Lecture : 1

Introduction of Rheumatic Diseases

Rheumatic diseases are several diseases characterized by inflammation that affects the connecting or supporting structures of the body — most commonly the joints, but also sometimes the tendons, ligaments, bones, and muscles. Some rheumatic diseases even affect the organs

Types of Rheumatic diseases:-

A- Degenerative arthropathies **(** Osteoarthritis)

B- Inflammatory arthropathies

((1- Rheumatoid arthritis **,** **2-**Ankylosing spondylitis **, 3-** Reactive arthritis (reactive arthropathy) **, 4-** Psoriatic arthropathy **, 5-** Juvenile Idiopathic Arthritis (JIA) **6-** Crystal arthropathies: (gout, pseudogout) **))**

C- Systemic conditions and connective tissue diseases

1-Lupus 2- Sjögren's syndrome 3- Scleroderma (systemic sclerosis)

4- Polymyositis 5- Dermatomyositis 7 -Mixed connective tissue disease

D - Soft tissue rheumatism

Local diseases and lesions affecting the joints and structures around the joints including tendons, ligaments capsules, bursae, stress fractures, muscles, nerve entrapment, vascular lesions, and ganglia. For example:

1-Low back pain 2- Tennis elbow

Autoimmune diseases	HLA Gene
Acute uveitis	**B27**
Ankylosing spondylitis	**B27**
Reiter syndrome	**B27**

Good pasture syndrome	**DR2**
Multiple sclerosis	**DR2 ,DR3**
Gravies disease	**DR3**
Myasthenia gravies	**DR3**
Rheumatoid arthritis **Systemic lupus**	**DR3** **DR4**
Type 1 insulin -dependent diabetes mellitus	**DR3 /DR4 heterozygous**
Pemphigus vulgaris	**DR4**
Hashimoto disease	**DR5**
Psoriasis vulgaris	**CW6**

Autoimmune diseases can result from damage inflicted on cells and tissues by humoral responses, cell-mediated immune responses, or both .

A. Humoral-associated autoimmune diseases

Some autoimmune diseases result from the binding of **self-reactive antibodies**, leading to type II and type I I I hypersensitivity responses. The antibodies activate complement lead to damage the cells and tissues. **Autoreactive T cells** are typically present as well, but their role is primarily the activation of the **autoreactive B cells** rather than directly attacking host cells. Examples of these autoimmune diseases include the following:

o Autoimmune hemolytic anemia: type II hypersensitivity

o Goodpasture syndrome: type II hypersensitivity

o Hashimoto thyroiditis: type I I hypersensitivity

o Rheumatic fever: type I I hypersensitivity

o Rheumatoid arthritis: type I I I hypersensitivity

o Systemic lupus erythematosus: type I I and type I I I hypersensitivity

B. Cell-mediated autoimmune diseases

Type IV hypersensitivity responses involve cell-mediated injury leading to autoimmune disease. These may include **cytotoxic T-cell** responses or **macrophages** driven by **DTH** responses.

• Insulin-dependent diabetes mellitus (type 1)

• Multiple sclerosis

• Reactive arthritis

• Rheumatoid arthritis

Rheumatoid arthritis provides an example of an autoimmune disease that involves both humoral and cell-mediated injury .

Lecture : 1

Inflammatory rheumatic diseases

1-Rheumatoid arthritis

RA :- is a chronic inflammatory autoimmune disease in which the immune response is directed against an individual's own tissue, including the joints, tendons, and bones, resulting in inflammation and destruction of these tissues.

RA can also affect other tissues throughout the body and cause problems in organs such as the **lungs, heart, and eyes**.

Affects **1-2%** of the adult population

Is more common among **women** than in men

Usually appears between ages **25 and 40** years

Rheumatoid arthritis that begins in people under **16** years of age is referred to as **juvenile idiopathic arthritis** or JIA (formerly **juvenile rheumatoid arthritis** or JRA).

Signs and symptoms

joint pain (in feet, hands, and knees,) swollen joints, tender joints , stiff joints, joint redness , joint warmth , loss of joint function, joint deformity**(swan neck, Boutonniere deformity)**

fever, limping,

polyarthritis,

loss of range of motion,

fatigue,

rheumatoid nodules,

anemia, and symptoms and signs that affect both sides of the body (**symmetry**).

What is the Causes of RA

The specific causes of RA are unknown, but some factors can increase the risk of developing the disease:-

1-Gander : disease is **two to three** times more common in women than in men. Experts believe this may be due to the effects of **estrogen** - a female hormone.

2-Age : RA may develop at any age .but most common in **40-60**.

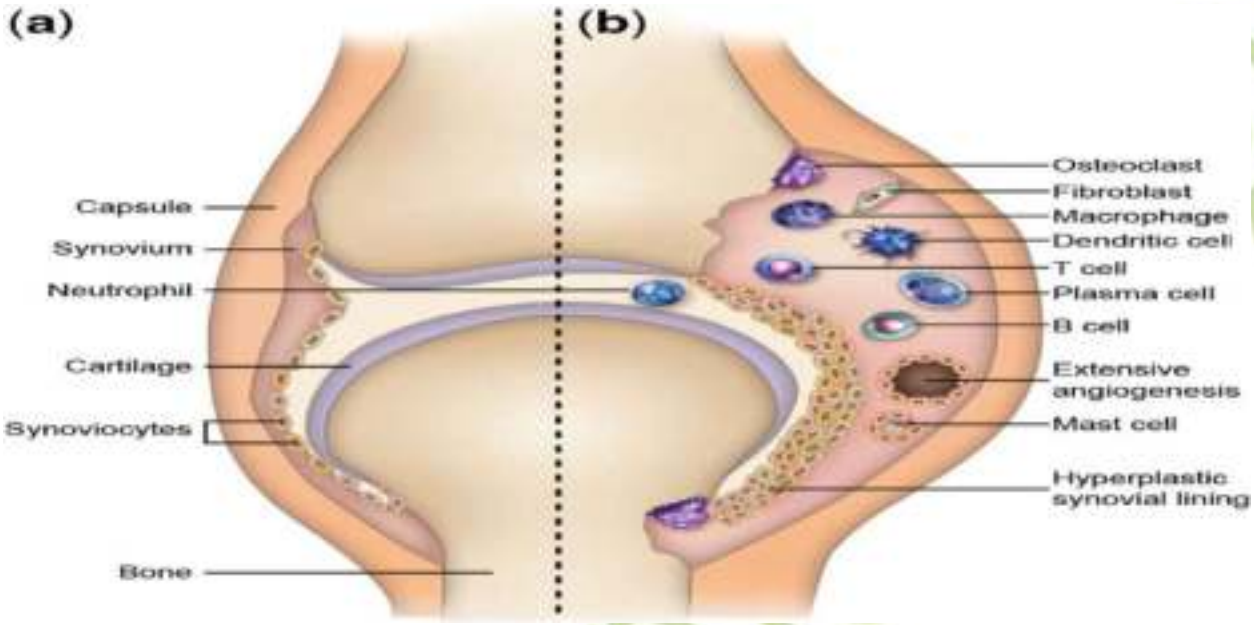
3-Genetic :patients with HLA **DR3,DR4** have risk with RA

4-Environmental behavior factors: exposure to air pollution ,insecticide ,mineral, obesity, response to trauma, emotional stress

5-Smoking : Regular smokers have a significantly higher risk of developing rheumatoid arthritis. Smoking makes the outlook for the disease worse.

6- Testosterone: Levels of testosterone that are **low** in men may predict a future development of rheumatoid arthritis.

Pathophysiology



1-Genetic,smoking ,bacteria, and synovial injury (hyperplasia) lead to **modulation of auto-Ag.**

2-Auto-Ag engulfed by macrophage and present to T-cells CD4(become auto-reactive)to activated it ,activated CD4stimulate B-cells to converted to plasma cells and produce Auto-Ab in lymph node .

3- CD4 T-cells ,Plasma cells ,neutrophils ,macrophage and auto-Ab inter the joints throughout the new formed blood vessel (angiogenesis)and began its action.

4-CD4 T-cells increase the inflammation ,and produce **IL-17** that activate macrophages and activation / proliferation of fibroblast lead to form **pannus**

5-Macrophage produce cytokine (TNF-a,IL-1,IL-6)lead to many function:

A-activation and proliferation of fibroblast together with T-cells action ,and the activate osteoclast to cause **bone erosion** .

B-direct activation of osteoblast to cause **bone erosion** .

C- assisted in inflammation.

D-Activate fibroblast to produce proteases that effect on chondrocyte to cause **cartilage degenerative** .

6- Neutrophil produce proteases that causes **cartilages degenerative.**

7-B-cells produce **two** types of Abs. **RF** (autoantibodies ,75% IgM directly against FC portion of IgG which form immune complex .and Anti-citrulinated protein Abs **ACPA** or **ACCP** (fibrin ,fillagrin) lead increase inflammation .

8-The mane cytokine is **TNF-a** play **major role** in pathophysiology .

9-Rheumatoid arthritis have two form of hypersensitivity:(**Type III** when production of auto-Ab by B-cells , **Type IV** when T-cells activate macrophage by IL-17.

Diagnosis

1- **Medical History** :- personal and family medical history as well as recent and current symptoms (pain, tenderness, stiffness, difficulty moving).

2- **Physical Exam** : examine each joint, looking for tenderness, swelling, warmth and painful or limited movement. The number and pattern of joints affected can also indicate RA. For example, RA tends to affect joints on both sides of the body.

3- Blood test : Anemia (hemolytic anemia ,normochromic normocytic) ,neutropenia,

4- **Inflammation test** :Erythrocyte sedimentation rate (**ESR**, or "sed rate") and C-reactive protein **(CRP)** level are markers of inflammation. A high ESR or CRP is not specific to RA, but when combined with other clues, such as antibodies, helps make the RA diagnosis.

5- Antibodies

Rheumatoid factor (RF) is an antibody found in about 80 percent of people with RA during the course of their disease. Because RF **can occur in other inflammatory diseases**, it's not a sure sign of having RA.

Anti-citrullinated protein antibodies (ACPAs) include(cyclic citrullinated peptide **ACC-P** and Anti mutated citrullinated vimentin **Anti-MCV**). Anti-MCV detected in sera of patients with RF negative . ACC-P occurs **primarily** in patients with RA. That

makes a positive anti-CCP test a stronger clue to RA. But anti-CCP antibodies are found in only 60 to 70 percent of people with RA and can **exist even before** symptoms start.

Antinuclear antibody(ANA) is also frequently found in people with rheumatoid arthritis.

6- Imaging Tests : An **X-ray**, **ultrasound** or **magnetic resonance imaging scan** may be done to look for joint damage, such as erosions – a loss of bone within the joint – and narrowing of joint space. But if the imaging tests don't show joint damage that doesn't rule out RA. It may mean that the disease is in an early stage and hasn't yet damaged the joints.

7- **Other tests :-** Liver enzyme (alkaline phosphatase) renal function test (Urea ,ceratinine) and Uric acid test

Differential diagnoses.

Osteoarthritis – distinguished with X-rays of the affected joints and blood tests, older age, starting pain less than an hour, asymmetric distribution of affected joints and pain worsens when using joint for longer periods.

Systemic lupus erythematosus (SLE) – distinguished by specific clinical symptoms and blood tests (antibodies against double-stranded DNA)

One of the several types of psoriatic arthritis resembles RA – nail changes and skin symptoms distinguish between them

Lyme disease causes erosive arthritis and may closely resemble RA – it may be distinguished by blood test in endemic areas

Reactive arthritis (previously Reiter's disease) – asymmetrically involves heel, sacroiliac joints and large joints of the leg. It is usually associated with urethritis, conjunctivitis, iritis, painless buccal ulcers.

Axial spondyloarthritis (including ankylosing spondylitis) – this involves the spine, although an RA-like symmetrical small-joint polyarthritis may occur in the context of this condition.

Hepatitis C – RA-like symmetrical small-joint polyarthritis may occur in the context of this condition. Hepatitis C may also induce Rheumatoid Factor auto-antibodies

Treatments

1-**NSAIDs : Nonsteroidal anti-inflammatory drugs (NSAIDs)** can relieve pain and reduce inflammation. Include **aspirin** ,**diclofenac** (voltaren) ,**ibuprofen**.

2-Steroids : Corticosteroid medications, such as **prednisone**, reduce inflammation and pain and slow joint damage .used in acute stage

3-DMARDs : Disease-modifying antirheumatic drugs These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from permanent damage. Common DMARDs include **methotrexate** (Trexall), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine).

4- **Biologic agents :** modified newer class of DMARDs includes **infliximab** (Remicade), **rituximab** (Rituxan).

5-Surgery :- in a final stage of disease , Hip and knee replacements are most common .

Vasculitis

- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss Syndrome)
- Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis)
- Polyarteritis nodosa
- Henoch–Schönlein purpura
- Serum sickness
- Giant cell arteritis, Temporal arteritis
- Takayasu's arteritis
- Behçet's syndrome
- Kawasaki's disease (mucocutaneous lymph node syndrome)
- Buerger's disease (thromboangiitis obliterans)
- Hereditary periodic fever syndromes

Lecture : 2

Inflammatory rheumatic diseases

2- Systemic lupus erythematosus

SLE :- is a chronic autoimmune disease characterized by the production of autoantibodies resulting from the dysfunction of T cells, B cells, and dendritic cells. These antibodies are principally anti-nuclear ضد النواة and induce an inflammatory response throughout the body**.**

Female: Male ratio of **9:1** during childbearing years 70% of SLE: females between ages **15-45** years **.**

Most common symptoms

1-Skin Rashes (Butterfly احمرار الوجنتين rash) 2- Mouth Sores (mouth ulcer)

3- Sunlight Sensitivity 4- Hair Loss (alopecia)

5-Swollen Lymph Nodes التهاب العقد 6- Fever حمى

7- Chest Pain الم الصدر 8- Extreme Fatigue اعياء

9- General Discomfort 10- Joints pain الم مفاصل 11- Difficulty Breathing

Types Of Lupus Disease :-

1-Systemic Lupus Erythematous (SLE)

Its affects many different organ systems in the body. It is marked by chronic inflammation, especially of the kidneys, joints, and skin. The cardiovascular and nervous systems can also be affected. قلبي وعائي

2-Lupus Limited to the Skin مقتصر على بشره فقط

The term "**chronic cutaneous lupus erythematosus**" refers to a specific form of lupus that is limited to the skin. . Five percent or more of the people with this form of lupus may develop SLE later in life. **Three types** of skin lupus exist:

a-chronic cutaneous lupus erythematosus (CCLE) (also known as Discoid Lupus Erythematosus [DLE]) newborn

b- sub-acute cutaneous lupus erythematosus (SCLE)

c- tumid lupus.

3-Drug-Induced Lupus Erythematosus

It is **temporary** and usually subsides within months of the time that the medication is stopped.

4- Neonatal Lupus Erythematosus

Affect the babies of women with certain autoantibodies, namely anti-Ro, anti-La, and anti-RNP. Usually neonatal lupus involves only the **baby's skin** and subsides on its own, even without treatment. 1-2% of infants with neonatal lupus experience **congenital heart block**.

5- Childhood Lupus

Children affects in the same manner as adult lupus, certain organs affected, such as the kidneys, requires more aggressive therapy than adult lupus

What causes lupus:- lupus develops in response to a combination of many factors

1-hormones :- estrogen may be regulates the severity of lupus. Estrogens are known modulators of immune system functions, influence cytokine production and are involved in the lupus disease process.

2-Genetic :- when one of two identical twins has lupus, there is an increased chance that the other twin will also develop the disease (In 30%),also associated with HLA DR3,DR4.

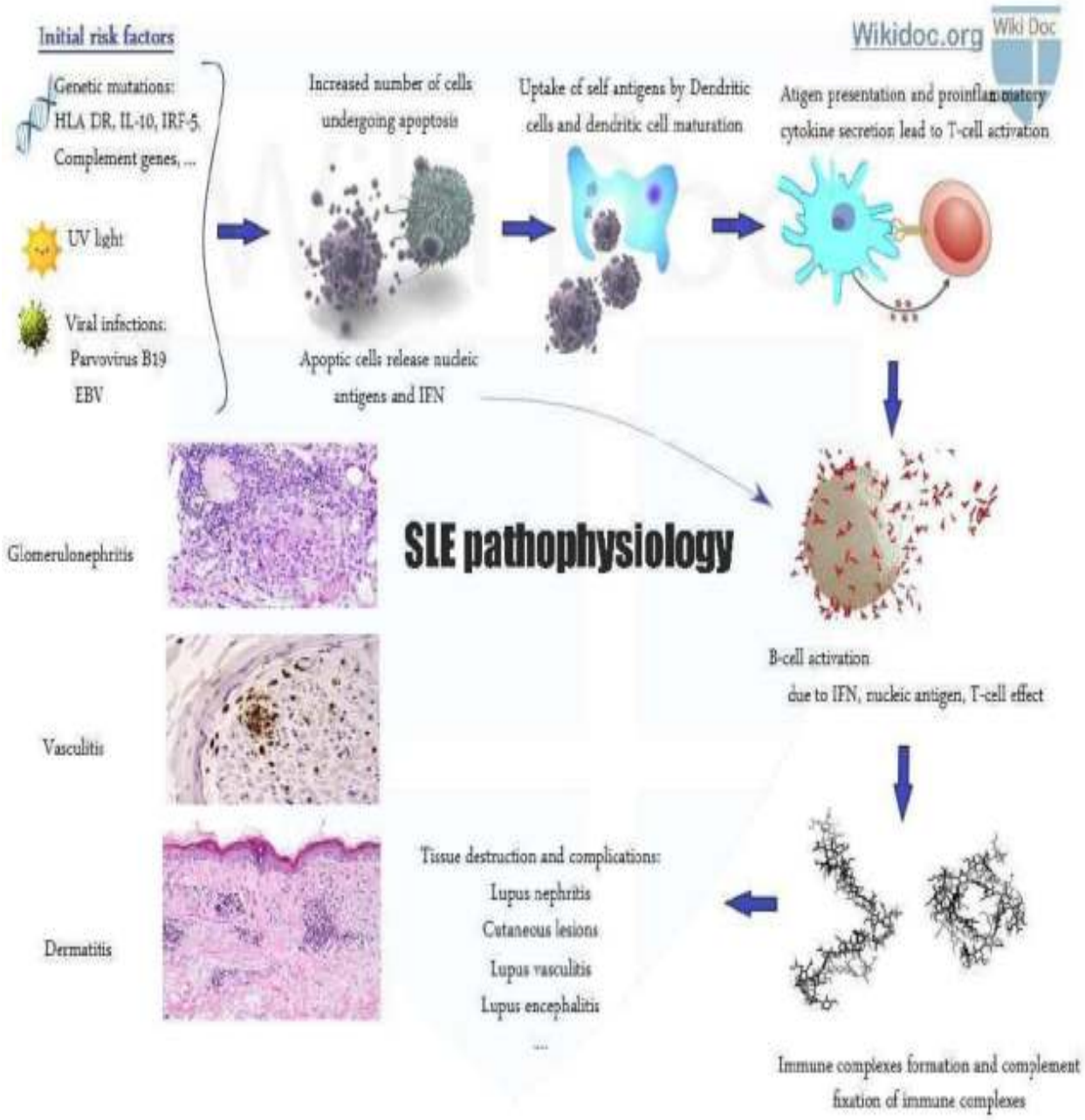
مهم جدا

3-**Environmental factor**: ultraviolet light ; infections (Epstein-Barr virus), and exposure to silica dust.

4- **medication : - Sulfa drugs**, which make a person more sensitive to the sun, such as: (trimethoprim-sulfamethoxazole) ,**Penicillin** :-amoxicillin; ampicillin .

Pathophysiology of SLE :-

- The development of systemic lupus erythematosus (SLE) is due to the activation of different mechanisms that may result in auto-immunity.
- The disease developmental process begins with the release of microparticles and proinflammatory cytokines from the cells that are undergoing apoptosis.
- Due to excess amount of apoptosis, the body is unable to clear these microparticles entirely, and these microparticles are presented to dendritic cells as antigens.
- Dendritic cells process these microparticles and mature, and present these as antigens to T-cells. T-cells, microparticles, and proinflammatory cytokines themselves trigger B-cell activation and autoantibody production.
- As a result, body tissues lose their self-tolerance. Affected patients are no longer entirely tolerant to all of their self-antigens, leading to development of an autoimmune disease and producing autoantibodies as a response.
- During disease progression, B cells and plasma cells that make autoantibodies are more persistently activated due to signaling abnormalities, causing them to make more autoantibodies. These autoantibodies are targeted predominantly to intracellular nucleoprotein particles.
- This increase in autoantibody production and persistence is supposed to be downregulated by anti-idiotypic antibodies or regulatory immune cells, but the massive immunologic response in SLE prevents this downregulation from taking place.
- After formation of immune complexes, the classical complement pathway is activated, which leads to the deposition of immune complexes in different organs and is responsible for flare ups and long term complications There are other factors such as genetic factors, hormonal abnormalities, and environmental factors that also play a role in the pathogenesis of SLE.



Criteria for diagnosis of SLE

SKIN :

1. Malar rash :- red or purplish and mildly scaly. Its shape of a **butterfly** and involves the bridge of the nose.

2. **Discoid rash :-** Erythematous hyper pigmented margins and flat scarred hypo pigmented centers

3. Photosensitivity : Rash over the sun exposed areas. Face, neck and V shaped area of chest

4. Oral ulcers:- Oral or nasopharyngeal ulceration, usually painless.

Systemic

5. Arthritis :- **Non erosive arthritis** Hand may show diffuse soft tissue swelling, **ulnar deviation**, **swan neck deformity**, MCP subluxation

6. Serositis 7. Renal disease. 8. Neurologic disease.

Lab :

9. **Hematologic disorders**:

-Hemolytic anemia

-Leukopenia ,(Lymphopenia)

-Thrombocytopenia

10. **Immunologic abnormalities**:

Anti-ds- DNA ,Anti- Sm ,Anti-phospholipid , False +ve VDRL

11. **Positive ANA .**

Laboratory diagnosis:-

1-Complete blood count: anemia, which commonly occurs in lupus.

2-Erythrocyte sedimentation rate :It may be **elevated** if you have lupus,

3-Kidney and liver assessment. kidneys and liver are functioning. Lupus can affect these organs.

4-Urinalysis. increased **protein** level or **red blood cells** in the urine, which may occur if lupus has affected your kidneys.

5-Antiphospholipid antibodies (lupus anticoagulant [LA], IgG and IgM anticardiolipin [aCL] antibodies; and IgG and IgM anti-beta2-glycoprotein [GP] I)

6-C3 and **C4** or **CH50** complement levels decrease levels due to consumption by Immune complex

7-The **LE cell (Lupus Erythematosus cell)** is a neutrophil or macrophage that has engulfed or phagocytized the (denaturated nuclear material) antibody-coated nucleus of another cell .

8-Anti nuclear antibodies (ANA) :- (also known as antinuclear factor or ANF) are autoantibodies that bind to contents of the cell nucleus. In normal individuals, the immune system produces antibodies to foreign proteins (antigens) but not to human proteins . In most cases, a positive ANA test indicates that your immune system has launched a misdirected attack on your own tissue — in other words, an autoimmune reaction.

A -Anti-dsDNA :- The anti-double stranded DNA (anti-dsDNA) test is used to help diagnose lupus (systemic lupus erythematosus, SLE) in a person who has a positive result on a test for antinuclear antibody (ANA) and has clinical signs and symptoms that suggest lupus. highly specific for SLE seen in approximately 70 percent of patients with SLE.

B –Extractable nuclear antigens (ENA) :- panel detects the presence of autoantibodies in the blood that react with proteins in the cell nucleus. These proteins are known as “extractable” because they can be removed from cell nuclei using saline and represent six main proteins (Ro, La, Sm, RNP, Scl-70 and Jo1).

a-Anti-Sm antibodies :- Anti-smooth muscle antibodies are antibodies formed against smooth muscle. are highly specific for SLE, but anti-Sm antibodies lack sensitivity (30%) .

b- Anti-Ro/SSA and **anti-La/SSB** antibodies are present in approximately 30 and 20 percent of patients with SLE, respectively; however, both antibodies are more commonly associated with Sjögren's syndrome .

c-Anti-U1 RNP antibodies are observed in SLE and mixed connective tissue disease (MCTD) .

9-Anti-ribosomal P protein antibodies have a high specificity for SLE, but have low sensitivity for SLE.

10- Biopsy :- sample of kidney tissue to determine the change and what the best treatment.

Treatments :- No permanent cure for SLE: treatment relieves symptoms

1-NSAIDs (non-steroidal anti-inflammatory drugs) **Aspirin ,ibuprofen** Reduce inflammation and pain .

2-Corticosteroids : Reduce inflammation Used after significant organ damage .

3-Antimalarial Drugs :- Hydroxychloroquine Reduces inflammation, protects against organ damage **,**Used for skin symptoms, joint pain .

4-DMARDs (disease-modifying antirheumatic drugs) :- **rituximab** Suppress B cell development, block B cell stimulation .

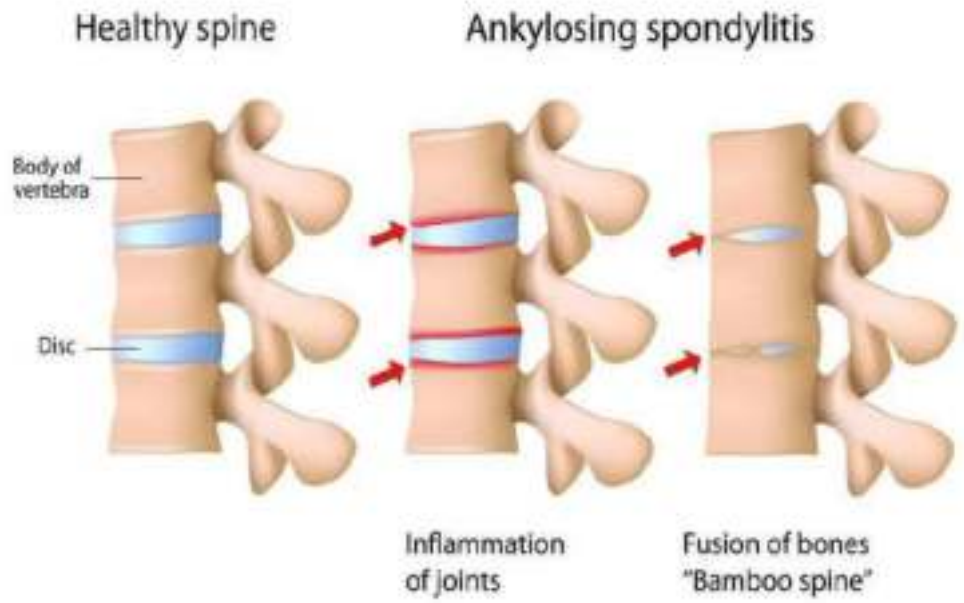
Lecture : 3

Inflammatory rheumatic diseases

3- Ankylosing spondylitis

Is a type of inflammatory arthritis disease that causes lower back pain. Symptoms, including hip pain and a stiff back that may come and go. Over time, vertebrae in the spinal column may fuse and become rigid (ankylosis). This fusing makes the **spine less flexible** and can cause difficult breathe deeply.

Ankylosing spondylitis affects **men** more often than women, occurs in late adolescence or **early adulthood**..



Sign and symptoms :-

1- stiffness and pain in your lower back in the early morning that lasts at least 30 minutes and then eases through the day or with activity
2- pain that wakes you in the night
3- pain in one or both buttocks and sometimes the backs of the thighs.

Causes :-

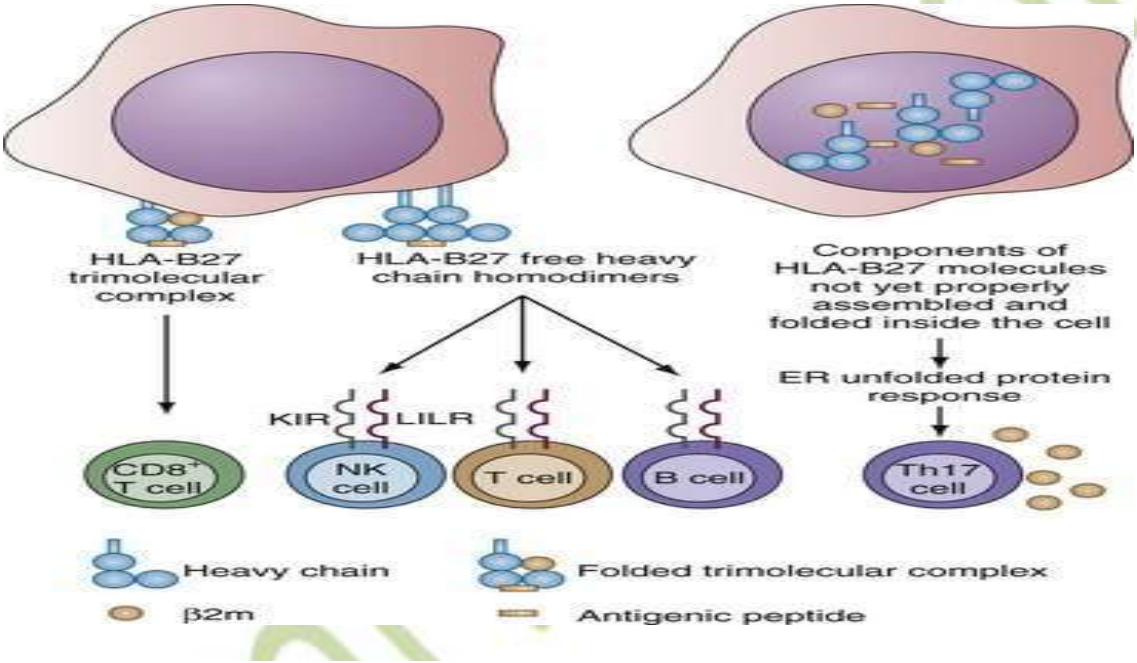
Unknown ,but genetic marker," a protein called **HLA-B27**. This marker is found in more than **95 percent** of people who have AS have a variation of the human leukocyte antigen-B gene (HLA-B). This changed, or mutated, gene produces a protein called HLA-B27 that increases disease risk.

Pathophysiology

In rheumatoid arthritis and spondyloarthropathy patients ,the inflamed synovium of peripheral joints exhibits similar characteristics. Three different structures of HLA-B27 and how they might induce the processes of arthritis. HLA-B27 is first generated as a free heavy chain, which inside the cell becomes associated and folded with β2-microglobulin (β2m) and antigenic peptide, and then becomes expressed on the cell surface as a trimolecular complex. It can also be

expressed on the cell surface as homodimers of heavy chains without β2m. ER, endoplasmic reticulum; KIR, killer-cell immunoglobulin-like receptor; LILR, leukocyte immunoglobulin-like receptor; NK, natural killer.

The arthritogenic peptide hypothesis postulates that in the case of ankylosing spondylitis, there is a breakdown of tolerance to certain self-peptides, and this breakdown is a consequence of mimicry between the self-peptides and certain pathogen-derived and arthritis-causing peptides.



Diagnosis :-

1-Rediographical feature:- X-ray , CT (Computed Tomography) , MRI (Magnetic Resonance Imaging), shows erosions and sclerosis.

2-Blood parameters:- increase CRP (c-reactive protein) and an increase in the ESR (erythrocyte sedimentation rate) .

3-Genetic testing : - HLA-B27

Treatments :-

1-Medication:- Disease-modifying anti-rheumatic drugs (DMARDs), (TNFα) blockers.

2- Surgery :- Surgical correction is also possible for those with severe flexion deformities.

3- Physical therapy

Lecture : 4

Inflammatory rheumatic diseases

4-Sjogrens syndrome

Sjögren's is a systemic, autoimmune, rheumatic disease that can affect many different body parts, especially the moisture-producing glands, and cause widespread dryness and other serious problems. Although dry mouth and dry eyes are the most common symptoms, dryness can also occur in the nose, sinuses, ears, throat, skin, and, in women, the vagina. There is speculation that, in men with Sjögren's, the prostate might be affected similarly to other organs.

Symptoms: -

The symptoms of Sjogren's can be different from person to person. You may have just one or two, or you may have many. By far, the most common symptoms are:

- Dry mouth that may have a chalky feeling or feeling or feel like cotton
- Dry eyes that may burn, itch, or feel gritty
- Dry throat, lips, or skin
- Dryness in your nose
- A change in taste or smell
- Swollen glands in your neck and face
- Skin rashes and sensitivity to UV light
- Dry cough or shortness of breath
- Feeling tired

- Trouble concentrating or remembering things
- Headache
- Dryness in the vagina in women
- Swelling, pain, and stiffness in your joints
- Heartburn, a sensation of burning that moves from your stomach to your chest
- Numbness or tingling in some parts of your body

Specific Tests for Sjögren's Syndrome

To make a Sjögren's syndrome diagnosis, doctors must see specific antibodies (blood proteins) in your blood. They also need to see a pattern of inflammation, found most often on the salivary glands of your lips, which is characteristic of Sjögren's syndrome.

Your doctor may recommend some or all of the following tests:

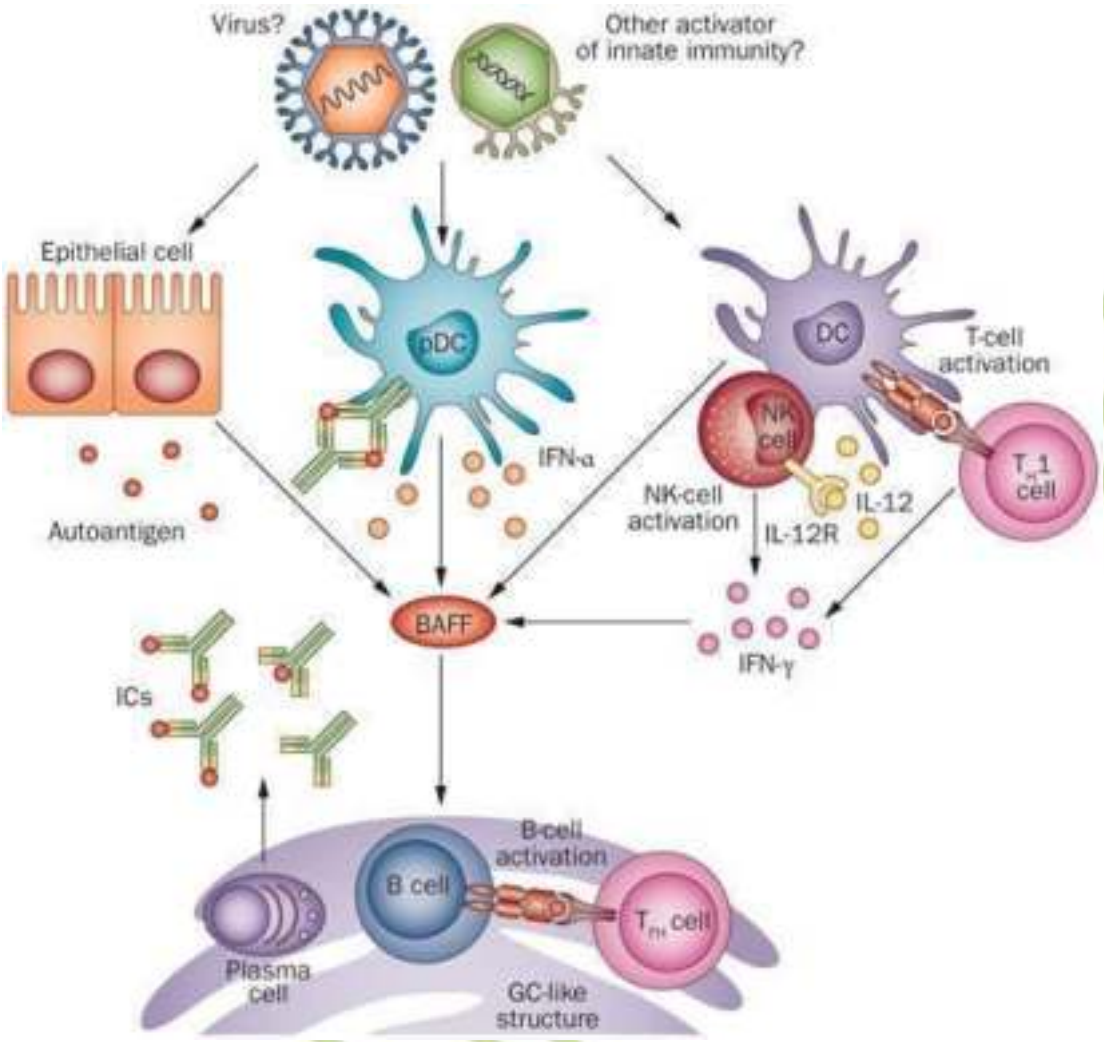
- Blood and urine tests, to look for the presence of antibodies common in Sjögren's syndrome. The results of an ANA (antinuclear antibody) test will determine if you have an autoimmune disorder.
- Schirmer's test, to see if your tear glands are producing enough tears to keep your eyes moist.
- Ocular surface staining to look closely at the surfaces of your eyes for damage and dryness.
- Salivary gland function scans, which look at the glands on the sides of your neck, below your ears and under your jaw.
- A biopsy of your lip to look for inflammation of the glands that produce saliva and tears. This test can determine the type of inflammation and the severity. A biopsy of the lip is performed because the salivary glands just under the lip's inner surface are the easiest glands to access.
- Sialometry, which measures the flow of saliva.
- Ultrasonography of the major salivary glands to reveal characteristic structural changes that can aid in diagnosis.

Pathophysiology of Sjögren's syndrome :-

- Sjögren's syndrome is a chronic autoimmune disease of largely unknown etiology and pathogenesis. The salivary and lacrimal glands are the main

target organs, and key cells and molecules involved in the autoimmune process have been detected in these glands.

- Chemokines, expressed by epithelial cells, can attract T cells and dendritic cells that produce proinflammatory cytokines, which stimulate the immune response and induce apoptosis in the acinar and ductal epithelial cells.
- The autoantigens SSA and SSB are translocated to the apoptotic blebs and trigger infiltrating B cells to produce autoantibodies against SSA and SSB.
- Germinal-center-like structures can form within glandular lymphocyte foci, facilitating the antigen-driven B-cell activation.
- Many of the autoimmune mechanisms described above can be induced by type I interferon (IFN), and activation of this system in patients with Sjögren's syndrome has been described.
- A possible scenario is that an initial viral infection induces type I IFN production in salivary glands with a subsequent activation of the adaptive immune system. Resultant autoantibodies form nucleic-acid-containing immune complexes that can trigger prolonged type I IFN production, leading to a self-perpetuating autoimmune reaction.
- Several potential therapeutic targets for Sjögren's syndrome exist within the type I IFN system.



Treatment

You'll need to take medicine throughout your life to help you manage your symptoms. You can buy some kinds in a drugstore without a prescription, while your doctor may need to prescribe stronger ones if those don't work well enough.

For instance, drops called "artificial tears" can keep your eyes from drying out. You'll need to use them regularly throughout the day. There are also gels that you put on your eyes at night. The advantage of the gels is that they stick to your eye's surface, so you won't need to apply them as often as the drops.

If artificial tears aren't helping, your doctor may prescribe drugs for your dry eyes, including:

- Cequa
- Lacrisert
- Restasis

Lacrisert is a tiny rod-shaped medicine. You put it into your eye with a special applicator, usually once or twice a day. Cequa and Restasis come in drops, which you use twice a day.

Another treatment option for dry eyes is a procedure called punctal occlusion. This is when your doctor puts tiny plugs into your tear ducts to block them up. This keeps tears from draining away too fast, meaning they stay on your eyes longer and help your eyes stay moist.

To help your dry mouth, your doctor may prescribe drugs that boost the amount of your saliva, including:

- Cevimeline (Evoxac)
- Supersaturated calcium phosphate rinse (NeutraSal)
- Pilocarpine (Salagen)

There are other treatments for some of the less common symptoms of Sjogren's syndrome. For instance, if you get yeast infections in your mouth, your doctor might prescribe antifungal medicine.

If you get heartburn, your doctor may give you medicines that curb the amount of acid in your stomach.

Your doctor may also suggest a medicine called hydroxychloroquine (Plaquenil) to treat your joint pain. It's a drug that's also used to treat malaria, lupus, and rheumatoid arthritis.

It's rare, but some people with Sjogren's get symptoms throughout the body, including belly pain, fever, rashes, or lung and kidney problems. For those situations, doctors sometimes prescribe prednisone (a steroid) or an anti-inflammation drug called methotrexate (Rheumatrex, Trexall).

Lecture : 5

Inflammatory rheumatic diseases

5- Behçet's disease

(BD) is a type of inflammatory disorder which affects multiple parts of the body.The most common symptoms include **painful mouth sores**, **genital sores**, inflammation of parts of the **eye**, and **arthritis**. Less commonly there may be inflammation of the brain or spinal cord, blood clots, **aneurysms**, or blindness, symptoms come and go.

Causes :- The primary cause is **not well known**, but consider **auto-inflammation of the blood vessels**. Some virus may be associated

Risk factors

Age :men and women in their **20s and 30sAge**, though children and older adults also can develop the condition.

Where you live. People from countries in the Middle East and Far East, including Turkey, Iran, Japan and China, are more likely to develop Behcet's.

Sex. While Behcet's disease occurs in both men and women, the disease is usually more **severe in men**.

Genes: HLA B51

Sign and symptoms

1-Sores : mouth **(canker sores) ,** skin (**acne-like sores),**genital **(scrotum or the vulva)**

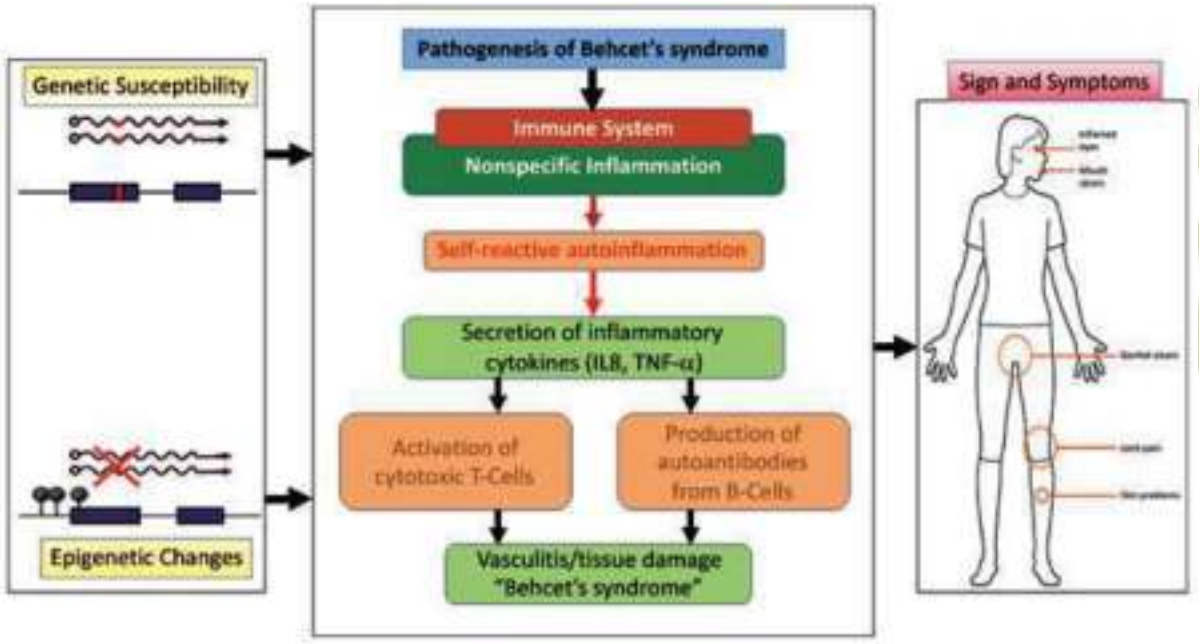
2- Eyes :Uveitis

2-Joints :-Joint swelling and pain

3-**Vascular system** :- aneurysms

4- Digestive and neurological system also involved

Pathogenicity of Behcet's disease



Diagnosis

There are no specific tests to confirm a diagnosis of Behcet's Disease. The diagnosis is based on clinical criteria. It may take several months or years for all the common symptoms of the disease to appear, often making it difficult to obtain a definitive diagnosis. The diagnosis is based on the occurrence of signs and symptoms of the disease and on positive clinical criteria referred to as the International Clinical Criteria for Behcet's Disease.

International Clinical Criteria for Behcet's Disease

An international group of physicians has established a set of guidelines to aid in the classification of Behcet's patients. The International Clinical Criteria for Behcet's Disease classification states patients must present with:

- Recurrent oral ulcerations (apthous or herpetiform) at least three times in one year.
- Additionally, patients must present any two of the following:
  - Recurrent genital ulcerations
  - Eye lesions (uveitis or retinal vasculitis) observed by an opthalmologist
  - Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules) found in adult patients not being treated with corticosteroids

- Positive "pathergy test" read by a physician within 24-48 hours of testing

Pathergy Test

- Doctors attempting to make a diagnosis of Behcet's Disease may order a pathergy test in an attempt to produce a pathergy reaction. The pathergy test is a simple procedure in which a small, sterile needle, is inserted into the skin of the forearm. Occurrence of a small red bump or pustule at the site of needle insertion one to two days following the pathergy test constitutes a positive result. A positive result indicates the immune system is overreacting to a minor injury. Although a positive pathergy test is helpful in the diagnosis of Behcet's Disease, only a minority of Behcet's patients demonstrate the pathergy phenomenon by having a positive test. Patients

Treatments

Corticosteroid ,

Anti –TNF like infliximab

Lecture : 5

Inflammatory rheumatic diseases

6- Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic, inflammatory disease of the joints and where tendons and ligaments connect to bone. It can start at any age and may affect children and **adults** .

The classic feature of psoriatic arthritis is **swelling of entire fingers** and **toes with a sausage-like appearance**. This often happens in association with changes to the nails such as small depressions in the nail **(pitting)**, thickening of the nails, and detachment of the nail from the nail bed. Skin changes consistent with psoriasis (e.g., red, scaly, and itchy plaques) frequently occur **before** the onset of psoriatic arthritis .

Approximately 40-50% of individuals with psoriatic arthritis have the **HLA-B27 genotype.**

Classification: -

1-Oligoarticular: **mild**. does **not** occur in the same joints on both sides of the body and involves **fewer than 3 joints**.

2-Polyarticular: affects **five or more** joints on both sides of the body simultaneously. This type is most **similar to rheumatoid arthritis**.

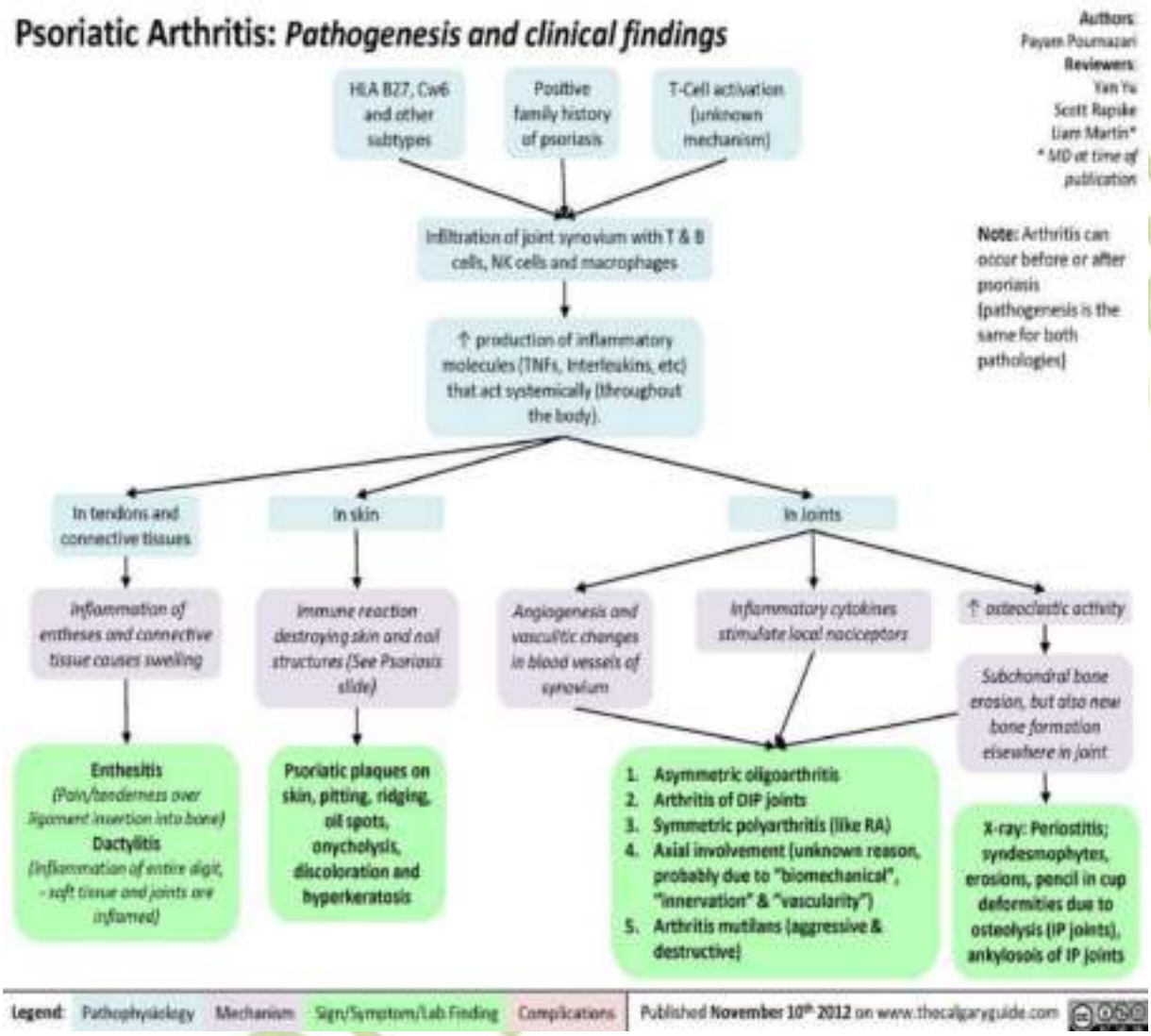
3-Arthritis mutilans :a **severe**, deforming and destructive arthritis. This condition can progress over months or years causing severe joint damage. Arthritis mutilans has also been called **chronic absorptive arthritis**

4-Spondyloarthritis : characterized by stiffness of the neck or the sacroiliac joint of the spine, but can also affect the hands and feet, in a similar fashion to **symmetric arthritis.**

5-Distal interphalangeal predominant : characterized by inflammation and stiffness in the joints nearest to the ends of the fingers and toes. **Nail changes are often marked**

Sign and symptoms :-Dactylitis, onycholysis, hyperkeratosis under the nails, joints symptoms .

Causes :Unknown ,but **HLA B27** associated



Diagnosis: **No definitive test** to diagnose psoriatic arthritis.

1- family history of psoriasis or psoriatic arthritis.

2- Laboratory tests :- Rheumatoid factor (RF). RF is an antibody that's often present in the blood of people with rheumatoid arthritis but not usually in the blood of people with psoriatic arthritis. This test can help your doctor distinguish between the two conditions. **A negative** test result for rheumatoid factor

3- Radiologic images

- **X-rays.** These can help pinpoint changes in the joints that occur in psoriatic arthritis but not in other arthritic conditions.
- **MRI.** This uses radio waves and a strong magnetic field to produce detailed images of both hard and soft tissues in your body. MRI can be used to check for problems with the tendons and ligaments in your feet and lower back..

Treatments :- NSAIDs , DMARDs

Lecture : 6

Gastrointestinal and liver diseases

1-Celiac disease

Celiac disease is an autoimmune disorder that's triggered when you eat gluten. It's also known as celiac sprue, nontropical sprue, or gluten-sensitive enteropathy.

Gluten is a protein in wheat, barley, rye, and other grains. It's what makes dough elastic and gives bread its chewy texture.

When someone with celiac disease eats something with gluten, their body overreacts to the protein and damages their villi, small finger-like projections found along the wall of their small intestine.

Sign and symptoms

- Diarrhea
- Fatigue
- Weight loss
- Bloating and gas
- Abdominal pain
- Nausea and vomiting Anemia, usually from iron deficiency

- Loss of bone density (osteoporosis) or softening of bone (osteomalacia)
- Itchy, blistery skin rash (dermatitis herpetiformis)
- Mouth ulcers
- Headaches and fatigue
- Nervous system injury, including numbness and tingling in the feet and hands, possible problems with balance, and cognitive impairment
- Joint pain
- Reduced functioning of the spleen (hyposplenism)

Causes:- Unknown , but many risk factors presents

1-**HLA DQ2 and HLA DQ8**

2- Autoimmune disease, such as type 1 diabetes, rheumatoid arthritis, or an autoimmune disease that affects the thyroid or the liver

3-Genetic disorder, such as Down syndrome or Turner syndrome

4-Family member who has the disease (**1 in 10**).

Diagnosis

1-Electrolytes and chemistries - Electrolyte imbalances; evidence of malnutrition

2-Hematologic tests - Anemia, low serum iron level, prolonged prothrombin time (PT)

3-Stool examination - Fat malabsorption

4-Oral tolerance tests - Lactose intolerance

5-Serology - Immunoglobulin A (IgA) antibodies

1-Anti- Gliadin IgA/IgG

2-Anti -Reticulin IgA

3-Anti- Endomysial IgA

4-Anti- Tissue Transglutaminase IgA

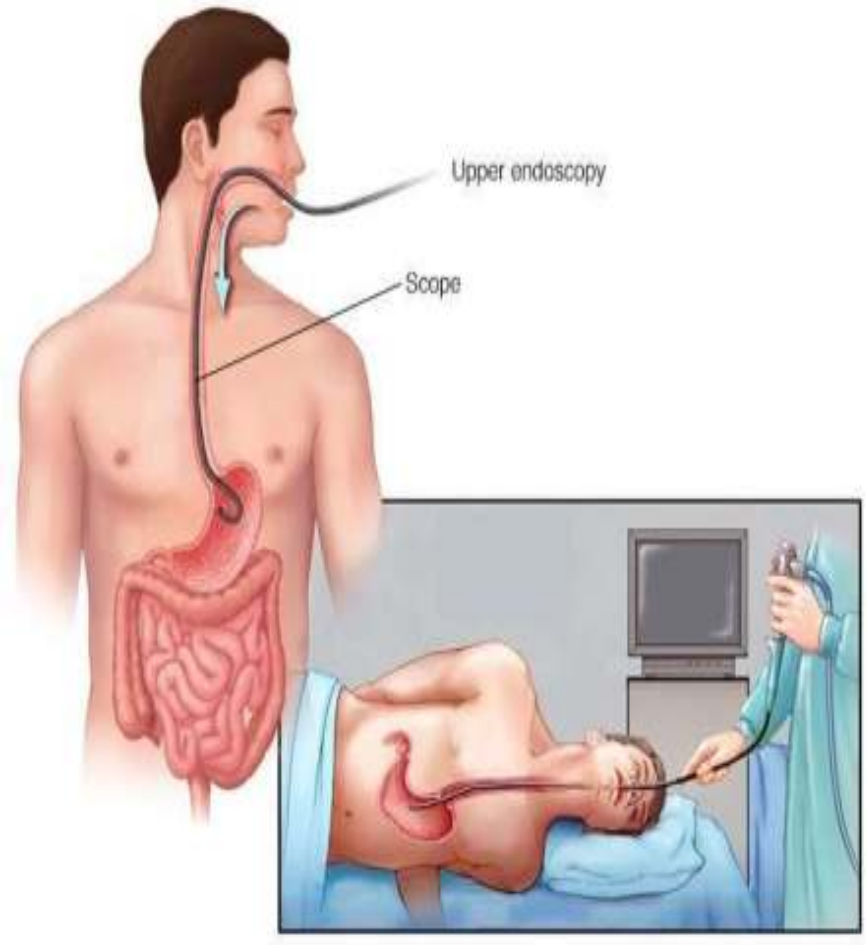
5- IgA deficiency: False-negatives 3-5% of celiac patients are IgA deficient

6-Imaging studies

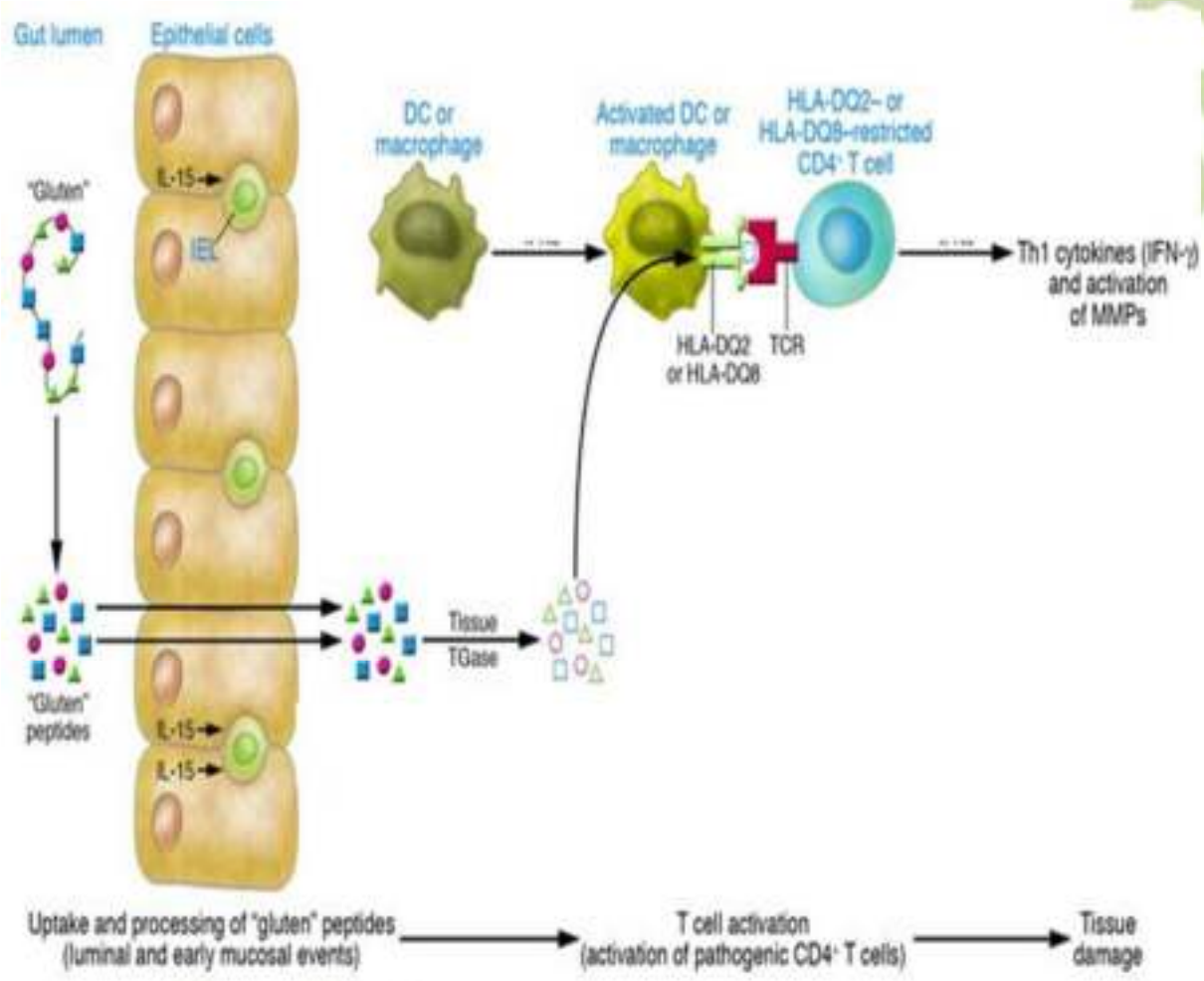
after barium ingestion is helpful to find dilatation of the small intestine, fragmentation or flocculation of the barium in the gut lumen.

7-Endoscopy and biopsy

Upper endoscopy with at **least 6 duodenal biopsies** is considered the **criterion standard** to help establish a diagnosis of celiac disease.



Pathophysiology



The pathogenesis of celiac disease into 3 major series of events: luminal and early mucosal events, activation of pathogenic CD4+ T cells, and subsequent events leading to tissue damage.

During the luminal and early mucosal events, key features include the ingestion of "gluten" by a genetically susceptible individual. Gluten is not fully digested because of its high proline content, and this gives rise to a number of large undigested gluten peptides.

The peptides gain access across the epithelial barrier to the lamina propria where they encounter tissue transglutaminase and antigen-presenting cells that express DQ2 or DQ8 that are ideally suited to bind those deamidated proline-rich peptides.

In a further series of events, the antigen-presenting cells present some of these peptides to DQ2 or DQ8 restricted populations of $CD4^+$ T cells, which become activated and release mediators that ultimately lead to tissue damage.

There are still many unknowns. These include the mechanism by which gluten peptides cross the epithelial barrier, the role of the intraepithelial lymphocytes in early and late disease pathogenesis, the role of IL-15 and type I interferons in disease pathogenesis, and the underlying basis for the release of tissue transglutaminase that leads to deamidation of gluten peptides.

Treatments :-

There is **no medication** that treats celiac disease .but should avoid gluten diet and take ***Gluten-Free Diet***

Lecture : 6

Gastrointestinal and liver diseases

2 -Pernicious anemia

Vitamin B12 deficiency anemia, of which pernicious anemia is a type, is a disease in which not enough red blood cells are present due to a lack of vitamin B12, technically refers to cases resulting from **not enough intrinsic factor**, it is often used to describe all cases of anemia due to not enough vitamin B12, Lack of intrinsic factor is most commonly due to an autoimmune attack on the cells that create it in the stomach.

Sign and symptoms

Come on slowly. If untreated, it can lead to neurological complications, and in serious cases, death.

skin sensations (**paresthesia),** tongue soreness (**glossitis**), and fatigue and general weakness. depressive mood, low-grade fevers, diarrhea, dyspepsia, weight loss, neuropathic pain, jaundice, sores at the corner of the mouth.

Causes

Lack of vitamin B-12(Cobalamine)

Vitamin B-12 plays a role in creating RBCs, so the body requires an adequate intake of vitamin B-12. Vitamin B-12 is found in: meat ,poultry ,shellfish ,eggs

dairy products

Lack of IF

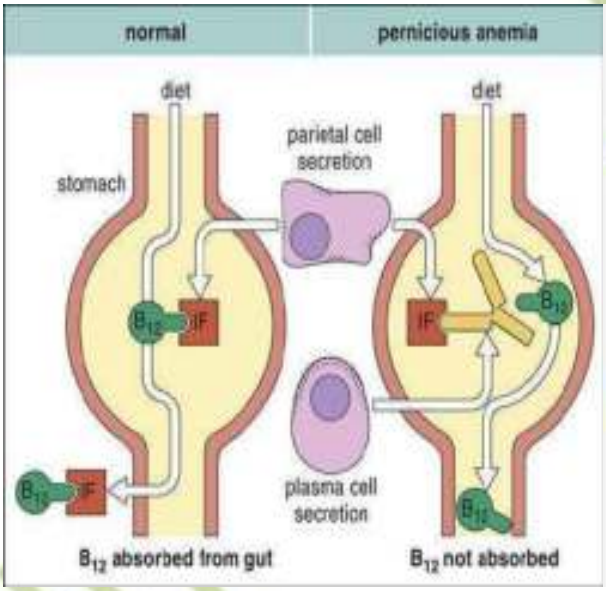
Your body also needs a type of **protein** called intrinsic factor (IF) to absorb vitamin B-12. IF is a protein produced by cells in the stomach. After you consume vitamin B-12, it travels to your stomach where it binds with IF. The two are then absorbed in the last part of your small intestine. In most cases of pernicious anemia, the body's immune system attacks and destroys the cells that produce IF in

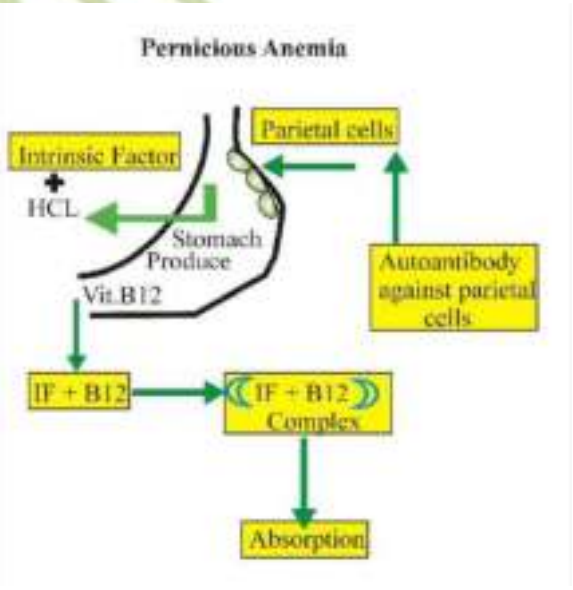
the stomach. If these cells are destroyed, the body can't make IF and can't absorb vitamin B-12.

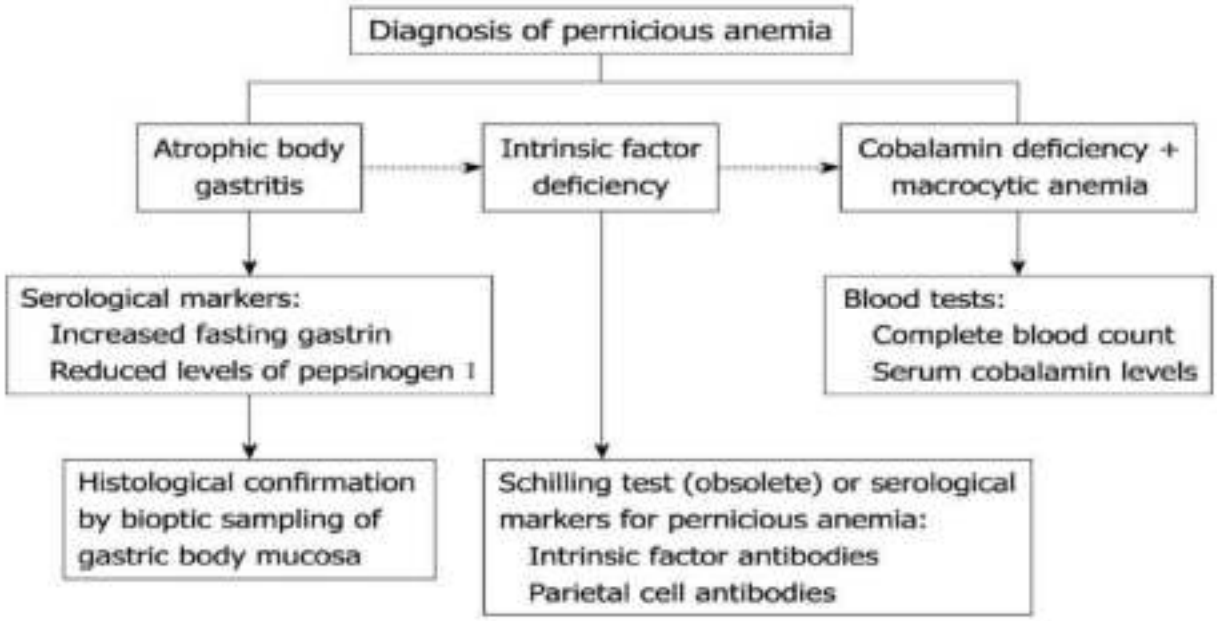
Macrocytes

Without enough vitamin B-12, the body will produce abnormally large red blood cells called macrocytes. Because of their large size, these abnormal cells may not be able to leave the bone marrow, where red blood cells are made, and enter the bloodstream. This decreases the amount of oxygen-carrying red blood cells in the bloodstream and can lead to fatigue and weakness.

Pernicious anemia is a type of macrocytic anemia. It's sometimes called megaloblastic anemia because of the abnormally large size of the red blood cells produced.







Treatment

- ***Cobalamin deficiency*** – Parenteral (i.m) – 1000 mcg daily for 1 week, weekly for next 4 weeks (*until hematocrit becomes normal*)
- Pernicious anemia and malabsorption – Monthly cobalamin supplementation.
- *Erratic absorption with oral formulations*
- **Folate deficiency** - folic acid(1 to 5 mg/day orally) for 3 – 4 weeks

Lecture : 6

Gastrointestinal and liver diseases
3-Diabetes mellitus

(DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period, Diabetes is due to either the pancreas **not producing enough insulin** or the cells of the body **not responding properly to the insulin** produced.

main types of diabetes mellitus:

1-**Type 1 DM** results from the pancreas's failure to produce enough insulin This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.

2-**Type 2 DM** begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is excessive body weight and not enough exercise.

3-**Gestational diabetes** is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

4-**Maturity onset diabetes of the young**

is an **autosomal dominant inherited** form of diabetes, due to one of several single-gene mutations causing defects in insulin production. It is significantly less common than the three main types. thus there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.

5-Other types

A- Prediabetes :- indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes.

B-Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than cause.

Sign and symptoms

polyuria (excessive urination)

polydipsia (increased thirst), dry mouth,

polyphagia (increased hunger),

fatigue, and weight loss , Blurred vision

Many type 1 diabetics are diagnosed when they present with **diabetic ketoacidosis**. The signs and symptoms of diabetic ketoacidosis include **dry skin**, rapid deep breathing, drowsiness, increased thirst, frequent urination, abdominal pain, and vomiting.

Causes:- Unknown ,but risk factor such as (genetic **HLA DR3,DR4**, family history, virus ,environment , (**age 4-7 in type 1 & above 10 in type 2**)

Pathophysiology of type1

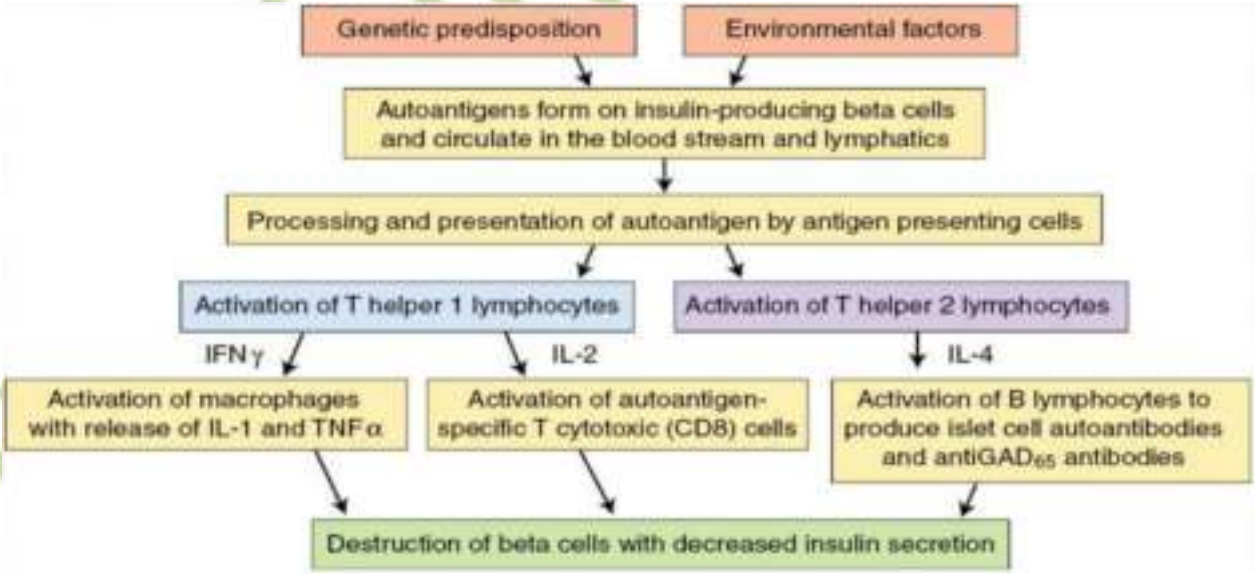


Figure 21-13 Pathophysiology of type 1 diabetes mellitus. *GAD*$_{65}$, glutamic acid decarboxylase; *INF*-γ Interferon-gamma; *IL*, interleukin; *TNF*-α, tumor necrosis factor-alpha.

Diagnosis

1-Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).

2-Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a **glucose tolerance test**.

3-Glycated hemoglobin (**hemoglobin A1C**) at or above 48 mmol/mol (≥ 6.5 DCCT %).also referred to as being **Hb1c or HGBA1C**) is a form of hemoglobin that is measured primarily to identify the **three-month** average plasma glucose concentration. The test is limited to a three-month average because the lifespan of a red blood cell is four months (120 days), **Normal levels of glucose produce a normal amount of glycated hemoglobin.**

Autoantibodies in DM

Test	Abbr	Description	Comments
Islet Cell Cytoplasmic Autoantibodies	**ICA**	Abs reacts with cytoplasmic components of all of the cells in the pancreatic islets(a $\beta\ \gamma\delta$. These antibodies occur in about 60% to 70% of newly diagnosed patients with IDDM,	providing strong evidence for an autoimmune origin and pathogenesis of the disease. The presence of ICA can be demonstrated for **years before the occurrence of symptoms**. The antibody tends to disappear with time.
Glutamic Acid Decarboxylase Autoantibodies	**GADA**	Tests for autoantibodies directed against beta cell protein (antigen) but is not specific to beta cells	Also one of the most commonly detected autoantibodies in newly diagnosed type 1 diabetics (about 70-80%)
Insulinoma-Associated-2	**IA-2A**	Tests for autoantibodies directed against beta cell antigens but is non-	Detected in about 60% of type 1 diabetics

Autoantibodies		specific	
Insulin Autoantibodies	**IAA**	Autoantibody targeted to insulin; insulin is the only antigen thought to be highly specific for beta cells.	Detected in about 50% of type 1 diabetic children; not commonly detected in adults

Genetic/other markers	T1DM	LADA	T2DM
Islet cell antibodies	Positive, may test positive before onset	Positive, helps differentiation from T2DM	Negative
Insulin autoantibody	Often detected	Often detected	Negative
Islet antigen 2	Often positive in newly diagnosed T1DM	Often detected	Negative
Glutamic acid decarboxylase antibody	Common in adults than in children	More common than in T1DM	Rare, positive may indicate LADA
HLA link	High	Low	Negative
Insulin/C-peptides	Very low	Low	Normal to high

T1DM: Type 1 diabetes mellitus, LADA: Latent autoimmune diabetes of adults, T2DM: Type 2 diabetes mellitus

Treatments

1. Taking insulin
2. Carbohydrate, fat and protein counting
3. Eating healthy foods
4. Exercising regularly and maintaining a healthy weight

Lecture : 7

Gastrointestinal and liver diseases

4- Ulcerative colitis

Is a disease that causes inflammation and sores (ulcers) in the lining of the large intestine (colon). It usually affects the lower section (**sigmoid colon**) and the **rectum**. But it can affect the entire colon.

There are five kinds of UC:

1-**ulcerative proctitis** (mildest form that affects the rectum only)

2-**proctosigmoiditis** (affects lower colon and rectum)

3-**left-sided colitis** (affects descending colon and rectum)

2-**Extensive colitis** (Extensive colitis involves the colon extending from the rectum to any point beyond the splenic flexure, but not including cecum.)

3-**pancolitis** (affects the whole colon and causes persistent bloody diarrhea)

Sign and symptoms

Ulcerative colitis symptoms can **vary, depending on the severity of inflammation** and where it occurs. Signs and symptoms may include:

Diarrhea, often with blood or pus

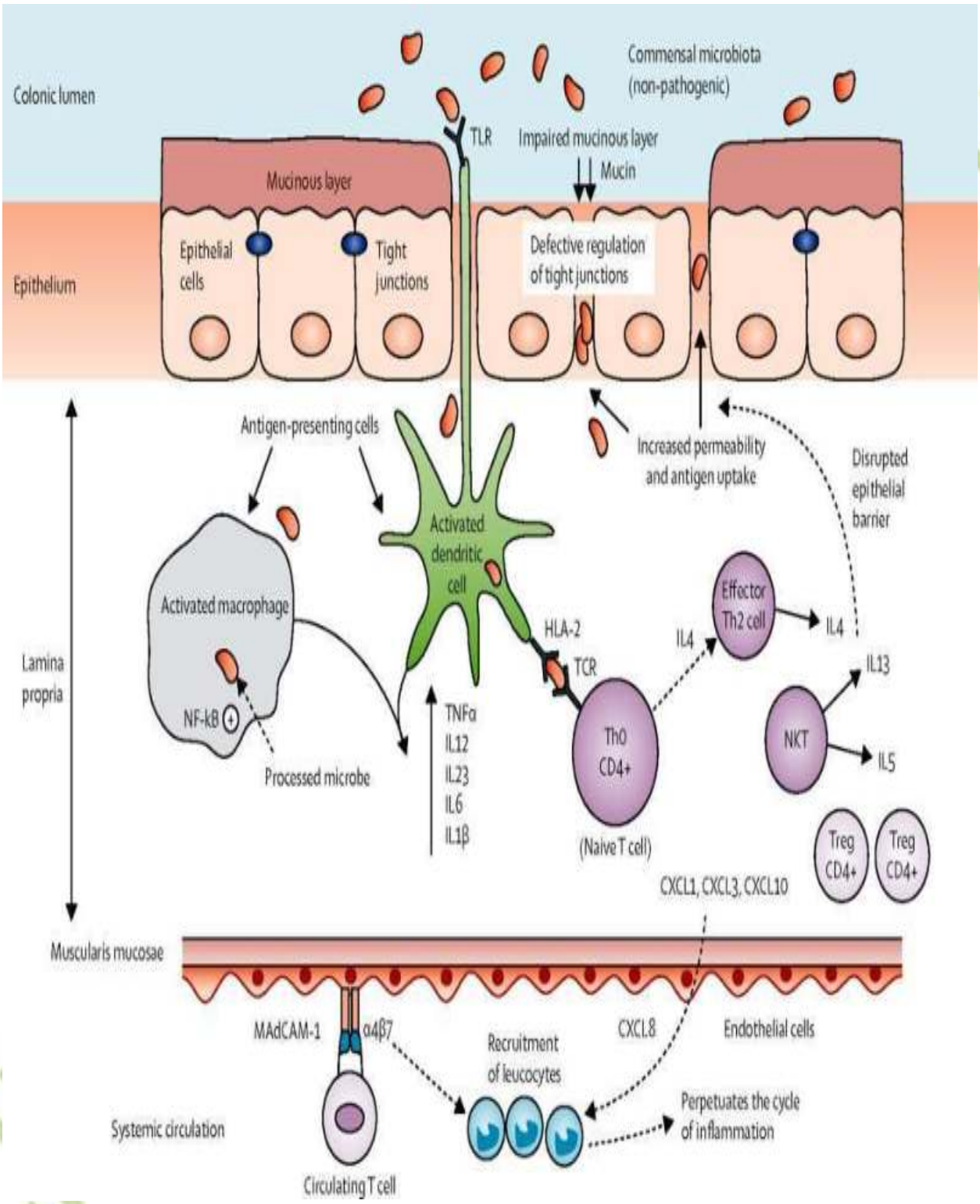
Abdominal pain and cramping

Rectal pain , Rectal bleeding — passing small amount of blood with stool

Urgency to defecate Weight loss Fatigue Fever

Causes :- Unknown --- risk factors

1-Genetic factors (HLA DR1,DR2,DR3) 2-environmental factors 3-Age :occur below 30 4-autoimmune factors 5-strees 6-infection 7-food allergy


Colonic lumen
Commensal microbiota
(non-pathogenic)
TLR
Impaired mucinous layer
Mucin
Mucinous layer
Epithelium
Epithelial cells
Tight junctions
Defective regulation of tight junctions
Antigen-presenting cells
Increased permeability and antigen uptake
Disrupted epithelial barrier
Activated dendritic cell
Activated macrophage
Lamina propria
NF-kB
Processed microbe
HLA-2
TCR
TNFα
IL12
IL23
IL6
IL1β
Th0 CD4+
(Naive T cell)
Effector Th2 cell
IL4
IL4
IL13
NKT
IL5
Treg CD4+
Treg CD4+
CXCL1, CXCL3, CXCL10
Muscularis mucosae
MAdCAM-1
α4β7
CXCL8
Endothelial cells
Recruitment of leucocytes
Perpetuates the cycle of inflammation
Systemic circulation
Circulating T cell

Diagnosis

Blood tests:- tests to check for anemia. Blood protein levels ,Blood sedimentation rates ,Body mineral levels ,RBC counts WBC counts

Stool sample:- White blood cells in your stool can indicate ulcerative colitis.

Colonoscopy:- take small samples of tissue (biopsy) for laboratory analysis. Sometimes a tissue sample can help confirm a diagnosis.

Flexible sigmoidoscopy.:-If your colon is severely inflamed, your doctor may perform this test instead of a full colonoscopy.

X-ray. :- use a standard X-ray of your abdominal area to rule out serious complications, such as a perforated colon.

CT scan:- reveal how much of the colon is inflamed.

Antibody Markers in Crohn's Disease and Ulcerative Colitis

Antibody marker	Crohn's disease	Ulcerative colitis
pANCA	±	+++
ASCA	+++	–
PAB	++	–
AEA-15	+++	+
AECA	+	++
Lymphocytotoxic	++	+
Anti-epithelial	+	++
Anti-p40	+	+++

PAB, pancreatic autoantibody; AEA-15, anti-erythrocyte antibody;AECA, anti–endothelial cell antibody; anti-p40, an antiepithelial autoantibody

The presence of antibodies against the yeast Saccharomyces cerevisiae (ASCA) and against neutrophils (pANCA) has been **used as diagnostic**

serological markers for inflammatory bowel disease (IBD) for many years. 1- **Positive ASCA** test with a **negative pANCA** test has a positive predictive value of 96% and a specificity of 97% **for Crohn's disease** (CD).

2-**ASCA−/pANCA+** predicts ulcerative colitis (UC) in 64%.

3- **both antibodies** have been found in other diseases, such as autoimmune liver disease, primary sclerosing cholangitis (pANCA), and in gluten sensitive enteropathy (ASCA).

Treatments

1-Anti-inflammatory drug :- corticosteroid ,5-aminosalicylates

2-Antibiotics.

3-Anti-diarrheal medications.

4-Pain relievers.

5-Iron supplements.

Lecture : 7

Gastrointestinal and liver diseases

5- Crohn's disease

Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. Prolonged inflammation results in damage to the GI tract.

symptoms of Inflammatory bowel disease (IBD)

- Persistent diarrhea
- Abdominal pain

- Rectal bleeding/bloody stools
- Weight loss
- Fatigue

Causes Of Inflammatory bowel disease (IBD)

The exact cause of IBD is unknown, but IBD is the result of a **defective immune system**. In IBD, the immune system responds incorrectly to [**environmental** triggers, which causes inflammation of the gastrointestinal tract. There also appears to be a **genetic component**—someone with a family history of IBD is more likely to develop this inappropriate immune response.

Diagnosis of Inflammatory bowel disease

IBD is diagnosed using a combination of **endoscopy** (for Crohn's disease) or **colonoscopy** (for ulcerative colitis) and **imaging studies,** such as contrast **radiography**, **magnetic resonance imaging (MRI), or computed tomography (CT)**.

Physicians may also check **stool samples** to make sure symptoms and blood tests to help confirm the diagnosis.

Crohn's disease

is a type of inflammatory bowel disease (**IBD**) that may affect **any part** of the gastrointestinal tract from **mouth to anus**, although it's most often found at the **end of the small intestine** (small bowel) and the **beginning of the colon** (large bowel).

Unlike with UC, Crohn's **isn't limited to the GI tract**. It may also affect the **skin, eyes, joints, and liver**. Since symptoms usually get worse after a meal, patients with Crohn's will often experience **weight loss due to food avoidance.**

Crohn's disease can cause **blockages of the intestine** due to scarring and swelling. Ulcers (sores) in the intestinal tract may develop into tracts of their own, known as **fistulas**. Crohn's disease can also **increase the risk for colon cancer** .

Symptoms include abdominal pain, diarrhea (which may be bloody if inflammation is severe), fever, abdominal distension, and weight loss.

erythema nodosum Bowel obstruction may occur as a complication of chronic inflammation, and those with the disease are at greater risk of colon cancer and small bowel cancer.

Diagnosis :-

Blood tests

1- complete blood count may reveal anemia, which commonly is caused by blood loss leading to iron deficiency or by **vitamin B_{12} deficiency**. Rarely autoimmune hemolysis may occur.

2- Ferritin levels help assess if iron deficiency is contributing to the anemia.

3- **Erythrocyte sedimentation rate (ESR) and C-reactive protein** help assess the degree of inflammation.

4- Testing for **Saccharomyces cerevisiae antibodies (ASCA)** and **anti - neutrophil cytoplasmic antibodies (ANCA)** has been evaluated to identify inflammatory diseases of the intestine[1] and to differentiate Crohn's disease from ulcerative colitis.-

Ulcerative colitis (UC)

Ulcerative colitis (UC) is a long-term condition that results in inflammation and ulcers of the colon and rectum. The primary symptoms of active disease are abdominal pain and diarrhea mixed with blood. Weight loss, fever, and anemia may also occur.

The cause of UC is unknown. Theories involve **immune system dysfunction, genetics, changes in the normal gut bacteria, and environmental factors**.

Diagnosis is typically by **colonoscopy with tissue biopsies.** It is a kind of inflammatory bowel disease (IBD) along with Crohn's disease and microscopic colitis.

Causes

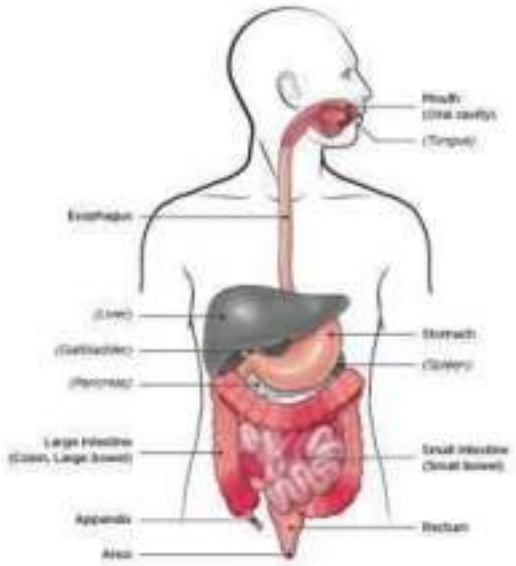
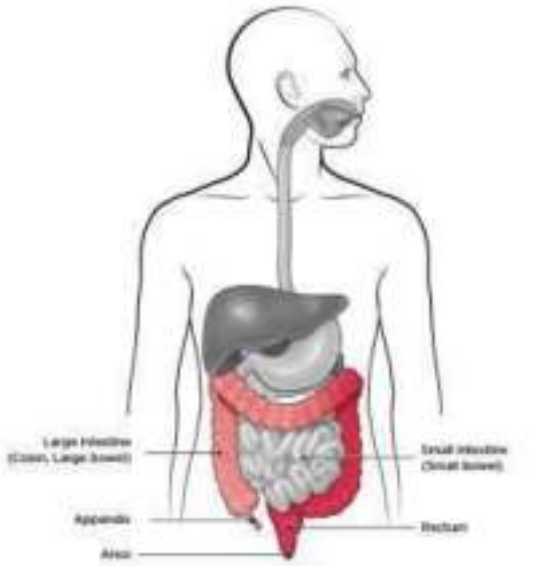
Ulcerative colitis is an autoimmune disease characterized by T-cells infiltrating the colon. No direct causes for UC are known, but factors such as genetics, environment, and an overactive immune system play a role.

Diagnosis

- A complete blood count is done to check for anemia; thrombocytosis, a high platelet count, is occasionally seen
- Electrolyte studies and kidney function tests are done, as chronic diarrhea may be associated with hypokalemia, hypomagnesemia and kidney injury.
- Liver function tests are performed to screen for bile duct involvement: primary sclerosing cholangitis.
- Imaging such as x-ray or CT scan to evaluate for possible perforation or toxic megacolon
- Stool culture and Clostridioides difficile stool assay to rule out infectious colitis
- Inflammatory markers, such as erythrocyte sedimentation rate or C-reactive protein
- Lower endoscopy to evaluate the rectum and distal large intestine (sigmoidoscopy) or entire colon and end of the small intestine (colonoscopy) for ulcers and inflammation

The differences between Crohn's disease and ulcerative colitis:

Crohn's Disease	Ulcerative Colitis
Can affect any part of the GI tract (from the mouth to the anus)—Most often it affects the portion of the small intestine before the large intestine/colon.	Occurs in the large intestine (colon) and the rectum

	
Damaged areas appear in patches that are next to areas of healthy tissue	Damaged areas are continuous (not patchy) – usually starting at the rectum and spreading further into the colon
Inflammation may reach through the multiple layers of the walls of the GI tract	Inflammation is present only in the innermost layer of the lining of the colon

Lecture : 11

Gastrointestinal and liver diseases

6- MALT lymphoma

Mucosa-associated lymphoid tissue (MALT)

The body's immune system is made up of a number of masses of lymphoid tissue or organs, as well as circulating leukocytes that originate from the bone marrow. The main lymphoid organs are:

- Bone marrow, thymus, tonsils, spleen and lymph nodes
- Mucosa-associated lymphoid tissue (MALT)
- Gut-associated lymphoid tissue (GALT)
- Bronchus-associated lymphoid tissue (BALT)
- Skin-associated lymphoid tissue (SALT)

MALToma is a form of lymphoma involving the mucosa-associated lymphoid tissue (MALT), frequently of the stomach, but virtually any mucosal site can be afflicted. It is a cancer originating from B cells in the marginal zone of the MALT, and is also called **extra nodal marginal zone B cell lymphoma**.

Lymphoma is a type of cancer. It happens when a growth of a lymphocyte population goes out of control.

There are 2 main types of lymphocytes: T lymphocytes (T cells) and B lymphocytes (B cells).

Mucosa-associated lymphoid tissue (MALT) lymphoma is a **type of low-grade B-cell Non-Hodgkin L.**

A MALT lymphoma can develop almost anywhere in the body, but it **most commonly develops in the stomach**. MALT lymphomas are normally divided into:

- **gastric (stomach) MALT lymphoma** – about a **third** of MALT lymphomas
- **non-gastric MALT lymphoma**, which most commonly affects the salivary glands, thyroid, lungs, skin, bowel or tissues around the eye.

Clinical features:-

These depend on the site involved:

Gastric MALT lymphomas may present with **dyspepsia**.

Nonspecific symptoms include fatigue, low-grade fever, nausea, constipation, weight loss and anemia.

Orbital MALT lymphomas may present with **blurred vision and visual field defects.**

Causes of MALT lymphoma

MALT lymphoma develops in areas where MALT tissue has formed and in epithelial tissues where lymphoid cells are not usually found. in response to:

- **inflammation** caused by a chronic (long-lasting) infection
- an **autoimmune condition**

Gastric MALT lymphoma has been strongly linked to infection by ***Helicobacter pylori***, a type of bacteria. This is a very common infection that doesn't usually cause serious problems but is also linked to stomach ulcers and indigestion.

- **Sjögren syndrome,** an autoimmune condition that causes dry mouth and dry eyes, may be linked to MALT lymphoma in the **salivary glands and lungs**.
- ***Chlamydia psittici*** infection, which can be caught from birds, including those kept as pets (eg parrots), may be linked to MALT lymphoma in the tissues surrounding the eye and **lacrimal (tear) glands**.
- **Hashimoto's thyroiditis**, an autoimmune inflammation of the thyroid gland, may be linked to MALT lymphoma in the thyroid.
- ***Borrelia burgdorferi*** infection, which causes Lyme disease and is carried by infected ticks, may be linked to MALT lymphoma of the **skin**.
- ***Campylobacter jejuni*** infection, a common cause of food poisoning, may be linked to MALT lymphoma of the **small bowel.**

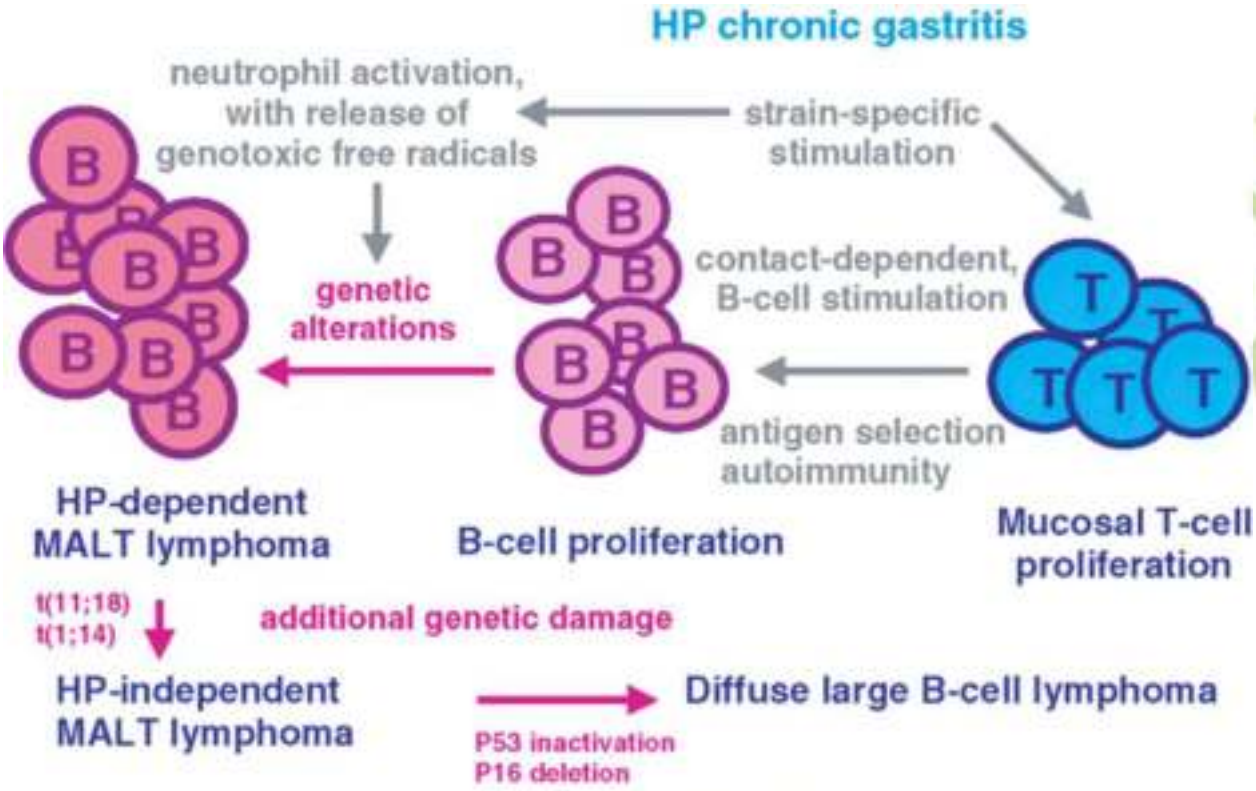
- **Rheumatoid arthritis** is linked to MALT lymphoma of the **lung**

Investigations:-

- General assessment: FBC, renal function tests, electrolytes, LFTs.
- Phenotyping of circulating lymphocytes, bone marrow lymphocytes or biopsy specimens.
- Imaging studies for disease staging:
- Barium contrast studies of the upper and lower gastrointestinal tract.
- CT scan and MRI scan & Endoscopy.

Pathogenesis of B-cell MALT gastric lymphomas

Schematic model of the origin and progression of a mucosa-associated lymphoid tissue (MALT) lymphoma. HPI stimulates the formation of lymphocytic infiltration of the gastric mucous membrane. As a result of direct antigenic stimulation and indirect stimulation (T-cells specific for HP), B-cells proliferate and can, at times, undergo a neoplastic transformation following the acquisition of genetic abnormalities, perhaps facilitated by the presence of free radicals. The accumulation of genetic abnormalities is associated with both a loss of dependency (as a result of antigenic stimulation) as well as a possible histological transformation. Tumors having at (11;18) (q21)/*AP12-MALT1* translocation do not respond to eradication of the infection, but they are rarely transformed into diffuse large B-cell lymphomas. Even lymphomas with a t(1;14) translocation appear to be independent of antigenic stimulation, yet they can undergo histological transformations. Tumors without these translocations present other genetic lesions that often respond to antibiotics; but they, too, can progress and become HP-independent, eventually transforming themselves into large-cell lymphomas following the inactivation of p53 and p16.



Treatments :-

1. Chemotherapy
2. Bone marrow aspiration
3. Radiotherapy .

Gastrointestinal and liver diseases

7- Autoimmune Liver Diseases

Autoimmune liver diseases occur when your body's immune system attacks the cells of your **liver** and **biliary system** (**bile ducts and gallbladder**). These conditions affect people of all ages and share common characteristics of other liver diseases such as **hepatitis**, **alcohol-induced liver disease** and **cirrhosis**.

There are three autoimmune liver diseases:

1- Autoimmune hepatitis

2- Primary sclerosing cholangitis

3- Primary biliary cirrhosis

Autoimmune hepatitis

formerly called **lupoid hepatitis**, is a chronic, autoimmune disease of the liver that occurs when the body's immune system attacks liver cells causing the liver to be inflamed.

Autoimmune hepatitis is **a serious condition** that may worsen over time **if not treated**. Autoimmune hepatitis can lead to **cirrhosis** and **liver failure**.

1-Cirrhosis occurs when **scar tissue replaces healthy liver tissue and blocks the normal flow of blood** through the liver.

2-Liver failure occurs when the **liver stops working** properly.

Classification:-

Four subtypes are recognized, but the clinical utility of distinguishing subtypes is limited.

	Type 1	Type 2	Type3	Type 4
Autoantibodies	**SMA, ANA, anti-actin, p-ANCA**	**Anti-LKM1, anti-Liver Cytosol 1 (anti-LC)**	**Anti-SLA, Anti-LP**	**No antibodies detected**
Age (year)	**10-20 and 45-70**	**2 - 14**	**30 - 50**	

Sign and symptoms :-

Autoimmune hepatitis may present **completely asymptomatic** (12–35% of the cases)

People usually present with **one or more nonspecific symptoms**, sometimes of long lasting duration, as **fatigue**, general ill health, **lethargy**, **weight loss**, mild **right upper quadrant pain**, **malaise**, **anorexia**, **nausea**, **jaundice** or **arthralgia** affecting the small joints. Rarely, **rash** or unexplained **fever** may appear. **Hepatomegaly** ,**splenomegaly**

Autoimmune hepatitis frequently appears **associated with other autoimmune conditions**, mainly celiac disease, vasculitis, and autoimmune thyroiditis.

Causes:-

60% of patients have chronic hepatitis that may **mimic viral hepatitis**, but without serologic evidence of a viral infection. The disease is strongly associated **with anti-smooth muscle autoantibodies. Risk factors**

- a family history of AIH
- HLA DRB1
- a history of bacterial or viral infections
- being female
- the use of certain medications, such as minocycline

Immune mechanism

In liver the **activate** circulating **T cells** through **antigen-presenting cells (APC).** Mechanism of Liver cell destruction via **cellular** and **humeral** mechanisms .

1-Cell-mediated cytotoxicity

-TH1 response (IL-2, IFN-γ, TNF-α) → clonal expansion of **cytotoxic T lymphocytes** that infiltrate and destroy hepatocytes.

-Genetic polymorphism that affects **TNF-α production** may facilitate this pathway**.**

2-Antibody-dependent cell-mediated cytotoxicity

TH2 response (IL-4,5,6,8,10,13) → **B cell stimulation** → Ab production →immunocyte complexes on hepatocyte surface → **targeted by NKT cells**

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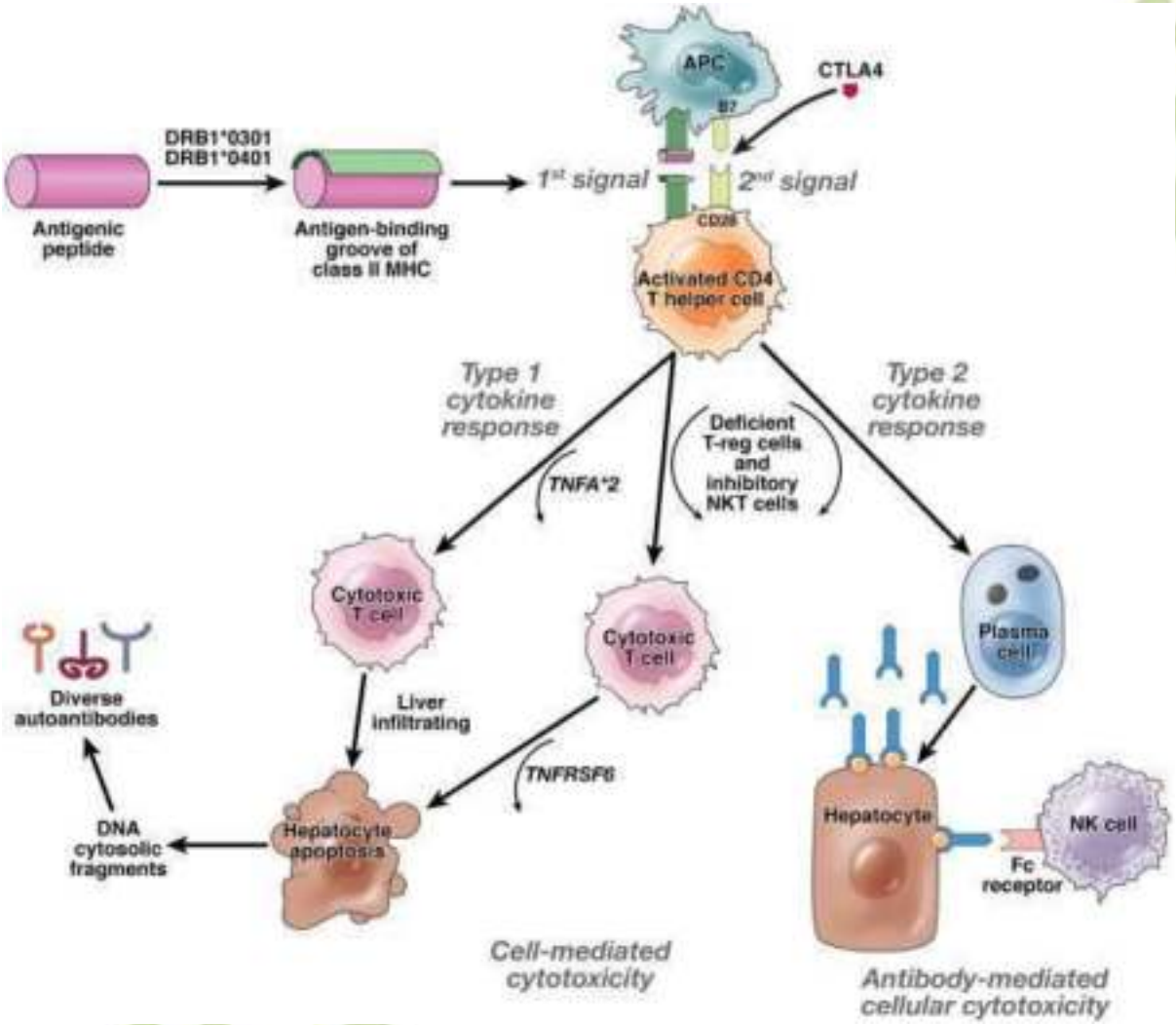


Diagnosis :-

The diagnosis of autoimmune hepatitis is best achieved with a **combination of clinical, laboratory**, and **histological** findings after **excluding other etiological factors** (e.g. viral, hereditary, metabolic, cholestatic, and drug-induced diseases).

1-Elevated serum **Alanine aminotransferase levels (ALT)** (1.5-50 times reference values)

2-Elevated **serum immunoglobulin levels**, primarily immunoglobulin G (**IgG**)

3-Mild to moderately elevated **serum bilirubin** and **alkaline phosphatase** – In 80-90% of patients; a sharp increase in the alkaline phosphatase reflect the development of **primary sclerosing cholangitis (PSC)** or the onset of **hepatocellular carcinoma** as a complication of cirrhosis

4-prolongation of **prothrombin time** – Markers of severe hepatic synthetic dysfunction,

A number of specific antibodies found in the blood

1-**antinuclear antibody (ANA)**,

2- **anti-smooth muscle antibody (SMA)**,

3- **anti-liver kidney microsomal antibodies (LKM-1, LKM-2, LKM-3)**,

4-**anti soluble liver antigen (SLA)**,

5-**liver–pancreas antigen (LP),** and

6-**anti-mitochondrial antibody (AMA))**

7-**increased Immunoglobulin G level**.

8- However, the diagnosis of autoimmune hepatitis always requires a **liver biopsy.**

Treatments

1-**Immunosuppressive glucocorticoids** such as **prednisone**, with or without azathioprine.

2-Liver transplantation .

Gastrointestinal and liver diseases

8- Primary biliary cholangitis

Primary biliary cholangitis (**PBC**), previously known as **primary biliary cirrhosis**, is an autoimmune disease of the liver.[1][2][3] It results from a slow, progressive destruction of the small bile ducts of the liver, causing bile and other toxins to build up in the liver, a condition called cholestasis. Further slow damage to the liver tissue can lead to scarring, fibrosis, and eventually cirrhosis.

Symptoms

More than half the people with primary biliary cholangitis do not have any noticeable symptoms when diagnosed. The disease may be diagnosed when blood tests are done for other reasons, such as routine testing.

Common early symptoms include:

- Fatigue
- Itchy skin

Later signs and symptoms may include:

- Dry eyes and mouth
- Pain in the upper right abdomen
- Swelling of the spleen (splenomegaly)
- Bone, muscle or joint (musculoskeletal) pain
- Swollen feet and ankles (edema)
- Buildup of fluid in the abdomen due to liver failure (ascites)
- Fatty deposits (xanthomas) on the skin around the eyes, eyelids or in the creases of the palms, soles, elbows or knees
- Yellowing of the skin and eyes (jaundice)

- Darkening of the skin that's not related to sun exposure (hyperpigmentation)
- Weak and brittle bones (osteoporosis), which can lead to fractures
- High cholesterol
- Diarrhea, which may include greasy stools (steatorrhea)
- Underactive thyroid (hypothyroidism)
- Weight loss

Causes

It's not clear what causes primary biliary cholangitis. Many experts consider it an autoimmune disease in which the body turns against its own cells. Researchers believe this autoimmune response may be triggered by environmental and genetic factors.

The liver inflammation seen in primary biliary cholangitis starts when certain types of white blood cells called T cells (T lymphocytes) start to collect in the liver. Normally, these immune cells detect and help defend against germs, such as bacteria and viruses. But in primary biliary cholangitis, they mistakenly destroy the healthy cells lining the small bile ducts in the liver.

Inflammation in the smallest ducts spreads and eventually damages other cells in the liver. As the cells die, they're replaced by scar tissue (fibrosis) that can lead to cirrhosis. Cirrhosis is scarring of liver tissue that makes it difficult for your liver to work properly.

Diagnosing : The basis for a definite diagnosis are:

- **Abnormalities** in liver enzyme tests are usually present and elevated gamma-glutamyl transferase and alkaline phosphatase are found in early disease. Elevations in bilirubin occur in advanced disease.
- **Antimitochondrial antibodies** are the characteristic serological marker for PBC, PBC patients have AMA against pyruvate dehydrogenase complex (PDC-E2), an enzyme complex that is found in the mitochondria.

- Other auto-antibodies may be present:
  Antinuclear antibody measurements are not diagnostic for PBC because they are not specific, but may have a role in prognosis.
  Anti-glycoprotein-210 antibodies, correlate with the disease's progression toward end-stage liver failure
  Anti-centromere antibodies often correlate with developing portal hypertension .

- **Abdominal ultrasound, magnetic resonance cholangiopancreatography or a CT scan** is usually performed to rule out blockage to the bile ducts. This may be needed if a condition causing secondary biliary cirrhosis, such as other biliary duct disease or gallstones, needs to be excluded.
- **A liver biopsy** may help, and if uncertainty remains as in some patients, an endoscopic retrograde cholangiopancreatography, an endoscopic investigation of the bile duct, may be performed.

Complications

As liver damage worsens, primary biliary cholangitis can cause serious health problems, including:

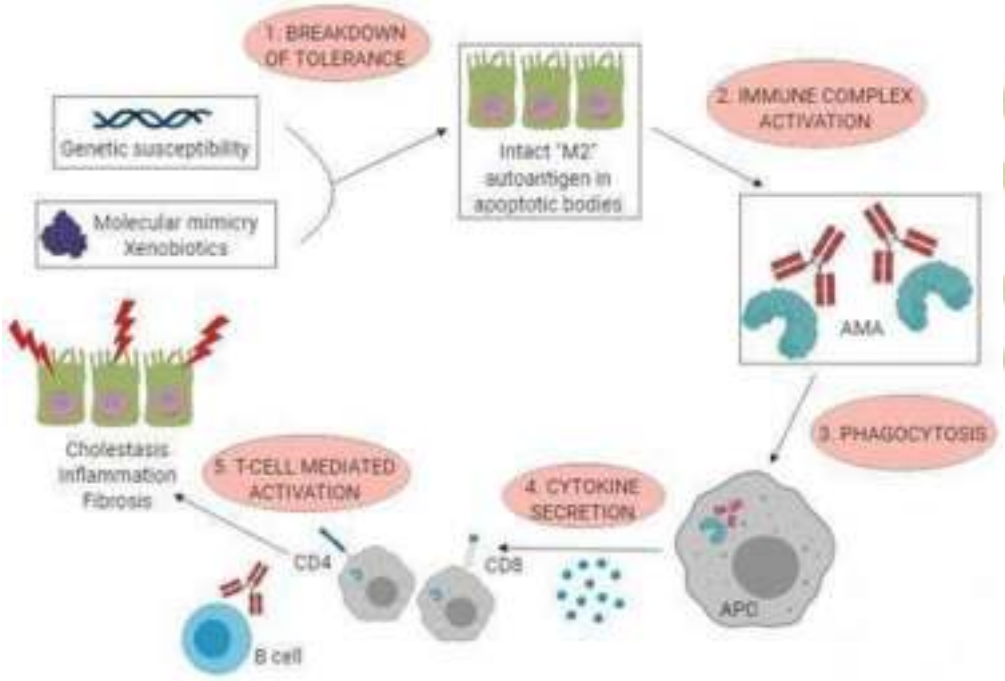
- **Liver scarring (cirrhosis).** Cirrhosis makes it difficult for your liver to work and may lead to liver failure. It indicates the later stage of primary biliary cholangitis.
- **Enlarged veins (varices).** When blood flow through the portal vein is slowed or blocked, blood may back up into other veins — usually those in your stomach and esophagus. Increased pressure may cause delicate veins to break open and bleed
- **Increased pressure in the portal vein (portal hypertension).** Blood from your intestine, spleen and pancreas enters your liver through a large blood vessel called the portal vein. When scar tissue from cirrhosis blocks normal blood flow through your liver, blood backs up. This causes increased pressure inside the vein

- **Enlarged spleen (splenomegaly).** Your spleen can become swollen with white blood cells and platelets because your body no longer filters toxins out of the bloodstream as it should.
- **Gallstones and bile duct stones.** If bile cannot flow through the bile ducts, it may harden into stones, causing pain and infection.
- **Liver cancer.** Liver scarring (cirrhosis) increases your risk of liver cancer. If you have liver scarring, you'll need regular cancer screening.
- **Weak bones (osteoporosis).** People with primary biliary cholangitis have an increased risk of weak, brittle bones that may break more easily.
- **Vitamin deficiencies.** A lack of bile affects your digestive system's ability to absorb fats and the fat-soluble vitamins, A, D, E and K. Because of this, some people with advanced primary biliary cholangitis may have low levels of these vitamins. These deficiencies can result in a variety of health problems, including night blindness and bleeding disorders.
- **High cholesterol (hyperlipidemia).** Up to 80% of people with primary biliary cholangitis have high cholesterol.
- **Decreased mental function (hepatic encephalopathy).** Some people with advanced primary biliary cholangitis and cirrhosis have personality changes and problems with memory and concentration.
- **Increased risk of other disease.** Primary biliary cholangitis is associated with metabolic or immune system disorders, including thyroid problems, limited scleroderma (CREST syndrome), rheumatoid arthritis, and dry eyes and mouth (Sjogren's syndrome).

Pathogenesis

The primary disease mechanism in PBC is thought to be T cell lymphocyte–mediated injury against intralobular biliary epithelial cells. This causes progressive destruction and eventual disappearance of the intralobular bile ducts. Molecular mimicry has been proposed as the initiating event in the loss of tolerance primarily to mitochondrial pyruvate dehydrogenase complex, E2, during which exogenous antigens evoke an immune response that recognizes an endogenous (self) antigen inciting an autoimmune reaction (Fig. **1**). Suspected mimics include xenobiotics**6** and bacterial and viral antigens.**7** AMA, a highly disease-specific autoantibody of PBC, targets four principal autoantigens, which are collectively

referred to as the "M2" subtype of mitochondrial autoantigens. In addition to the humoral response, T cell responses including $CD4^+$ and $CD8^+$ T cells target the same antigen and are involved in the destruction of biliary epithelial cells. The resultant cholestasis with noxious bile acids causes "foamy" degeneration of hepatocytes and perpetuates the cycle of injury.



Figure

Model of the pathogenesis of PBC. In a genetically susceptible individual, environmental triggers lead to loss of tolerance to the mitochondrial antigen through molecular mimicry. Intact mitochondrial antigens in cholangiocytes undergoing apoptosis in the presence of AMAs and macrophages leads to an innate immune response and further enhancement of adaptive immune responses.

Gastrointestinal and liver diseases

9- Primary sclerosing Cirrhosis

Primary sclerosing cholangitis, or PSC, is a chronic disease in which the bile ducts inside and outside the liver become inflamed and scarred, and eventually narrowed or blocked.

Symptoms

Primary sclerosing cholangitis is often diagnosed before symptoms appear when a routine blood test or an X-ray taken for an unrelated condition shows liver abnormalities.

Early signs and symptoms often include:

- Fatigue
- Itching
- Yellow eyes and skin (jaundice)
- Abdominal pain

Signs and symptoms that may appear as the disease progresses include:

- Fever
- Chills
- Night sweats
- Enlarged liver
- Enlarged spleen
- Weight loss

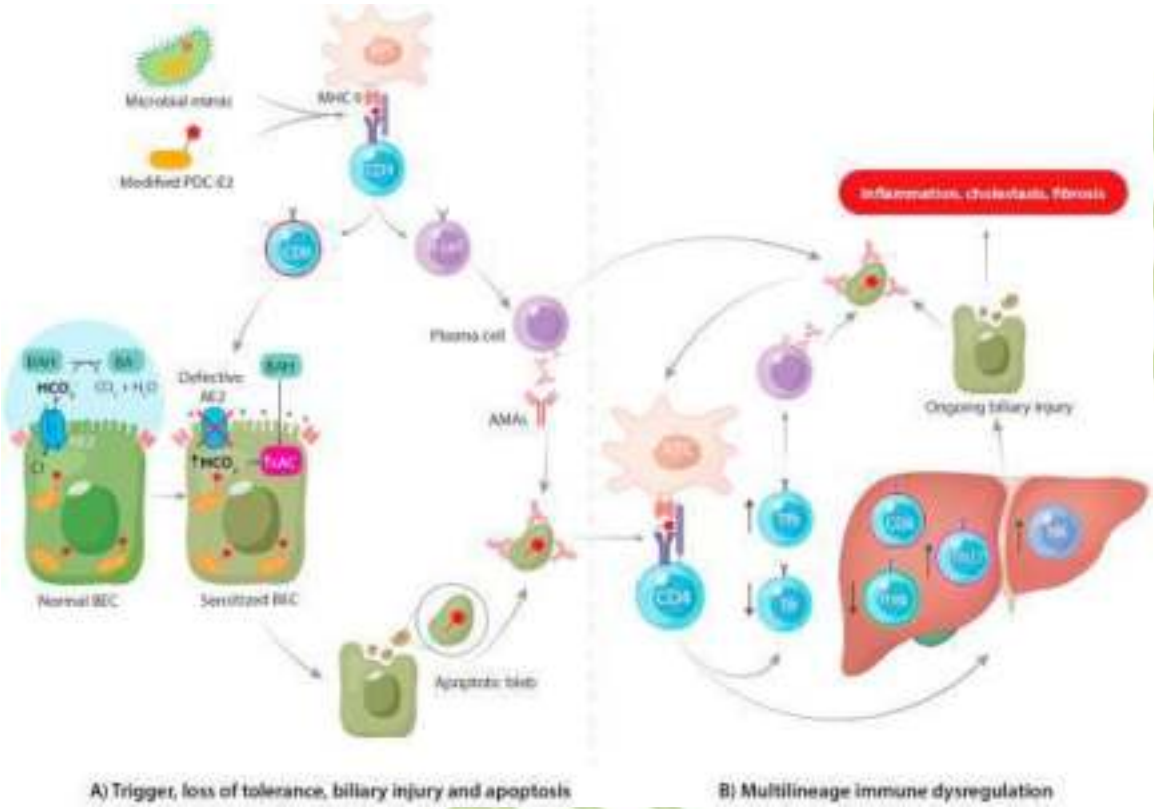
Causes

The exact cause of primary sclerosing cholangitis is unknown, and its pathogenesis is improperly understood. Although PSC is thought to be caused by autoimmune disease, it does not demonstrate a clear response to immunosuppressant's. Thus, many experts believe it to be a complex, multifactorial (including immune-mediated) disorder and perhaps one that encompasses several different hepatobiliary diseases.

Complications

Complications of primary sclerosing cholangitis may include:

- **Liver disease and failure.** Chronic inflammation of the bile ducts throughout your liver can lead to tissue scarring (cirrhosis), liver cell death and, eventually, loss of liver function.
- **Repeated infections.** If scarring of the bile ducts slows or stops the flow of bile out of the liver, you may experience frequent infections in the bile ducts.
- **Portal hypertension.** Your portal vein is the major route for blood flowing from your digestive system into your liver. Portal hypertension refers to high blood pressure in this vein.
- **Thinning bones.** People with primary sclerosing cholangitis may experience thinning bones (osteoporosis). Your doctor may recommend a bone density exam to test for osteoporosis every few years. Calcium and vitamin D supplements may be prescribed to help prevent bone loss.
- **Bile duct cancer.** If you have primary sclerosing cholangitis, you have an increased risk of developing cancer in the bile ducts or gallbladder.
- **Colon cancer.** People with primary sclerosing cholangitis associated with inflammatory bowel disease have an increased risk of colon cancer. If you've been diagnosed with primary sclerosing cholangitis, your doctor may recommend testing for inflammatory bowel disease, even if you have no signs or symptoms, since the risk of colon cancer is elevated if you have both diseases



Treatments for PSC

There is currently no established cure for PSC. However, medical therapy may help to alleviate symptoms such as itching, infection, and malnutrition. Surgery or endoscopic procedures may be performed to address blockage in the bile ducts and improve bile flow.

If a patient's condition advances to liver failure, liver transplantation may be recommended. Although PSC can recur after transplant, a liver transplant is curative in the majority of cases.

Diagnosis

1- Liver function blood test
2- **MRI of your bile ducts.** Magnetic resonance cholangiopancreatography uses magnetic resonance imaging (MRI) to make images of your liver and bile ducts and is the test of choice to diagnose primary sclerosing cholangitis.
3- X-rays of your bile ducts. A type of bile duct X-ray called endoscopic retrograde
4- Liver biopsy.

Primary Biliary Cholangitis (PBC) vs Primary Sclerosing Cholangitis (PSC)

Primary Biliary Cholangitis (PBC)		Primary Sclerosing Cholangitis (PSC)
Inflammation of **intrahepatic bile ducts** which may lead to fibrosis and cirrhosis	Site of Involvement	Inflammation of both **intra and extrahepatic bile ducts** (10-15% only intrahepatic affected)
♀ Female > male (9:1 ratio)	Gender	♂ Male > female
Often asymptomatic; Pruritus, fatigue, abdominal pain; Jaundice after years	Features	Pruritus, fatigue, cholangitis
Cholestatic picture with raised ALP, GGT	Liver function tests	Cholestatic picture with raised ALP, GGT
Anti-mitochondrial antibody (AMA) M2 subtype positive in 98% of PBC	Investigation	ERCP/MRCP shows **beaded appearance** of bile ducts
Sjogren's syndrome (seen in 80% of PBC) Rheumatoid arthritis Systemic sclerosis	Associated conditions	80% of those with PSC have inflammatory bowel disease (usually UC)
Cirrhosis	Complications	↑ Risk of cholangio and colorectal carcinoma Cirrhosis
• Cholestyramine for pruritus • Ursodeoxycholic acid – **improves survival** and delay transplantation • Liver transplantation	Treatment	• Cholestyramine for pruritus • Ursodeoxycholic acid – may improve LFTs but **does not improve survival** • Liver transplantation

GRAM PROJECT

Glomerulonephritis (GN)

also known as glomerular nephritis, is a term used to refer to several kidney diseases (usually affecting both kidneys). Many of the diseases are characterized by **inflammation** either of the **glomeruli** or of the **small blood vessels** in the kidneys.

it may present with isolated **hematuria and/or proteinuria** (blood or protein in the urine); or as a nephrotic syndrome, a nephritic syndrome, acute kidney injury, or chronic kidney disease.

Diagnosing the pattern of GN is important because the **outcome and treatment differs** in different types. **Primary causes** are intrinsic to the kidney. **Secondary causes** are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (SLE, vasculitis), or diabetes.

Primary glomerulonephritis

1-Membranous glomerulonephritis

(MGN) is a slowly progressive disease of the kidney affecting mostly people between ages of 30 and 50 years, usually Caucasian .It is the second most common cause of nephrotic syndrome in adults,

Signs and symptoms Some people may present as nephrotic syndrome with proteinuria, edema with or without renal failure. Others may be asymptomatic.

Causes and classification

Primary/idiopathic

The cause of the disease is idiopathic (of unknown origin or cause). This can also be referred to as *idiopathic membranous nephropathy*. One study has identified antibodies to an **M-type phospholipase A_2 receptor** .

Secondary

- **autoimmune conditions** (e.g., systemic lupus erythematosus)
- **infections** (e.g., syphilis, malaria, hepatitis B, hepatitis C)
- **drugs** (e.g., captopril, NSAIDs, penicillamine, probenecid).
- **inorganic salts** (e.g. gold, mercury).

- **tumors**, frequently solid tumors of the lung and colon

Pathogenesis

MGN is caused by **immune complex formation in the glomerulus**. The immune complexes are formed by binding of antibodies to antigens in the glomerular **basement membrane**. The antigens may be **part** of the basement membrane, or deposited from elsewhere by **the systemic circulation**. The immune complex serves as an activator that triggers a response from the **C5b - C9 complements**, which form a membrane attack complex (MAC) on the glomerular epithelial cells. This, in turn, stimulates release of **proteases and oxidants by the mesangial and epithelial cells**, damaging the capillary walls and causing them to become "leaky".

Morphology

By light microscopy, the basement membrane is observed to be **diffusely thickened**. Using Jones' stain, the GBM appears to have a **"spiked" or "holey" appearance**.

On electron microscopy, **subepithelial deposits** that nestle against the glomerular basement membrane seems to be the cause of the thickening. Also, **the podocytes lose their foot processes**. As the disease progresses, the **deposits will eventually be cleared, leaving cavities in the basement membrane**. These cavities will later be **filled with basement membrane-like material**, and if the disease continues even further, the glomeruli will become **sclerosed** and finally **hyalinized.**

Treatment of secondary membranous nephropathy is guided by the treatment of the **original disease**. For treatment of idiopathic membranous nephropathy, the treatment options include **immunosuppressive drugs** and non-specific anti-proteinuric measures. Recommended first line therapy often includes: **cyclophosphamide** alternating with a **corticosteroid**.

2-Post-infectious glomerulonephritis

Acute proliferative glomerulonephritis is a disorder of the glomeruli (glomerulonephritis), or small blood vessels in the kidneys. It is a common complication of bacterial infections, typically skin infection by *Streptococcus* bacteria types 12, 4 and 1 (impetigo) but also after streptococcal pharyngitis, for which it is also known as *postinfectious* or *poststreptococcal glomerulonephritis*. It can be a risk factor for future albuminuria. In adults, the

signs and symptoms of infection may still be present at the time when the kidney problems develop, and the terms *infection-related glomerulonephritis* or *bacterial infection-related glomerulonephritis* are also used.

Signs and symptoms Hematuria , Oliguria ,Edema ,Hypertension ,Fever (headache, malaise, anorexia, nausea).

The pathophysiology of this disorder is consistent with an **immune-complex-mediated mechanism**, a type III hypersensitivity reaction. This disorder produces proteins that have different antigenic determinants, which in turn have an affinity for sites in the glomerulus. As soon as binding occurs to the glomerulus, via interaction with properdin, the complement is activated. Complement fixation causes the generation of additional inflammatory mediators .

Diagnosis

Kidney biopsy ,Complement profile ,Imaging studies ,Blood chemistry studies

Clinically, acute proliferative glomerulonephritis is diagnosed following a differential diagnosis between (and, ultimately, diagnosis of) staphylococcal and streptococcal impetigo.

Serologically, diagnostic markers can be tested; specifically, the **streptozyme test** is used and measures multiple streptococcal antibodies: antistreptolysin, antihyaluronidase, antistreptokinase, antinicotinamide-adenine dinucleotidase, and anti-DNAse B antibodies.

Treatment: blood pressure (BP) control: A low-sodium diet may be needed when hypertension is present. In individuals with oliguric acute kidney injury, the amount of potassium should be controlled.

3-IgA nephropathy (IgAN)

also known as **IgA nephritis**, **Berger disease** or **synpharyngitic glomerulonephritis** , is a disease of the kidney (or nephropathy); specifically it is a form of glomerulonephritis or an inflammation of the glomeruli of the kidney.

IgA nephropathy is the **most common glomerulonephritis worldwide.** Primary IgA nephropathy is characterized by **deposition of the IgA antibody in the glomerulus**.

There are other diseases associated with glomerular IgA deposits, the most common being **IgA vasculitis** (formerly known as **Henoch–Schönlein purpura [HSP**

In IgA nephropathy there is a **slow progression** to chronic kidney failure in 25–30% of cases during a period of 20 years.

Signs and symptoms

hematuria, which usually starts **within a day or two** of a non-specific upper respiratory tract infection, as opposed to post-streptococcal glomerulonephritis, which occurs some time (**weeks**) after initial infection, **Groin pain**, **proteinuria**, the patients may **not** have any symptoms .

Pathophysiology

deposits of immunoglobulin A (IgA) in a granular pattern in the mesangium .but no clear known explanation for the accumulation of the IgA. Exogenous antigens for IgA have **not been identified** in the kidney, but it is possible that this antigen has been **cleared before** the disease manifests itself. It has also been proposed that **IgA itself may be the antigen.**

A recently advanced theory focuses on **abnormalities of the IgA1 molecule in glomerular** mesangium. A similar mechanism has been claimed to underlie Henoch–Schönlein purpura.

Diagnosis

1-Ultrasound of the kidney and cystoscopy are usually done first to pinpoint the source of the bleeding. These tests would rule out kidney stones and bladder cancer, two other common urological causes of hematuria.

2-The history and association with respiratory infection can raise the suspicion of IgA nephropathy.

3- A kidney biopsy is necessary to confirm the diagnosis. The biopsy specimen shows proliferation of the mesangium, with IgA deposits on immunofluorescence and electron microscopy. However, patients with isolated microscopic hematuria (i.e. without associated proteinuria and with normal kidney function) are not usually biopsied since this is associated with an excellent prognosis.

4- A urinalysis will show red blood cells, usually as red cell urinary casts. Proteinuria.

5-Other blood tests done to aid in the diagnosis include **CRP** or **ESR**, **complement levels**, **ANA**, and **LDH**. **Protein electrophoresis** and **immunoglobulin levels** can show increased IgA in 50% of all patients.

2- Glomerulonephritis associated with systemic disease

1-Henoch–Schönlein purpura (HSP)

also known as **IgA vasculitis**, **anaphylactoid purpura**, **purpura rheumatica**, and **Schönlein–Henoch purpura**, is a disease of the skin, mucous membranes, and sometimes other organs that most commonly affects **children**. In the skin, the disease causes palpable purpura (small, raised areas of bleeding underneath the skin), often with joint pain and abdominal pain. With kidney involvement, there may be a loss of small amounts of blood and protein in the urine (hematuria and proteinuria, the kidney involvement proceeds to chronic kidney disease. HSP is often preceded by an infection, such as a throat infection.

HSP can develop after infections with streptococci (β-haemolytic, Lancefield group A), hepatitis B, herpes simplex virus, parvovirus B19, Coxsackievirus, adenovirus, Helicobacter pylori,measles, mumps, rubella, Mycoplasma and numerous others

HSP is **a systemic vasculitis** (inflammation of blood vessels) and is characterized by **deposition of immune complexes** containing the antibody immunoglobulin A (IgA); the exact cause for this phenomenon is **unknown**. Henoch–Schönlein purpura is a small-vessel vasculitis in which complexes of immunoglobulin A (IgA) and complement component 3 (C3) are deposited on arterioles, capillaries, and venules.

Diagnosis

Like IgA nephropathy ,also The platelet count may be **raised**, and distinguishes it from diseases where low platelets are the cause of the purpura, such as idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura.

serum complement levels are normal.

2- Lupus nephritis (also known as SLE nephritis)

is an inflammation of the kidneys caused by systemic lupus erythematosus . It is a type of glomerulonephritis in which the glomeruli become inflamed. As the result of SLE, the cause of glomerulonephritis is said to be **secondary** .

Classification:-

1-Class I disease (**minimal mesangial glomerulonephritis**) in its histology has a normal appearance under a light microscope, but mesangial deposits are visible under an electron microscope. At this stage urinalysis is normal.

2-Class II disease (**mesangial proliferative glomerulonephritis**) is noted by mesangial hypercellularity and matrix expansion. Microscopic haematuria with or without proteinuria may be seen. Hypertension, nephrotic syndrome, and acute kidney insufficiency are very rare at this stage.

3-Class III disease (**focal glomerulonephritis**) is indicated by sclerotic lesions involving less than 50% of the glomeruli, which can be segmental or global, and active or chronic, with endocapillary or extracapillary proliferative lesions. Under the electron microscopy, subendothelial deposits are noted, and some mesangial changes may be present. Immunofluorescence reveals positively for IgG, IgA, IgM, C3, and C1q. Clinically, haematuria and proteinuria are present, with or without nephrotic syndrome, hypertension, and elevated serum creatinine.

4-Class IV disease (**diffuse proliferative nephritis**) is both the **most severe**, and the **most common subtype**. More than 50% of glomeruli are involved. Lesions can be segmental or global, and active or chronic, with endocapillary or extracapillary proliferative lesions. Under electron microscopy, subendothelial deposits are noted, and some mesangial changes may be present. Clinically, haematuria and proteinuria are present, frequently with nephrotic syndrome, hypertension, hypocomplementemia, elevated anti-dsDNA titres and elevated serum creatinine.

5-Class V disease (**membranous glomerulonephritis**) is characterized by diffuse thickening of the glomerular capillary wall (segmentally or globally), with diffuse membrane thickening, and subepithelial deposits seen under the electron microscope. Clinically, stage V presents with signs of nephrotic syndrome. Microscopic haematuria and hypertension may also been seen. Stage V also can also lead to thrombotic complications such as renal vein thromboses or pulmonary emboli.

6- Class VI, or **advanced sclerosing lupus nephritis**.It is represented by global sclerosis involving more than 90% of glomeruli, and represents healing of prior inflammatory injury. **Active glomerulonephritis is not usually present**. This

stage is characterised by slowly progressive kidney dysfunction, with relatively bland urine sediment. Response to immunotherapy is usually poor. A tubuloreticular inclusion within capillary endothelial cells is also characteristic of lupus nephritis, and can be seen under an electron microscope in all stages. It is not diagnostic however, as it exists in other conditions such as HIV infection. It is thought to be due to the chronic interferon exposure.

The pathophysiology

of lupus nephritis has autoimmunity contributing significantly. Autoantibodies direct themselves against nuclear elements. The characteristics of nephritogenic autoantibodies (lupus nephritis) are: antigen specificity directed at nucleosome, high affinity autoantibodies form intravascular immune complexes, autoantibodies of certain isotypes activate complement.

The diagnosis

of lupus nephritis depends on **blood tests**, **urinalysis, X-rays**, ultrasound scans of the kidneys, and a **kidney biopsy**. On urinalysis, a nephritic picture is found and red blood cell casts, red blood cells and proteinuria is found. The World Health Organization has divided lupus nephritis into five stages based on the biopsy.

Vasculitis associated glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN)

is a syndrome of the kidney that is characterized by a **rapid loss of renal function**,(within 3 months)With **glomerular crescent formation** seen on kidney biopsies. If left untreated, it rapidly progresses **into acute renal failure.**

1-Type 1: characterized by the presence of autoantibodies directed against the glomerular basement membrane , **anti-GBM glomerulonephritis**. The antibodies are directed against a particular protein found in the GBM, **type IV collagen**, more specific **α3 chain** some cases of type I RPGN are also associated with antibodies directed against the **basement membrane of lung alveoli**, producing **Goodpasture syndrome**.

features anti-GBM antibodies alone; these cases are considered idiopathi

Goodpasture syndrome (GPS)

is a rare autoimmune disease in which antibodies attack the basement membrane in lungs and kidneys, leading to bleeding from the lungs and kidney failure. It is thought to attack the alpha-3 subunit of type IV collagen, which has therefore been referred to as Goodpasture's antigen.often leading to **death** .

Signs and symptoms: coughing up blood, chest pain, blood in the urine, protein in the urine, unexplained swelling of limbs or face, high amounts of urea in the blood, and high blood pressure.

Cause: unknown, but exposure to tobacco smoke, certain gene mutations (***HLA-DR15***), infection (such as influenza A), cocaine inhalation.

Pathophysiology: GPS causes the abnormal production of anti-GBM antibodies, by the plasma cells of the blood. The anti-GBM antibodies attack the alveoli and glomeruli basement membranes. These antibodies bind their reactive epitopes to the basement membranes and activate the complement cascade, leading to the death of tagged cells. T cells are also implicated. It is generally considered a type II hypersensitivity reaction.

Diagnosis: often difficult, biopsy, especially the kidney, anti-GBM antibodies, cytoplasmic antineutrophilic antibodies .

Treatment: plasmapheresis, immunosuppressant drugs, especially cyclophosphamide, prednisone

Diagnosis of HSP

No specific diagnostic laboratory test is available to assess for markers of HSP. The following general laboratory tests may be helpful for excluding other diagnoses and evaluating renal function:

Antinuclear antibody (ANA) and rheumatoid factor (RF)

Factors VIII and XIII

Urinalysis

Complete blood count (CBC)

Platelet count

Erythrocyte sedimentation rate (ESR)

Stool guaiac test:- is one of several methods that detects the presence of fecal occult blood.The test involves placing a faecal sample on guaiac paper (extracted from the wood resin of Guaiacum trees) and applying hydrogen peroxide which, in the presence of blood, yields a blue reaction product within seconds.

Blood urea nitrogen (BUN) and creatinine

Amylase and lipase

Electrolytes

Plasma D-dimer:- is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two D fragments of the fibrin protein joined by a cross-link

Plasma thrombin-antithrombin (TAT) complex, prothrombin fragment (PF)-1, and PF-2

Prothrombin time (PT) and activated partial thromboplastin time (aPTT)

Serum IgA

Antistreptolysin O (ASO)

CH50

C3 and C4 Immunocomplexes of IgG and IgA

Respiratory disease

1- 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.

Alternative Names

Interstitial lung disease - drug induced

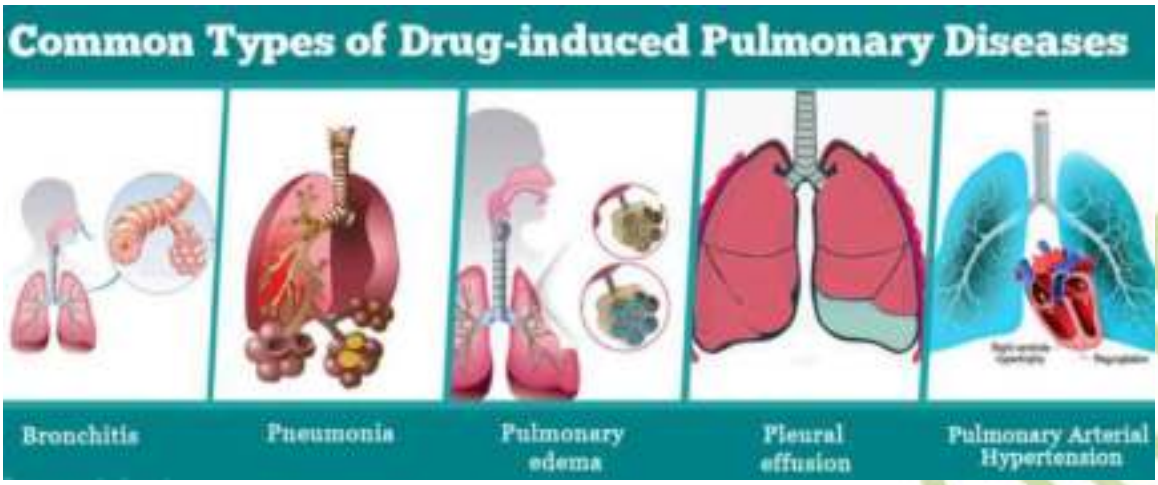
What is the most common drug-induced respiratory problem?

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:

- Allergic reactions like asthma or pneumonitis
- Lymph node swelling
- Alveolar haemorrhage, i.e. bleeding into lung sacs
- Bronchitis, i.e., inflammation of the airways
- Pneumonia
- Pulmonary edema, i.e., fluid accumulation in the lungs
- Pleural effusion i.e., fluid accumulation around the lungs
- Pulmonary fibrosis i.e., formation of scar tissue in the lungs
- Pulmonary arterial hypertension
- 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.

Patients with drug-induced lung diseases will give a history of drug intake before the reaction. Sometimes, the doctor will have to specifically ask for such a history. 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. This information can help your healthcare provider diagnose and decide the treatment of certain lung disorders.
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

Respiratory disease

2- Chronic 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 . Chronic eosinophilic pneumonia is not truly chronic;

rather it is an acute or subacute illness that recurs (thus, a better name might be recurrent eosinophilic pneumonia). The prevalence and incidence of chronic eosinophilic pneumonia are unknown. Etiology is suspected to be an allergic diathesis. Most patients are nonsmokers.

Symptoms and Signs of Chronic Eosinophilic Pneumonia

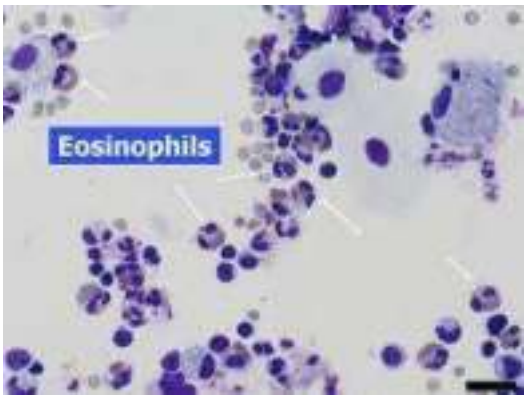
Patients with chronic eosinophilic pneumonia often present with fulminant illness characterized by

1- Cough & fever
2- Progressive breathlessness
3- Wheezing, and night sweats.
4- Asthma accompanies or precedes the illness in > 50% of cases.
5- Patients with recurrent symptoms may have weight loss.

Diagnosis of Chronic Eosinophilic Pneumonia

Diagnosis of chronic eosinophilic pneumonia is suspected in patients with characteristic symptoms and typical radiographic appearance.

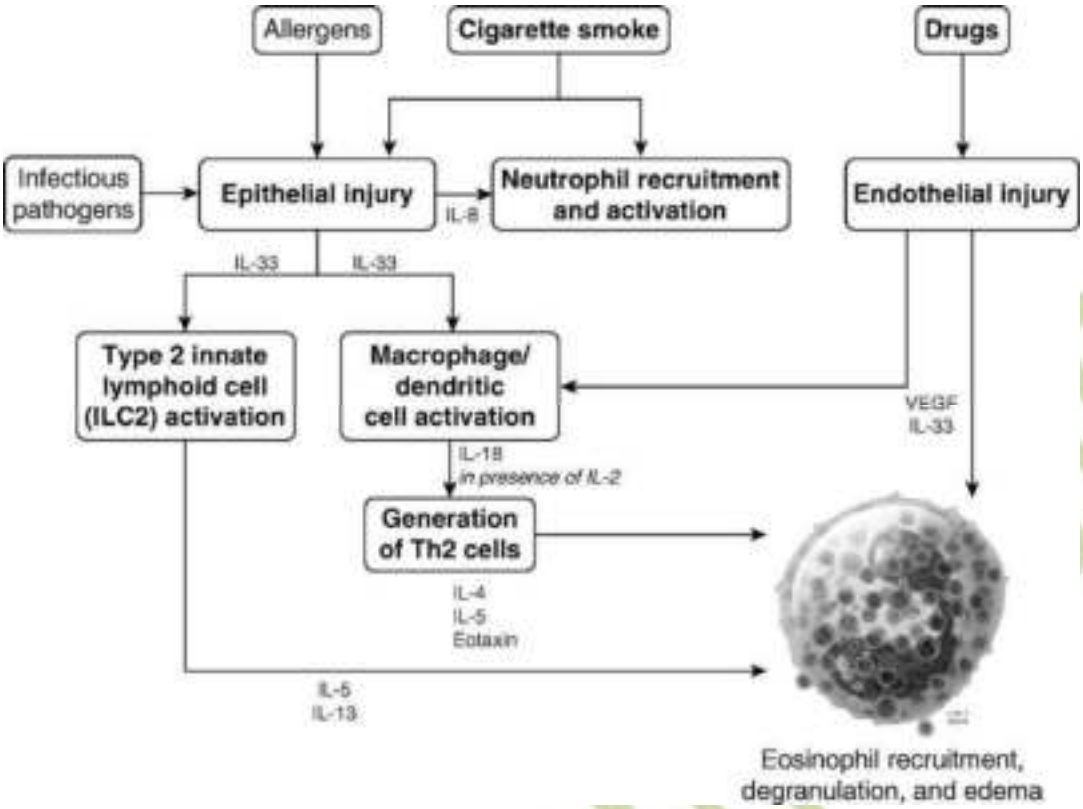
- Chest x-ray and high-resolution CT (HRCT)
- Exclusion of infectious causes of pneumonia
- Bronchoalveolar lavage
- Complete blood count (CBC)
- Peripheral blood eosinophilia count , peripheral eosinophilia is often present in chronic eosinophilic pneumonia.
- Sedimentation rate (ESR)
- Bronchoalveolar lavage is usually done to confirm the diagnosis. Eosinophilia > 40% in bronchoalveolar lavage fluid is highly suggestive of chronic eosinophilic pneumonia; serial bronchoalveolar lavage examinations may help document the course of disease.



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.



Respiratory disease

3- 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 your body. Some commonly seen problems are given specific names related to the source of the allergen, including farmer's lung and bird fancier's lung.

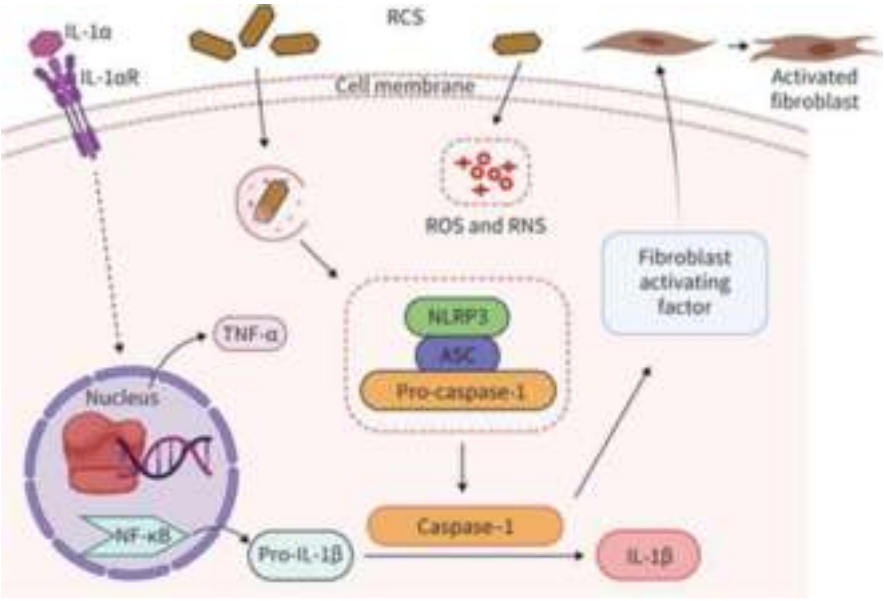
4. Histoplasmosis is caused by breathing fungal spores from soil that has been contaminated by bird or bat droppings. Some occupations that may expose workers to spores are farmers, pest control workers, poultry keepers, construction workers and landscapers.

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 before the late 1970s.

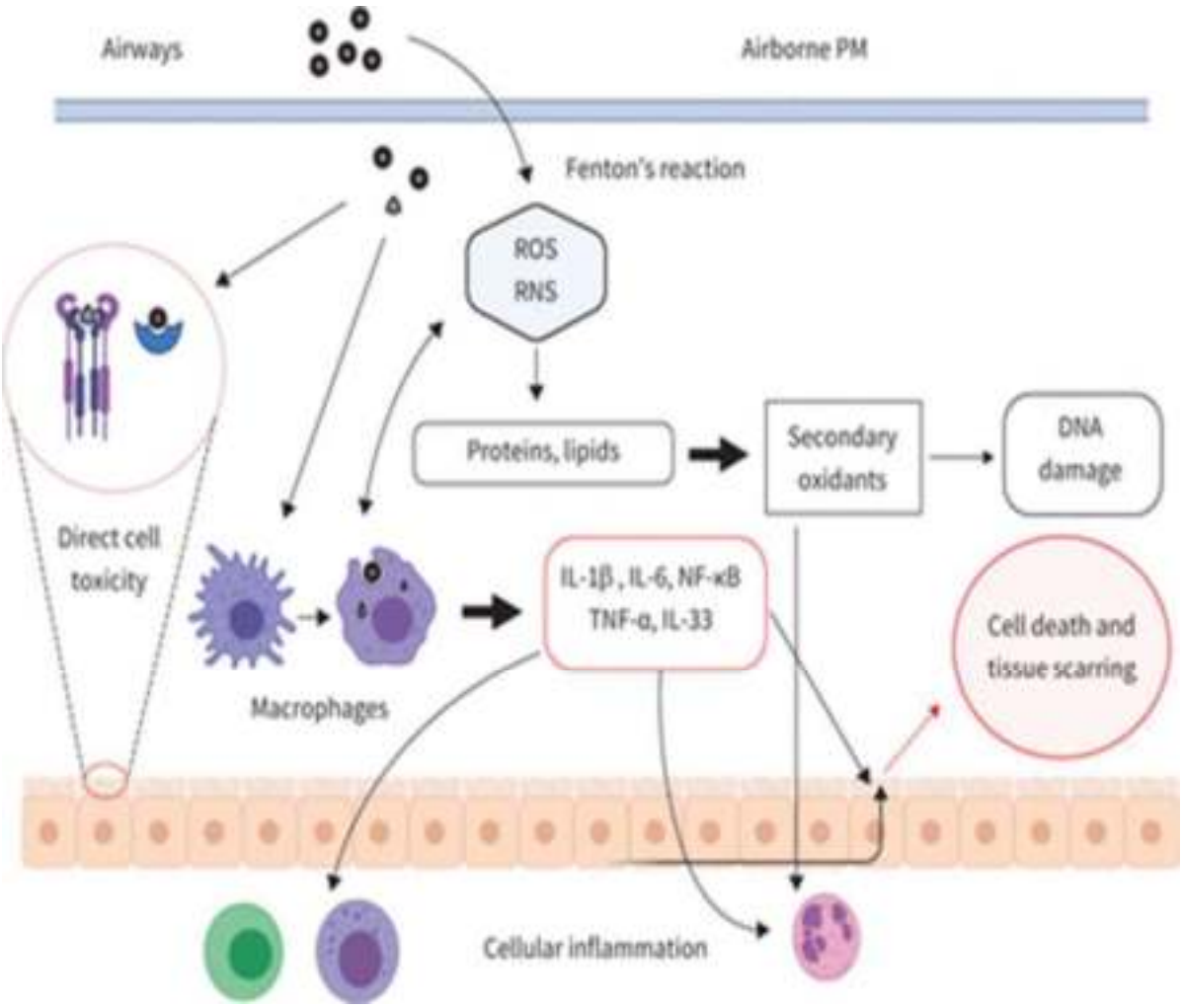
6. Coal workers pneumoconiosis, commonly known as black lung disease, occurs when coal dust is inhaled. Continued exposure to coal dust causes scarring in the lungs.

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.

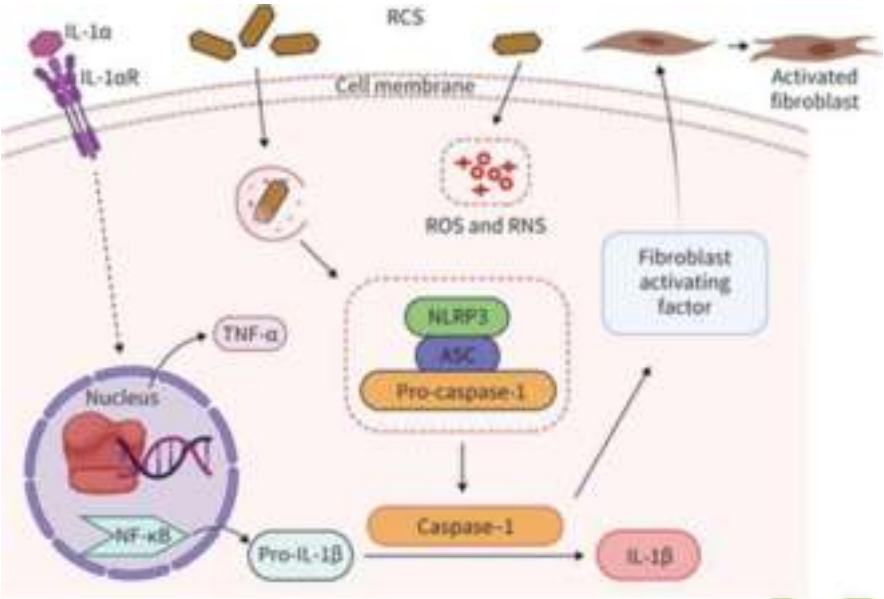
8. Work-related asthma accounts for 15 percent to 23 percent of new adult asthma cases in the United States. According to one study, men working in forestry and with metals and women in the service industries (waitresses, cleaners, and dental workers) have the highest risk for occupational asthma.



Pathogenesis of reactive crystalline silica (RCS). The illustration depicts the interaction of RCS with lung epithelial cells and subsequent activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome pathway and production of pro-inflammatory cytokine interleukin (IL)-1β, free radicals and fibroblast-activating factor leading to fibrosis. Created with BioRender.com. ROS: reactive oxygen species; RNS: reactive nitrogen species; ASC: apoptosis-associated speck-like protein containing a caspase activation and recruitment domain; TNF: tumour necrosis factor; NF-κB: nuclear factor-κB.



Mechanisms of dust particulate matter (PM) toxicity. Schematic representation depicting ambient airborne PM with various cellular mechanisms and triggering cascade reactions, *i.e.* cellular inflammation, reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, cytokine production and DNA damage, leading to cell death and scar tissue formation. Created with BioRender.com. IL: interleukin; NF-κB: nuclear factor-κB; TNF: tumour necrosis factor.



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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.

Respiratory disease

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, beer and wine
9. Gastroesophageal reflux disease (GERD), a condition in which stomach acids back up into your throat

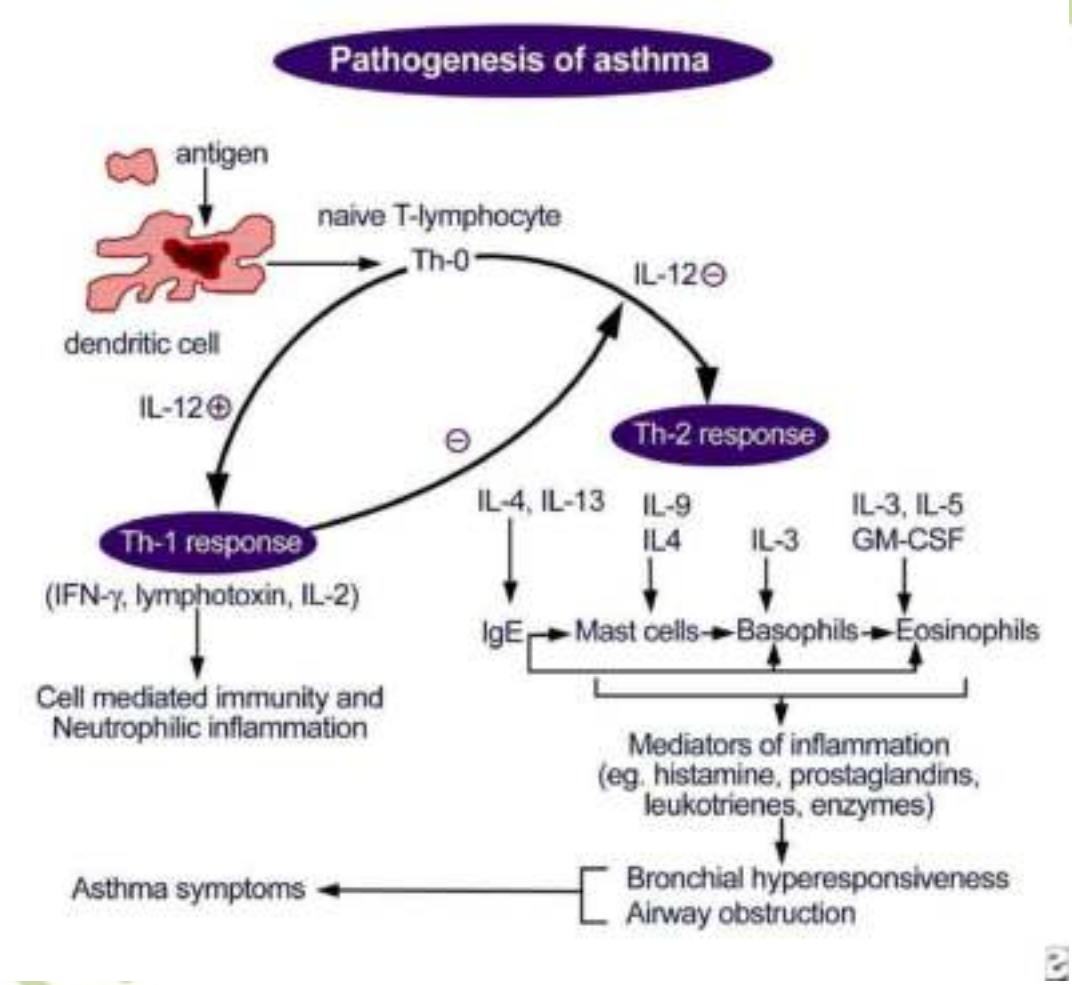
pathophisiology

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.

There is an early and late response in asthma. A trigger initiates the airway inflammatory response in asthma. After inhalation, these triggers may stimulate resident airway mast cells and cause cross-linking of immunoglobulin E on the mast cell surface. This will result in the release of histamine and will induce the production of prostaglandins, leukotrienes, and other enzymes. 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

Physical exam: Your doctor will do a physical exam to look for signs of asthma or other related conditions. They will look at your ears, eyes, nose, throat, skin, and listen to your chest and lungs. They will measure your height and weight to assess

your overall health and use it with your lung function tests. They will also use a device called a pulse oximeter. It goes on your finger and measures the level of oxygen in your blood. You may also need an X-ray of your lungs or sinuses.

Lung function tests: To confirm asthma, your doctor may have you take one or more breathing tests known as 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 your breathing.

Lung function tests are often done before and after inhaling a medicine known as a bronchodilator [brahn-ko-DIE-ah-lay-tor]. This medicine opens your airways. If your lung function improves a lot with use of a bronchodilator, you probably have asthma. Your doctor may prescribe a trial with asthma medicine to see if it helps.

Common tests used to assess your airways include:

- **Spirometry:** A type of lung function test that measures how much you breathe in and out and how fast you breathe out.
- **FeNO test (exhaled nitric oxide):** A test that helps assess inflammation in the airways.
- **Bronchial provocation or "trigger" tests:** Tests that measure if your lungs are sensitive to certain irritants or triggers.

Allergy tests: A visit with an allergy specialist may be beneficial. Most people with asthma have allergies that trigger or worsen their asthma.

Blood tests: Your doctor may order blood tests to check your immune system. They will check the levels of a white blood cell called eosinophils and an antibody called immunoglobulin E (IgE). If your levels are high, this may be a sign of severe asthma.

Complete Pulmonary Function Testing

Your asthma care provider may want to determine your lung volumes and diffusing capacity. This is often done if your asthma diagnosis is unclear. The test

requires you to sit inside a special box that helps determine how much air you breathe in and out.

1. **Lung Volumes:** Your asthma care provider may order body plethysmography test to determine your lung volumes. Asthma may cause certain changes in lung volumes that will assist your asthma care provider in diagnosing or treating your asthma.

2. **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. **Chest X-Ray**

A chest X-ray is a test commonly performed for patients who wheeze. An asthma care provider will usually order one to make sure there is not some other condition that may be causing your symptoms like a lung infection. With asthma, the chest X-ray is likely to show air trapping or hyper-expansion.

4- Bronchoprovocation Challenge Testing

When your asthma provider orders a bronchoprovocation test, you will inhale a specific substance through a nebulizer, often methacholine or histamine. This is done to see if your lungs become irritated, hyperresponsive, and lead to the development of asthma symptoms. The test has a high negative predictive value. This means that if the test is negative it is unlikely you have asthma. It is often done when your asthma provider suspects asthma but is not able to make a clear diagnosis. Unlike looking for improvement in lung function, the bronchoprovocation test is attempting to provoke asthma symptoms to make a diagnosis.

5- Arterial Blood Gas (ABG)

An arterial blood gas (ABG) is an arterial blood sample used to determine how well blood is oxygenated—a marker for oxygen exchange between the lungs and the blood. Commonly, a blood sample will be obtained from one of the arteries near your wrist. This test may likely be performed during an acute asthma exacerbation and is more reliable than pulse oximetry.

6- Allergy Testing

The relationship between allergies and asthma has been known for a long time. Allergens you normally breathe in can increase the inflammatory reaction and hyperresponsiveness in your lungs. However, your healthcare provider cannot reliably determine if a particular allergen is responsible for your symptoms on clinical grounds alone. Because of this, your asthma care provider may recommend allergy testing. Not all asthmatics are tested. But if you have persistent asthma, your asthma care provider will probably recommend testing.

7- Fractional Exhaled Nitric Oxide (FeNO)

Fractional exhaled nitric oxide testing detects and measures a gas produced by cells in the airways when they are inflamed as a result of allergic or eosinophilic asthma. The presence of this gas, nitric oxide, can help diagnose asthma or determine how well anti-inflammatory medications—typically inhaled corticosteroids (ICSs)—are controlling asthma.[1]

The test is simple and noninvasive: It involves exhaling slowing and steadily (rather than forcefully, as is the case of other lung function tests) into a handheld instrument. The device measures the amount of nitric oxide in the breath in parts per billion (PPB). FeNO takes place in a healthcare provider's office and the results of the test are available immediately.[2]

FeNo testing was one focus of a National Institutes of Health panel of experts who issued updated guidelines for asthma management in December 2020. According to their recommendations, FeNO testing should not be used alone to diagnose or monitor asthma, but can be helpful as an add-on test when a person's symptoms and spirometry and other tests aren't conclusive.

The guidelines apply only to adults and children 5 and over. The panel advised against FeNO testing for younger children as a way to assess wheezing, as studies show it to be an unreliable way to predict if they ultimately will develop asthma

Treatment of asthma

You have options to help manage your asthma. Your healthcare provider may prescribe medications to control symptoms. These include:

- **Bronchodilators:** These medicines relax the muscles around your airways. The relaxed muscles let the airways move air. They also let mucus move more easily through the airways. These medicines relieve your symptoms when they happen and are used for intermittent and chronic asthma.
- **Anti-inflammatory medicines:** These medicines reduce swelling and mucus production in your airways. They make it easier for air to enter and exit your lungs. Your healthcare provider may prescribe them to take every day to control or prevent your symptoms of chronic asthma.
- **Biologic therapies for asthma:** These are used for severe asthma when symptoms persist despite proper inhaler therapy.

You can take asthma medicines in several different ways. You may breathe in the medicines using a metered-dose inhaler, nebulizer or another type of asthma inhaler. Your healthcare provider may prescribe oral medications that you swallow.

Difference between asthma and pneumonia

The main difference is that asthma is a chronic, noninfectious condition, whereas pneumonia is a lung infection.

Asthma causes inflammation and narrowing of the airways. It mainly affects the bronchioles, which are the tiny branches of the airways in the lungs.

Asthma is not a curable disease, though a person can manage its symptoms with the right medications. Asthma triggers can lessen over time and as a person learns to manage their illness.

Pneumonia is an infection that can occur in one or both of the lungs. It causes inflammation in the air sacs, not the bronchioles.

Pneumonia can cause the lungs to fill with fluid, making breathing painful and difficult. It is treatable.

While asthma and pneumonia can cause many similar symptoms, they are different diseases with different treatment and care approaches.

Respiratory disease

5- Non-allergic bronchitis

Non-allergic bronchitis

Non-allergic bronchitis is sometimes called acute bronchitis, as symptoms may onset suddenly and are typically brief.

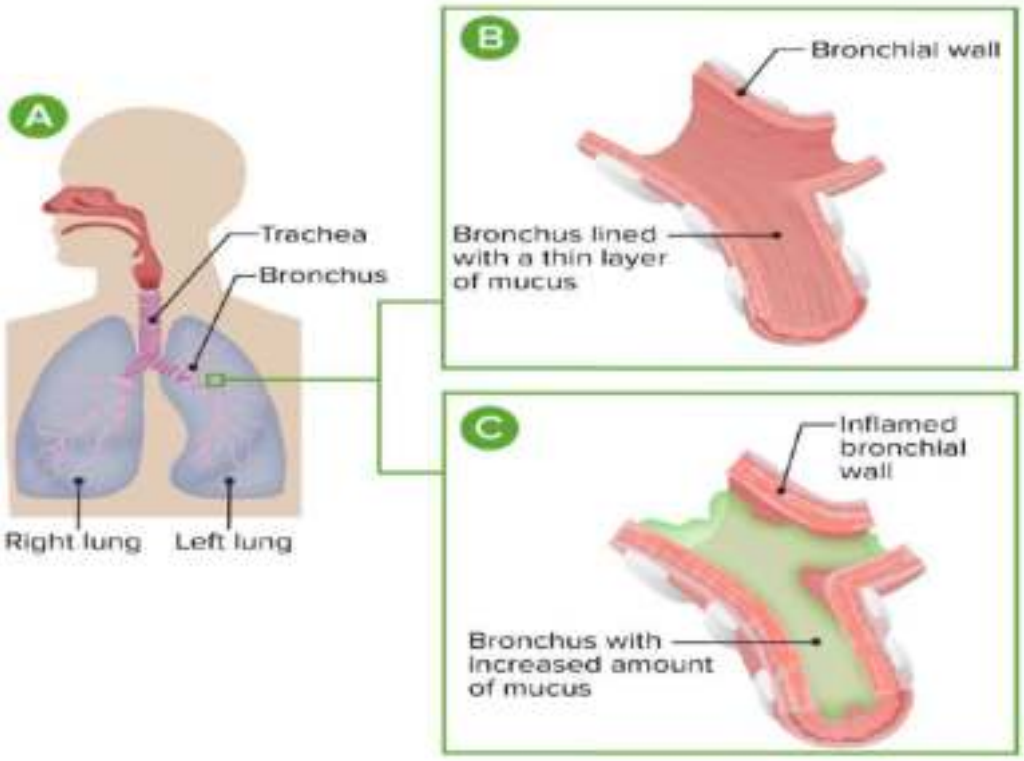
Acute bronchitis is defined as a self-limiting lower respiratory tract infection or is an inflammation of air tubes (bronchial tubes) that bring oxygen into the lungs. It is a form of lower respiratory tract infection that can be caused by bacteria, virus, or airborne irritants. If you have chronic upper respiratory health conditions like asthma, you may be more susceptible to acute bronchitis. To distinguish this condition from common colds and other upper respiratory ailments. Bronchitis refers specifically to infections causing inflammation in the bronchial airways, whereas pneumonia denotes infection in the lung parenchyma resulting in consolidation of the affected segment or lobe.

Mostly, acute bronchitis develops suddenly and typically clears up in 3 to 10 days. Since it is a temporary condition and generally does not lead to any permanent breathing difficulties, acute bronchitis treatment is neither prolonged nor complicated.

Symptoms of Acute Bronchitis

Each person is different, and symptoms will vary depending on the cause of inflammation. The symptoms associated with acute bronchitis are similar to those of the cold and flu and last less than 3 weeks .

- Coughing with or without mucus
  - A runny nose
  - A sore throat
  - Sneezing
  - Fever & chills
  - Breathing difficulties
  - Extreme fatigue
- Mild headache
- Mild body ache



Causes

A virus usually causes acute bronchitis. Bacteria can sometimes cause acute bronchitis. But, even in these cases, taking antibiotics is NOT advised and will not help you get better.

Diagnosed of Acute Bronchitis

Acute bronchitis usually develops suddenly and can persist for 3 to 10 days. For many people, bronchitis will disappear without any treatment at all. If you visit the doctor, your diagnosis will include:

- Lung examination, possibly through an X-ray if they sound congested.
- Questions about any recent illnesses, shortness of breath, or other breathing difficulties.
- Throat cultures and blood tests may be used to rule out other health conditions.

Treatment

Treatment of acute bronchitis is typically divided into two categories: antibiotic therapy and symptom management. Physicians appear to deviate from evidence-based medical practice in the treatment of bronchitis more than in the diagnosis of the condition.

1-Antibiotic

Because of the risk of antibiotic resistance and of *Clostridium difficile* infection in the community, antibiotics should not be routinely used in the treatment of acute bronchitis, especially in younger patients in whom pertussis is not suspected. Although 90 percent of bronchitis infections are caused by viruses, approximately two thirds of patients in the United States diagnosed with the disease are treated with antibiotics.

Symptoms management

Because antibiotics are not recommended for routine treatment of bronchitis, physicians are challenged with providing symptom control as the viral syndrome progresses. Common therapies include antitussives, expectorants, inhaler medications, and alternative therapies. Several small trials and Cochrane reviews help guide therapy for symptom control.

Dermatitis

also known as **eczema**, is a group of diseases that results in inflammation of the skin. These diseases are characterized by **itchiness, red skin, and a rash**. In cases of short duration there may be small blisters while in long-term cases the skin may become thickened. The area of skin involved can vary from small to the entire body.

Dermatitis is a group of skin conditions that includes **atopic dermatitis**, **allergic contact dermatitis**, **irritant contact dermatitis**, and **stasis dermatitis**. The exact cause of dermatitis is **often unclear**. Cases may involve a combination **of irritation, allergy, and poor venous return.** The type of dermatitis is generally determined by the person's history and the location of the rash. For example, irritant dermatitis often occurs on the hands of people who frequently get them wet. Allergic contact dermatitis occurs upon exposure to an allergen causing a hypersensitivity reaction in the skin.

Signs and symptoms:-

It's a **vary**, from **skin rashes** to **bumpy rashes** or including **blisters**. Although every type of dermatitis has different symptoms, there are certain signs that are common for all of them, including **redness of the skin, swelling, itching and skin lesions with sometimes oozing and scarring**. Although the location may vary.

The cause of dermatitis is unknown but is presumed to be a combination of **genetic** and **environmental** factors.

Classification:-

A type of dermatitis may be described by **location (e.g., hand eczema), by specific appearance (eczema discoid), or by possible cause (varicose eczema).**

Common types

1-Atopic dermatitis is an allergic disease believed to have a hereditary component and often **runs in families** whose members have asthma. Itchy rash is particularly noticeable on **head and scalp, neck, inside of elbows, behind knees, and buttocks**. It is very common in developed countries, and rising. Irritant contact dermatitis is sometimes misdiagnosed as atopic dermatitis.

2-Contact dermatitis is of two types: **allergic** (resulting from a delayed reaction to an allergen, such as poison ivy, nickel, or Balsam of Peru), and **irritant** (resulting from direct reaction to a detergent, such as sodium lauryl sulfate, for example).

Some substances act both as **allergen and irritant (wet cement**, for example). Other substances cause a problem after **sunlight exposure**, bringing on phototoxic dermatitis. About three quarters of cases of **contact eczema are of the irritant type, which is the most common occupational skin disease..**

3-Seborrhoeic dermatitis or seborrheic dermatitis (**"cradle cap" in infants**) is a condition sometimes classified as a form of eczema that is closely related to **dandruff**. It causes dry or greasy peeling of the scalp, eyebrows, and face, and sometimes trunk. In newborns it causes a thick, yellow, crusty scalp rash called **cradle cap**.

Less common types

1-Dyshidrosis (dyshidrotic eczema, pompholyx, vesicular palmoplantar dermatitis) only occurs on palms, soles, and sides of fingers and toes. Tiny opaque bumps called vesicles, thickening, and cracks are accompanied by itching, which gets worse at night. **A common type of hand eczema**, it worsens in warm weather.

2-Discoid eczema (**nummular eczema, exudative eczema, microbial eczema)** is characterized by round spots of oozing or dry rash, with clear boundaries, often on lower legs. It is usually worse in winter. Cause is unknown, and the condition tends to come and go.

3-Venous eczema (gravitational eczema, stasis dermatitis, varicose eczema) occurs in people with impaired circulation, varicose veins, and edema, and is particularly **common in the ankle area of people over 50**. There is redness, scaling, darkening of the skin, and itching. The disorder predisposes to leg ulcers.

4-Dermatitis herpetiformis (Duhring's disease) causes intensely itchy and typically symmetrical rash on arms, thighs, knees, and back. **It is directly related to celiac disease**, can often be put into remission with appropriate diet, and tends to get worse at night.

5-Neurodermatitis (lichen simplex chronicus, localized scratch dermatitis) is an itchy area of thickened, pigmented eczema patch that results from habitual rubbing and scratching. Usually there is **only one spot**. Often curable through behavior modification and anti-inflammatory medication. Prurigo nodularis is a related disorder showing multiple lumps.

6-Autoeczematization (id reaction, autosensitization) is an eczematous reaction to an infection with parasites, fungi, bacteria, or viruses. It is completely curable with the clearance of the original infection that caused it. The appearance varies depending on the cause. It always occurs some distance away from the original infection.

7-There are eczemas overlaid by viral infections (eczema herpeticum or vaccinatum), and eczemas resulting from underlying disease (e.g., lymphoma). Eczemas originating from ingestion of medications, foods, and chemicals, have not yet been clearly systematized.

Pathophysiology :-

All eczemas are characterized by **spongiosis** which allows inflammatory mediators to accumulate. Different dendritic cells subtypes, such as Langerhans cells, inflammatory dendritic epidermal cells and plasmacytoid dendritic cells have a role to play.

Diagnoses

An accurate diagnosis requires an examination of the entire skin surface and a careful health history. It is important for a doctor to rule out curable conditions caused by infectious organisms. Occasionally, a sample of **skin (biopsy)** may be sent for examination in a laboratory.

Management

Lifestyle :-Bathing once or more a day is recommended, usually for five to ten minutes in warm water. Soaps should be avoided

Moisturizers :-Moisturizing agents (also known as emollients) are recommended at least once or twice a day.

Medications :-There is little evidence for antihistamine; they are thus not generally recommended. Sedative antihistamines.

Corticosteroids:-

Eosinophilic pneumonia

(EP) is a disease in which an eosinophil, a type of white blood cell, accumulates in the lung pulmonary infiltrates (bronchoalveolar lavage fluid) or in tissue (lung biopsy specimens). These cells cause disruption of the normal air spaces(alveoli).

Epidemiology

The epidemiologic factors to be considered include exposure to certain **parasites** (in endemic regions), **toxic products (inhalation)**, **medications and illicit drugs**, as well as a **history of asthma and atopy**.

Signs and symptoms:-

Most types of eosinophilic pneumonia have **similar signs** and symptoms. Prominent and nearly universal signs and symptoms include **cough, fever, difficulty breathing, and night sweats**. **Acute eosinophilic pneumonia** typically follows a rapid course. **Fever and cough** may develop only **one or two** weeks before **breathing difficulties** progress to the point of **respiratory failure** requiring mechanical ventilation. **Chronic eosinophilic** pneumonia usually follows a slower course. Symptoms accumulate over several months and include **fever, cough, difficulty breathing, wheezing, and weight loss**. Individuals with CEP are often misdiagnosed with asthma before CEP is finally recognized.

Classification of EP based on clinical-radiological presentation and etiology.

Principal forms of pulmonary eosinophilia (based on clinical-radiological present

1) Simple pulmonary eosinophilia
2) Chronic eosinophilic pneumonia
3) Acute eosinophilic pneumonia
4) Allergic bronchopulmonary aspergillosis
5) Pulmonary eosinophilia associated with a systemic disease:

• Churg-Strauss syndrome
• Hypereosinophilic syndrome

Etiology of the forms of pulmonary eosinophilia

1) Primary or idiopathic

2) Secondary

a) Known cause

- Drugs
- Parasites
- Toxic products/irradiation
- Fungal and mycobacterial infection

b) Diseases that can lead to pulmonary eosinophilia

- **Diffuse lung diseases**: cryptogenic organizing pneumonia; hypersensitivity pneumoı idiopathic pulmonary fibrosis; Langerhans cell histiocytosis; sarcoidosis.
- **Malignant diseases**: leukemia; lymphoma; lung cancer; adenocarcinoma involving multiple organs; squamous carcinoma involving multiple organs.
- **Connective tissue diseases**: rheumatoid arthritis; Sjögren's syndrome.

1-Simple EP :- or Löffler's syndrome or **Loeffler's syndrome** is a disease in which eosinophils accumulate in the lung in response to a parasitic infection. migratory pulmonary infiltrates in patients with eosinophilia and few or no pulmonary symptoms .Pulmonary infiltrates are peripheral, with a pleural base. **Drugs and ascariasis are the most common causes of this syndrome**. In **one third of cases, simple pulmonary eosinophilia is idiopathic**. The **prognosis is excellent**. The use of corticosteroids is rarely necessary, and spontaneous resolution occurs within **30 days**.

caused by the parasites *Ascaris lumbricoides*, *Strongyloides stercoralis* and the hookworms *Ancylostoma duodenale* and *Necator americanus*.

Cardiac damage caused by the damaging effects of eosinophil granule proteins (ex. major basic protein) is known as Loeffler endocarditis and can be caused by idiopathic eosinophilia or eosinophilia in response to parasitic infection.

2- acute eosinophilic pneumonia lead to **acute respiratory failure, fever, diffuse pulmonary infiltrate and severe eosinophilia in the BALF or in lung tissue**.

Histological examination **reveals eosinophil infiltration and edema in the alveolar spaces and interstitium**, including the interlobular septa. In the lung tissues, there is

a release of eosinophil chemotactic cytokines, all of which accumulate and are seen in the BALF, **without an increase in the blood**. This explains **tissue eosinophilia without peripheral eosinophilia**. Pulmonary eosinophilia presents the greatest number of eosinophils in lung tissue, which is why, through the **granules containing toxic proteins**, **the tissue injury is so severe**. Since the proteolytic potential of eosinophils is lower than is that of neutrophils, the acute lung injury is **reversible and there are no sequelae**

3- Chronic eosinophilic pneumonia or Carrington's disease:-

is a rare disorder characterized by the massive accumulation of eosinophils in the lungs (pulmonary eosinophilia). They are usually produced in response to **allergens, inflammation or infection** (especially parasitic ones) and are particularly active in the respiratory tract. In CEP, **eosinophils also accumulate in the bloodstream** (peripheral eosinophilia). Common symptoms include shortness of breath (dyspnea), cough, fatigue, night sweats, low grade fevers, and unintended weight loss. The **exact cause of CEP is unknown (idiopathic).**

4-**Eosinophilic granulomatosis with polyangiitis** (EGPA), also known as **Churg-Strauss syndrome** (CSS) or **allergic granulomatosis**, is an extremely rare autoimmune condition that **causes inflammation of small and medium-sized blood vessels** (vasculitis) in persons with a history of airway allergic hypersensitivity (atopy).

It usually manifests in three stages.

The **early (prodromal) stage** is **marked by airway inflammation;** almost all patients experience asthma and/or allergic rhinitis.

The **second stage** is characterized by abnormally **high numbers of eosinophils** (hypereosinophilia), which causes **tissue damage, most commonly to the lungs and the digestive tract**.

The **third stage** consists of **vasculitis**, which can eventually lead to **cell death and can be life-threatening.**

Diagnostic markers:- include eosinophil granulocytes and granulomas in affected tissue, and antineutrophil cytoplasmic antibodies (ANCA) against neutrophil granulocytes.

The criteria for diagnosis of Churg–Strauss syndrome lists these criteria:

- Asthma
- Eosinophilia, i.e. eosinophil blood count greater than 500/microliter, or hypereosinophilia, i.e. eosinophil blood count greater than 1,500/microliter
- Presence of mononeuropathy or polyneuropathy
- Unfixed pulmonary infiltrates
- Presence of paranasal sinus abnormalities
- Histological evidence of extravascular eosinophils

if at least four of these six criteria are positive

Radiological manifestations

Pulmonary infiltrates, characterized by foci of air-space consolidation and focal ground-glass opacities, can be seen in pulmonary eosinophilia of all causes. However, there are certain presentations that are considered typical, or at least suggestive, of one of three groups: CEP; and AEP, ABPA (Allergic bronchopulmonary aspergillosis)

In eosinophilia, unlike in neutrophilic inflammation, cavitation is rare. Nevertheless, cavitation can occur in certain cases of ABPA and CSS, as well as in cases of certain parasitic infections, such as filariasis and hydatidosis.

Laboratory findings

Peripheral eosinophilia occurs in virtually all cases, either in the initial presentation or during the course of the disease. Eosinophilia is **not always severe in blood samples**, with eosinophil counts of 500-1,000 cells/mm3, **or it can even be absent from the initial clinical presentation, thereby making diagnosis difficult.**

Increased eosinophil counts in the air spaces, common to various causes of pulmonary eosinophilia, result in severe eosinophilia in the BALF and is the principal method of confirming the diagnosis of AEP and CEP. In such cases, eosinophils account for more than 25% of the cells in the BALF.

Eosinophilic pneumonia due to parasites almost always occurs during **larval migration** to the lungs. Initially (in the pulmonary infiltrate phase) **parasitological stool examination results are negative**, because the worms are still in the larval

phase and therefore do not produce eggs. Stool examination results remain negative for up to **8 weeks** after the onset of pulmonary symptoms.

Histopathological findings

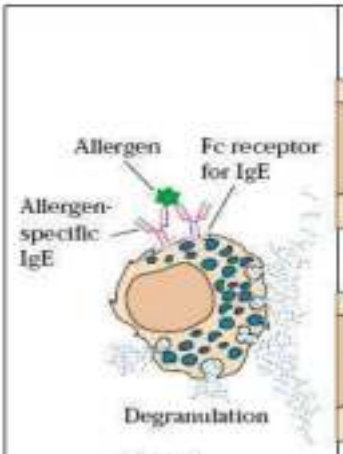
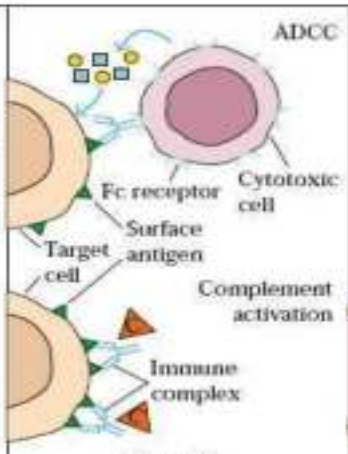
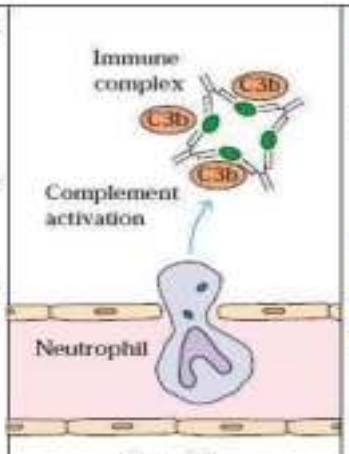
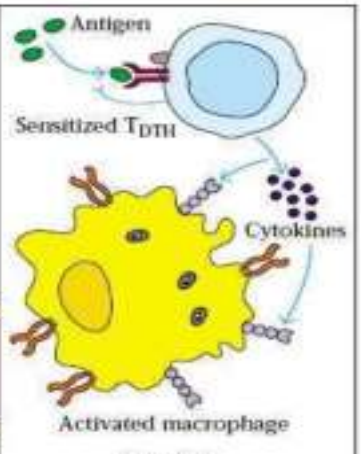
Lung biopsy (transbronchial or by thoracotomy) is **not a prerequisite** for the diagnosis of pulmonary eosinophilia. Biopsy is performed to **rule out the hypotheses**

Alternative names	Often mentioned disorders	Mediators	Description

of infection and neoplasia, as well as to make the differential diagnosis with other interstitial diseases and cryptogenic organizing pneumonia, or to confirm CSS.

Histopathological findings that are common to virtually all causes include **intra-alveolar exudate of histiocytes and eosinophils**, also present in the interstitium, as well as **eosinophilic microabscesses**, **macrophages containing Charcot-Leyden crystals** and findings of bronchiolitis obliterans or organizing pneumonia. **Small focal areas of interstitial fibrosis**, as well as intra-alveolar necrosis and even a **certain degree of vasculitis**, can occur, although without granulomas. **Granulomas**, as well as being present in ABPA, are indicative of parasitic infections and CSS.

Allergy (immediate)	Atopy ,Anaphylaxis ,Asthma ,Churg-Strauss Syndrome	IgE	Fast response which occurs in minutes, rather than multiple hours or days. Free antigens cross link the IgE on mast cells and basophils which causes a release of vasoactive biomolecules. Testing can be done via skin test for specific IgE.
Cytotoxic, antibody-dependent	Autoimmune hemolytic anemia ,Rheumatic heart disease ,Thrombocytopenia ,Erythroblastosis fetalis ,Goodpasture's syndrome ,Graves' disease Myasthenia gravis	IgM or IgG (Complement) MAC	Antibody (IgM or IgG) binds to antigen on a target cell, which is actually a host cell that is perceived by the immune system as foreign, leading to cellular destruction via the MAC. Testing includes both the direct and indirect Coombs test.[3]
Immune complex disease	Serum sickness ,Arthus reaction ,Post streptococcal glomerulonephritis ,Membranous nephropathy ,Reactive arthritis ,Lupus nephritis ,Systemic lupus erythematosus ,Extrinsic allergic alveolitis(hypersensitivity pneumonitis)	IgG (Complement) Neutrophils	Antibody (IgG) binds to soluble antigen, forming a circulating immune complex. This is often deposited in the vessel walls of the joints and kidney, initiating a local inflammatory reaction.
Delayed-type hypersensitivity,[2][3] cell-mediated immune memory response, antibody-independent	Contact dermatitis, including Urushiol-induced contact dermatitis (poison ivy rash).,Mantoux test ,Chronic transplant rejection ,Rheumatoid arthritis ,Multiple sclerosis,Coeliac disease ,Hashimoto's thyroiditis	T-cells	Helper T cells (specifically Th1 helper t cells) are activated by an antigen presenting cell. When the antigen is presented again in the future, the memory Th1 cells will activate macrophages and cause an inflammatory response. This ultimately can lead to tissue damage.
Autoimmune disease, receptor mediated	Graves' disease ,Myasthenia gravis	IgM or IgG (Complement)	

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

Hypersensitivity

(also called **hypersensitivity reaction** or **intolerance**) undesirable Hypersensitivity reactions require a pre-sensitized (immune) state of the host. They are classified in four groups.reactions produced by the normal immune system, including allergies and autoimmunity. They are usually referred to as an over-reaction of the immune system and these reactions may be damaging, uncomfortable, or occasionally fatal.

Allergy

Type of hypersensitivity reactions of the immune system. Allergy may involve more the one type of reaction.An allergy is an immune reaction to something that does not affect most other people. Substances that often cause reactions are:

Pollen ,Dust mites ,Mold spores ,Pet dander ,Food ,Insect stings,, Medicines

Penicillin allergy

Is an abnormal reaction of your immune system to the antibiotic drug penicillin.

Signs and symptoms

penicillin allergy include **hives, rash and itching ,Fever ,Swelling ,Shortness of breath ,Wheezing ,Runny nose , watery eyes .Severe reactions include anaphylaxis**, a life-threatening condition that affects multiple body systems.

Causes :- Penicillin allergy occurs when your **immune system becomes hypersensitive to the drug -mistakenly reacting to the drug as a harmful substance**. Before the immune system can become sensitive to penicillin, you have to be **exposed to the medication at least once**. If and when your immune system misidentifies penicillin as a harmful substance, it **develops an antibody to the** drug. The **next time you take the drug**, **these specific antibodies flag it and direct immune system attacks on the substance**.

Penicillins include:- Amoxicillin ,Ampicillin ,Dicloxacillin ,Nafcillin,Oxacillin,Penicillin G,Penicillin V ,Piperacillin ,Ticarcillin.

Mechanism :- There are two mechanisms for a drug allergy to occur: IgE or non-IgE mediated. In IgE-mediated reactions, also known as Immunoglobulin E mediated reactions, drug allergens bind to IgE antibodies, which are attached to mast cells and basophils, resulting in IgE cross-linking, cell activation and release of preformed and newly formed mediators.

Diagnosis:-

Skin tests :-Administers a small amount of the suspect penicillin to your skin with a tiny needle. A positive reaction to a test will cause a red, itchy, raised bump. but some kinds of drug reactions cannot be detected by skin tests.

IgE levels may be elevated in patients who are atopic, but the level does not necessarily correlate with clinical symptoms.

The tryptase level can be elevated, which is indicative of mast cell degranulation. False-negative results can occur.

An elevated eosinophil count may be observed in patients with atopic disease.

RAST (fluorenzymeimmunoassay): measures antigen-specific IgE.

Graded challenge:-you receive up **to five doses** of the suspect penicillin, **starting with a small dose** and increasing to the desired dose. If you reach the therapeutic dose with no reaction, If you are allergic to one type of penicillin, your doctor may recommend a graded challenge with a type of penicillin or cephalosporin that's less likely — because of known chemical properties — to cause an allergic reaction. This would enable your doctor to identify an antibiotic that can be used safely.

Insect bites and stings

Occur when an insect is agitated and seeks to defend itself through its natural defense mechanisms, or when an insect seeks to feed off the bitten person. Some insects inject formic acid, which can cause an immediate skin reaction often

resulting in redness and swelling in the injured area. Stings from fire ants, bees, wasps and hornets are usually painful, and may stimulate a dangerous allergic reaction called anaphylaxis for at-risk patients, and some wasps can also have a powerful bite along with a sting. Bites from mosquitoes and fleas are more likely to cause itching than pain.

Signs and symptoms

The reaction to a sting is of three types. 1-**The normal reaction** involves the area around the bite with redness, itchiness, and pain. 2-**A large local reaction** occurs when the area of swelling is greater than 5 cm. 3-**Systemic reactions** are when symptoms occur in areas besides that of the bites.

Hypersensitivity

(also called **hypersensitivity reaction** or **intolerance**) undesirable Hypersensitivity reactions require a pre-sensitized (immune) state of the host. They are classified in four groups.reactions produced by the normal immune system, including allergies and autoimmunity. They are usually referred to as an over-reaction of the immune system and these reactions may be damaging, uncomfortable, or occasionally fatal.

Type I: IgE mediated immediate reaction

Type II: Antibody-mediated reaction (IgG or IgM antibodies)

Type III: Immune complex-mediated reaction

Type IV: Cytotoxic, cell-mediated, delayed hypersensitivity reaction

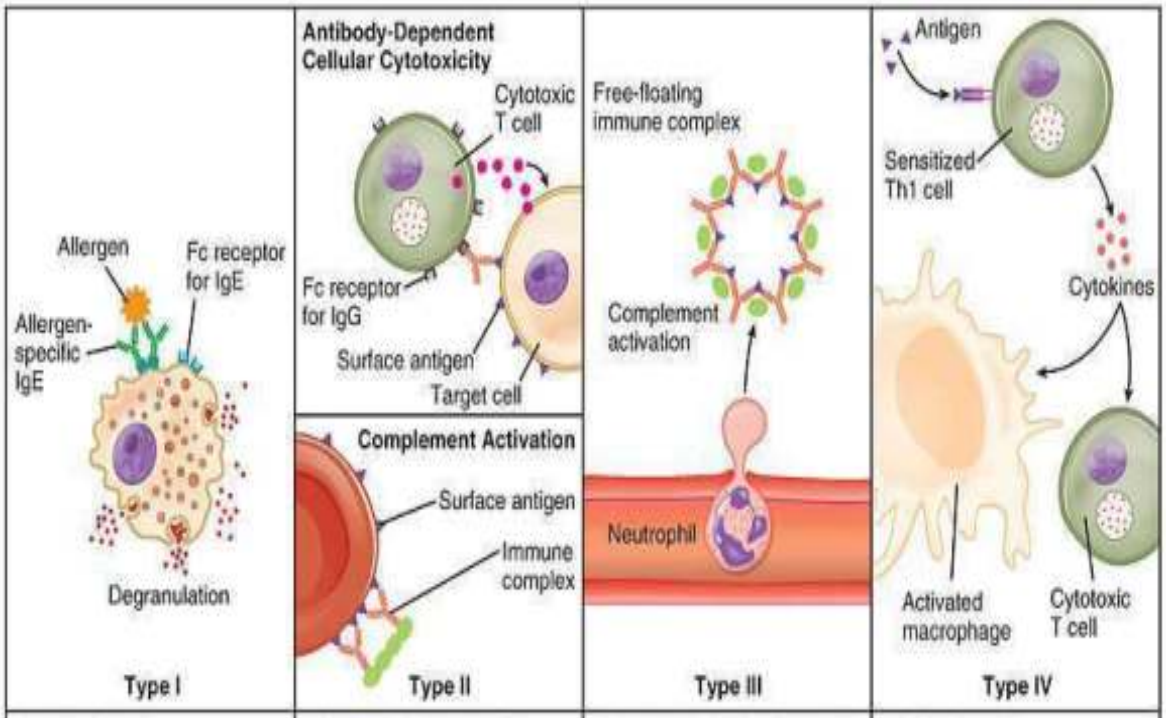
Diagnosis of hypersensitivity

The **RAST** (Radioallergosorbent test) is a laboratory test performed on blood. It tests for the amount of specific IgE antibodies in the blood which are present if there is a "true" allergic reaction.

The **MELISA® test** (Memory Lymphocyte Immuno Stimulation Assay) **measures hypersensitivity to numerous metals, including mercury, by placing a series of**

metals into contact with the white blood cells of the person being tested and then monitoring the reaction. An innovative diagnostic tool.

Type	Description	Method of Detection
I	An immediate reaction that can result in an anaphylactic reaction	Provocation test, Skin test, IgE RAST
II	Cytotoxic reaction mediated by IgM and IgG antibody responses to host tissue	IgG serum test
III	IgG and IgM antibodies form immune complexes with antigens in the blood	IgG serum test
IV	Delayed reaction that is mediated by memory T cells	Skin test, MELISA®



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

Endocrinology

Immunological thyroid disease

Graves' Disease

Graves' disease is an autoimmune disease that affects the thyroid gland. The gland produces too much thyroid hormone, a condition known as hyperthyroidism. Thyroid hormones regulate body temperature, heart rate and metabolism. An overactive thyroid causes problems with organs like the heart, as well as bones and muscles. Treatments can help.

Introduction to Graves' Disease:

Graves' disease is a thyroid-specific autoimmune disorder in which the body makes antibodies to the thyroid-stimulating hormone receptor (TSHR), leading to hyperthyroidism, or an abnormally strong release of hormones from the thyroid gland. Normally, the release of thyroid hormones is mediated by thyroid-stimulating hormone (TSH), a hormone secreted by the pituitary gland that binds to TSHR to stimulate the thyroid to release thyroid hormones. This normal cycle is self-regulating: the hormones secreted by the thyroid keep more TSH from being produced

The thyroid is a butterfly-shaped gland located at the base of the neck just below the Adam's apple. The thyroid produces hormones that help regulate many functions in the body.

- Autoimmunity against the thyroid gland generates two opposite pathogenic processes: thyroid hyperplasia in Graves' disease and thyroid destruction in Hashimoto's thyroiditis.

- Three different mechanisms have been sequentially proposed to be responsible for autoimmune thyrocyte depletion: first, antibody-mediated destruction through immune-complex deposition; second, T-cell-mediated destruction through the release of cytotoxic granules after specific target recognition; and third, death-receptor-mediated induction of apoptosis.

The onset of symptoms of Graves' disease is usually gradual, often taking several weeks or months to develop.

Graves' disease causes hyperthyroidism, which speeds up certain body functions. There are many symptoms of hyperthyroidism. You may experience some of these symptoms and not others, or many of them at the same time.

Symptoms of hyperthyroidism can include:

- Rapid heartbeat (palpitations).
- Feeling shaky and/or nervous.
- Weight loss.
- Increased appetite.
- Diarrhea and/or more frequent bowel movements.
- Thin, warm and moist skin.
- Intolerance to heat and excessive sweating.
- Difficulty sleeping, such as insomnia.
- Enlarged thyroid gland (goiter).
- Hair loss and change in hair texture (brittle).
- Menstrual changes.
- Muscle weakness.

If you're experiencing these symptoms, see your healthcare provider.

Graves' disease can also cause eye disease symptoms, including:

- Gritty, irritated eyes.
- Swelling of the tissues around your eyes (puffy eyes).
- Bulging eyes.
- Light sensitivity.
- Pressure or pain in your eyes.
- Blurred or double vision.

This is called Graves' ophthalmopathy or orbitopathy or thyroid eye disease. Only about a third of people with Graves' disease develop this condition. If you're experiencing these symptoms, it's important to see your eye doctor (optometrist or ophthalmologist).

Rarely, people with Graves' disease develop a lumpy, reddish thickening of the skin on their shins known as pretibial myxedema (called Graves' dermopathy). It's usually painless and mild, but it can be painful for some peop

How is Graves' disease diagnosed?

Your healthcare provider will ask about your symptoms and medical history, including your family history of thyroid disease, and perform a physical exam. They may also order the following tests to confirm a Graves' disease diagnosis:

- **Thyroid blood tests**: These blood tests check the level of thyroid hormone in your blood and amounts of thyroid-stimulating hormone (TSH). A low TSH level indicates that your thyroid gland is producing too much hormone. The overproduction causes your pituitary gland to make less TSH.

- **Thyroid antibody blood tests**: These tests help identify different types of autoimmune thyroid conditions. The two types of antibodies linked with Graves' disease include TSI (thyroid-stimulating antibodies) and TBII (thyrotropin binding inhibitory immunoglobulins).
- **Thyroid uptake and scan**: In this test, you take a small amount of radioactive iodine orally. Your provider will check to see how much of the radioactive iodine your thyroid absorbs. High levels of iodine absorption can be a sign of Graves' disease.
- **Doppler blood flow measurement (Doppler ultrasound)**: This test uses sound waves to detect increased blood flow in your thyroid due to Graves' disease. Your provider may order this test if radioactive iodine uptake is not a good option for you, such as during pregnancy or breastfeeding.

How is Graves' disease treated?

Graves' disease is a lifelong (chronic) condition. However, treatments can keep your thyroid hormone levels in check. Medical care may even make the disease temporarily go away (remission).

Treatments for Graves' disease include:

- **Beta-blockers**: Beta-blockers, such as propranolol and metoprolol, are often the first line of treatment for Graves' disease. These medications regulate your heart rate and protect your heart until other hyperthyroidism treatments take effect. These medications don't stop thyroid hormone production.
- **Antithyroid medications**: Antithyroid medications, such as methimazole (Tapazole®) and propylthiouracil, block your thyroid's production of thyroid hormone. In a small percentage of people, these

medications cause skin rashes and low white blood cell count, which may increase your risk of infection. Rarely, liver disease develops.

- **Radioiodine therapy**: This therapy involves taking one dose of radioactive iodine in pill or liquid form. Over two to three months, radiation slowly destroys thyroid gland cells. (The rest of your body isn't exposed to radiation.) As your thyroid gland shrinks, hormone levels return to normal. People who are pregnant or breastfeeding shouldn't get this treatment. If you have this treatment, you'll likely eventually develop hypothyroidism (underactive thyroid), which requires medication. But hypothyroidism is easier to treat than hyperthyroidism and it causes fewer long-term health problems.
- **Surgery**: A thyroidectomy involves surgically removing all or part of your thyroid gland. After surgery, some people produce too little thyroid hormone (hypothyroidism). If you develop this condition, you may need to take thyroid replacement hormone medications, such as levothyroxine (Synthroid®), for the rest of your life.

Antithyroid medication, radioiodine therapy and surgery all have benefits and risks, and there's no consensus in the medical community on which treatment is the best option. It's important to discuss all three options in detail with your provider to make the best choice for you.

Hashimoto's Disease

Hashimoto's disease affects the thyroid gland. It's also called Hashimoto's thyroiditis, chronic lymphocytic thyroiditis or autoimmune thyroiditis. can lead to hypothyroidism, when the thyroid gland is affected and gradually stops producing

enough hormones to keep the body working properly. Hashimoto's is more common in middle-aged women than men and can cause fatigue and weight gain.

Hashimoto's hypothyroidism happens when the thyroid gland doesn't make enough thyroid hormones to meet the body's needs because its immune system has damaged it.

Thyroid hormones regulate metabolism, which is how you turn food into energy. Without enough energy, your body cannot operate normally and its functions begin to slow down.

How is Hashimoto's disease diagnosed?

First, your healthcare provider will take your medical history and perform a physical exam. He or she will feel your thyroid gland to determine if it is enlarged. Blood tests are also ordered. These include:

- **Thyroid stimulating hormone (TSH) test:** A high TSH level most commonly means the thyroid gland is not producing enough T4 hormone. This lab is usually most consistent with a diagnosis of hypothyroidism or subclinical hypothyroidism.
- **Free T4 test:** A low T4 level suggests that the person has hypothyroidism.
- **Antithyroid antibody test:** Presence of antibodies indicates a higher risk of developing Hashimoto's hypothyroidism.

The most common imaging test that may be ordered is an ultrasound of your thyroid gland. The ultrasound shows the size and appearance of the thyroid and if there are any nodules or growths in your neck area.

How is Hashimoto's disease treated?

If Hashimoto's disease does progress to hypothyroidism, usual treatment is a synthetic (man-made) form of thyroid hormone called levothyroxine (Synthroid®, Tirosint®, Levoxyl®, Levothroid®, Unithroid®).

This drug restores the normal function of the thyroid. You'll need to take it every day for the rest of your life. Your providers and you will figure out how to adjust your dose to make sure that your hypothyroidism is kept under control.

Symptoms

Hashimoto's disease progresses slowly over the years. You may not notice signs or symptoms of the disease. Eventually, the decline in thyroid hormone production can result in any of the following:

- Fatigue and sluggishness
- Increased sensitivity to cold
- Increased sleepiness
- Dry skin
- Constipation
- Muscle weakness
- Muscle aches, tenderness and stiffness
- Joint pain and stiffness
- Irregular or excessive menstrual bleeding
- Depression
- Problems with memory or concentration
- Swelling of the thyroid (goiter)
- A puffy face

- Brittle nails
- Hair loss
- Enlargement of the tongue

Causes

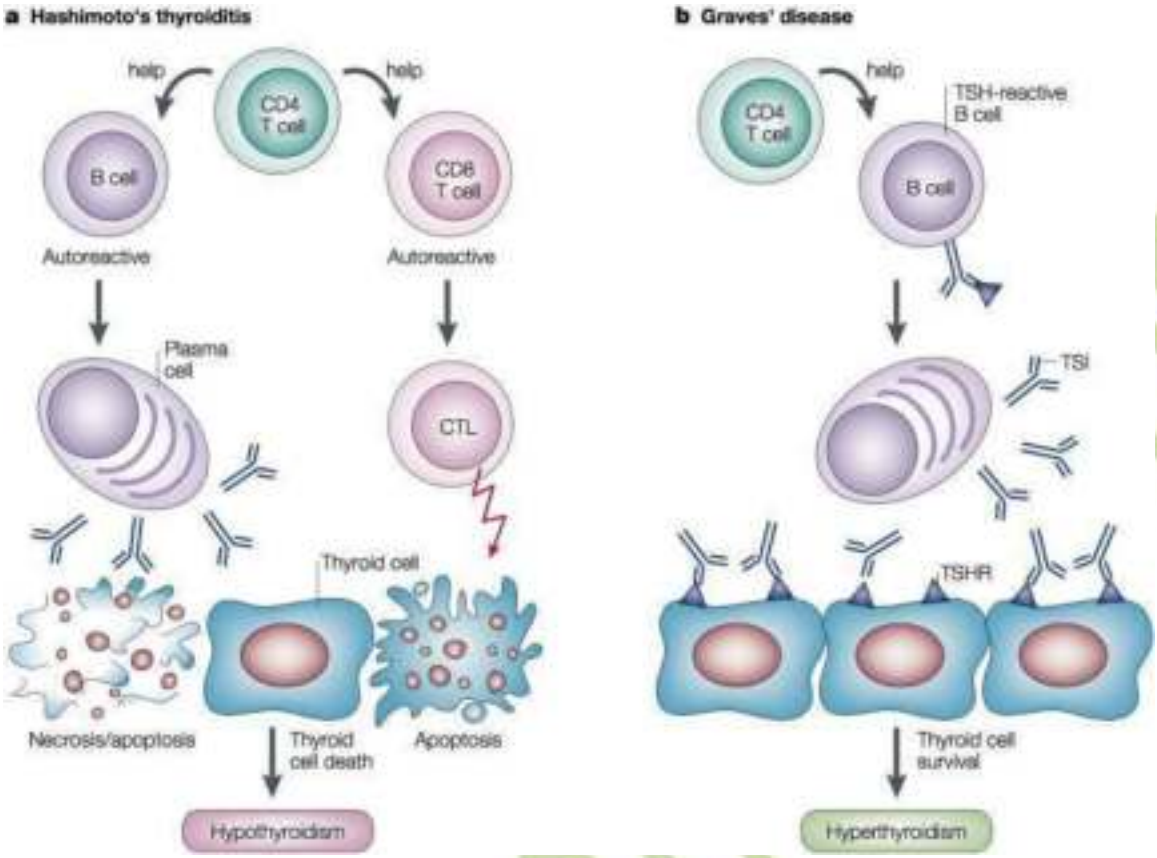
Hashimoto's disease is an autoimmune disorder. The immune system creates antibodies that attack thyroid cells as if they were bacteria, viruses or some other foreign body. The immune system wrongly enlists disease-fighting agents that damage cells and lead to cell death.

What causes the immune system to attack thyroid cells is not clear. The onset of disease may be related to:

- Genetic factors
- Environmental triggers, such as infection, stress or radiation exposure
- Interactions between environmental and genetic factors

| Pathogenesis of Hashimoto's disease (A) and GD (B)

. (A) Autoreactive CD4 + T cells in HT induce antibody production by B cells. The antibodies bind to the basal membrane of the thyroid follicle, activate complement, and induce necrosis of thyrocytes. The activation of cytotoxic CD8 + T cells leads to the induction of apoptosis by action of perforin. Finally, the expression of Fas (CD95) and FasL (CD95L) by thyrocytes perpetuates HT. (B) Autoreactive CD4 + T cells in GD induce only anti-thyroid-stimulating hormone receptor antibody-producing B cells. These antibodies act stimulatory by increasing I2 metabolism (cAMP/PKA) and promoting proliferation and survival (PI3K/PKC/ERK) of thyrocytes. Blocking antibodies are characterized by lack of effect (not shown), and neutral antibodies activate various pathways, such as PI3K/Akt, mTOR/p70S6K, and MAPK/ERK1/2 and induce thyrocyte apoptosis. Abbreviations: GD, Graves' disease; HT, Hashimoto's thyroiditis; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; p70S6K, ribosomal protein S6 kinase beta-1; PKC, protein kinase C; PI3K, phosphatidylinositol 3,4,5, triphosphate kinase; PKA, protein kinase; mTOR, mammalian target of rapamycin.



Diagnosis

A number of conditions may lead to the signs and symptoms of Hashimoto's disease. If you're experiencing any of these symptoms, your health care provider will conduct a thorough physical exam, review your medical history and ask questions about your symptoms.

Testing thyroid function

To determine if hypothyroidism is the cause of your symptoms, your provider will order blood tests that may include the following:

- **TSH test.** Thyroid stimulating hormone (TSH) is produced by the pituitary gland. When the pituitary detects low thyroid hormones in the blood, it sends TSH to the thyroid to prompt an increase in thyroid hormone production. High TSH levels in the blood indicates hypothyroidism.

- **T-4 tests.** The main thyroid hormone is thyroxine (T-4). A low blood level of T-4 confirms the findings of a TSH test and indicates the problem is within the thyroid itself.

Antibody tests

More than one disease process can lead to hypothyroidism. To determine if Hashimoto's disease is the cause of hypothyroidism, your health care provider will order an antibody test.

The intended purpose of an antibody is to flag disease-causing foreign agents that need to be destroyed by other actors in the immune system. In an autoimmune disorder, the immune system produces rogue antibodies that target healthy cells or proteins in the body.

Usually in Hashimoto's disease, the immune system produces an antibody to thyroid peroxidase (TPO), a protein that plays an important part in thyroid hormone production. Most people with Hashimoto's disease will have TPO antibodies in their blood. Lab tests for other antibodies associated with Hashimoto's disease may need to be done.

Treatment

Most people with Hashimoto's disease take medication to treat hypothyroidism. If you have mild hypothyroidism, you may have no treatment but get regular TSH tests to monitor thyroid hormone levels.

T-4 hormone replacement therapy

Hypothyroidism associated with Hashimoto's disease is treated with a synthetic hormone called levothyroxine (Levoxyl, Synthroid, others). The synthetic hormone works like the T-4 hormone naturally produced by the thyroid.

The treatment goal is to restore and maintain adequate T-4 hormone levels and improve symptoms of hypothyroidism. You will need this treatment for the rest of your life.

Monitoring the dosage

Your heath care provider will determine a dosage of levothyroxine that's appropriate for your age, weight, current thyroid production, other medical conditions and other factors. Your provider will retest your TSH levels about 6 to 10 weeks later and adjust the dosage as necessary.

Once the best dosage is determined, you will continue to take the medication once a day. You'll need follow-up tests once a year to monitor TSH levels or any time after your provider changes your dosage.

A levothyroxine pill is usually taken in the morning before you eat. Talk to your doctor if you have any questions about when or how to take the pill. Also, ask what to do if you accidentally skip a dose. If your health insurance requires you to switch to a generic drug or a different brand, talk to your doctor.

Precautions

Because levothyroxine acts like natural T-4 in the body, there are generally no side effects as long as the treatment is resulting in "natural" levels of T-4 for your body.

Too much thyroid hormone can worsen bone loss that causes weak, brittle bones (osteoporosis) or cause irregular heartbeats (arrhythmias).

Effects of other substances

Certain medications, supplements and foods may affect your ability to absorb levothyroxine. It may be necessary to take levothyroxine at least four hours before these substances. Talk to your doctor about any of the following:

- Soy products
- High-fiber foods
- Iron supplements, including multivitamins that contain iron

- Cholestyramine (Prevalite), a medication used to lower blood cholesterol levels
- Aluminum hydroxide, which is found in some antacids
- Sucralfate, an ulcer medication
- Calcium supplements

T-3 hormone replacement therapy

Naturally produced T-4 is converted into another thyroid hormone called triiodothyronine (T-3). The T-4 replacement hormone is also converted into T-3, and for most people the T-4 replacement therapy results in an adequate supply of T-3 for the body.

For people who need better symptom control, a doctor also may prescribe a synthetic T-3 hormone (Cytomel) or a synthetic T-4 and T-3 combination. Side effects of T-3 hormone replacement include rapid heartbeat, insomnia and anxiety. These treatments may be tested with a trial period of 3 to 6 months.

Tumors and Tumor Markers

Tumor immunology

The proliferation of normal cells is carefully regulated. However, such cells when exposed to chemical carcinogens, irradiation and certain viruses may undergo mutations leading to their transformation into cells that are capable of uncontrolled growth, producing a tumor or neoplasm.

The tumor may be:

- Benign, if it is not capable of indefinite growth and the host survives.
- Malignant, if the tumor continues to grow indefinitely and spreads (metastases). This uncontrolled growth may be due to up regulation of **oncogenes**

(cancer-inducing genes) and/or down regulation of **tumor suppressor genes** (that normally inhibit tumor growth often by inducing cell death).

Tumor associated antigens

There are 2 main types of tumor antigens:

- Tumor-specific transplantation antigens (TSTA) which are **unique to tumor cells and not expressed on normal cells.**
- Tumor associated transplantation antigens (TATA) that are expressed by **tumor cells and normal cells.**

Tumor-associated developmental antigens or onco-fetal antigens:-

These include alpha-fetoprotein (AFP) and carcino-embryonic antigen (CEA) found secreted in the serum. AFP is found in patients with hepatocellular carcinoma whereas CEA is found in colon cancer. These are important in diagnosis. **AFP is produced only as a secreted protein whereas CEA is found both on cell membranes and in secreted fluids.**

Viruses that cause human tumors include:

DNA viruses

- Papova (papilloma, polyoma) viruses: Papilloma virus causes cervical cancer.
- Hepatitis virus: Hepatitis B virus causes hepatocellular cancer.
- Adenoviruses may also be tumorigenic
- Certain types of Herpes Virus (CMV and EBV)

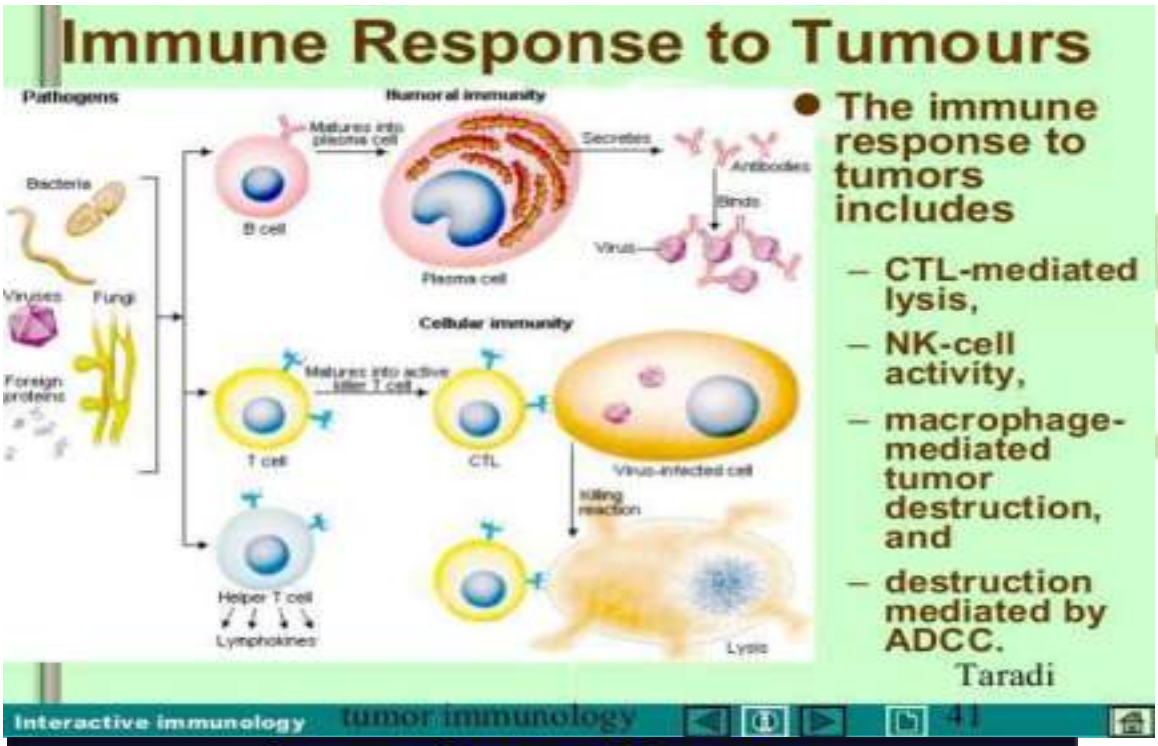
RNA viruses

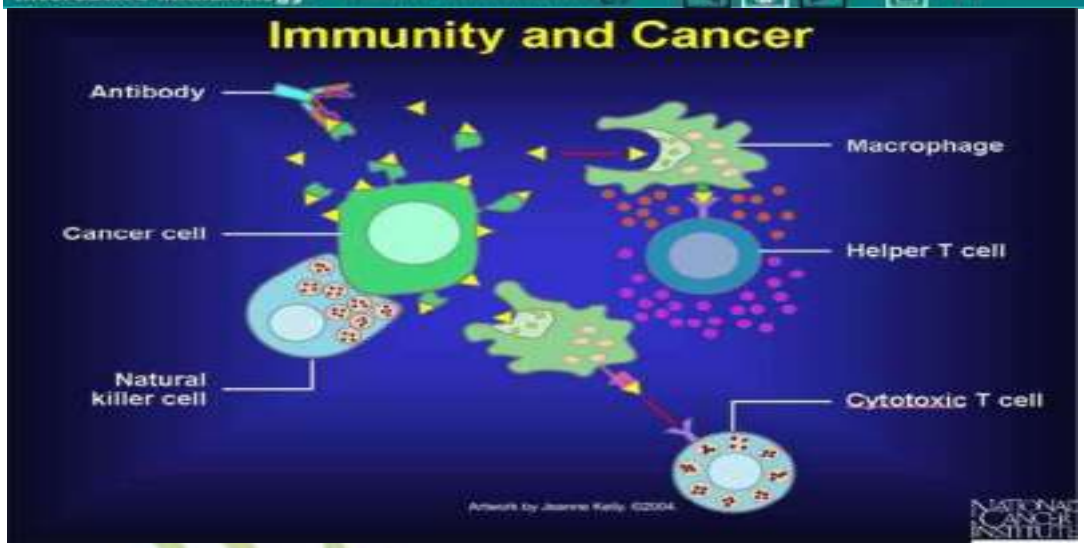
- Retroviruses: Human T- lymphotropic viruses (HTLV-I and HTLV-II) causes T-cell leukemias.

Immunity against Tumor : There is several anti-tumor immune reactivity in human;

1. Cell-mediated immunity plays a critical role in tumor rejection.

2. The T helper (Th) cells recognize the tumor antigens that may be shed from tumors and internalized, processed and presented in association with class II MHC on antigen presenting cells. These Th cells, will produce cytokines. provide help to B cells in antibody production.
3. Cytokines such as **IFN-gamma γ** may also activate macrophages to be tumoricidal
4. The Th cells also provide help to tumor-specific cytotoxic T cells (CTLs) $CD8^+$ and NK cell by inducing their proliferation and differentiation.
5. The CTLs recognize tumor antigens in the context of class I MHC and mediate tumor cell lysis.
6. In tumors with decreased MHC antigens, natural killer (NK) cells are important in mediating tumor rejection.





Tumor Marker (TM):-

T.M or also known as biomarkers are indicators of cellular, biochemical, molecular, or genetic alterations by which neoplasia can be recognized. It is

measurable biochemical that are associated with a malignancy, **they are substances found at higher than normal levels in some peoples with cancer.**

Classification:- The T.M. is either produced by the tumor cells (tumor derived) or by the body in response to tumor cells (Tumor associated).

1. **Tumor Specific Antigens**: - Present on tumor cells and not on any normal cells.
2. **Tumor Associated Antigens: -** Are present on tumor cells and also on some normal cells in response to the tumor.

Clinically associated useful of TMs :-

• Diagnostic and distinguish benign from malignant disease

• Correlate with the amount of tumor present (so-called tumor burden)

• Allow subtype classification to more accurately stage patients

• Be prognostic, either by the presence or absence of the marker or by its concentration

• Guide choice of therapy and predict response to therapy

Type of T.Ms. (specific and /or sensitive)

As like other laboratory Testing, T.Ms. test must be both **specific and sensitive.**

Specificity: - If either the T.Ms. it self or the test used to detect or measure it is not specific enough, there is a chance that the results could suggest a tumor is presents, or growing despite treatment, when it is not (a false positive). High specificity – not present in other diseases, non-tumors and in healthy subjects

Sensitivity: - If the T.Ms. or the test is not sensitive enough, the result may suggest a tumor is not present when it actually is or that is responding to treatment, when it is not (A false Negative). High sensitivity – detectable at the beginning of the disease

Main Examples of T.Ms. in cancers:-

Protein Tumor Markers :

- Carcinoembryonic antigen (CEA)
- α- Fetoprotein (AFP) .
- Carbohydrate Antigen (CA . 19-9) . (CA . 125). monitoring of ovarian CA
- Prostate-Specific Antigen (PSA) .
- CA 15-3 – monitoring of breast CA
- CA 72 CA 72-4– monitoring of gastric CA
- CA 19 CA 19-9 9 for monitoring of pancreas CA (and bile ducts)
- Human Chorionic Gonadotropin in Testicular Germ Cell Tumors

The following examples for T.Ms. often associated with cancer:-

1. Carciniembryonic Antigen (CEA) :- It is an oncofetal protein that is normally present during fetal life but can be seen in low concentration in healthy adults. This may be found at elevated levels in patients with cancer of the colon and rectum. CEA itself is secreted into the circulation and is also found in the mucous secretions of the stomach, small intestine, and biliary tree.

2. α- Fetoprotein(AFP):- It is an oncofetal antigen synthesized by hepatocytes and endodermally , it is used for the detection of Hepatocellular carcenoma (HCC) .It raised in testicular cancer. Elevated levels are also seen in hepatitis, inflammatory bowel disease, and cirrhosis. Prognosis The AFP concentration reflects tumor size.

3. Prostate – Specific Antigen (PSA):- Is a serine protease that is formed in the prostatic epithelium and secreted into the prostatic ducts. Its function is to digest the gel that is formed in seminal fluid after ejaculation. Normally only small amounts of PSA leak into the circulation . PSA levels are high in man with prostate cancer, prostatitis or being prostatic hyperplasia (BPH)..

4. Carbohydrate Antigen – 125 (CA-125):- This protein is found on the surface **of ovarian cancer cells** and can be detected with a blood test , An increased in CA -125 may be caused by another type of cancer , including endometrial, peritoneal of fallopian tube cancer or anon- cancerous condition , pelvic inflammatory diseases , cirrhosis.

5. Carbohydrate Antigen 19-9: Serum marker for pancreas cancer But its use is limited to monitoring response to therapy, not as a diagnostic marker. Because CA 19-9 epitope is normally present within the biliary tree.

6. DNA-Based Markers:

Specific mutations in oncogenes , tumor -suppressor genes, and mismatch repair genes can serve as biomarkers. **These mutations may be germline . e.g. proto-oncogene ,** or **somatic mutations such p53 mutations. RB gene mutation**

7. Human Chorionic Gonadotropin (HCG) :

A glycoprotein hormone , Normally secreted by placental tissue with highest circulating levels occurring at 60 days of gestation. elevation occurs during pregnancy and in patients with trophoblastic neoplasms.. Maybe elevated in some benign conditions – peptic ulcer disease, inflammatory intestinal disease and cirrhosis .

8. Other types of Tumor markers

a. **Tissue and organ specific antigens** :- PSA , Thyroglobulin (TG) , Squamous cell carcinoma (SCC) , Hormone receptors , C- Peptide .

b. **Nonspecific antigens (Paraneoplastic production)**:- Ferritin , Lactate dehydrogenase (LDH) , B2- Micro globulin , ACTH , ADH and Parathyroid hormones.

Transplantation

Immunology of transplantation

Graft or Transplant: Transfer of living cells, tissues and organs from one part of the body to another or from one individual to another.

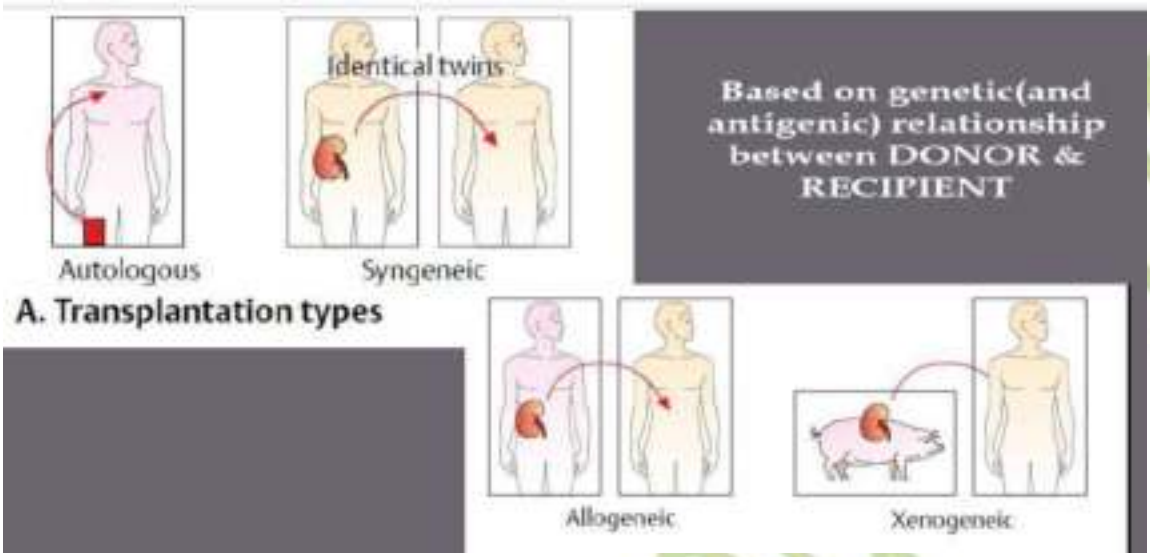
The transplantation mainly based on:

1. Organ or tissue transplanted
2. Anatomical site of origin of transplant & site of its placement:
   a. Orthotopic: normal sites
   b. Heterotopic: abnormal sites
3. Genetic compatibility and antigenic relationship.
4. Fresh or stored transplanted tissue :

Types of Transplantation:-

1. Autologous .

2. Syngeneic.
3. Allogenic .
4. Xenogeneic .



Auto grafting (Autologous) -

Transfer of self-tissue from one body site to another in the same individual, it should:

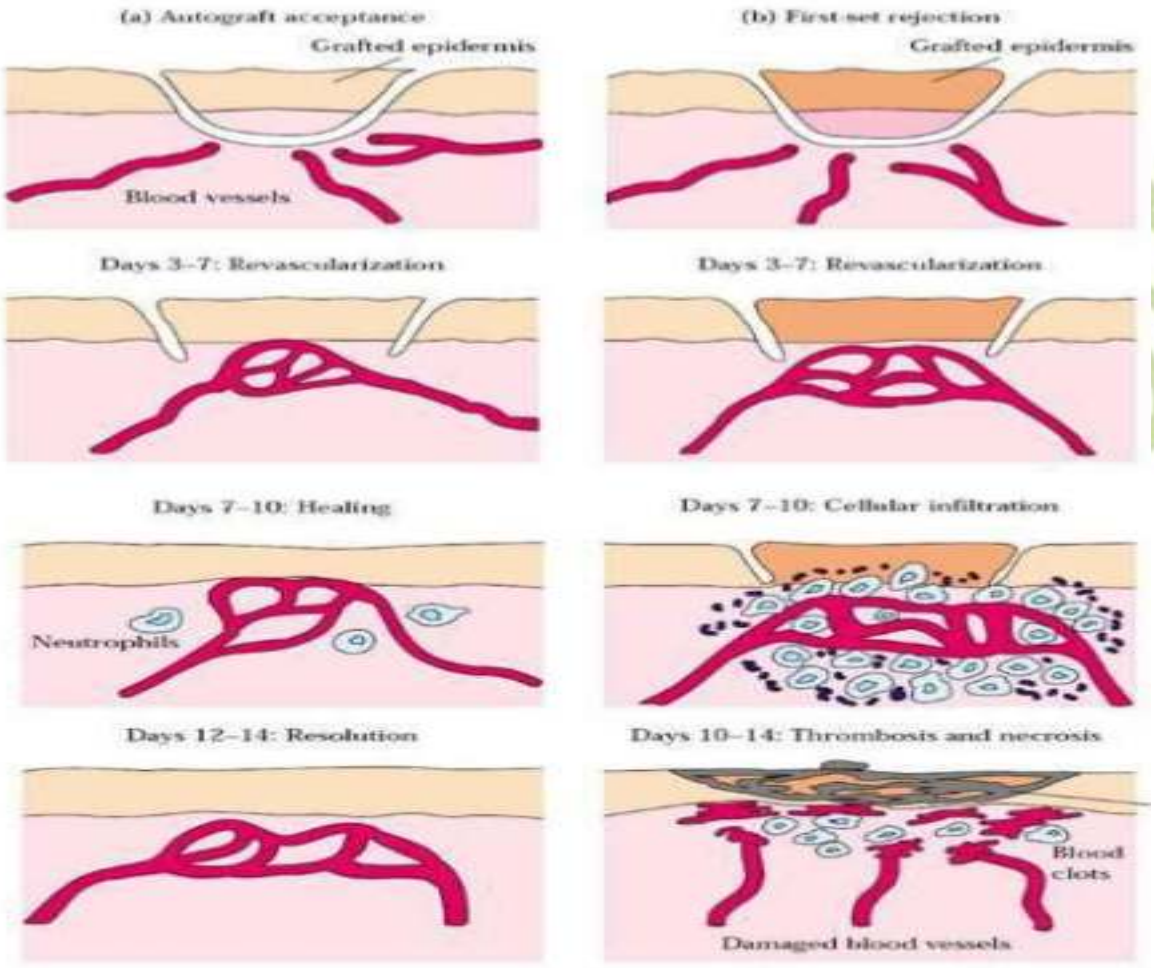
• **Genetic homology** of the tissue- immune system does not respond (Skin,hiar grafts) Auto graft acceptance epidermis:-

1. After 3- 7 days have revascularization of blood vesicles.
2. 7 – 10 days healing.
3. 12 -14 neutrophil resolution,

Allograft reaction:-

First Set Response :- Skin graft from a genetically unrelated animal of same species . Initial acceptance , Thrombosed and necrosed Mainly by T lymphocytes .

- After 3- 7 days have revascularization of blood vesicles .
- 7 – 10 cellular infiltration ,
- 10 -14 thromboses and necrosis ,
- > 14 day damaged blood vesicles and rejection the implanted tissues.

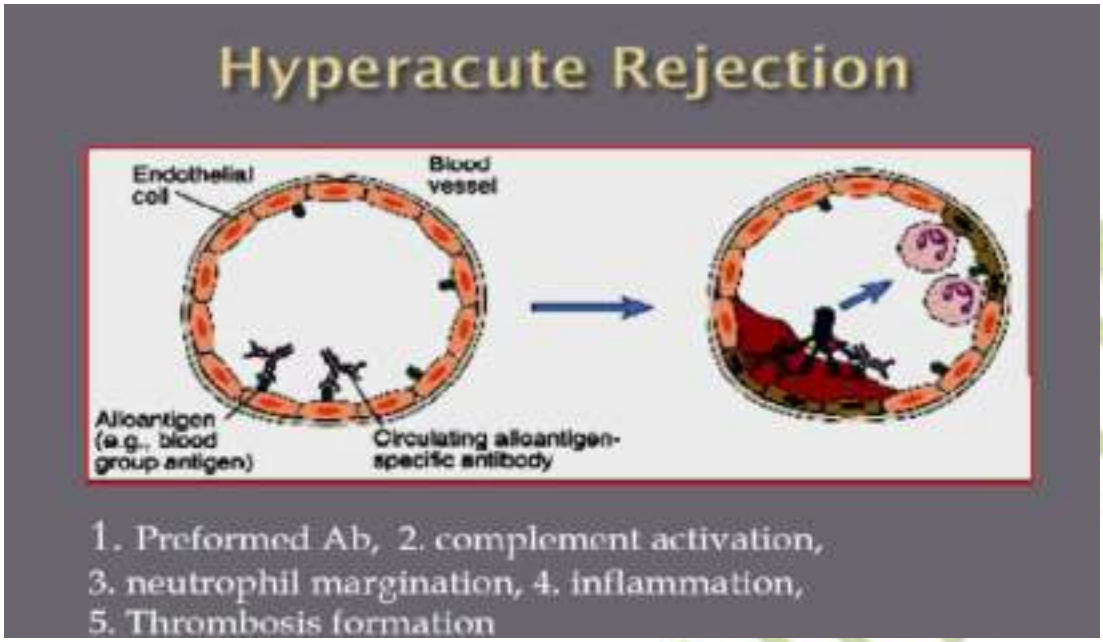


Second Set Response :- If an animal has rejected a graft by the first set response, another graft from the same donor is applied – rejected in an accelerated manner , Mainly by antibodies

Effecter mechanism of allograft rejection:-

- **Hyper acute Rejection**

a. Pre-existing specific antibodies in high titers in the host circulation bind to donor endothelial antigens.
b. Activates Complement Cascade.
c. Characterized by thrombotic occlusion of graft
d. Graft remains pale
e. Rejected within minutes or hours, even without an attempt at vascularization



Immunological Enhancement: -

Humoral antibodies can **act in opposition to CMI by inhibiting graft rejection.**

- **Afferent inhibition**: Combine with antigens released from graft so that they are unable to initiate an immune response
- **Central inhibition**: Antibodies may combine with lymphoid cell, by a negative feedback, render them incapable of responding to the antigens of the graft.
- **Efferent inhibition**: By coating the surface of cells in the graft so that sensitized lymphocytes are kept out of contact with them .

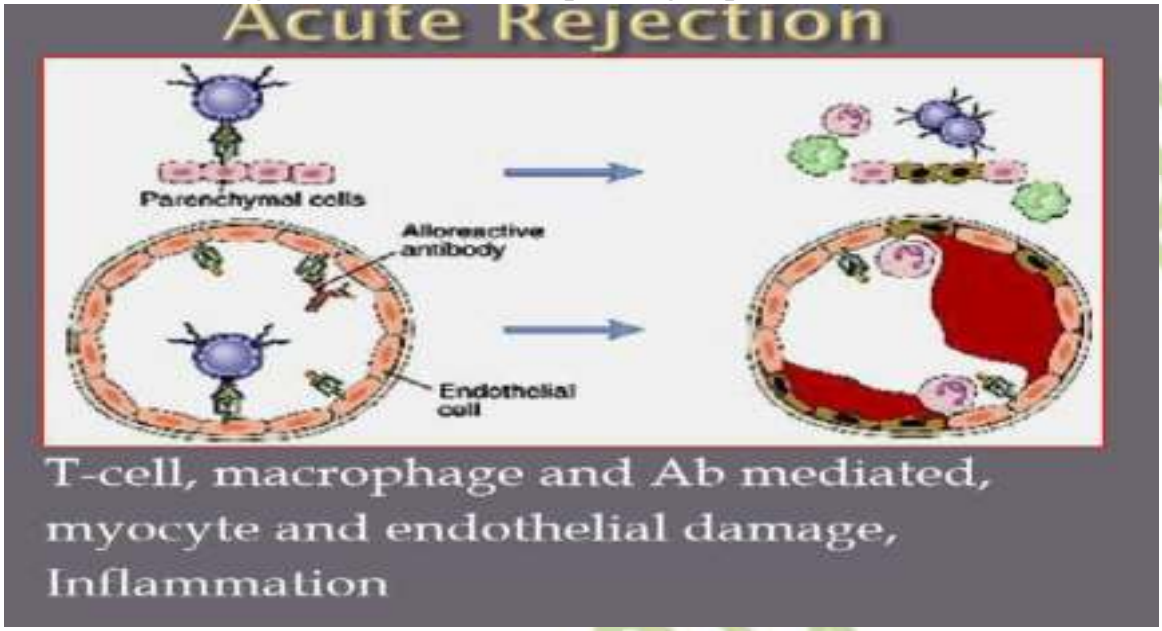
Acute Rejection: -

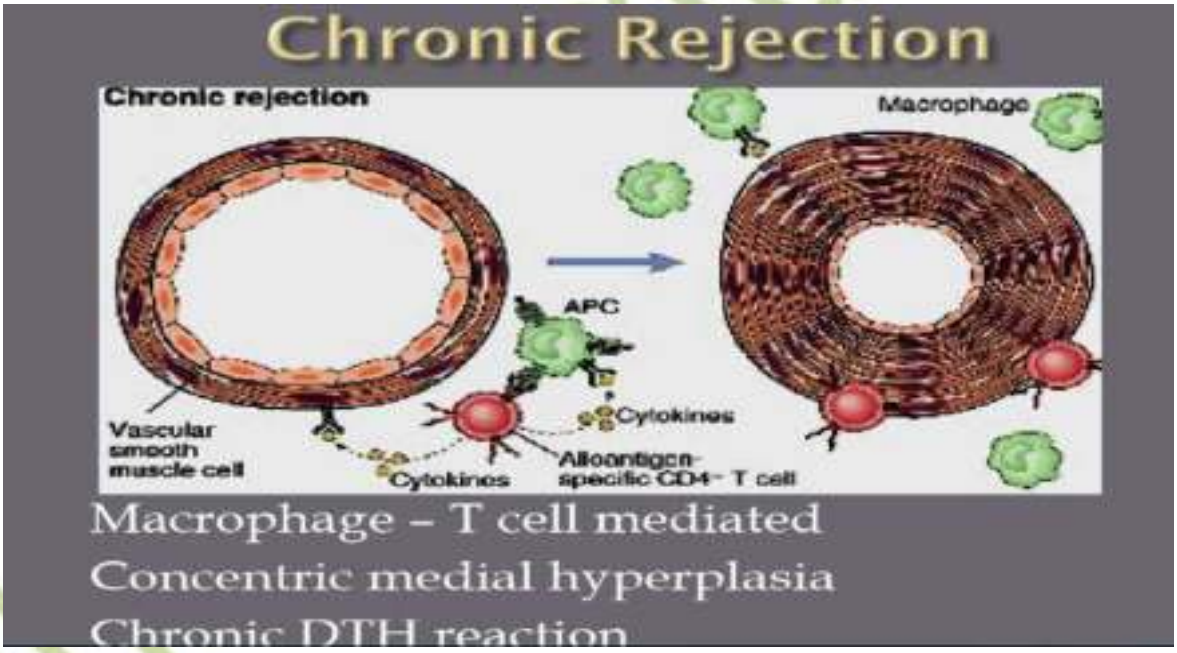
- Vascular and parenchymal injury mediated by T cells and antibodies that usually begin after first week of transplantation if **no immunosuppressant therapy**
- Incidence is high (30%) for the first 90 days.

Chronic Rejection :-

- Occurs in most solid organ transplants
- Heart, Kidney, Lung, Liver
- Characterized by :
    a. Fibrosis

b. Vascular abnormalities
c. Loss of graft function over a prolonged period.





Histocompatibility antigens.

Antigens that participate in graft rejection are called transplantation or histocompatibility antigens :

- ABO blood group
- HLA system (MHC restricted allograft Rejection)

Histocompatibility Testing :-

- ABO blood grouping
- HLA compatibility:
- Tested by HLA typing and tissue matching
- HLA typing identifies the HLA antigens expressed on the surface of leucocytes

Methods of HLA – Typing :-

- Microcytotoxicity test .
- Molecular methods
  a. RFLP with southern blott
  b. PCR using sequence specific primers.
- Tissue matching .

Micro Cytotoxicity: -

Tests for complement mediated lysis of peripheral blood lymphocytes with a standard set of typing sera. Micro-cytotoxicity assay, utilizes serum with known anti-HLA antibodies that recognize particular HLA loci (HLA-A, HLA-B, HLA-C, HLA-DQ, HLA-DR /not DP) in order to match genetically similar individuals in hopes of performing a tissue transplantation.

Graft-versus-host (GVH) reaction: -

Graft rejection is due to the reaction of the host to the grafted tissue, Host-versus-graft response , The contrary situation, in which the graft mounts an immune response against the antigens of the host, is known as: Graft-versus-host (GVH) reaction.

Essential Component Required for (GVH)

The GVH reaction occurs when the following conditions are present:

1. The graft contains immunocompetent T cells.
2. The recipient possesses transplantation antigens that are absent in the graft.
3. The recipient must not reject the graft.

When grafted tissue has mature T cells, they will attack host tissue leading to GVHR. Major problem for bone marrow transplant.

Methods to overcome GVHR :

- Treat bone marrow to deplete T cells.
- Use autologous bone marrow.
- Use umbilical cord blood.

Caused by the reaction of grafted mature Tcells in the marrow inoculum with alloantigens of the host

- Acute GVHD :- Characterized by epithelial cell death in the skin, GI tract, and liver .
- Chronic GVHD :- Characterized by atrophy and fibrosis of one or more of these same target organs as well as the lungs

+