



IMMUNOPATHOLOGY

Part 1 – Hypersensitivities and Allergic Responses



DISORDERS OF IMMUNITY

1/ Type I Hypersensitivity - Anaphylactic-Type Reaction

2/ Type II Hypersensitivity - Cytotoxic Antibody-Mediated Reaction

3/ Type III Hypersensitivity - Immune Complex-Mediated Reaction

4/ Type IV Hypersensitivity - Cell Mediated, Delayed Reaction

Hypersensitivity is when an otherwise healthy immune system has an undesirable exaggerated response to a foreign substance (or perceived foreign substance) that damages the body's own cells.



Type I Hypersensitivity - Anaphylactic-Type Reaction

- Mediated by IgE and mast cells or basophils

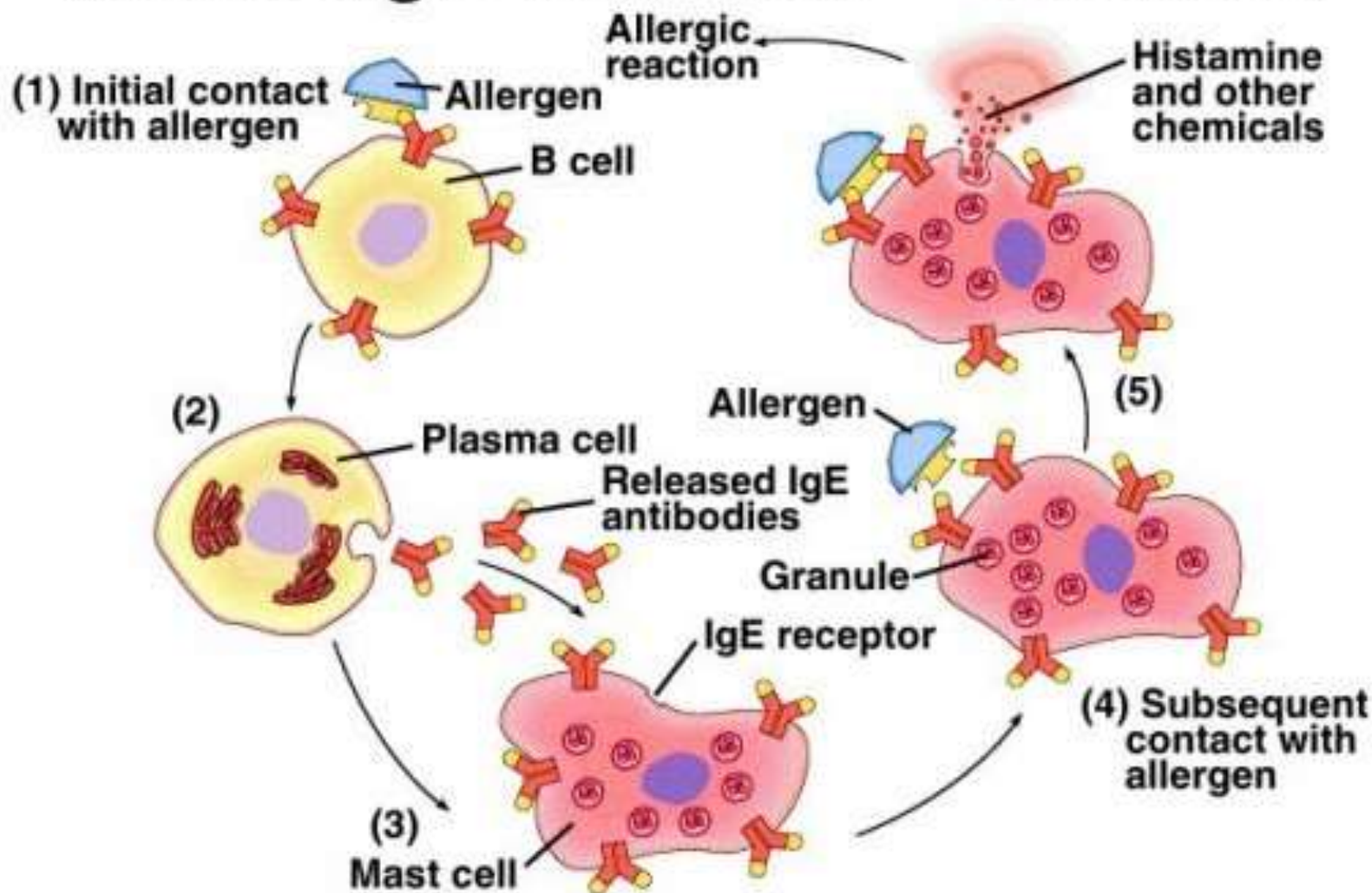
Example:

- Ag (pollen) sensitizes B-Lymphocytes to become plasma cells producing IgE (in tissues)
- IgE attaches to mast cells, causing a massive release of histamine within a few seconds
- Re-exposure to Ag → Ag-Ig complex on surface of mast cells => release of HISTAMINE = immediate response
- The more frequent the exposures, the larger the amount of histamine released and the greater the reaction.



Ricki Lewis, Life, 3e. Copyright © 1998 The McGraw-Hill Companies, Inc. All rights reserved.

An Allergic Reaction — Overview

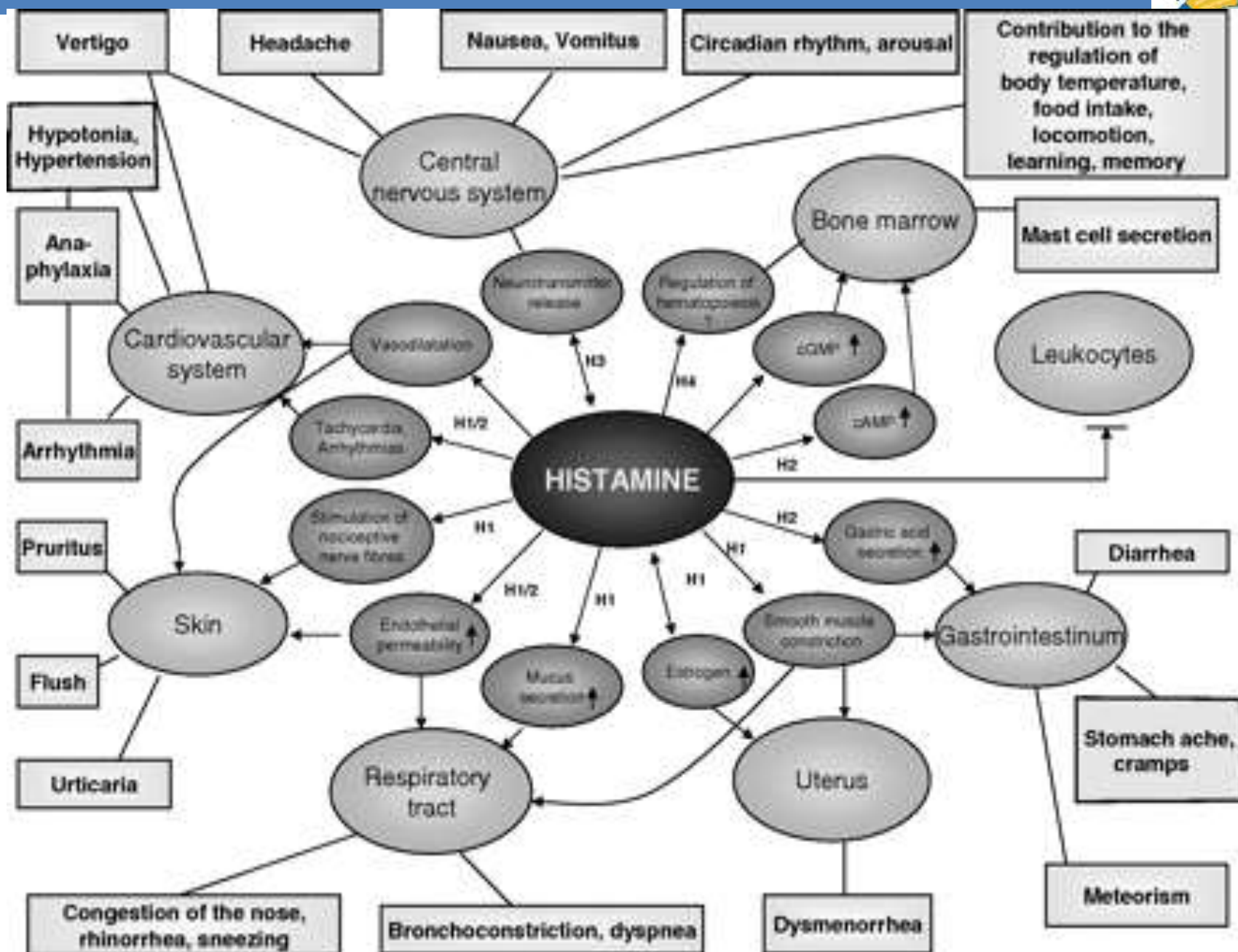




Type I Hypersensitivity - Anaphylactic-Type Reaction

EFFECTS OF HISTAMINE:

- increased vascular permeability => edema and accumulation of inflammatory cells
- Vaso-dilation
- production of mucus
- Broncho-constriction
- Itching
- Initial reaction is almost immediate (within minutes)
- Late response (4 - 6 hours later) - mediated by slow-reacting substances of anaphylaxis (typical of asthma)





Clinical Examples

HAY FEVER (allergic rhinitis)

- allergy to pollen, dust, dandruff

Signs and Symptoms:

- itching (nose, eyes)
- sneezing, nasal congestion and/or discharge
- conjunctivitis, edema (eyelids)

Therapy:

- antihistamines
- desensitization to specific allergens (injections)



Clinical Examples

ATOPIC DERMATITIS (eczema)

- 10% of all children
- Genetic predisposition – hyper-production of IgE
- Exposure - direct skin contact, diet, unknown
- Later in life - development of hay fever or asthma is a possibility

Therapy:

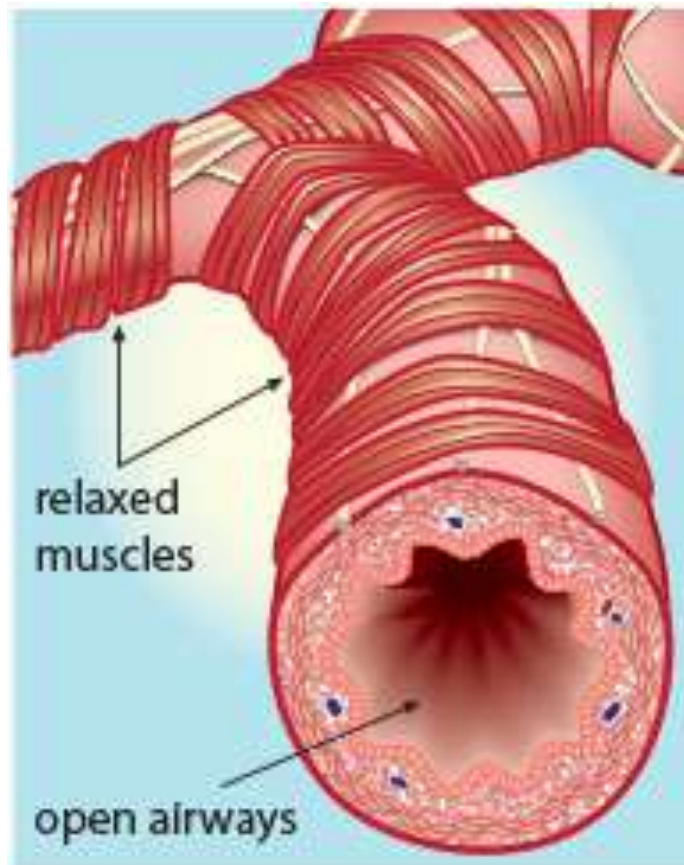
- Corticosteroid ointments
- Diet changes



Clinical Examples

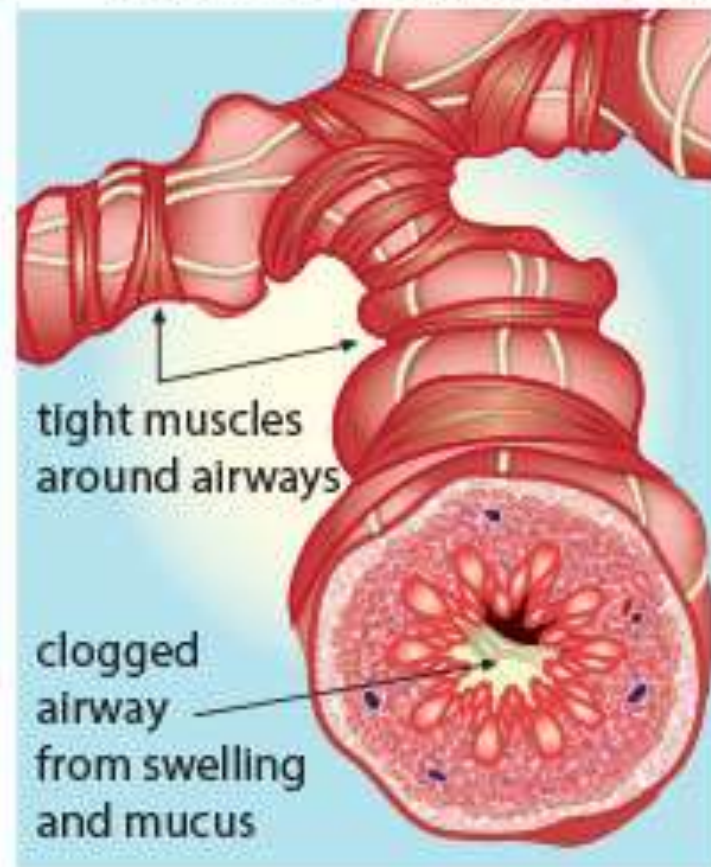
ASTHMA

- triggers: pollen, dust mites, molds, some foods, emotional upset, aspirin, sulfating agents, exercise, cold air, cigarette smoke, preservatives
- EARLY PHASE (ACUTE):
- spasm of smooth muscles in bronchioles (=bronchoconstriction)
- excessive mucus production



Normal Bronchiole

Asthmatic Bronchiole



http://coreem.net/content/uploads/2015/06/Asthma-healthcare-online.org_.jpg



LATE PHASE (CHRONIC):

- inflammation, fibrosis, edema, necrosis of bronchial epithelium

Signs and Symptoms:

- dyspnea, cough, wheezing, chest tightness, tachycardia, fatigue, moist skin, anxiety

Therapy:

- Adrenergic drugs during acute attack and other bronchodilators
- Long term management: corticosteroid inhalers and other anti-inflammatories



Clinical Examples

ANAPHYLACTIC SHOCK

= life threatening, severe, systemic response to allergen to which the body was previously sensitized

- Insect bites - bee sting, wasps, hornets, fire ants
- IV injection of anesthetics or radiographic contrast media
- Drug reactions – penicillin or Aspirin specially if I.V.I
- Severe allergy to some foods – peanuts, shellfish



ANAPHYLACTIC SHOCK:

Signs and Symptoms:

- Shock = result of massive release of histamine => drop in B.P.
- Choking = laryngeal edema
- Wheezing = bronchial spasm
- Pulmonary edema
- Circulatory collapse due to vasodilation and increased permeability of capillaries

Therapy:

- EpiPen = epinephrine (adrenaline) to stimulate vasoconstriction and heart action => restoring normal B.P., bronchodilators



2/ Type II Hypersensitivity – Cytotoxic Antibody-Mediated Reaction

- Mediated by cytotoxic Ig (antibody). Plasma cells create IgG or IgM antibodies.
- Antibodies form antigen-antibody complex. Leads to destruction through complement activation, hindering cellular function, attracting NK cells, macrophages etc.
- Antigen may be extrinsic or intrinsic
- Intrinsic Ag - proteins, RNA, DNA
- Extrinsic Ag - some drugs and other chemicals



Clinical Examples

HEMOLYTIC ANEMIA

- Antigen on RBCs recognized by the immune cells as foreign => destruction
- Antibodies are created to destroy RBCs either in the circulation or in the liver and spleen.
- Can often go on for months before detection
- Caused by genetic defects in RBC formation, burns, infections, other autoimmune conditions, drug reactions, lead poisoning



Clinical Examples

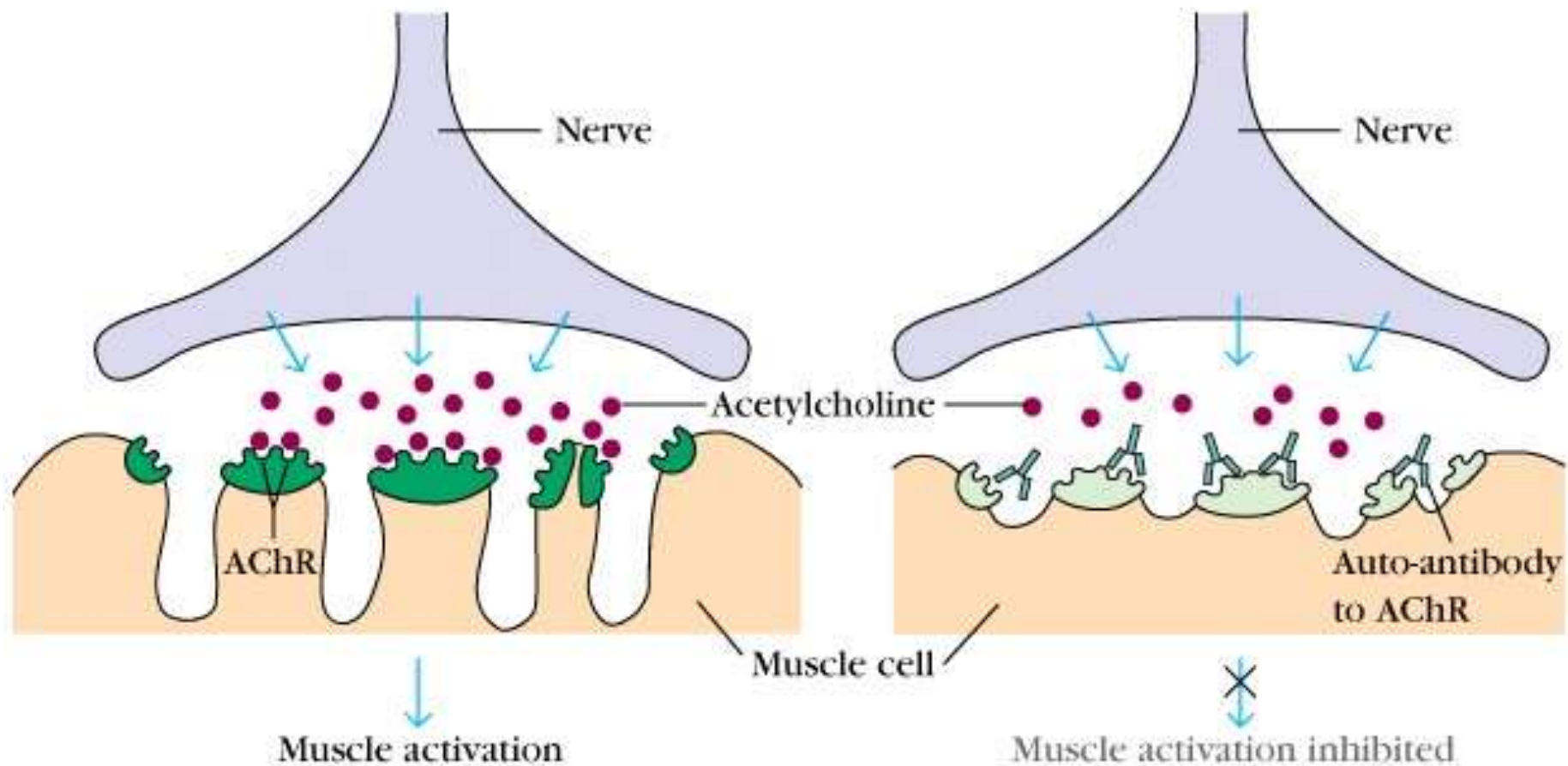
MYASTHENIA GRAVIS

- autoimmune disease marked by severe muscle weakness:
- Mediated by Ig to the receptor for acetylcholine (ACH) on skeletal muscle cells
- => receptors for ACH blocked (later destroyed) => progressive weakness → paralysis
- Therapy:
 - Immuno-suppressant drugs
 - Anticholinesterase agents



Neuromuscular Junction

BLOCKING AUTO-ANTIBODIES (Myasthenia gravis)





SYMPTOMS

- **Eye muscles**
- Drooping of one or both eyelids (ptosis).
- Double vision (diplopia)
- **Face and throat muscles**
- Altered speaking (dysarthria)
- Difficulty swallowing (dysphagia)
- Problems chewing
- Limited facial expressions
- **Neck and limb muscles**
- Weakness in arms, legs, neck, fingers etc.
- Weakness in the chest muscles sometimes
- occurs. If this is severe, myasthenic crisis
- may result .

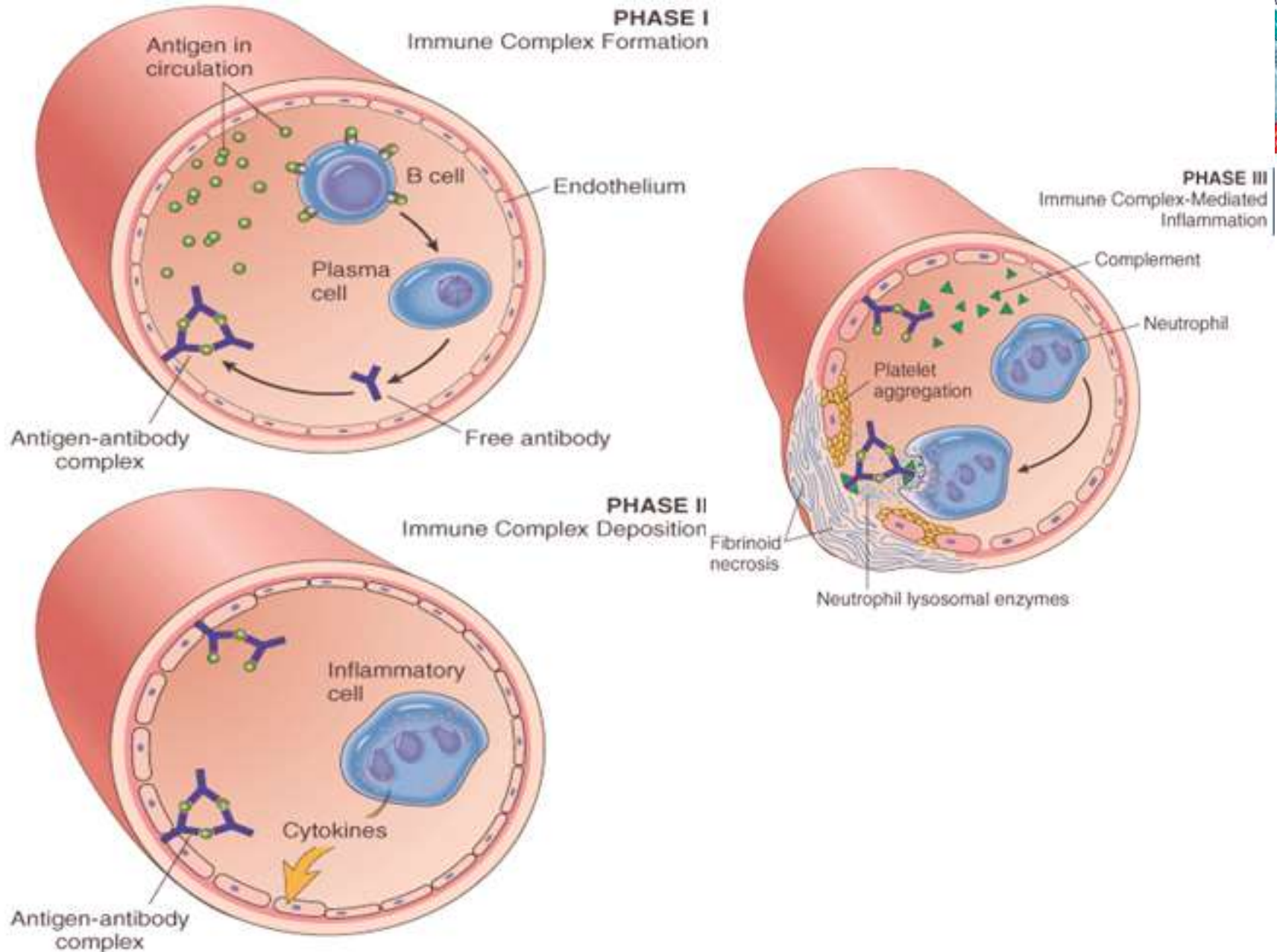




3/ Type III Hypersensitivity - Immune Complex-Mediated Reaction

- mediated by immune complexes (Ag-Ig) circulating in blood
- Complexes form and can deposit anywhere in the body
- → “trapped” in various organs (**kidneys**, brain, pleura, pericardium)
- → triggering inflammatory response

<https://www.youtube.com/watch?v=bJqQcBUlfol>





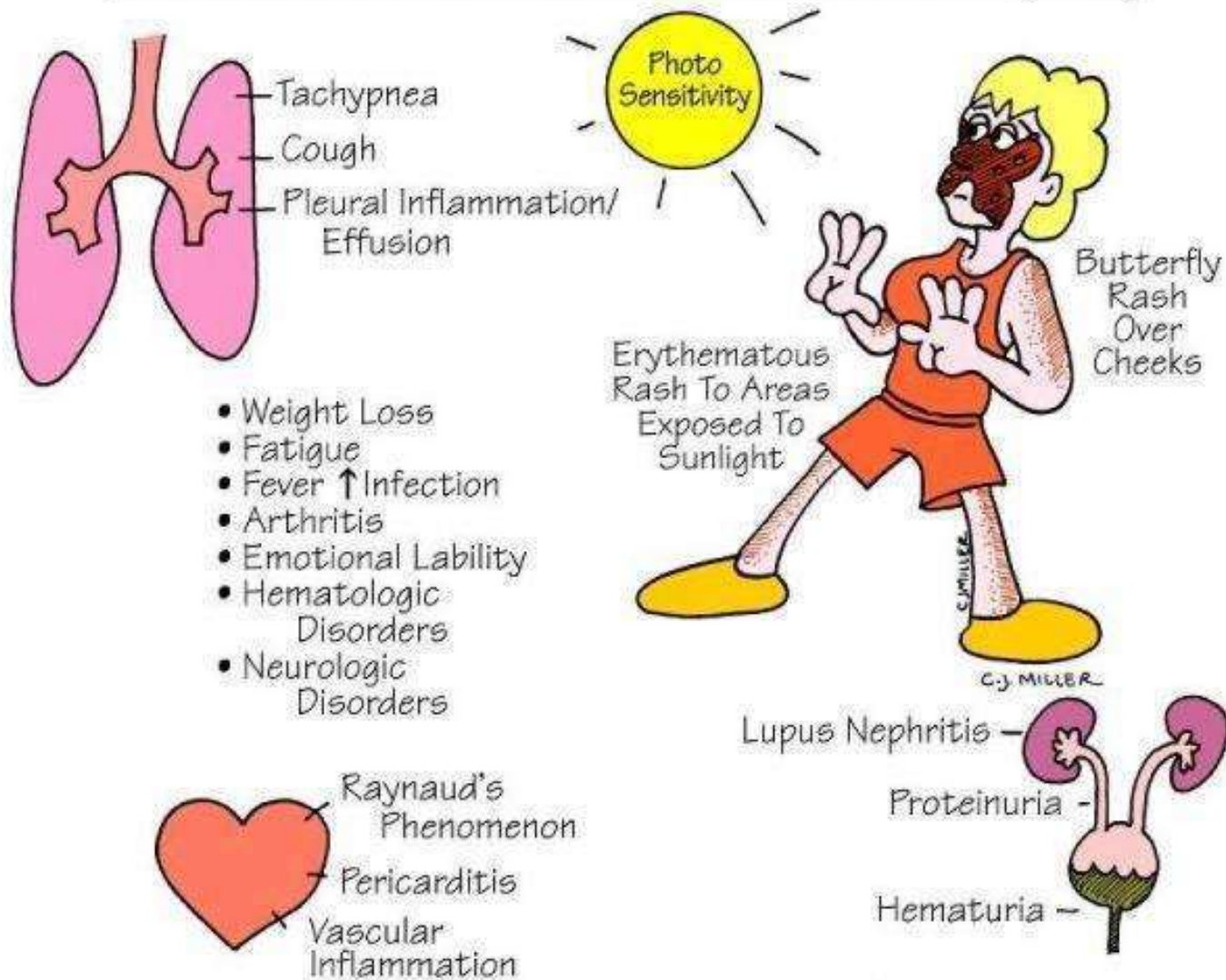
Clinical Examples

SYSTEMIC LUPUS ERYTHEMATOSIS (SLE)

- Ag-Ig complexes deposited in kidney, joints, skin, etc..
- Cause is unknown but thought to be related to:
 - Genetics
 - Other autoimmune conditions
 - Side effect of some drugs – “drug induced lupus”
- Therapy: corticosteroids



SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)



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Clinical Examples

POST STREPTOCOCCAL GLOMERULONEPHRITIS

- An infection of streptococcal bacteria that begins usually in the skin or throat
- In RARE cases, 1-3 weeks after infection without antibiotics, complexes of Ig and streptococcal Ag circulate in blood → glomerular basement membrane of the kidney
- Immune cells attack the complexes causing large amounts of inflammation



Clinical Examples

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

- Signs and Symptoms:
 - Changes to electrolytes (increased potassium in the blood)
 - High blood pressure
 - Decreased urine output, bloody urine
- Therapy: self-limiting disease
 - Goes away on its own after a couple weeks, but rarely can lead to chronic kidney failure
 - Often use antibiotics and immune suppressants to manage



4/ Type IV Hypersensitivity - Cell Mediated, Delayed Reaction

- Involves T-Lymphocytes and macrophages
- A secondary immune response that occurs 48-72 hours after the exposure (vs. anaphylaxis which occurs within seconds-minutes)
- Antigen captured by antigen-presenting cells to T Cells who attack self cell with similar characteristics of antigen
- Form large complexes of immune cells in a cluster, known as a “granuloma”



Clinical Examples

CONTACT DERMATITIS

- allergy to various allergens (rubber gloves, gold rings, poison ivy)
- reaction to Mycobacterium Tuberculosis, M. Leprae, various fungi → formation of granulomas
- <https://www.youtube.com/watch?v=exWgB3OhN50>
(Minute 16+)



Clinical Examples

TRANSPLANT REJECTION

- A person receives an organ transplant in which their immune system recognizes as foreign
- Antigens on the surface of the organ are not matched close enough to those of the recipient
- Reactions can begin within seconds (giving the wrong type of blood), weeks or even years (low level of constant inflammation and damage to the organ)
- Most common: decrease organ function, pain, swelling, fever, flu-like symptoms



Autoimmune Diseases

- Immune response is based on the ability of the immune system to distinguish between self and non-self.
- Auto-tolerance develops during fetal life (ability to prevent an immune response to something foreign)
- Breakdown of auto-tolerance = autoimmune diseases (immune system begins fighting cells/tissues that are normal)
- ETIOLOGY is unknown
- Autoimmune diseases are HYPERSENSITIVITY REACTIONS to own tissues
 - Myasthenia Gravis
 - Systemic Lupus Erythematosus



Immunodeficiency Diseases

- Primary (congenital) – genetic defects
- Secondary (acquired) - due to infections (HIV/AIDS), metabolic diseases, cancer, iatrogenic
- Involvement: B-Lympho, T-Lympho, generalized

Diagnosis:

- Lymphopenia = low lymphocyte count in peripheral blood
- Deficiency of B Lymphocytes → low levels of serum Ig
- All immuno-deficiencies cause reduced resistance to infections



Clinical Examples

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

- Severe genetic mutations in both T- and B-lymphocytes
- Results in severe bacterial, viral, and fungal infections early in life that lead to death
- Don't usually survive past first year of life



David Vetter – “Bubble Boy”



Lived in a specially constructed sterile plastic bubble from birth until death at the age of 12



Clinical Example

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Cause - HIV - Human Immunodeficiency Virus

Course:

- Initial response to HIV invasion is a flu-like illness
- Over the next 2 to 10 years, the virus slowly destroys T-lymphocytes
- **When levels fall below 200**, the individual is considered “immuno-deficient” – diagnosis of AIDS
- primary disease lowers immunity then one or more opportunistic infections or malignancies produce fatal symptoms



Pathologies typical for AIDS patients:

- pneumocystis carinii pneumonia (PCP)
- Kaposi's Sarcoma
- Rare, benign skin cancer usually found in elderly Jewish or Italian men; progresses rapidly in AIDS patients; arises from endothelial cells of blood vessels and produces painless purple skin lesions that resemble bruises
- Lymphoma
- Tuberculosis
- **Persistent diarrhea** (due to bacterial and viral infections and also due to AIDS treatment) **more than 1 month = AIDS until prove otherwise**
- leukoplakia (white patches on mucous membrane caused by Epstein-Barr virus)
- Toxoplasmosis
- severe herpes simplex infections
- severe herpes zoster infections (shingles)
- severe candida albicans infections
- neurologic complications (neuritis, neuropathy, neoplasms, AIDS dementia)



Signs and Symptoms of AIDS

- **T helper (CD4 lymphocyte) count < 200/mm³ of blood** (normal is 1200)
- 1st stage
 - mild mononucleosis-like symptoms (fatigue, fever, swollen glands, headache)
- 2nd stage - lasts several years
 - Chronically swollen lymph nodes
 - Opportunistic infections develop
 - Dementia as virus invades CNS
 - Most individuals reaching this stage die within 2 years



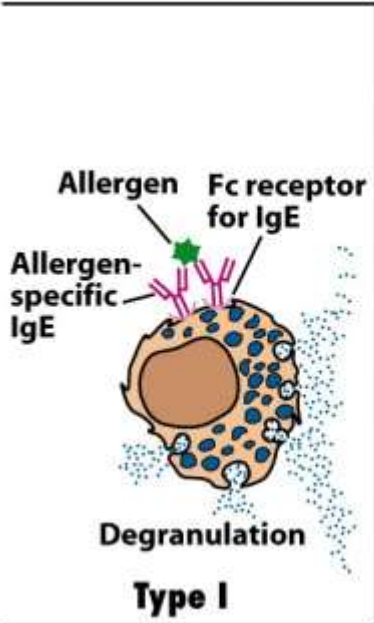
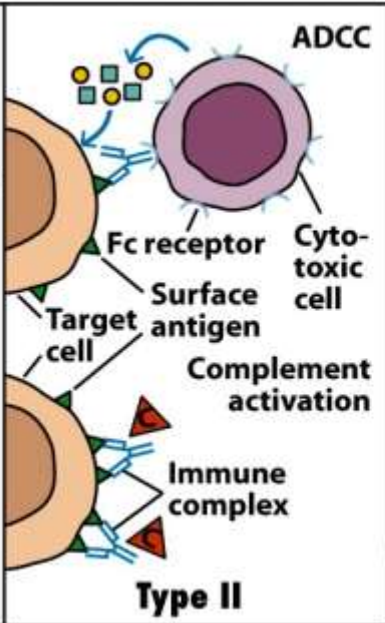
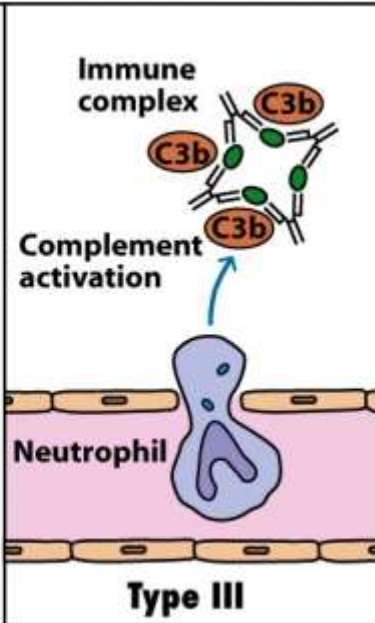
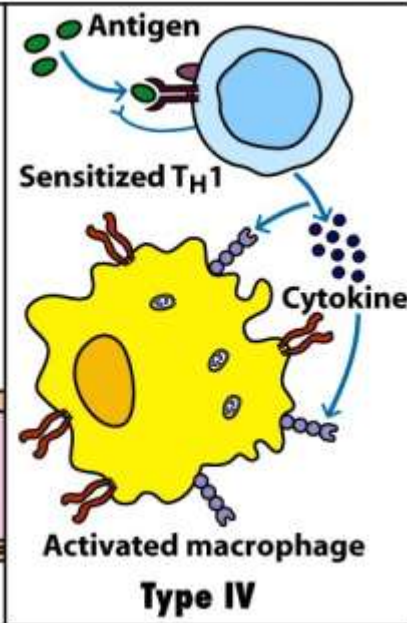
 <p>Type I</p>	 <p>Type II</p>	 <p>Type III</p>	 <p>Type IV</p>
IgE-Mediated Hypersensitivity	IgG- or IgM-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
<p>Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.</p>	<p>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.</p>	<p>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.</p>	<p>Sensitized T_H1 cells shown above release cytokines that activate macrophages or T_C cells that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.</p>
<p>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.</p>	<p>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.</p>	<p>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.</p>	<p>Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.</p>

Figure 15-1
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