin antibody): SLE and others