Republic of Iraq Ministry of Higher Education and Scientific Research

Training package
In

Clinical Immunology

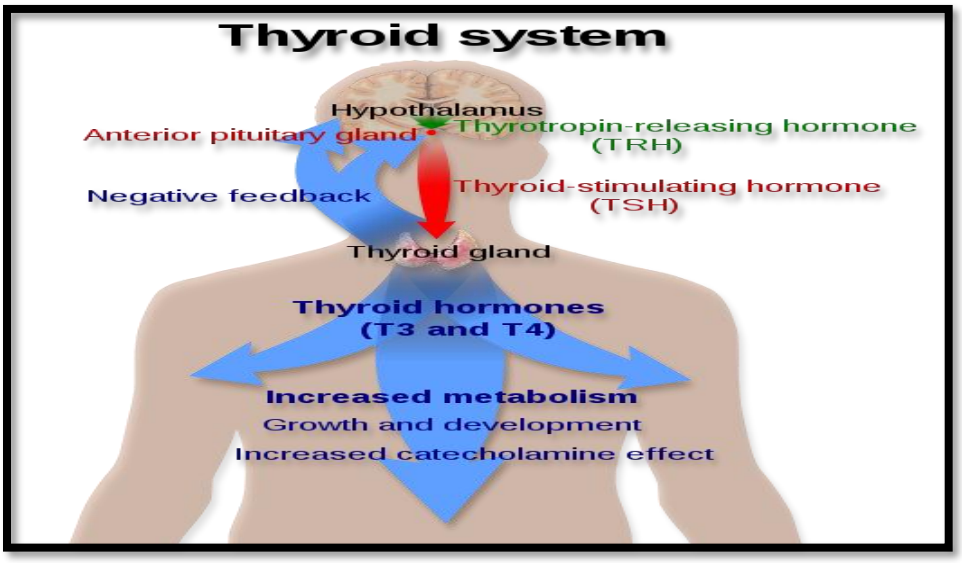
Students of fourth class of
Medical Laboratory Techniques Department

Lecture No. 1

Thyroid gland

The human thyroid gland is a major component of the endocrine system. Thyroid hormones perform many important functions. They exert powerful and essential regulatory influences on growth, differentiation, cellular metabolism, and general hormonal balance of the body, as well as on the maintenance of metabolic activity and the development of the skeletal and organ system.

The hormones Thyroxine (T4) and Triiodothyronine (T3) are secreted from the thyroid gland and regulated by a sensitive feedback system involving the hypothalamus and pituitary gland. The hypothalamus is an endocrine gland in the brain releases the thyrotropin releasing hormone (TRH), which stimulates the pituitary to release the thyroid stimulating hormone (TSH). This causes the thyroid to release T3 and T4 and these in turn regulate the release of TRH and TSH via a feedback control mechanism.



Synthesis of T3 and T4

Thyroglobulin (Tg) is a large tyrosine-rich protein bind to iodine after oxidation of iodide, a reaction catalysed by thyroid peroxidase (TPO) and release monoiodotyrosin (MIT) and di-iodotyrosine (DIT). Then peroxidase links 2 DIT to

form T4 or one DIT and one MIT to form T3 released by thyroid gland cells in the circulation. In liver deiodinases enzymes covert about 1/3 of the T4 into T3.

Oxidation

Iodide ⟶ Iodine + Thyroglobulin (Tg) ⟶ Monoiodotyrosin + Di-iodotyrosine
. TPO

Monoiodotyrosine + Diiodotyrosine ⟶ Triiodothyronine (T3)

Diiodotyrosine + Diiodotyrosine ⟶ Thyroxine (T4)

T4 and T3 may stay free in plasma or bind to several serum proteins mainly; thyroid binding globulin (TBG), transthyretin and albumin. Only about 0.02% of T4 and 0.3% of T3 is free in plasma.

Thyrotoxicosis is a characteristic feature of overproduction of the thyroid hormone; Thyroxine (T4) and Triiodothyronine (T3). This is known as hyperthyroidism in which the level of these hormones increased above normal level of blood. Thyrotoxicosis can occur for other reasons as ingestion of exogenous thyroid hormone as tablets, toxic thyroid adenoma, thyroiditis and anti-arrhythmic drug.

Autoimmune thyroid disease is broadly classified into categories on the basis of the effect on gland function:

1- **Autoimmune hyperthyroidism** is seen in **Graves's disease**
2- **hypothyroidism** is seen in **Hashimotos thyroiditis**.

Patient's serum also containing different types of auto-antibody that directed against different thyroid self antigens mainly Tg, Tpo, thyroid growth stimulating Ig (TGI) and thyroid stimulating hormone receptor (TSH-R).

Two types of anti-TSH-R antibodies may exist in the patient serum:

1. Stimulatory (Thyroid Stimulating Ig or TSI).
2. Blocking or inhibitory (Thyroid Binding Inhibitory Ig or TBII).

Graves's disease

It is the most common cause of hyperthyroidism which driven by an autoimmune mechanism. Graves's disease has a peak incidence in the 3rd and 4th decades and is found in approximately 0.1-0.5 % of the general population. It is more common in women than man (7:1). Predispositions to Graves's disease include living in an area of high iodine intake, Female sex hormones, stress and possession of HLA-DR3, which confer a relative risk of disease.

In Graves's disease the dominant type of anti-TSH-R Abs is the TSI, however, the presence of both types of Ab (TSI &TBII) in some patients may explain the fluctuation from over activity to under activity of the gland. The TSI mimic the TSH in its action, even more, it has a more prolonged action on the activation of thyroid gland cells than TSH do.

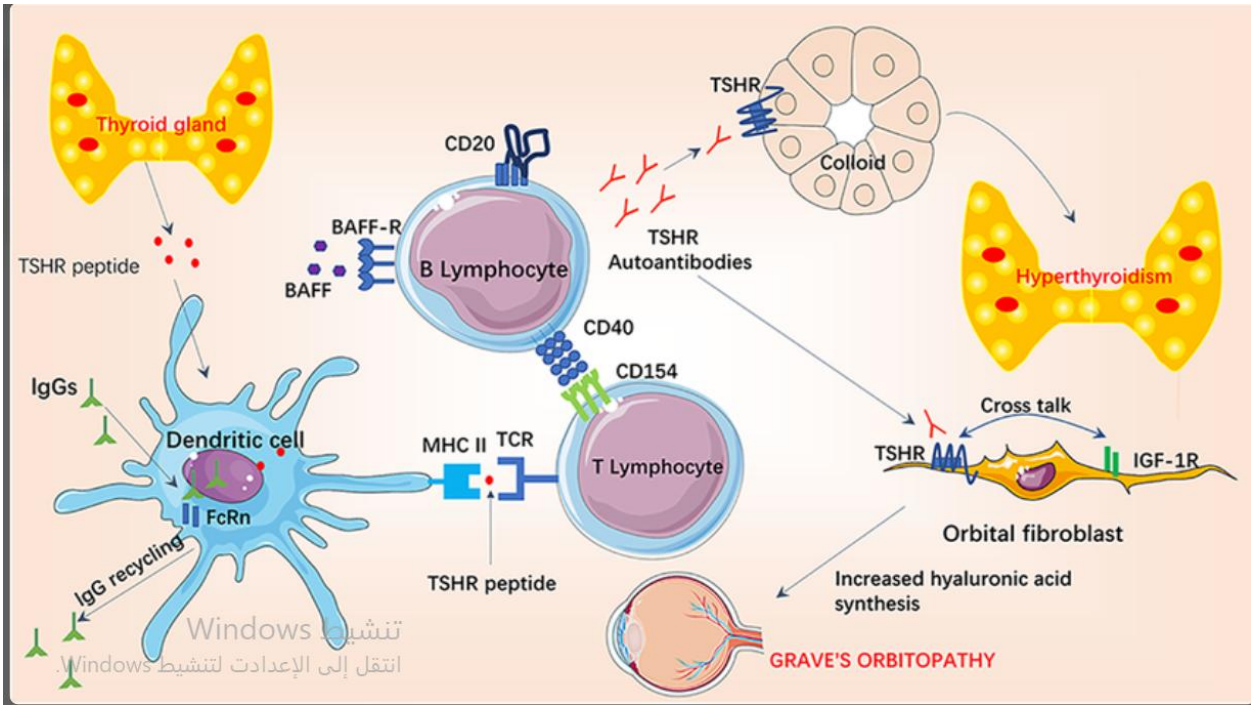
Symptoms

Patients typically present with the symptoms or signs of hyperthyroidism (palpitations, tachycardia, arrhythmias, heat intolerance, increased appetite with weight loss, diarrhea, weakness and proximal myopathy, nervousness and tremor). One characteristic feature of Graves's disease is eye disease characterized by protrusion of the eyeball and lid retraction resulting from tissue inflammation in the retro-orbital space. **Goiter** which is an enlargement or hypertrophy of the thyroid tissue is of diffuse pattern in Graves's disease.

Pathogenesis of Graves's disease

Pathogenesis of Graves's disease depends on the humoral and cell-mediated immunity participation. However, T cells (T_H2, $CD8^+$) are responsible for the glandular thyroid T cells infiltration, whereas the antibodies are acting as a disturbing factor for the normal physiological function of the gland. A clear application for that is the autoimmune syndrome in neonates which is caused by the transplacental transfer of IgG which cause a transient disturbance in the endocrine physiology that disappears with time after birth in proportion with the half-life time of IgG without any significant damage of the target organs.

The level of thyroid Abs in pregnant women with **Graves's disease** and **Hashimotos thyroiditis** decreased during pregnancy, but increased again after word.



Hashimotos thyroiditis

Hashimotos thyroiditis (autoimmune thyroiditis) is a chronic disease typically characterized by enlargement (goiter) and dense lymphatic infiltration of the thyroid gland. It is four times more common in women and has incidence of approximately 0.5% in the general population; the incidence peaks in middle age.

Causes of Hashimotos thyroiditis

- HLA-DR5 gene most strongly implicated conferring a relative risk. In addition, HT may be associated with polymorphism of CTLA-4 gene.
- Environmental factors (high iodine intake, infection as chronic HCV, certain drugs, exposure to radioactive isotypes, presence of other autoimmune diseases as celiac disease and type 1 diabetes.

Pathogenesis of **Hashimotos thyroiditis** depends on the humoral and cell-mediated immunity participation. However, T cells ($CD4^+$ (T_H1), $CD8^+$) are responsible for the destruction of thyroid tissue that targeting the auto antigens Tg and Tpo. Microbial mimicry by viral or bacterial antigens may drive this destructive mechanism.

Symptoms of Hashimotos thyroiditis

Patients usually complain of goiter as the main symptom, with an enlarged, firm, sometimes nodular thyroid gland on examination. At presentation, patients may still be euthyroid, but with time the pathological processes result in loss of thyroid tissue and hypothyroidism. Symptoms and signs of hypothyroidism may be seen at the first consultation (fatigue, cold intolerance, dryness of skin, anorexia, weight gain, menstrual disturbance, huskiness of voice, mental slowing, abnormal reflexes).

Graves's disease	**Hashimotos thyroiditis**
1. Hyperactivity	1. Fatigue, lethergy
2. Weight loss with increase of Appetite	2. Weight again
3. Heat intolerance	3. Cold intolerance
4. Thirst/polyuria	4. Dry coarse skin
5. Diffuse goiter	5. Rubbery, nodular goiter
6. Ophthalamopathy, eyelid Retraction, exophthalmous, peri-orbital odema	6. Facial edema (myxodema)
7. Tachycardia	7. Mostly bradycardia
8. Free T3 ↑ Free T4 ↑ Total T3 ↑ Total T4 ↑ Anti-Tg N(rarely ↑ in few cases) Anti-TPO N (slightly in 50% of cases) Anti-TSH-R ↑ TSH ↓	8. Free T3 N- ↓ Free T4 ↓ Total T3 N- ↓ Total T4 ↓ Anti-Tg ↑ Anti-TPO ↑ Anti-TSH-R N TSH ↑
9. Treatment Anti-thyroid drugs Radioactive iodine Thyroidectomy	9. thyroxine
10. TH2	10. TH1

Lecture No. 2

Diabetes mellitus

Diabetes is a state of high blood sugar (hyperglycemia) in which different mechanisms lead to deficiency of insulin and/ or impaired insulin action and persistent hyperglycemia and is classified into:

1. **Insulin-dependent diabetes mellitus** (IDDM) or type1.
2. **Non-insulin-dependent diabetes mellitus** (NIDDM) or type 2.
3. **Gestational diabetes mellitus.**

Type 1 diabetes mellitus

Type 1 diabetes mellitus (type 1 DM or T1DM) is a major clinical problem in both children and adults. It is an organ-specific autoimmune disease represents 10-15% of all diabetes. Healthy human islets of Langerhans are composed of a core of some 80% β cells (making the glucose-regulating hormone insulin), with a mantle of other endocrine cells types, producing glucogan (α cells), somatostatin (δ cells) and pancreatic polypeptide (PP cells) making up the remainder.In type 1 DM, the hyperglycemia results from insufficient insulin secretion by β cells in the islets of Langerhans of the pancreas.

Causes

1. Genetic: DR3/DQ2 or DR4/DQ8 haplotypes have strong link for the incidence of the disease, but other genetic associations (non HLA) are CTLA-4 (cytotoxic lymphocyte associated protein 4) also found in many family that play a role in the onset of type 1 DM.
2. Environmental factors:
    - Seasonal variation in the incidence rate (peaks in autumn and winter).
    - Infection with pathogens that have specific tropism toward the pancreatic tissue, mumps and coxsakie viruses. Similarities in the protein sequence of these viruses and certain islet cell cytoplasmic (ICA), glutamic acid decarboxylase (GAD) would initiate molecular mimicry mechanism in tolerance breakdown.

Immunopathogenesis

A virus infection in the pancreatic β islets cells leads to inflammation, damaged and releasing β cells antigens, their recruit antigen presenting cells (dendritic cells) which capture the virus protein and auto antigens released from the damaged β islets

cells to local lymph node and present them to T cells. T cells are activated to eradicate the virus. Inadvertently, T cells are activated against β cells and the slow process of β cells damage starts. In type 1 DM insulin production is failed due to destruction of β cells in the islets of Langerhans in pancreatic tissue without any destruction in the other cells as (α or δ cells) which is mediated by specific immune response).

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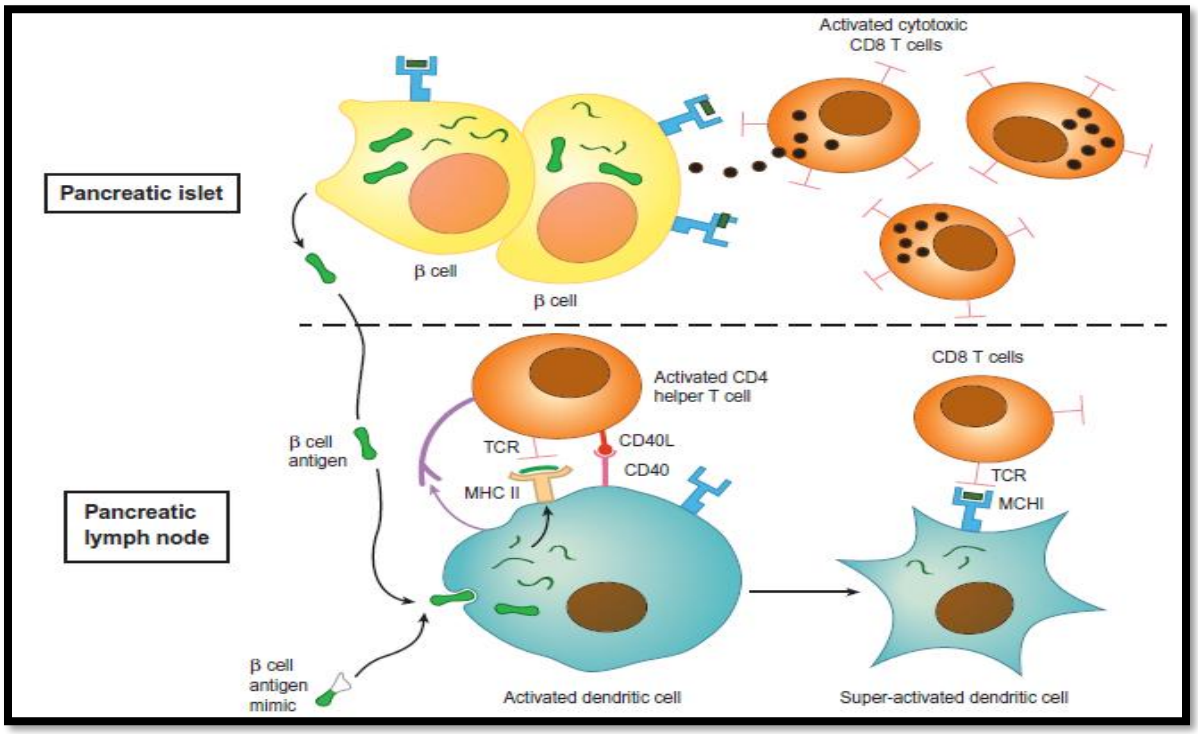


Figure: Immune mechanisms of β-cell destruction in type 1diabetes.

Features of islet autoantigens in type 1 DM

Autoantigens	Islet specific	Function	Autoantibody
Insulin	Yes, and β cells specific	Regulates glucose	Insulin autoantibody (IAA)
glutamic acid decarboxylase	No, present in other islet cells and CNS	Catalyses synthesis of γ-amino butyric acid (GABA), a negative neurotransmitter	glutamic acid decarboxylase autoantibody (GADA)

		probably regulates insulin release.	
Islet tyrosine phosphatase	No, present in other islet cells and CNS	Unknown	insulinoma-2 associated autoantibody (IA-2A)
Zinc transport 8	Yes, and β cells specific	Zinc transport	Zinc transport 8 autoantibody (ZNT8A)

Clinical features

Many pre- or subclinical stages occur in the DM patient before clinical diagnosis can be done:

1. Stage 1: the cell mass and function of β cells is normal but individuals who carry genetic susceptibility alleles to type 1 suffer exposure to an environmental stimulus triggering islets inflammation (insulitis). The release of sequestered or altered self antigens explains in part the later development of islet Autoantibodies that mark the recognition of stage 2.
2. Stage 2: serological evidence of humoral and cell-mediated autoimmunity indicated by the appearance of different types of autoantibody as islet cell cytoplasmic autoantibody (ICA), glutamic acid decarboxylase autoantibody (GADA), insulinoma-2 associated autoantibody (IA-2A) or insulin autoantibody (IAA). This occurs without any clinical metabolic signs. However, during this stage, there can be a 50% decline in β cells mass without detectable abnormalities by any form of glucose tolerance testing.
3. Stage 3: The earliest functional β cells abnormalities which manifestation by the intravenous glucose tolerance test (IVGTT) which decrease.
4. Stage 4: intolerance to oral glucose challenges appears as indicated by oral glucose tolerance test (OGTT).
5. Stage 5: after 1-2 years of glucose intolerance upon oral testing, atypical history of polyuria, polydipsia, polyphagia with weight lose impaired visual acuity, tingling or numbness in the hands or feet resulting from sensory nerve changes are identified. Finally by a true hyperglycemia a full diagnosis can be

done. If diabetes is undiagnosed or untreated, failure to metabolize glucose will result in the breakdown of fat, leading to ketonemia and ketoacidosis, which may be accompanied by nausea and hyperventilation before life-threatening ketoacidotic coma .

Addison's disease

Addison's disease, also known as primary adrenal insufficiency, is predominantly an autoimmune disorder where the body's immune system mistakenly attacks and damages the adrenal glands . This immune-mediated assault primarily targets the outer layer of the adrenal glands, known as the adrenal cortex, where vital hormones like cortisol and aldosterone are produced .

Addison's disease can affect people of all ages, though it is most commonly diagnosed in adults between 30 and 50 years old . Specifically, the disease leads to an underproduction of cortisol (a glucocorticoid) and often aldosterone (a mineralocorticoid) . The damage typically affects the outer layer of the adrenal glands, called the adrenal cortex . The destruction of the adrenal cortex cells by the immune system leads to an insufficient production and functions of these hormones .

- **Cortisol (a glucocorticoid)**: Essential for the body's response to stress (such as illness, injury, or surgery), maintaining blood pressure, heart function, immune system, and blood glucose levels .

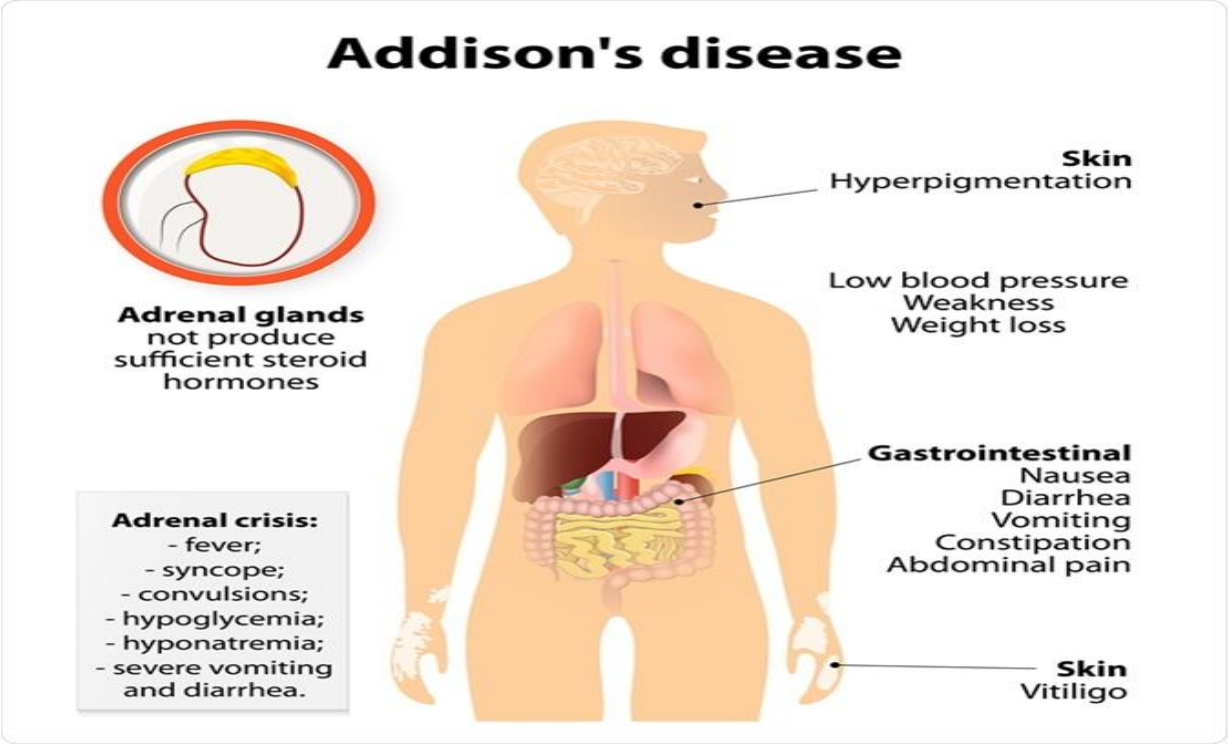
- **Aldosterone (a mineralocorticoid)**: Regulates the balance of sodium and potassium in the blood, which in turn controls fluid volume and blood pressure

Immunopathogenicity of Addison’s disease

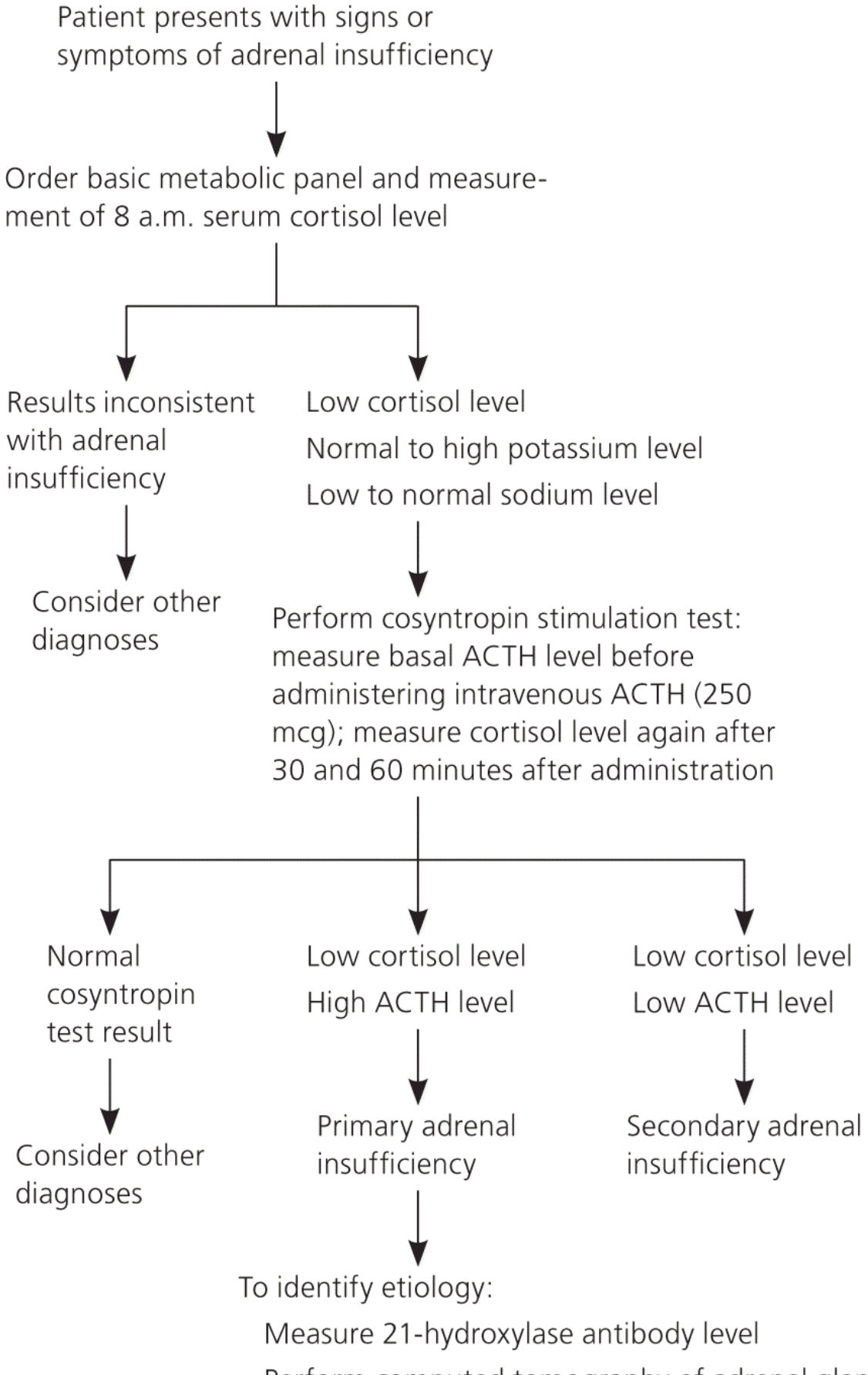
The immunopathogenicity of Addison’s disease, specifically **Autoimmune Addison’s Disease (AAD)**, is characterized by the chronic, immune-mediated destruction of the adrenal cortex. The disease involves a complex, long-term autoimmune attack, primarily driven by T cells, which leads to the selective loss of steroid-producing cells in all three layers of the adrenal cortex .The primary antigen targeted by the immune system is the enzyme **21-hydroxylase (21OH)**, which is crucial for the synthesis of cortisol and aldosterone in the adrenal cortex.

Autoantibodies against 21OH (21OHAb) are present in over 90% of patients at diagnosis.The destruction is caused by a cell-mediated immune response, where cytotoxic T lymphocytes (CD8+) and T helper cells (CD4+) infiltrate the adrenal cortex, replacing it with fibrous tissue. **Cytotoxicity(** CD8+ T cells)directly kill adrenocortical cells. 21OH autoantibodies bind to adrenal cortex cells and activate complement or attract immune cells to kill them. Activated macrophages and T cells produce cytokines like Interferon-gamma (IFN-γ) and TNF- α, which induce apoptosis in adrenal cells.

General Symptoms:



Diagnosis of Adrenal Insufficiency



Lecture No. 3

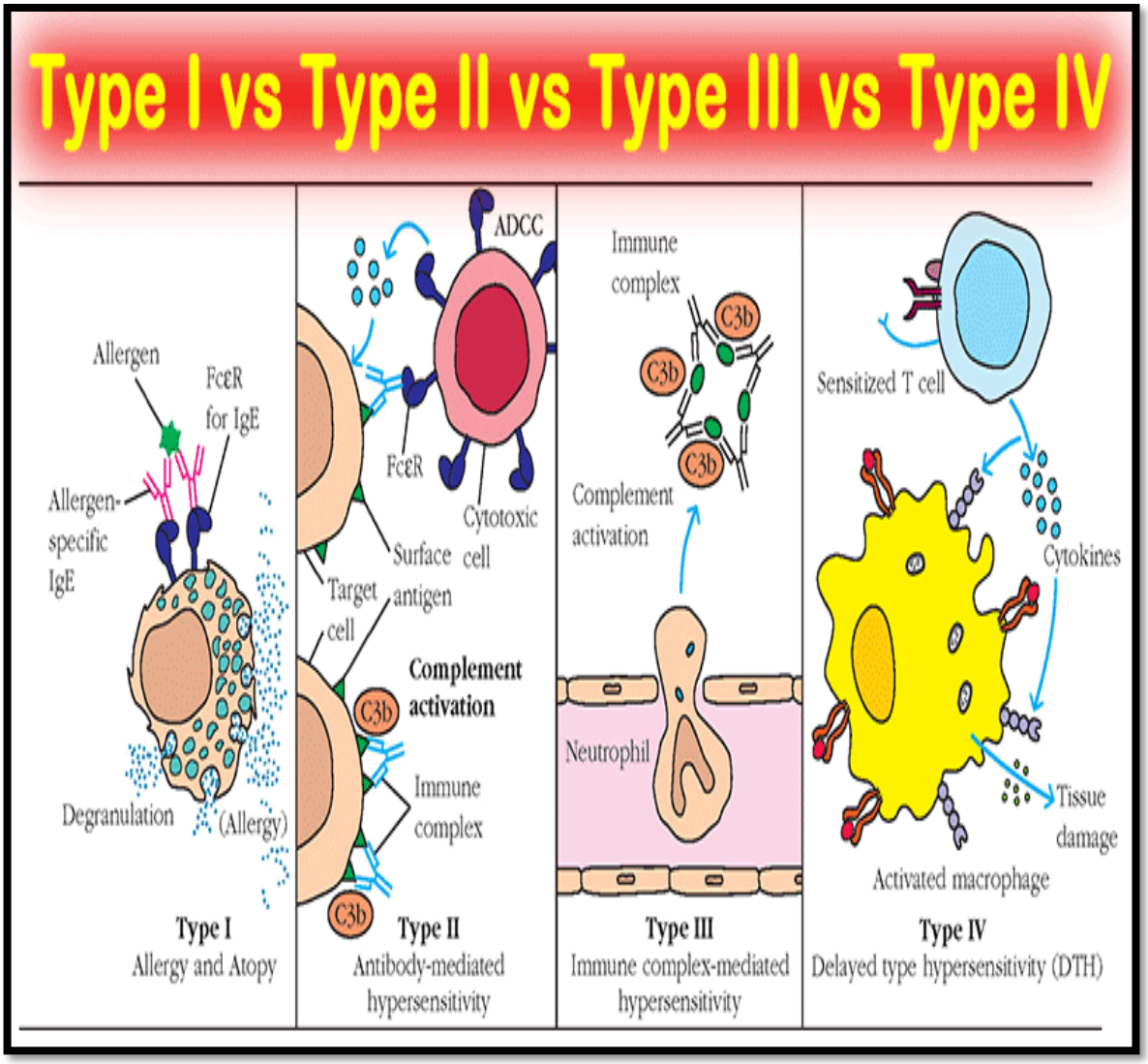
Hypersensitivity

Hypersensitivity, which is defined as an exaggerated response to atypically harmless antigen that results in injury to the tissue, disease, or even death. Antigens that trigger allergic reactions are called **allergens.**

Classification of hypersensitivity reactions:

Table 26-1 Classification of Hypersensitivity Reactions

	Type of Reaction			
Parameter	**I**	**II**	**III**	**IV**
Reaction	Anaphylactic	Cytotoxic	Immune complex	T cell–dependent
Antibody	IgE*	IgG, possibly other immunoglobulins	Antigen-antibody complexes (IgG, IgM)*	None
Complement involved	No	Yes*	Yes*	No
Cells involved	Mast cells, basophils, granules (histamine)*	Effector cells (macrophages, polymorphonuclear leukocytes)*	Macrophages, mast cells	Antigen-specific T cells
Cytokines involved	Yes*	No	Yes*	Yes (T cell cytokines)*
Comparative description	Antibody mediated, immediate	Antibody dependent; complement or cell mediated	Immune complex mediated (immune complex disease)	T cell-mediated, delayed type
Mechanism of tissue injury	Allergic and anaphylactic reactions	Target cell lysis; cell-mediated cytotoxicity	Immune complex deposition, inflammation	Inflammation, cellular infiltration
Examples	Anaphylaxis Hay fever Asthma Food allergy	Transfusion reactions Hemolytic disease of newborn Thrombocytopenia	Arthus reaction Serum sickness Systemic lupus erythematosus	Allergy or infection Contact dermatitis



Testing of Hypersensitivity

1. In Vitro Tests: Total IgE

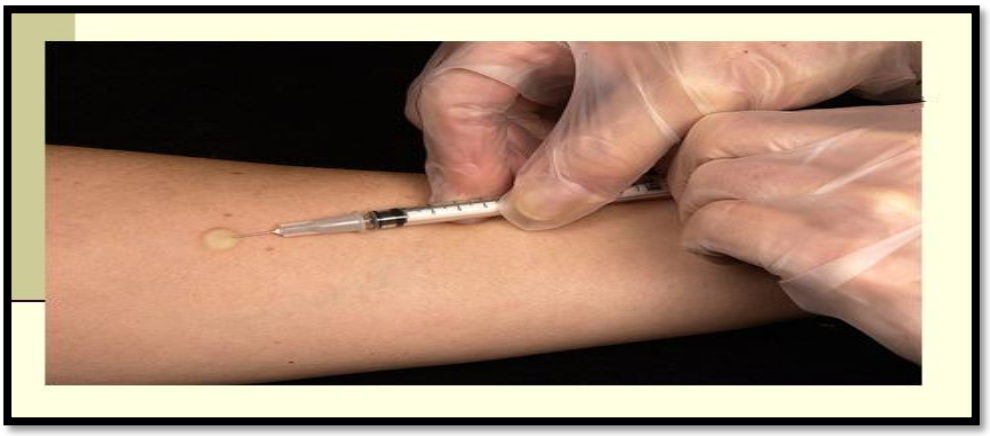
Testing Principles In vitro tests involve measurement of either total IgE or antigen-specific IgE. These are less sensitive than skin testing but usually are less traumatic to the patient. Total IgE testing has become more important as a screening test before a patient is referred to an allergy specialist**.** Total serum IgE testing is used clinically to aid in diagnosis of allergic rhinitis, asthma, or other allergic conditions that may be indicated by patient symptoms

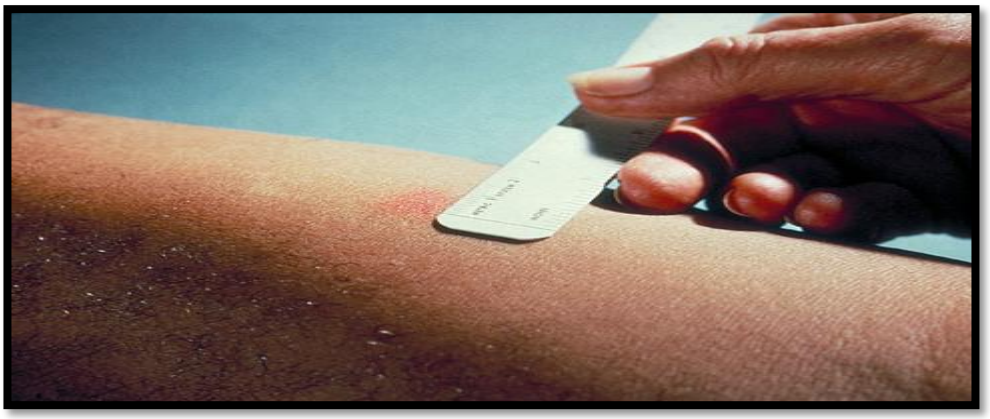
2. Antigen-Specific IgE Testing

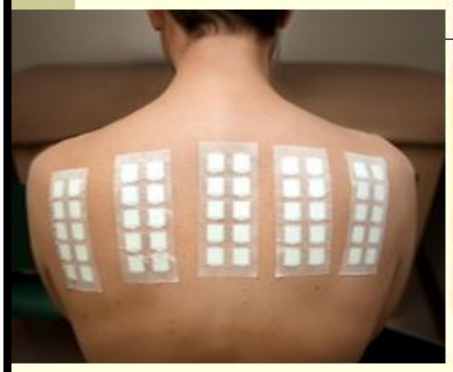
The original commercial testing method for determining specific IgE was known as the **radioallergosorbent test (RAST),** introduced in 1966. Principles of the test remain the same, but newer testing methods involve the use of enzyme or

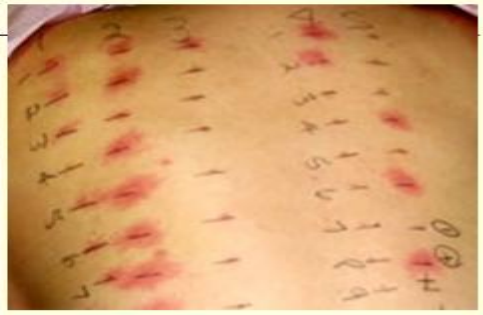
fluorescent labels rather than radioactivity. Allergen-specific IgE testing is safer to perform than skin testing and is easier on some patients, especially children or apprehensive adults, and the sensitivity now approaches that of skin testing. It is especially useful in detecting allergies to common triggers such as ragweed, trees, grasses, molds, animal dander, milk, and egg albumin.

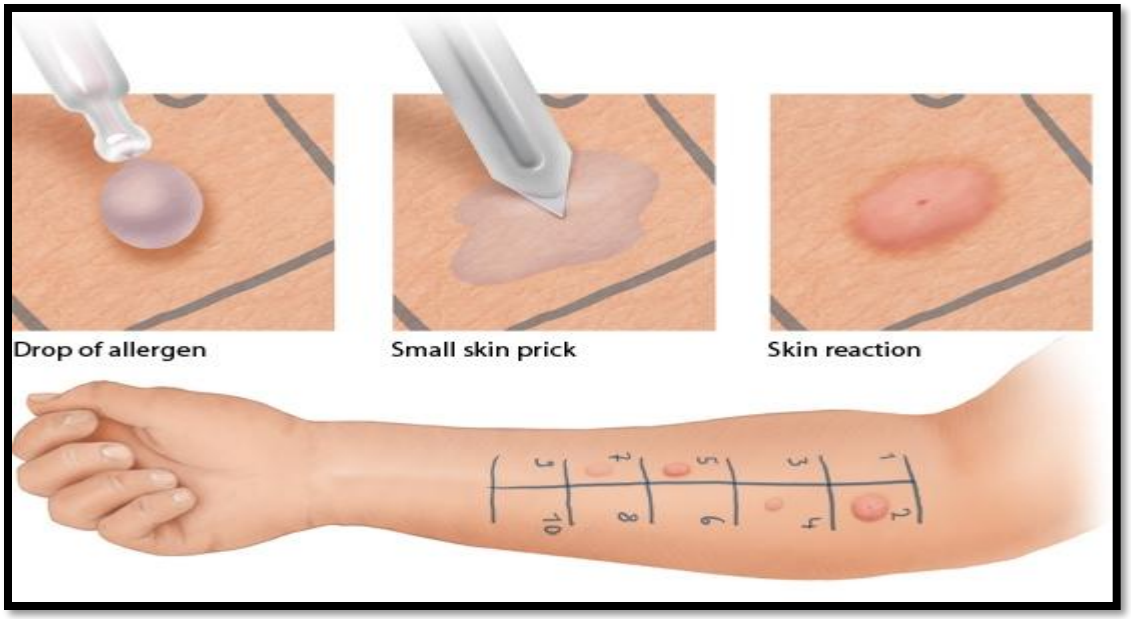
3. **The patch test** is considered the gold standard in testing for contact dermatitis. This must be done when the patient is free of symptoms or when he or she at least has a clear test site. A nonabsorbent adhesive patch containing the suspected allergen is applied on the patient's back, and the skin is checked for a reaction over the next 48 hours. Redness with papules or tiny blisters is considered a positive test. Final evaluation is conducted at 96 to 120 hours. All readings should be done by a skilled evaluator. False negatives can result from inadequate contact with the skin.
4. Skin testing can be performed by a skin puncture test (SPT) to assist in the identification of foods that may provoke IgE-mediated, food induced allergic reactions
5. **MELISA** (**Memory Lymphocyte Immunostimulation Assay**) is a blood test that detects type IV hypersensitivity to metals, chemicals, environmental toxins and molds. Type IV hypersensitivity reactions, particularly to nickel, are well established and may affect 20% of the population
6. **The oral food challenge (OFC**) remains the gold standard for the diagnosis of food allergy. During the OFC, a standard serving size of the allergen is divided into 4–7 servings and administered over 60–90 minutes, with each dose being given 15–20 minutes apart. The initial amount fed to the patient is typically a very small proportion of the total serving, and each successive dose administers a larger amount of protein. At the first sign of an objective reaction, the OFC is stopped and appropriate treatment administere











Lecture No. 4

Asthma

A chronic disease in which the bronchial airways in the lungs become narrowed and swollen, making it difficult to breathe. Symptoms include wheezing, coughing, tightness in the chest, shortness of breath, and rapid breathing. An asthma attack may be brought on by pet hair, dust, smoke, pollen, mold, exercise, cold air, or stress.

Asthma signs and symptoms include:

1. Shortness of breath
2. Chest tightness or pain
3. Wheezing when exhaling, which is a common sign of asthma in children
4. Trouble sleeping caused by shortness of breath, coughing or wheezing
5. Coughing or wheezing attacks that are worsened by a respiratory virus, such as a cold or the flu

Types of asthma

1. Allergic asthma
2. Seasonal asthma
3. Non allergic asthma
4. Exercise induced asthma
5. Difficult asthma
6. Childhood asthma

Causes

It isn't clear why some people get asthma and others don't, but it's probably due to a combination of environmental and inherited (genetic) factors. Exposure to various irritants and substances that trigger allergies (allergens) can trigger signs and symptoms of asthma. Asthma triggers are different from person to person and can include:

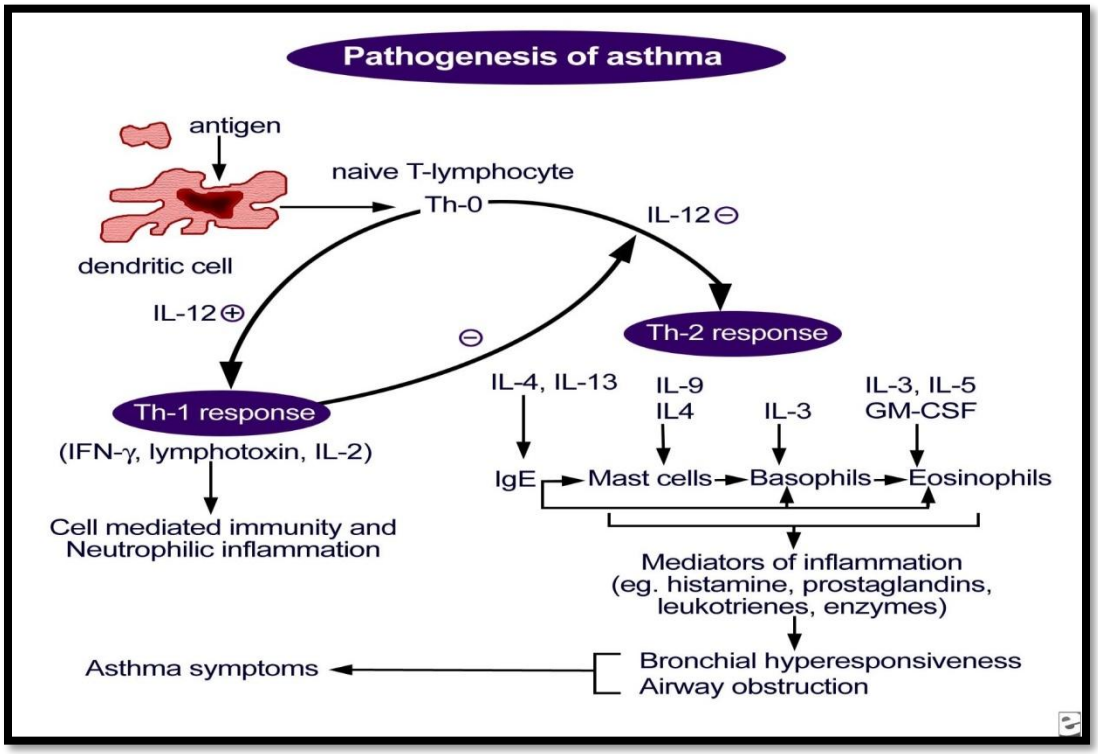
1. Airborne allergens, such as pollen, dust mites, mold spores, pet dander or particles of cockroach waste
2. Respiratory infections, such as the common cold
3. Physical activity
4. Cold air
5. Air pollutants and irritants, such as smoke
6. Certain medications, including beta blockers, aspirin, and nonsteroidal anti-inflammatory drugs, such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve)
7. Strong emotions and stress
8. Sulfites and preservatives added to some types of foods and beverages, including shrimp, dried fruit, processed potatoes .
9. Gastroesophageal reflux disease (GERD), a condition in which stomach acids back up into your throat

Pathophysiology of asthma

There are two phases of an asthma exacerbation, which include the early phase and late phase. The early phase is initiated by IgE antibodies that are sensitized and released by plasma cells. These antibodies respond to certain triggers in the environment, such as the risk factors listed above. IgE antibodies then bind to high-affinity mast cells and basophils. When a pollutant or risk factor gets inhaled, the mast cells release cytokines and eventually de-granulate. Released from mast cells are histamine, prostaglandins, and leukotrienes. Simultaneously, cytokines derived from the mast cell will signal other inflammatory cells and their mediators to the lung. The result is airway inflammation, increased vascular permeability, mucus secretion, bronchospasm, and wheezing. These events are referred to as the *early asthmatic response* because they occur within minutes. A major component of the early response is bronchospasm.

The *late asthmatic response* is delayed by hours. It is caused by a multitude of inflammatory cells continuing the inflammatory process. Of the inflammatory cells,

the T cells play an important role. Antigen presenting cells may present a variety of allergenic antigens to chronically activated T helper cells. These cells then secrete multiple cytokines that maintain and intensify the local inflammatory response. Many other inflammatory cells, including mast cells and eosinophils, will respond to the T cells' cytokines. These inflammatory cells will produce cytokines, which amplify the cellular response and the inflammatory reaction. There is a migration of inflammatory cells from the circulation into the pulmonary vasculature and the airway submucosa. A central component to the inflammatory process as well as treatment is the arachidonic acid pathway, which leads to the generation of leukotrienes.



Diagnosis

1- Physical exam

2-**Lung function tests :-** These are also called (pulmonary function tests.) Lung function tests detect how well you inhale (breathe in) and exhale (breathe out) air from your lungs. These tests measure breathing.

Lung function tests are often done before and after inhaling a medication known as a bronchodilator. This medicine opens the airways. If lung function improves a lot with a bronchodilator, the patient likely has asthma.

Common Lung function tests used to assess airways include:

a. **Spirometry:** A type of lung function test that measures how much you breathe in and out and how fast you breathe out.
b. **FeNO test (exhaled nitric oxide):** A test that helps assess inflammation in the airways.
c. **Bronchial provocation or "trigger" tests:** Tests that measure if lungs are sensitive to certain irritants or triggers such as methacholine or histamine.
d. **Diffusion Capacity:** Diffusion capacity measures how well oxygen flows from the lungs into your blood. Poor diffusion indicates damage to the lung where the oxygen and blood meet in the lungs. Diffusion capacity is usually normal in asthmatics.

3- Allergy tests
4- Blood tests: measured the levels of immunoglobulin E (IgE) and Eosinophil . If the levels are high, this could be a sign of severe asthma.
5-**Chest X-Ray:-**in asthma, the chest X-ray is likely to show air trapping or hyperexpansion.

Lecture No. 5

Allergic Rhinitis

Allergic rhinitis, commonly known as hay fever, is an allergic reaction that occurs when the immune system overreacts to airborne particles called allergens. These allergens can include pollen from trees, grasses, and weeds, as well as dust mites, mold spores, and pet dander.

Symptoms of Allergic Rhinitis

Allergic rhinitis is characterized by inflammation of the nasal membranes, leading to symptoms such as:

1- Sneezing 2- Nasal congestion (blocked nose)

3-Runny nose (rhinorrhea) 4- Itchy nose, throat, and eyes 5- Watery eyes

These symptoms typically arise shortly after exposure to allergens and can vary in severity depending on the individual and the level of allergen exposure.

Immunopathogenicity of Allergic Rhinitis

Allergic rhinitis (AR) is primarily characterized by an immunoglobulin E (IgE)-mediated hypersensitivity reaction to environmental allergens. The immunopathogenicity of allergic rhinitis involves a complex interplay of immune cells, mediators, and genetic factors that lead to the clinical symptoms associated with the condition. The immunopathogenicity process occur through several stages

1. Sensitization Phase

The immunopathogenic process begins with sensitization to allergens, which are typically harmless environmental substances such as pollen, dust mites, and animal dander. During this phase:

- **Antigen Presentation**: Allergen particles are captured by antigen-presenting cells (APCs) in the nasal mucosa. These cells process the allergens and present them to naive T lymphocytes.
- **T Cell Activation**: The interaction between APCs and T cells leads to the differentiation of naive T cells into T helper type 2 (Th2) cells. This is a critical step, as Th2 cells are responsible for orchestrating the allergic response.
- **IgE Production**: Activated Th2 cells secrete cytokines (e.g., IL-4, IL-5, and IL-13) that stimulate B cells to produce allergen-specific IgE antibodies. These IgE molecules bind to high-affinity IgE receptors (FcεRI) on mast cells and basophils, sensitizing them to future exposures to the same allergen.

2. Early Phase Response

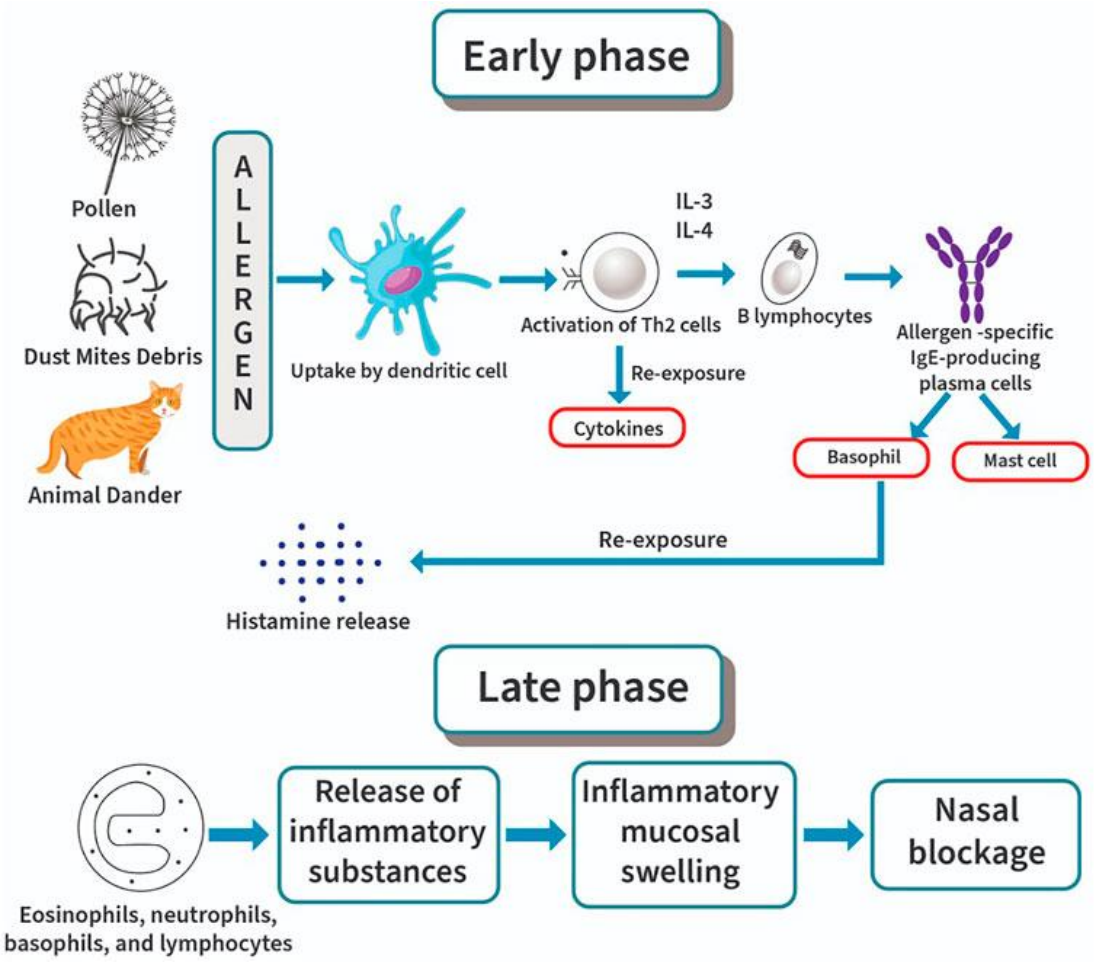
Upon re-exposure to the allergen, the following occurs:

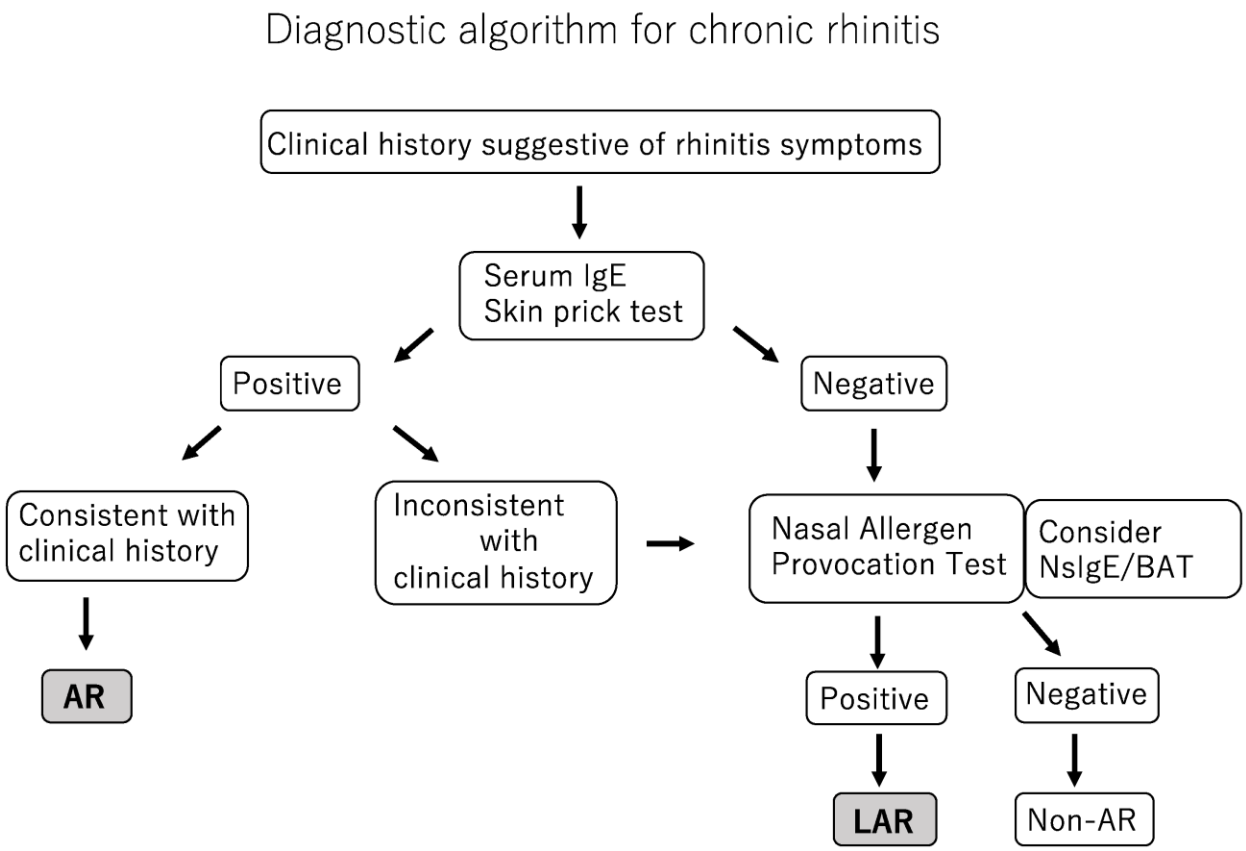
- **Mast Cell Activation**: The allergen cross-links the IgE on sensitized mast cells, leading to their activation and degranulation. This releases a variety of mediators, including histamine, leukotrienes, and prostaglandins, which cause immediate symptoms such as sneezing, itching, and nasal congestion.
- **Vascular Changes**: Histamine and other mediators increase vascular permeability and cause vasodilation, contributing to nasal congestion and rhinorrhea (runny nose).

3. Late Phase Response

The late phase of allergic rhinitis occurs several hours after allergen exposure and is characterized by:

- **Inflammatory Cell Recruitment**: The initial mediators released by mast cells attract other immune cells, including eosinophils, neutrophils, and T lymphocytes, to the site of inflammation. This recruitment is mediated by chemokines and cytokines.
- **Chronic Inflammation**: The accumulation of these inflammatory cells leads to sustained inflammation in the nasal mucosa, resulting in prolonged symptoms and potential tissue remodeling over time.
- **Nasal Hyperresponsiveness**: The chronic inflammation can lead to increased sensitivity of the nasal mucosa to various stimuli, resulting in hyperreactivity to non-allergic triggers such as smoke or strong odors.





Lecture No. 6

Atopic dermatitis

Atopic dermatitis, commonly known as **eczema**, is a chronic inflammatory skin condition characterized by dry, itchy, and inflamed skin . It is not contagious and cannot be spread from person to person . While it often begins in infancy or childhood, it can affect individuals at any age and may persist into adulthood .

Symptoms of Atopic dermatitis

Atopic dermatitis typically manifests with a very itchy rash that can appear anywhere on the body, common symptoms include:

- Red, dry patches of skin .
- Rashes that may secretion, weep clear fluid, or bleed when scratched .

- Thickening, hardening, and scaling of the skin .
- Small, fluid-filled bumps or crusting .
- Discoloration of the skin (red, purple, brown, or gray), which can darken or lighten in affected areas, especially in individuals with darker skin tones .

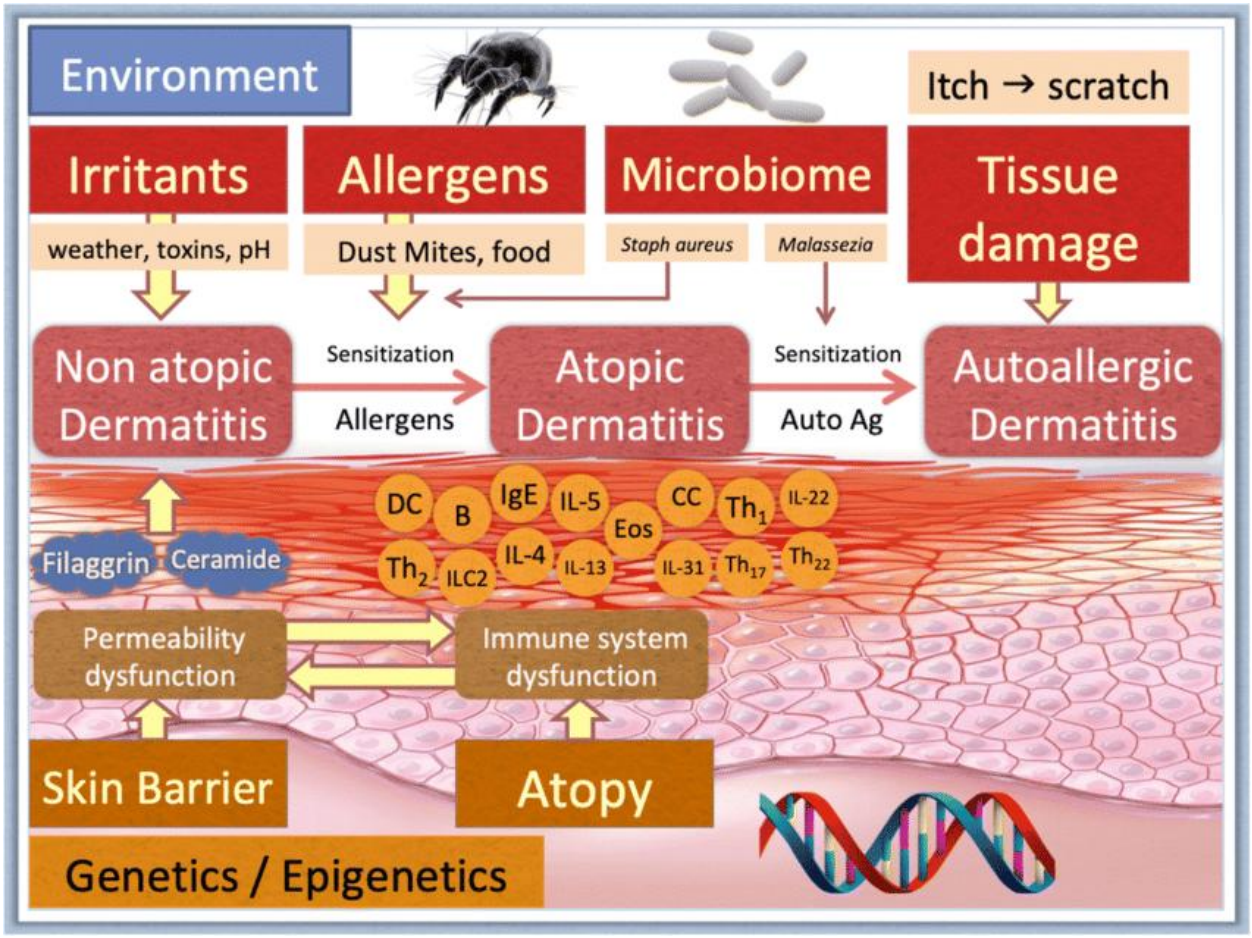
The itching can be severe and prolonged, often leading to sleep disturbances and potential skin infections from scratching . Atopic dermatitis often occurs in periods of worsening symptoms, known as flares, followed by periods of improvement or remission .

Causes and Risk Factors

The exact cause of atopic dermatitis is not fully understood, but it is believed to involve a combination of genetic, immune system, and environmental factors .

- **Genetics**: There is a higher chance of developing atopic dermatitis if there is a family history of the condition, hay fever, or asthma . Some individuals may have a genetic variant that prevents their skin from forming a strong protective barrier, making it more susceptible to irritants and allergens .
- **Immune System**: The immune system in individuals with atopic dermatitis can become confused and overactive, leading to inflammation in the skin . It is increasingly recognized as an immune-driven disease .
- **Environmental Factors**: These can trigger flares by affecting the skin's protective barrier, allowing moisture to escape . Common triggers include:
    - Exposure to tobacco smoke and air pollutants .
    - Fragrances and other compounds in skin products and soaps .
    - Excessively dry skin .
    - Heat and sweat, stress, dust mites, pet dander, mold, pollen .
    - Cold and dry air .
    - Certain foods (e.g., eggs, cow's milk) can be triggers in infants and children .

Pathogencity of Atopic dermatitis



Diagnosis of Atopic dermatitis

- The diagnosis is made on **history, examination and skin testing** (skin prick test evokes a wheal and flare response but not eczematous lesions, it is possible to replicate eczema like plaques by patch testing with allergens such as house dust mite extracts in sensitive individual), with **the total serum IgE level** also usually raised and IgE directed against airborne and food allergens is a prominent feature.

Lecture No. 7

Contact dermatitis

Contact dermatitis is an inflammatory skin disease caused **T_H1-cell mediated (type IV) hypersensitivity** to external agents (see figure below) which come into contact with the skin. These agents (known as **haptens**) are usually molecules of relatively of low molecular weight (<1 KDa) and are not immunogenic, but they can penetrate the epidermis and bind to certain proteins in the skin (carrier proteins) and become highly reactive molecules.

Classification

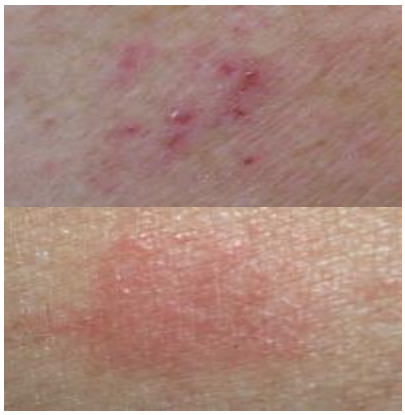
1. Acute toxic dermatitis.
2. Cumulative dermatitis.
3. Allergic Contact dermatitis.

Pathogenesis

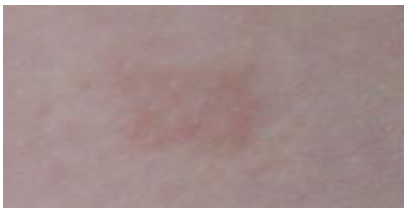
Two phase of pathogenesis are recognized: an **induction phase**, from time of initial antigen contact to sensitization of T lymphocytes, and an **elicitation phase**, from antigen re-exposure to the appearance of dermatitis. In **the induction phase**, Langerhans cells bind the hapten-carrier protein complex and present it in association with MHC class II antigens to T lymphocytes ($CD4^+$). Induction of cellular immunity to a contact skin sensitizer can occur within 7-10 days of first contact but it usually happens after many months or years of exposure to small amounts of antigens. Individual sensitivity varies according to the nature of the agent, its concentration and the genetic susceptibility of the person exposed. Re-exposure to the relevant antigen triggers **the elicitation phase** which produce dermatitis. In this phase, effector T lymphocytes carried via the circulation to the skin meet the antigen (composed of hapten complexed to carrier protein) presented by Langerhans cells and other antigen-presenting cells in the epidermis. Activation of T lymphocytes releases cytokines which cause induce skin inflammation, with keratinocytes proliferation, hyperplasia of the epidermis and consequent protective thickening.

Diagnosis

The diagnosis of contact dermatitis depends on **a careful medical history, the distribution of the lesions, and patch testing**. In the patch test, a suspected contact sensitizer is applied to normal skin (usually on the upper back) and covered for 48h. The reaction is read after 2 and 4 days. In a positive response, there is inflammation and induration at the test site.

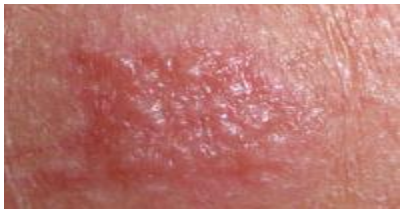


Irritant reaction

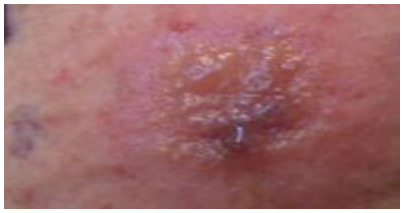


+/- reaction

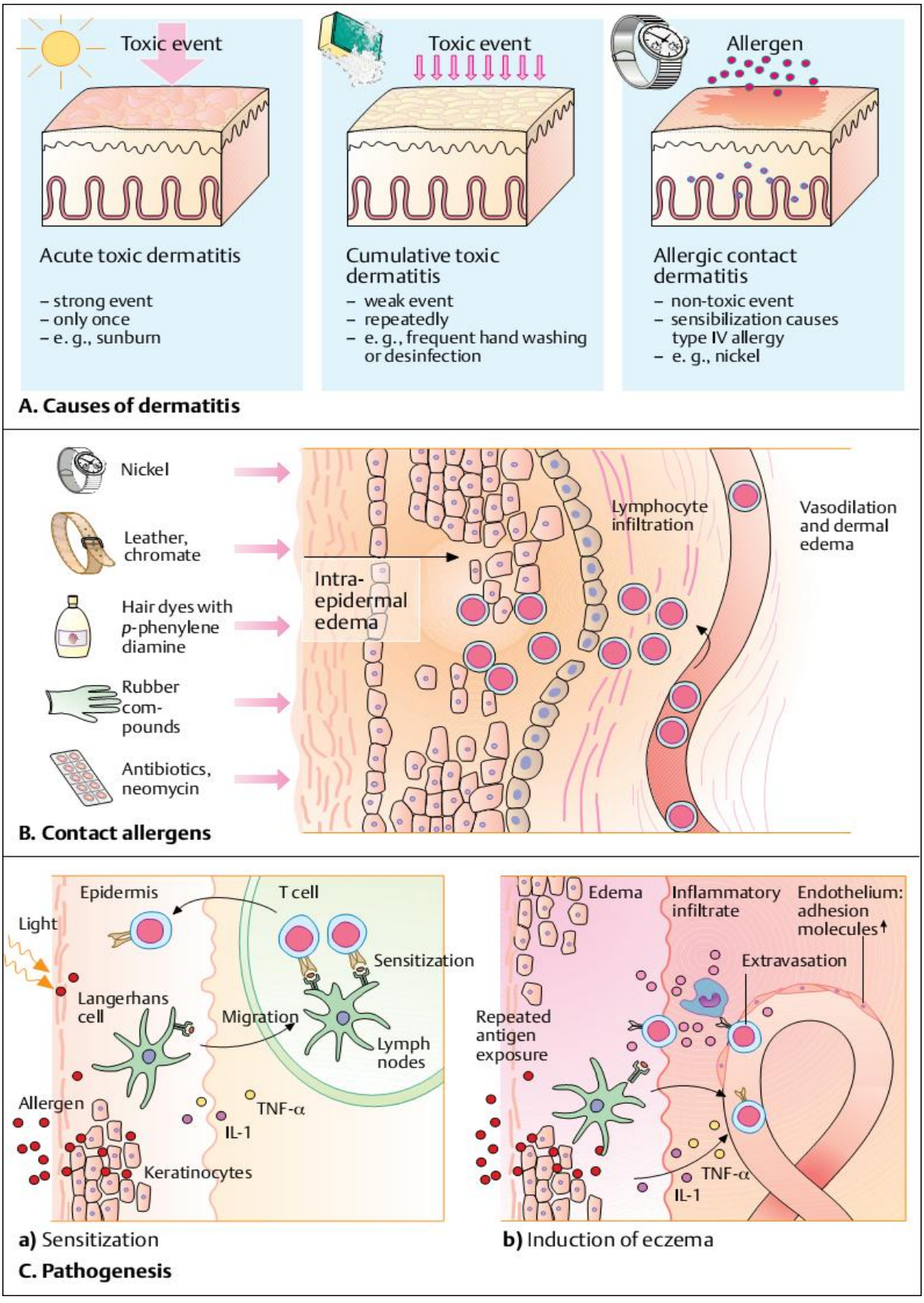
+ reaction



++ reaction



+++ reaction


Toxic event
Acute toxic dermatitis
– strong event
– only once
– e. g., sunburn
Toxic event
Cumulative toxic dermatitis
– weak event
– repeatedly
– e. g., frequent hand washing or desinfection
Allergen
Allergic contact dermatitis
– non-toxic event
– sensibilization causes type IV allergy
– e. g., nickel
A. Causes of dermatitis
Nickel
Leather, chromate
Hair dyes with p-phenylene diamine
Rubber com-pounds
Antibiotics, neomycin
Intra-epidermal edema
Lymphocyte infiltration
Vasodilation and dermal edema
B. Contact allergens
Epidermis
T cell
Light
Sensitization
Langerhans cell
Migration
Lymph nodes
Allergen
TNF-α
IL-1
Keratinocytes
a) Sensitization
Edema
Inflammatory infiltrate
Endothelium: adhesion molecules
Extravasation
Repeated antigen exposure
TNF-α
IL-1
b) Induction of eczema
C. Pathogenesis

Lecture No. 8

Respiratory disease

Drug-Induced Pulmonary Disease

Drug-induced pulmonary disease is lung disease brought on by a bad reaction to a medicine. Pulmonary means related to the lungs.

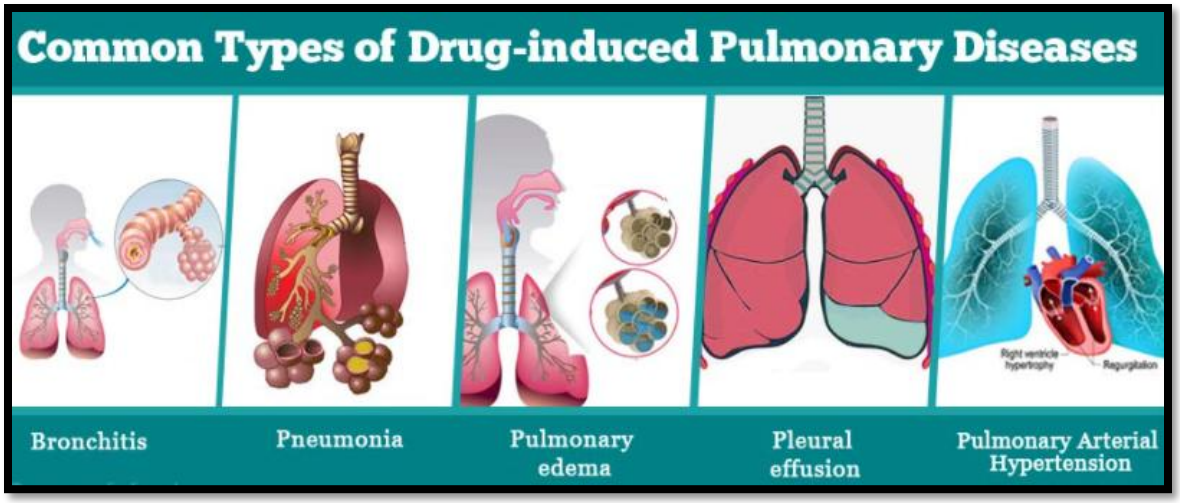
What is the most common drug-induced respiratory problem?

Interstitial pneumonitis (ie, inflammation of the lung interstitium, such as the alveolar septa) is the most common manifestation of drug-induced lung disease.

The Common Types of Drug-induced Pulmonary Diseases

There are different types of lung or pulmonary diseases caused by drugs are:

1. **Allergic reactions** like asthma, hypersensitivity pneumonitis, or eosinophilic pneumoni
2. **-Lymph node swelling**
3. **Alveolar haemorrhage**, i.e. bleeding into lung sacs .
4. **Bronchitis,** i.e., inflammation of the airways .
5. **Pneumonia**
6. **Pulmonary edema**, i.e., fluid accumulation in the lungs .
7. **Pleural effusion** i.e., fluid accumulation around the lungs .
8. **Pulmonary fibrosis i**.e., formation of scar tissue in the lungs .
9. **Pulmonary arterial hypertension**i.e defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise .
10. **Lung failure.**



Many medicines and substances are known to cause lung disease in some people. These include:

- Antibiotics, such as nitrofurantoin and sulfa drugs
- Heart medicines, such as amiodarone
- Chemotherapy drugs such as bleomycin, cyclophosphamide, and methotrexate
- Street drugs

Symptoms

Symptoms may include any of the following:

- Bloody sputum
- Chest pain
- Cough
- Fever
- Shortness of breath
- Wheezing

Diagnosis of Drug-induced Pulmonary Diseases

It has always been a challenge for pulmonologists to diagnose drug-induced pulmonary disease. The medications can cause reactions in varied forms, which makes it difficult for pulmonologists to identify the drug or its reaction.

Tests that could detect changes in the lungs include the following:

1. **Imaging tests like chest x-ray and chest CT scan .**
2. **Lung function tests :** The primary purpose of pulmonary function testing is to identify the severity of pulmonary impairment**.** The tests measure lung volume, capacity, rates of flow, and gas exchange.
3. **Bronchoscopy** : is a procedure to look directly at the airways in the lungs using a thin, lighted tube (bronchoscope). The bronchoscope is put in the nose or mouth. It is moved down the throat and windpipe (trachea), and into the airways **.**
4. **Blood tests to rule out SLE-like reactions as a cause of the lung disease**
5. Lung Biopsy, in rare cases

Lecture No. 9

Eosinophilic Pneumonia

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by an abnormal and marked accumulation of eosinophils in the interstitium and alveolar spaces of the lung causing inflammation and damage. Causes include smoking, allergic reactions and parasitic infections. EP may occur suddenly or worsen slowly.

What are the types of eosinophilic pneumonia?

There are three main types of eosinophilic pneumonia. They include:

- **Acute eosinophilic pneumonia:** This type worsens quickly as your blood oxygen level falls. Most patients with AEP completely recover with treatment.
- **Chronic eosinophilic pneumonia:** This type worsens slowly, over days or weeks. If untreated, it may persist over weeks or months and result in severe symptoms.
- **Löffler syndrome (simple pulmonary eosinophilic, or SPE):** This form of eosinophilic pneumonia may cause no symptoms or only mild symptoms such as a dry cough. Löffler syndrome occurs due to a parasitic infection (roundworms). With treatment, the condition typically resolves within one month.

Causes of Eosinophilic pneumonia

Eosinophilic pneumonia has many causes, both infectious and noninfectious. But healthcare providers don't always know the exact cause.

Common noninfectious triggers include:

- Allergic reactions.
- Fungus (usually aspergillosis).
- Inhaled toxins, such as chemical fumes or particulate metals (found in the air) or dust.
- Medication, including commonly used antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors (SSRIs).
- Smoking, especially if you've had a change in cigarette smoking habits (starting smoking for the first time or smoking more often).
- Underlying conditions, including cancer, autoimmune disease or inflammatory disease.

The symptoms of eosinophilic pneumonia

Signs of eosinophilic pneumonia vary, depending on the type and cause. Common symptoms include:

- Cough.
- Fever.
- Shortness of breath (dyspnea).

Acute eosinophilic pneumonia can worsen quickly, often within two weeks. Symptoms are usually more severe in people who smoke and may include:

- Chest pain.
- Chills.
- Fatigue.
- Muscle aches or muscle pain (myalgia).

Without prompt diagnosis and treatment, the oxygen in your blood may fall to dangerously low levels. This can lead to acute respiratory failure in a few hours, requiring emergency treatment.

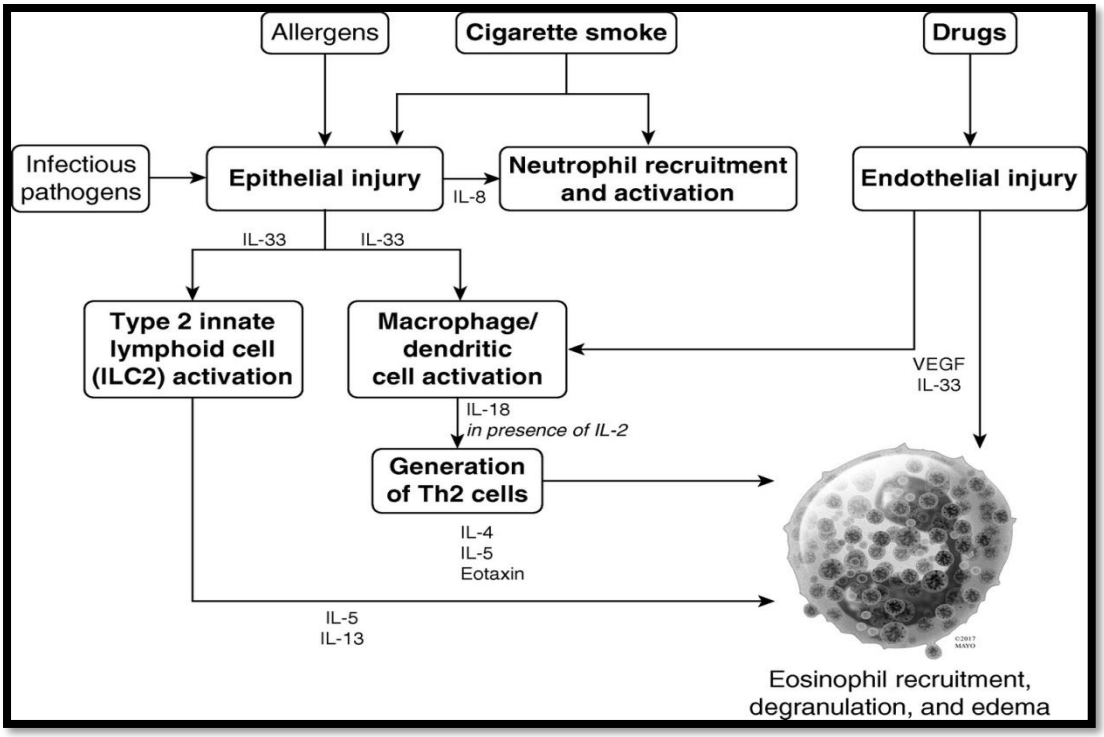
Common symptoms include:

- Shortness of breath that worsens.
- Night sweats.
- Unexplained weight loss.
- Wheezing.

Pathogenicity of Chronic Eosinophilic Pneumonia

The pathophysiological role of eosinophils in autoimmune diseases is not well defined; however, it has been shown that the production of pro-inflammatory cytokines stimulates and activates different cell groups, and can simultaneously induce autoantibodies and/or increased infiltration of eosinophils in various tissues, without an underlying autoimmune disease.

A proposed model for the pathogenesis of acute eosinophilic pneumonia. IL-33 may be released by damaged epithelial cells responding to noxious stimulants such as allergens, infectious pathogens, and other inhalational toxins, including cigarette smoke. IL-33 and vascular endothelial grow factor (VEGF) may also be released by endothelial cells after drug-induced injury. In addition to IL-33, acute exposure to cigarette smoking induces epithelial cell release of IL-8, which mediates recruitment and activation of neutrophils. An additional source of IL-33 in the lung may be the activation of innate type 2 lymphoid cells, which have the capacity to rapidly generate IL-33 in response to certain stimuli. Subsequent generation and binding of IL-33 to cells expressing its receptor (ST2), including macrophages and dendritic cells, may lead to recruitment and activation of T-helper cell type 2 (Th2)-polarized T lymphocytes and production of cytokines like IL-5, which further promote recruitment and activation of eosinophils in the lung tissue. Eosinophils may also migrate into the lung because of chemokine gradients and increased permeability in the context of endothelial injury.



Diagnosis of Eosinophilic pneumonia

- medical history and travel.
- physical exam.
- Blood tests, including a complete blood count, to detect abnormalities.
- Broncho alveolar lavage (BAL) is the most important test to diagnose EP. Uses a flexible tube (bronchoscope) to collect fluid from your lungs to look for signs of disease.
- Chest x-ray and CT scan.
- Peripheral blood eosinophilia count , peripheral eosinophilia is often present in chronic eosinophilic pneumonia.
- Sedimentation rate (ESR)
- **Lecture No. 10**

Occupational lung diseases

Occupational or work-related lung diseases are lung conditions that have been caused or made worse by long-term exposure to certain irritants in the workplace. Dust particles, chemicals, fungal spores, and certain animal droppings are examples of exposures that may increase your risk of developing occupational lung disease.

There is no cure for occupational lung diseases. Controlling your exposure to lung irritants and treatment can help slow the disease progression, lessen symptoms, and improve your quality of life. If you smoke, quit. Smoking can cause or worsen lung disease.

The symptoms of an occupational lung disease

- Coughing
- Shortness of breath
- Chest pain
- Chest tightness
- Abnormal breathing pattern .

Types of occupational lung diseases

- Asthma.
- Bronchiolitis obliterans.
- COPD.(Chronic obstructive pulmonary disease)
- Hypersensitivity pneumonitis.
- Lung cancer.
- Mesothelioma.
- Pneumoconiosis.

The difference between inorganic and organic dust

Inorganic refers to any substances that do not contain carbon, excluding certain simple carbon oxides, such as carbon monoxide and carbon dioxide.

Organic refers to any substances that do contain carbon, excluding simple carbon oxides, sulfides, and metal carbonates .

Exposure to environmental and occupational lung irritants may put you at risk of developing chronic lung disease, including:

1. **Silicosis** is caused by breathing in tiny bits of silica, a mineral found in sand, quartz, and many other types of rock. Silicosis mainly affects workers exposed to silica dust in jobs such as construction and mining.
2. **Coccidioidomycosis or Valley fever** is an infection caused by breathing in the spores of the fungus Coccidioides found in the soil. Valley fever mainly affects workers exposed to dust storms or areas where contaminated soil is being disturbed, in jobs like construction or farming.
3. **Hypersensitive pneumonitis** is caused when you breathe in a specific substance (allergen) that triggers an allergic reaction in the body.

4. **Histoplasmosis** is caused by breathing fungal spores from soil that has been contaminated by bird or bat droppings. Some occupations that may expose workers to spores are farmers, pest control workers, poultry keepers, construction workers and landscapers.
5. **Asbestosis** is a naturally occurring mineral used as an insulation material and as a fire retardant. The main group at risk for asbestosis is people who worked in mining, milling, manufacturing, installation, or removal of asbestos products .
6. **Coal workers pneumoconiosis**, commonly known as black lung disease, occurs when coal dust is inhaled. Continued exposure to coal dust causes scarring in the lungs.
7. **Mesothelioma** is a rare type of cancer that occurs in the lining of the lungs and less commonly the lining of the abdomen. Asbestos exposure is the primary risk factor for mesothelioma. Occupations such as mining or milling, electricians, plumbers, pipe-fitters, insulators, or even remodelers of older homes still have a high risk of exposure.
8. **Work-related asthma:-** Men working in forestry and minerals and women working in service industries (waitresses, cleaners, and dental workers) are most likely to develop occupational asthma.

Diagnose of an occupational lung disease

- **Pulmonary function tests**: diagnostic tests that help to measure the lungs' ability to move air into and out of the lungs effectively. The tests are usually performed with special machines into which the person must breathe.
- **Microscopic examination** from biopsy or autopsy of tissue, cells, and fluids from the lungs
- **Measurement of respiratory or gas exchange functions**
- **Examination of airway or bronchial activity**

How can occupational lung diseases be prevented?

The best prevention for occupational lung diseases is avoidance of the inhaled substances that cause lung diseases and Do not smoke. Smoking can actually increase the risk for occupational lung disease.

Lecture No. 11

Tumor

Tumor is an overgrowth (uncontrolled growth) of tissues and cells in certain organs in the body which result in a mass of tissue that has result in destruction of normal architecture of the tissue and lost the normal function of the healthy original tissue.

Tumor can be generally classified into

1. **Benign tumor:** cluster of tumor cells that are localized in a restricted area in the body without the ability to move to other areas in the body.
2. **Malignant tumor:** cluster of tumor cells that can move and invade (**metastasis**) other adjacent and far away tissues.

Metastasis means spreading of the invasion tumor cells from the primary focus of tumor to other parts of the body via blood or lymph circulation to form a secondary focus of tumor.

Tumor classifications

A. According to the involved tissue:
   1. **Carcinoma:** Tumor of epithelial cells.
   2. **Sarcoma:** Tumor of muscle and connective tissues.
   3. **Adenoma:** Tumor of the glandular tissue which is benign.
   4. **Adenocarcinoma:** Tumor of the glandular tissue which is malignant.

B. According to the system or organ:
   1. **Lymphoma:** Tumor of lymph nodes.
   2. **Leukemia:** Tumor of the blood, bone marrow and immune system.
   3. **Hepatocarcinoma:** Tumor of the liver.
   4. **Astrocytoma, gilioma, retinoblastoma, neuroblastoma:** Tumor of the central nervous system.

Causes

1. **Environmental:** there are so many environmental carcinogenic factor including:
   A. Chemical carcinogens: including wide range of food preservatives, dyes, smokes and many others.

B. **Physiological carcinogens:** including UV light, X ray, nuclear radiation and many others.
C. **Biological carcinogens:** including mostly viruses and some bacteria:
    1. Hepatitis B virus (HBV) and (HCV) can cause hepatocellular carcinoma in chronically infected persons.
    2. Epstein Barr virus (EBV) can cause Burkitt's lymphoma.
    3. Human T lymphocyte virus-1 (HTLV-1) can cause T cell leukemia.
    4. Human papilloma virus (HPV) can cause cervical carcinoma in women.
    5. Helicobacter pylori can cause gastric carcinoma.
    6. Human herpes virus-8 (HHV-8) can cause Kaposi sarcoma in AIDS patients.

2. **Genetic:** many of the people with tumors have certain genetic constitutions which indicate a familial association of tumors like breast cancer and ovarian cancer.
3. **Hormonal:** hormonal changes (mainly in women) may trigger certain types of tumors. The best example of that is the breast cancer which occurs more commonly in women with
    1. Pregnancy at old ages (>35 years).
    2. Early age of menstruation.
    3. Late onset of menopause.
    4. Post menopausal hormone replacement therapy.

Tumor antigens

In tumor, there are many antigens (which they are not found normally or found in different forms or quantities) are expressed on the tumor cells surface or generalized inside the tumor cell. The earliest classification of tumor antigens was based on their patterns of expression.

1. **Tumor-specific antigens:** Antigens that are expressed on tumor cells but not on normal cells were called tumor-specific antigens; some of these antigens are **unique** to individual tumors **(chemical carcinogens)**, whereas others are **common**, shared among tumors of the same type **(viral carcinogens)**.
2. **Tumor-associated antigens:** Many of tumor antigens that expressed in case of tumor could also expressed in normal cells but either with low level or at different development stage. For examples

A. **Alpha-feto protein (αFP):** is a protein that secreted by the liver of embryo, but it should be disappear after birth. When it appears again in adult serum it may indicate liver and gonadal (testes) cancer.
B. **Carcino-embryonic antigen(CEA):** this types of antigens is expressed in certain tumors of the gastrointestinal tract (as colonic cancer),however it can also expressed in the patient serum with inflammation of pancreas (pancreatitis) or inflammation of colon (colitis). The presence of CEA is not specific to the tumor only and not diagnostic. However it can used to monitor the response to therapy against colonic cancer by measuring its level in the patient serum.
C. **Cancer testes antigens:** these antigens are expressed normally in the tissue of the testes, but when expressed in other tissue as lung or breast it indicates tumors of these organs.
D. **Mutated antigen:** certain antigens are found normally in the body, but when they mutated they change into tumor antigens example: protein 53 (P53) this protein normally inhibit cellular proliferation.
E. **Melanoma-melanocyte differentiation antigens:** certain enzymes like tyrosinase enzyme is found normally in skin cells (melanocytes) in small amount, but it also found in skin tumor cells (melanoma) in large amount (quantitative difference). **Example (tyrosinase enzyme, melanoma antigen recognized by T cells)**

Immune responses to tumors

Innate immunity

The role of **macrophages** in anti-tumor immunity is largely inferred from the demonstration that invitro, activated macrophages can kill many tumor cells more efficiently than they can kill normal cells.

NK cells kill many types of tumor cells, especially cells that have reduced class I MHC expression and can escape killing by CTLs. Invitro, NK cells can kill virally infected cells and certain tumor cell lines, especially hematopoietic tumors.

Adaptive immunity

The effector mechanisms of both cell-mediatedimmunity and humoral immunity have been shown to kill tumor cells in vitro.

Cell-mediated immunity

The principal mechanism of tumor immunity is killing of tumor cells by CD8 CTLs.

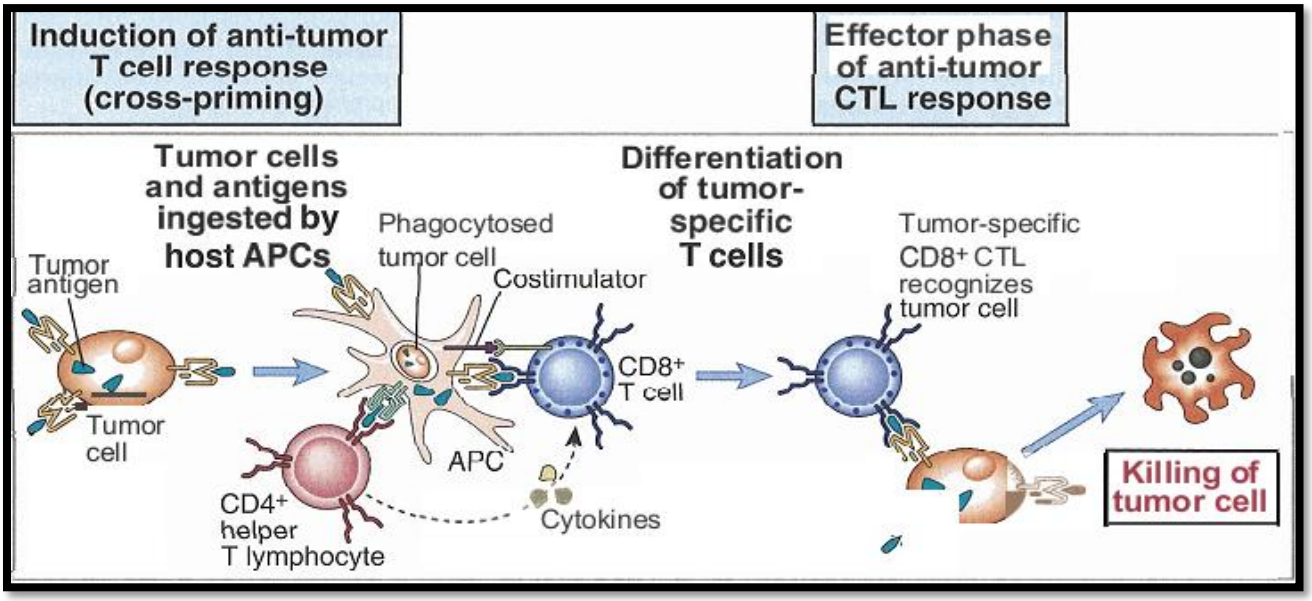


Figure: lnduction of T cell responses to tumors. antigens.

Humoral immunity

Tumor-bearing hosts may produce antibodies against various tumor antigens. For example, patients with serum antibodies against EBV encoded antigens expressed on the surface of the lymphoma cells. Antibodies may kill tumor cells by activating complement or by antibody-dependent cell-mediated cytotoxicity, in which Fc receptor-bearing macrophages or NK cells mediate the killing. However, the ability of antibodies to eliminate tumor cells has been demonstrated largely invitro, and there is little evidence for effective humoral immunity against tumors.

Evasion of immune responses by tumors

Many malignant tumors possess mechanisms that enable them to evade or resist host immune responses:

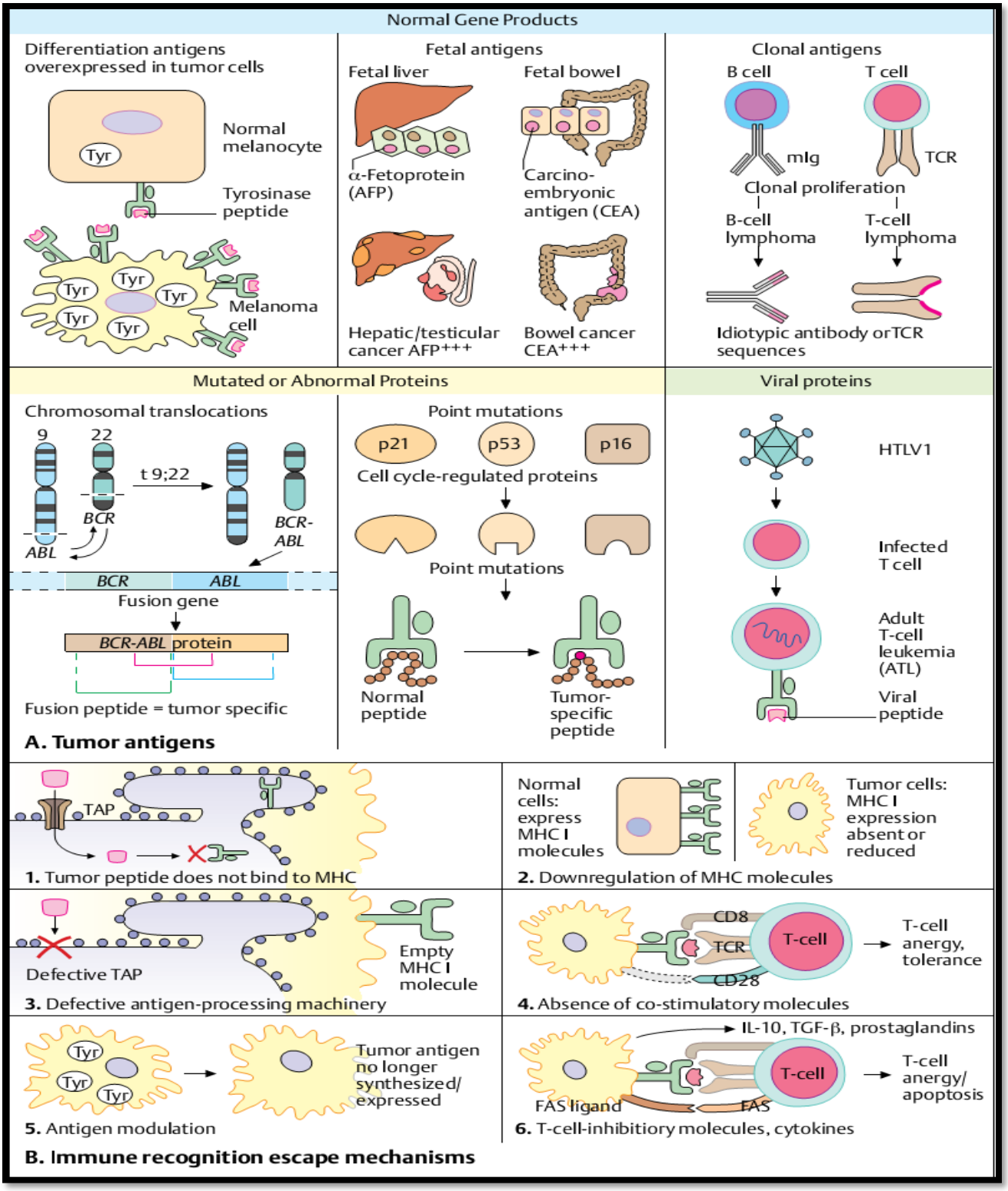
1. Class I MHC expression may be down-regulated on tumor cells so that they cannot be recognized by CTLs.
2. Tumors lose expression of antigens that elicit immune responses.

3. Tumors may fail to induce CTLs because most tumor cells do not express costimulators or class II MHC molecules.
4. The products of tumor cells may suppress anti-tumor immune responses.
5. Tumor antigens may induce specific immunologic tolerance.

Diagnosis

1. **Histopathology:** by taking a biopsy of the tumor mass and recognize the transforming cells.
2. **Enzymatic:** measuring certain enzymes that may change during the course of the disease.
3. **Clinical presentation.**
4. **Immunodiagnosis:** in many occasions immunodiagnosis is more sensitive and can diagnosis tumor more early than other diagnostic methods. This method depends basically on the detection of tumor antigens (markers) in the patient serum or tissue biopsy. Generally, there are two method for that:
    1. **In vivo method** which means injecting of radiolabelled mAb against suspected tumor marker in the body then to follow any binding reaction between the Ab and the Ag inside the body by a device called immune-scintigraphy. This method is used to monitor the level of CEA in people with colonic cancer.
    2. **In vitro method** which means taking sample (blood or tissue) from the patient and reacting it with the specific Ab for the expected tumor marker. This method is used to detect α-feto protein in the serum of patients with suspected liver tumors.

Other application for this method is to use an anti-MHC-class I Ab with breast biopsy to detect the presence or absence of MHC-class I molecules on breast cells. Breast cells with tumor are usually lack the presence of these molecules on their surfaces (IFAT method).



Lecture No. 12

Transplantation

Transplantation is the process of taking cells, tissues, or organs, called **a graft**, from one individual and placing them into a different individual.A graft transplanted between two genetically different individuals of the same species is called an **allogeneic graft (or allograft)**.

Transplantation of tissues from one individual to a genetically nonidentical recipient leads to a specific immune response called **rejection** that can destroy the graft. The antigens recognised during rejection are referred to as **alloantigens**. The key alloantigens are those encoded by the MHC. In humans these are known as **HLA** molecules is to present peptide antigen to a complementary T cell receptor.

Allogeneic MHC molecules may be presented on donor APCs to recipient T cells (**direct allorecognition**), or the alloantigens may be picked up by host APCs that enter the graft or reside in draining lymphoid organs and be processed and presented to T cells as peptides associated with self MHC molecules (**indirect allorecognition**).

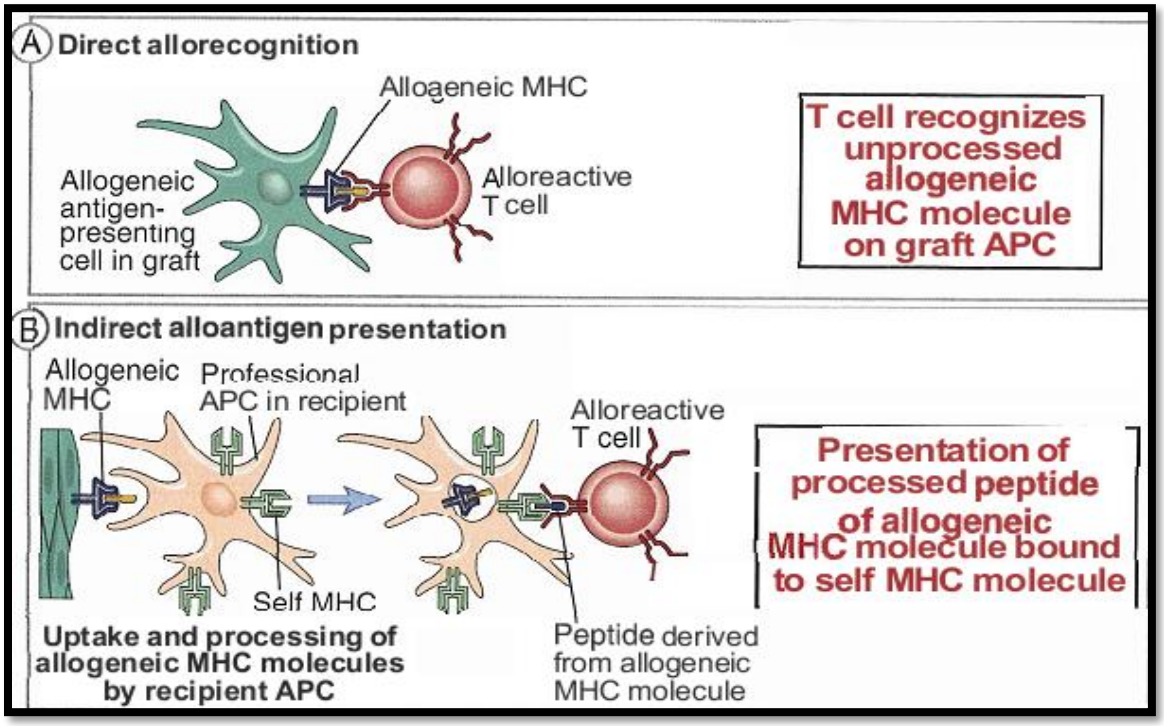


Figure: Direct and indirect alloantigen recognition.

Ty

- **Autograft or autologous transplant:** the organ/tissue is transplanted within the same individual. It does not undergo rejection.
- **Syngraft or syngeneic transplant:** the organ/tissue is transplanted between genetically identical subjects, such as monozygotic twins or inbred laboratory animals. It does not undergo rejection.
- **Allograft or allogeneic transplant:** the organ/tissue is transplanted between genetically non-identical members of the same species. It is rejectes unless immunosuppression is instituted.
- **Xenograft or xenogeneic transplant:** the organ/tissue is transplanted between members of the different species. It is rejected hyperacutely.

Classification of rejection

Rejection can be classified according to the timescale of its appearance and to the immune mechanism involved (see Table.1)**.**

Table.1 Classification of rejection

Type	Time after transplantation	Probable mechanism
Hyperacute	Minutes	Preformed antibodies
Accelerated acute	1-5 days	T lympocytes
Acute	From 2nd	T lympocytes
Chronic	Months or years	Antibodies, complement, adhesion molecules

In classical immune responses, it is the balance between the different components of the immune system that decrees the magnitude and manifestation of the rejection process. Once a naïve helper CD4 cell designated to T_H0 has recognized as alloantigen, presented by a professional antigen-presenting cell such as a dendritic cell, which is singularly competent in providing the co-stimulation signals needed to arouse naïve cells, it can become either a T_H1 or a T_H2 cell according to the microenvironment it encounters and the nature of the alloantigenic stimulus. If the surrounding medium is rich in IL-12 a macrophage-derived cytokines, the naïve T_H0 CD4 cell will commit itself to the T_H1 phenotype and function and orchestrate the activation of CD8 cytotoxic T cells and of macrophage through the release of IL-2

and IFN-γ. If ,however, the prevailing cytokine is IL-4, the naïve CD4 cell will differentiate into the T_H2 phenotype, and though the secretion of IL-4 and IL-10 will direct the activation of B lympocytes and antibody production.

Graft-versus-host reaction

Immunocomponent cells from thegraft recognise alloantigens of the recipient and the recipient develops a disorder known as **the graft-versus-host (GVH) reaction**. This reaction is common after transplantation of **bone marrow**, even when the matching between donor and recipient has been stringent. When GVH becomes symptomatic the term **graft-versus-host disease (GVHD)** is more appropriate. GVHD has been described not only following bone marrow transplantation but also, occasionally, after **liver transplantation** and even after **blood transfusions**. GVHD can be divided into two distinct entities: **acute disease**, occuring in the first 1 or 2 months after transplantation, and **chronic disease**, developing at least 2 or 3 months after transplantation.

In humans, GVHD typically affects **the skin, liver, intestinal tract and immune system** and appears within days or weeks after bone marrow transplantation. In **mild GVH** reactions, patients manifest erythema of the palms, soles and ears. Hepatic signs of mild reactions are limited to asymptomatic hyperbilirubinaemia, and gastrointestinal involvement is indicated by mild diarrhoea, in the case of **sever GVHD**, the skin lesions can include a necrolytic disorder, characterized by blister formation and desquamation. Severe liver abnormalities include jaundice, elevation of alkaline phosphatase, which denotes cholestasis, and of transaminase, a sign of liver cell damage. Sever gastrointestinal GVHD includes abdominal pain and diarrhea, with life-threating electrolyte abnormalities. These manifestations are the result of injury to the epithelial cells of the target organs. Mild GVH may resolve spontaneously or with mild immunosuppressive treatments. Sever GVH is usually unresponsive to treatments and has a fatal outcomes.

Lecture No. 13

Autoimmune hemolytic anemia (AIHA)

In this disease, red blood cells (RBC) survive for a shorter time than in normal (less than 120 days) due to immune mechanism destructions of these RBC. In all conditions, the immune destruction is mediated by autoantibodies against certain components of the RBCs. AIHA are classified according to the thermic activity of the autoantibodies:

1. **Warm antibody hemolytic anemias** bind more efficiently to RBC at 37 C.
2. **Cold antibody hemolytic anemias** bind more efficiently to RBC at 4 C.

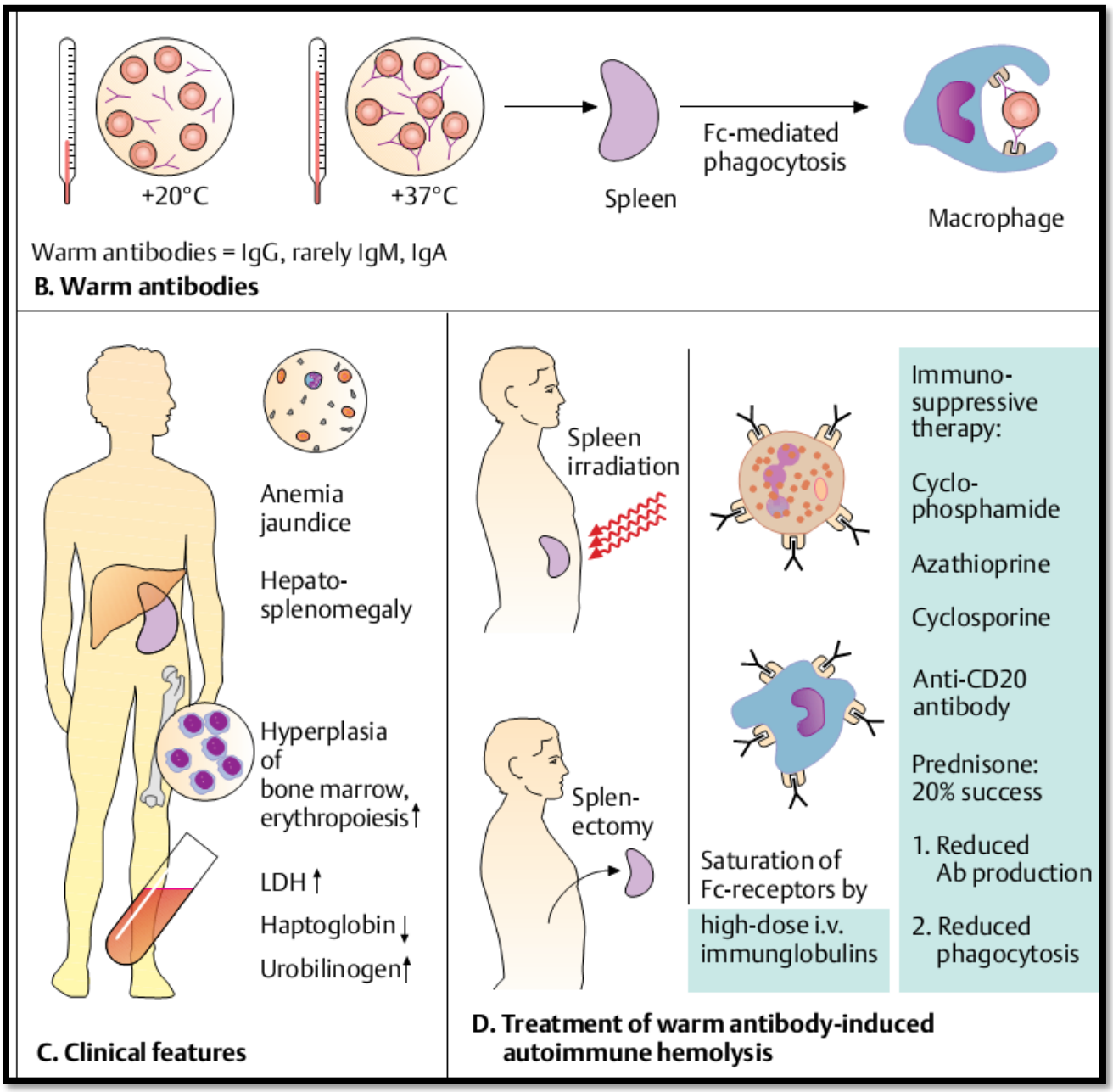
In all types of AIHA, there are autoantibody against certain components of the RBC surface which are attached to the patients RBC or free in the serum. In many occasion, complement may participate in the reaction to produce an Ab-Ag-complement complex. The screening test that used for the diagnosis of AIHA is called (Coombs test) which can demonstrate the presence of these autoantibody either attached to the patients RBC or free in serum. Coombs test could be direct or indirect.

Warm antibody hemolytic anemias

Affects all ages and mostly over 30 years of age and could be transient or persistent. About the half of the cases are idiopathic and the other half are due to secondary causes (lymphoproliferation, autoimmune disease as SLE, drugs and infections).the commonest pathogenesis of hemolytic anemia is the destruction of the opsonized RBC (with IgG and/or C3) by splenic macrophages and liver kupffers cells.

With warm antibodies, erythrocyte lysis takes place mainly in the RE system; the serum concentration of the hemoglobin-binding protein haptoglobin decreases only if there is severe hemolysis. Hepatosplenomegaly occurs due to the increased rate of hemolysis in the spleen and liver. Intracellular enzymes, such as lactate dehydrogenase (LDH), are released. Erythropoiesis is stimulated in the bone marrow, and reticulocytes are increased. The freed hemoglobin is reduced to bilirubin, which binds to glucuronate in the liver and is excreted in the bile. Hyperbilirubinemia, which leads to yellowish discoloration of the sclera and skin (jaundice), is frequently seen. Urobilinogen, another degradation product, cause dark discoloration of the urine.

Most cases are positive for direct Coombs test (50% are positive for both IgGand C3, 40% are positive for only IgG, 10% are positive for only C3). About 35% are positive for free autoantibody (indirect Coombs test).



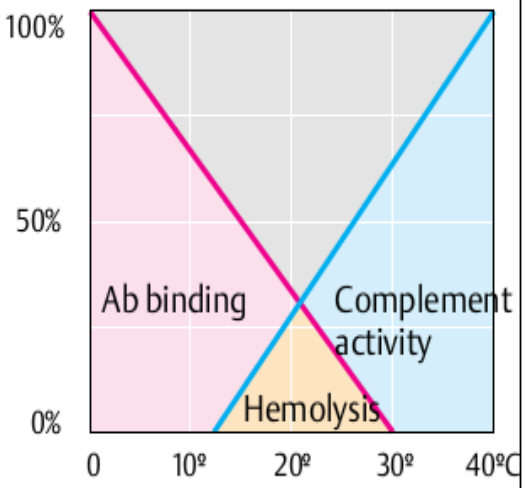
Cold antibody hemolytic anemias

Cold antibodies are usually IgM and only occasionally IgG. Accordingly, they can cause agglutination of erythrocytes and are therefore called agglutinins.It is a disease of elderly people (over60years) mainly due to primary (idiopathic causes) and rarely

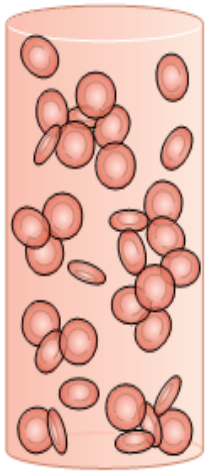
due to secondary cause (infections, lymphoproliferation). They are most commonly observed following infections, especially by Mycoplasma, Epstein-Barr virus, or cytomegalovirus, and rarely after bacterial diseases. These infections usually lead to the formation of polyclonal cold reactive antibodies that bind to erythrocytes most efficiently at low temperature. In most cases, cold antibodies are directed against I antigen, which is mainly expressed on mature RBCs, but also on some pathogens. Some malignant lymphatic diseases may lead to secretion of monoclonal agglutinins. Monoclonal agglutinins may be directed against both I and i antigen (immature fetal erythrocytes).

All patients have IgM coated RBC at 4c, but on warming the blood these Abs detached from RBC, however, fixed C3d can still be detected by direct Coombs test. The commonest pathogenesis of hemolysis is complement mediated mechanism. Free cold auto-Ab (cold agglutinins) are also found in the patients serum.

Since the temperature in the capillaries of the skin can drop below 30 C, the cold agglutinins cause the erythrocytes to clump together. This intravascular agglutination process leads to capillary obstruction, which manifests as acrocyanosis (bluish discoloration of the fingers, ears, and tip of the nose) or livedo reticularis (reddish/bluish reticular pattern of the skin). Trophic lesions (ulcer, necrosis) may occur in sever forms.



2. Thermic amplitude



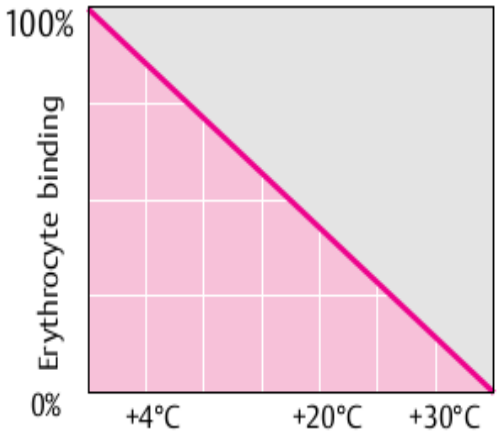
- Falsely high MCV
- Falsely low erythrocyte count

3. Changes in blood chemistry

- Anemia
- Acrocyanosis
- Livedo reticularis
- Trophic disorders

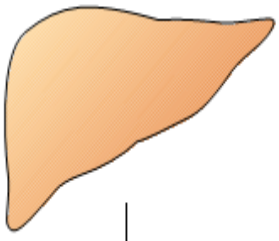
4. Clinical symptoms

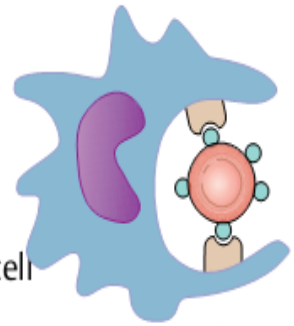
A. Autoimmune hemolysis by cold antibodies



Cold antibodies
= IgM, rarely IgG

Intravascular hemolysis or



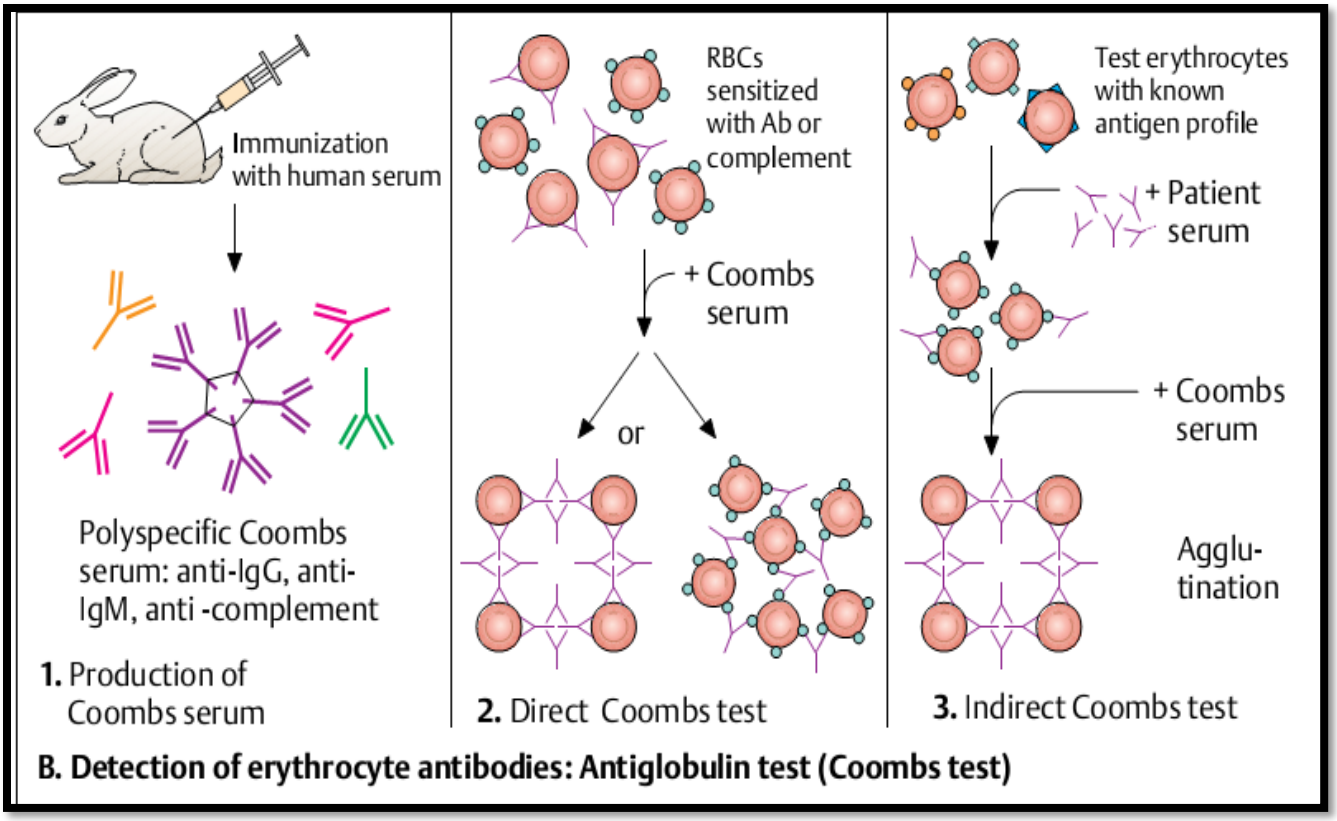


Kupffer cell

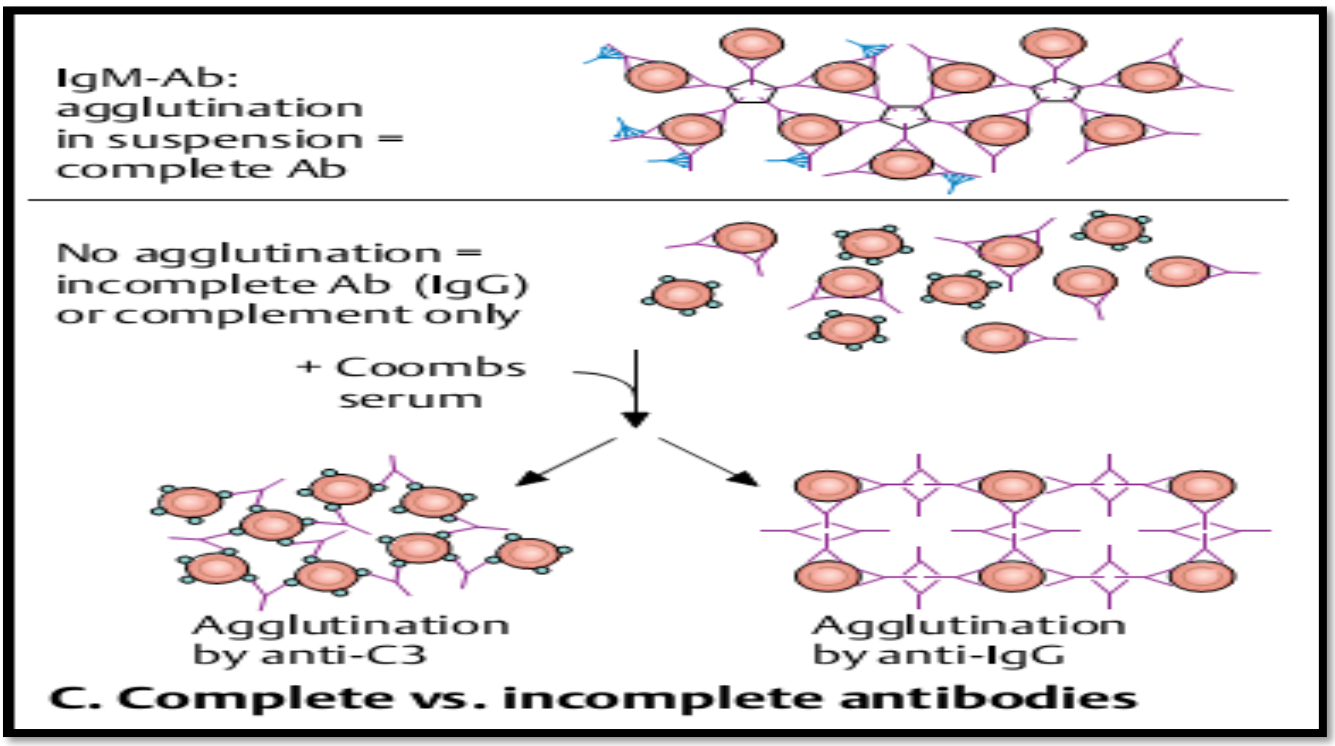
C3-receptor-mediated phagocytosis

B. Mechanisms of hemolysis

C. Therapy



B. Detection of erythrocyte antibodies: Antiglobulin test (Coombs test)

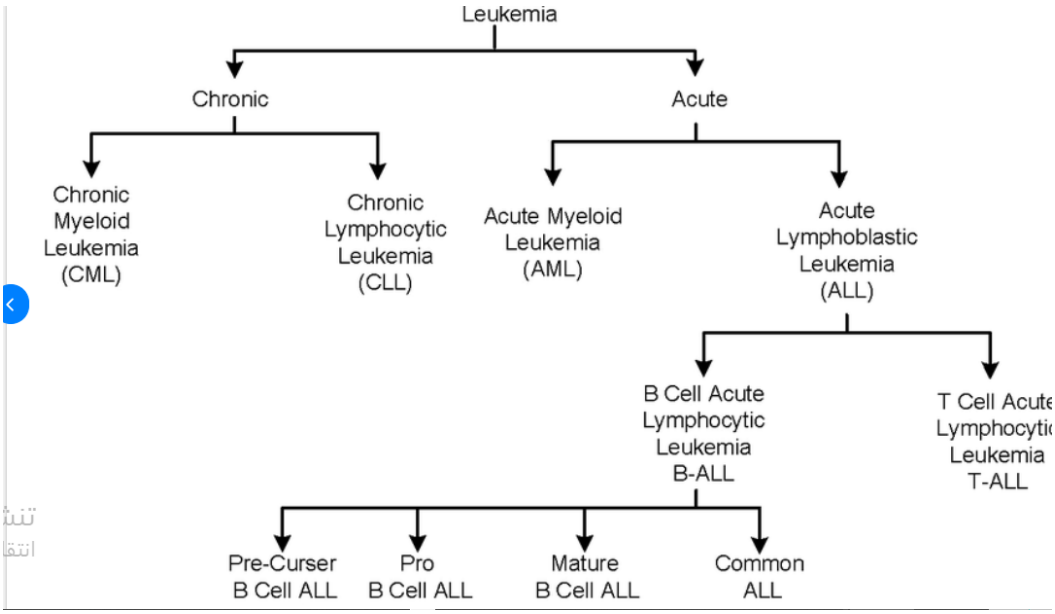


C. Complete vs. incomplete antibodies

Lecture No. 14 & 15

Acute & Chronic Leukemia
&
Lymphoid and Myloid Leukemia

Leukemia is a form of cancer that originates in the blood and blood-forming tissues, such as the bone marrow, primarily affecting white blood cells . It is classified based on its speed of progression and the type of cells involved, leading to the two main categories: acute leukemia and chronic leukemia



Acute Leukemia

Acute leukemia is a group of aggressive hematologic malignancies characterized by the rapid proliferation of immature blood cells, known as blasts, in the bone marrow . These immature cells are unable to perform their normal functions and multiply quickly, causing the disease to worsen rapidly . The term "acute" signifies its rapid progression . Immediate and aggressive treatment is necessary to achieve the best possible outcome .

Characteristics of acute leukemia include:

- **Rapid Progression** It develops quickly, with symptoms often appearing shortly after the condition begins .

- **Immature Cells** The abnormal blood cells are immature (blasts) and cannot carry out normal bodily functions .
- **Severity** It is typically more severe than chronic leukemia .
- **Affected Populations** While anyone can develop acute leukemia, it is more prevalent in children, teenagers, and young adults .
- **Types** Examples include Acute Lymphocytic Leukemia (ALL), which is common in young children and affects lymphocytes, and Acute Myelogenous Leukemia (AML), which is common in adults .

Clinical Symptoms of Acute Leukemia

General Symptoms

1-Fatigue and Weakness

2- Fever and Infections: Frequent or severe infections due to a lack of functional white blood cells .

3- Night Sweats **4-** Unexplained Weight Loss **5-**Bleeding and Bruising

6- Petechiae: Tiny red or purple spots under the skin caused by bleeding .

7- Prolonged Bleeding: Difficulty stopping bleeding due to low platelet counts

8- Pale Skin: A washed-out appearance due to anemia .

9- Shortness of Breath: Often linked to anemia or high white blood cell counts .

10- Headaches or Neurological Symptoms: In some cases, acute leukemia can affect the central nervous system, causing headaches, confusion, or blurred vision

Bone and Joint Symptoms

1-Bone Pain or Tenderness: Common in children and adults, often affecting the legs, chest, or hips .

2-Joint Pain: Discomfort in the joints, which may be mistaken for other conditions like arthritis **3-**Swelling and Enlargement
4-Swollen Lymph Nodes **5-**Enlarged Liver or Spleen

classification of acute leukemia

The classification of **acute leukemia** is primarily based on the type of blood cell affected (lymphoid or myeloid) and the characteristics of the leukemia cells.

Acute leukemia is broadly divided into two main categories:

1. **Acute Lymphoblastic Leukemia (ALL)**:
    - Affects immature lymphoid cells (lymphoblasts).
    - Most common in children but can also occur in adults.
    - Subtypes include:
        - **B-cell ALL**: The most common subtype, further classified based on genetic abnormalities (e.g., B-ALL with BCR-ABL1 fusion, ETV6-RUNX1 fusion).
        - **T-cell ALL**: Less common, often associated with mediastinal masses or thymic involvement .
2. **Acute Myeloid Leukemia (AML)**:
    - Affects immature myeloid cells (myeloblasts).
    - More common in adults, particularly those over 60 years old.
    - Subtypes are classified based on morphology, cytogenetics, and molecular markers .

Chronic Leukemia

Chronic leukemia involves more mature blood cells that replicate or accumulate at a slower rate . These cells may function normally for a period of time . The "chronic" designation indicates its slow progression . As a result, symptoms may take months or even years to manifest, and patients may initially experience few to no symptoms . It is often discovered incidentally during routine medical examinations . Chronic leukemia is defined by the indolent proliferation of white blood cells .

Characteristics of chronic leukemia include:

- **Slow Progression** It progresses slowly, with symptoms potentially taking months or years to appear .
- **More Mature Cells** It involves more mature blood cells compared to acute leukemia .
- **Severity** It tends to be less severe than acute leukemia .
- **Affected Populations** Most patients with chronic leukemia are older adults .

- **Types** Examples include Chronic Lymphocytic Leukemia (CLL), the most common chronic adult leukemia, and Chronic Myelogenous Leukemia (CML) . Some forms of chronic leukemia may initially require a watchful waiting approach before treatment .

Types of Chronic Leukemia

1-Chronic Lymphocytic Leukemia (CLL)

2. Chronic Myeloid Leukemia (CML)

Chronic Lymphocytic Leukemia (CLL) Symptoms

CLL primarily affects lymphocytes, a type of white blood cell, and is more common in older adults. Symptoms often develop gradually and may include:

1-Swollen Lymph Nodes: Painless lumps in the neck, underarms, stomach, or groin .

2-Fatigue: Persistent tiredness due to anemia or the disease itself .

3-Frequent Infections: Caused by a weakened immune system due to abnormal lymphocytes .

4-Night Sweats: Excessive sweating, especially at night .

5-Unexplained Weight Loss: Losing weight without trying .

6-Pain or Fullness Below the Ribs: Often due to an enlarged spleen .

7-Easy Bleeding or Bruising: Caused by low platelet counts .

8-Petechiae: Tiny red spots under the skin caused by bleeding .

Pathogenicity of Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia (CLL) is a malignancy of mature B-lymphocytes driven by genetic abnormalities, impaired DNA damage response, and chronic B-cell receptor (BCR) signaling. It involves clonal accumulation in blood, marrow, and lymph nodes, heavily supported by microenvironmental survival signals.

- **Genetic & Molecular Aberrations:** Common, non-random alterations include deletions in 13q14 (often the first hit), 11q22-23 (ATM), and 17p13 (\(TP53\)), as well as trisomy 12. These mutations disrupt cell cycle regulation and DNA repair.
- **BCR Signaling & Antigen Stimulation:** CLL cells are continuously activated via BCR signaling, which supports survival and proliferation. This is often driven by self-antigens or microbial antigens, with stereotyped receptors suggesting antigen-driven selection.
- **Tumor Microenvironment:** Malignant cells reside in "proliferation centers" within lymph nodes, interacting with T-cells, nurselike cells, and stromal cells that provide essential survival, anti-apoptotic signals.
- **Epigenetic Landscape:** The CLL genome shows widespread DNA hypomethylation, which affects gene expression and contributes to the malignant phenotype.
- **Clinical Progression:** The disease is preceded by Monoclonal B-cell Lymphocytosis (MBL). It is characterized by slow accumulation but can transform into more aggressive forms, such as Richter syndrome.

2. Chronic Myeloid Leukemia (CML) Symptoms

CML affects myeloid cells and is characterized by the presence of the Philadelphia chromosome. Symptoms are often mild in the early stages and worsen as the disease progresses:

Fatigue and Weakness: Common due to anemia or the disease itself .

Night Sweats: Drenching sweats, particularly at night .

Unexplained Weight Loss: Significant weight loss without dietary changes .

Fever: Persistent or recurrent fever .

Bone and Joint Pain: Discomfort in bones or joints, especially as the disease progresses .

Abdominal Discomfort or Fullness: Often caused by an enlarged spleen, leading to a feeling of fullness after eating small amounts .

Shortness of Breath: Due to anemia or lung infections .

Easy Bleeding or Bruising: Caused by low platelet levels .

Pathogenicity of Chronic Myeloid Leukemia (CML)

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm caused by a specific genetic mutation that leads to the uncontrolled proliferation of hematopoietic stem cells. The hallmark of CML is the BCR-ABL1 fusion gene, which results from a chromosomal translocation known as the Philadelphia chromosome.

1. Genetic Basis:

A. The Philadelphia Chromosome

Chromosomal Translocation: CML is characterized by a reciprocal translocation between chromosomes 9 and 22, denoted as t(9;22)(q34;q11). This translocation creates the BCR-ABL1 fusion gene, which encodes a constitutively active tyrosine kinase .

B. BCR-ABL1 Oncoprotein:

The BCR-ABL1 protein drives the pathogenesis of CML by activating multiple downstream signaling pathways that promote cell proliferation, inhibit apoptosis, and disrupt normal hematopoiesis .

2. Molecular Mechanisms

The BCR-ABL1 oncoprotein leads to several molecular changes that contribute to the development and progression of CML

3. Disease Phases

CML progresses through three distinct phases, each with unique pathological features:

A-Chronic Phase:

Characterized by the proliferation of mature granulocytes with minimal symptoms.

Over 85% of patients are diagnosed in this phase .

B-Accelerated Phase:

Additional cytogenetic abnormalities emerge, leading to increased proliferation of immature cells.

C-Blast Phase:

Resembles acute leukemia, with a dominance of immature blast cells and rapid disease progression .

4. Role of the Tumor Microenvironment

The bone marrow microenvironment supports the survival and proliferation of leukemic cells by providing growth factors and cytokines.

This interaction further enhances the effects of the BCR-ABL1 oncoprotein .

5. Clonal Evolution

As CML progresses, additional mutations and chromosomal abnormalities accumulate, contributing to disease progression and resistance to therapy .

Chromosomal Instability in Chronic Myeloid Leukemia: Mechanistic Insights and Effects

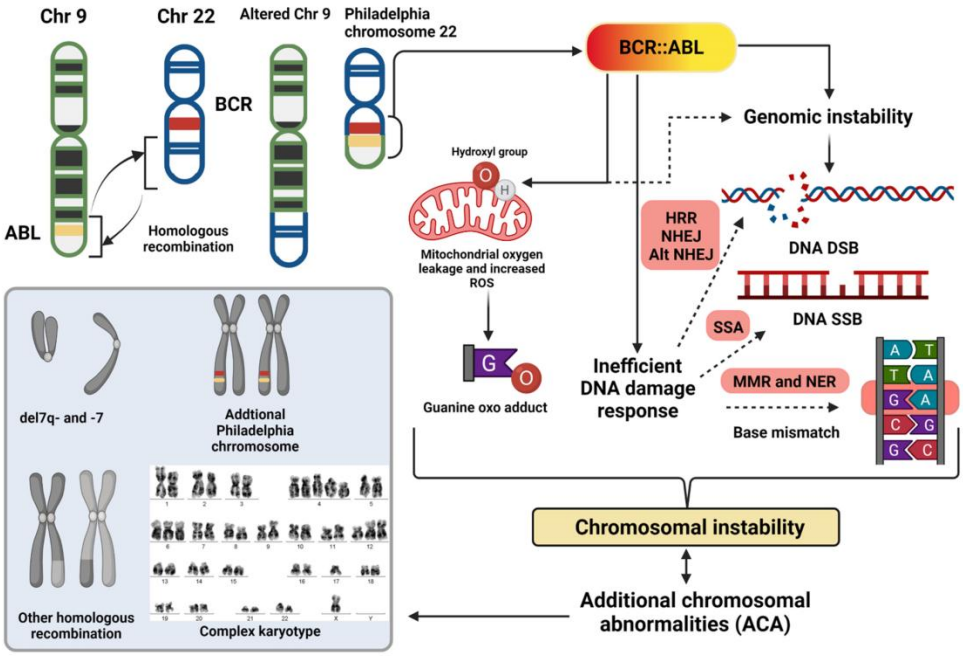


Table Comparing

Chronic Lymphocytic Leukemia & Acute Lymphoblastic Leukemia

Characteristics	Chronic Lymphocytic Leukemia	Acute Lymphoblastic Leukemia
Definition	A type of leukemia with abnormal malignant B cells.	A type of leukemia affecting the stem cells of either B or T cells.
Age group(s) affected	Mostly adults, rare in children.	Mostly children under 15 years of age or adults over 45.
Symptoms	Fever, night sweats, weight loss, no appetite, swollen lymph nodes and glands.	Night sweats, fever, no appetite, easy bruising, bleeding gums, fatigue, dizziness, low blood platelets and low blood cell counts.
Complications	Infections and death.	Infections, bleeding, kidney failure, and death.
Survival	87% at 5 years	68% at 5 years

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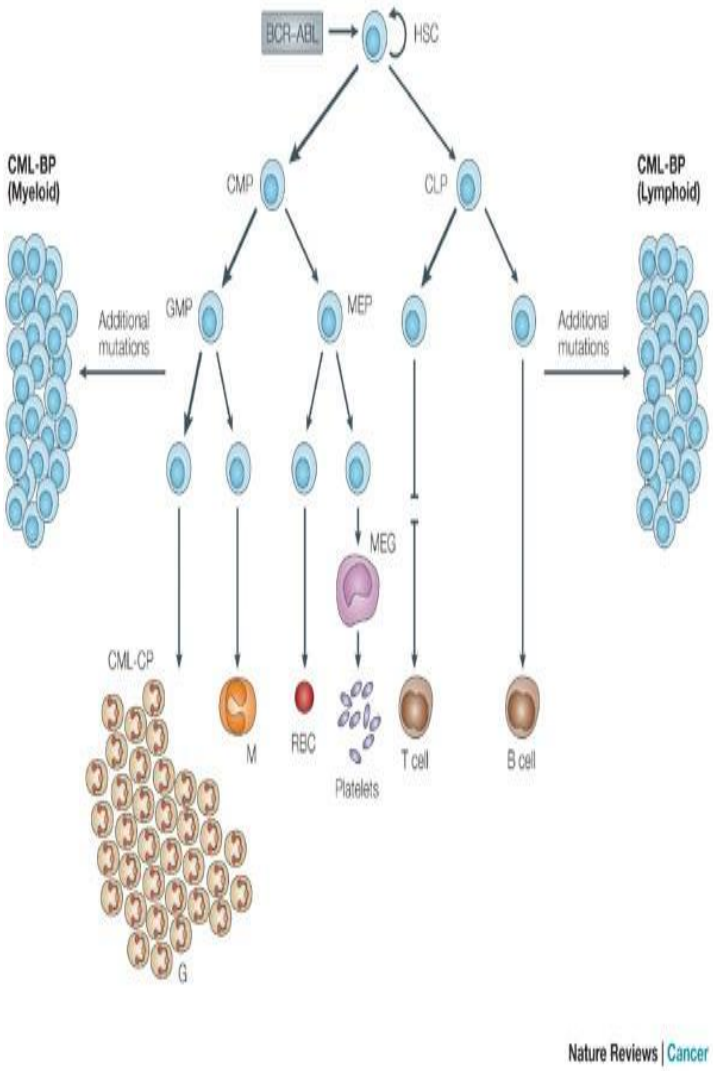
Mechanisms of BCR–ABL in the pathogenesis of chronic myelogenous leukaemia



Differences Between Acute and Chronic Lymphocytic Leukemia (ALL vs. CLL)

Differences Between Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML)

Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML) are both types of blood cancers originating in the myeloid cells of the bone marrow.

	Acute Myeloid Leukemia	chronic myeloid leukemia
1. Disease Progression	Progresses rapidly and aggressively. Involves immature white blood cells (blasts) that do not function properly. Symptoms appear quickly, often within days or weeks .	Progresses slowly over months or years. Involves more mature, but still abnormal, white blood cells. symptoms appear slowly
2. Genetic Abnormalities	Characterized by various genetic mutations, such as FLT3, c-KIT, and TP53. No single hallmark genetic abnormality defines AML.	Defined by the presence of the Philadelphia chromosome (BCR-ABL fusion gene), a specific genetic abnormality caused by a translocation between chromosomes 9 and 22.This genetic marker is a key target for treatment.
3. Symptoms	Fatigue, fever, and shortness of breath. bleeding (due to thrombocytopenia). Bone pain, frequent infections, and petechiae (small red spots under the skin caused by bleeding).	Often asymptomatic in the early (chronic) phase. Symptoms, when present, may include fatigue, weight loss, night sweats, and an enlarged spleen (causing abdominal discomfort).

4. Diagnosis	Diagnosed by the presence of more than 20% myeloblasts in the bone marrow or blood.	Diagnosed by detecting the Philadelphia chromosome or BCR-ABL fusion gene through genetic testing.
5. Prognosis	Prognosis depends on age, genetic mutations, and response to treatment. Without treatment, AML progresses rapidly and is often fatal within weeks or months.	Prognosis has improved significantly with the advent of TKIs. Many patients achieve long-term disease control and can live normal lives with proper treatment.
classification	Subtypes are classified based on genetic mutations and cell characteristics.	Classified into three phases: chronic, accelerated, and blast phase, based on disease progression.