

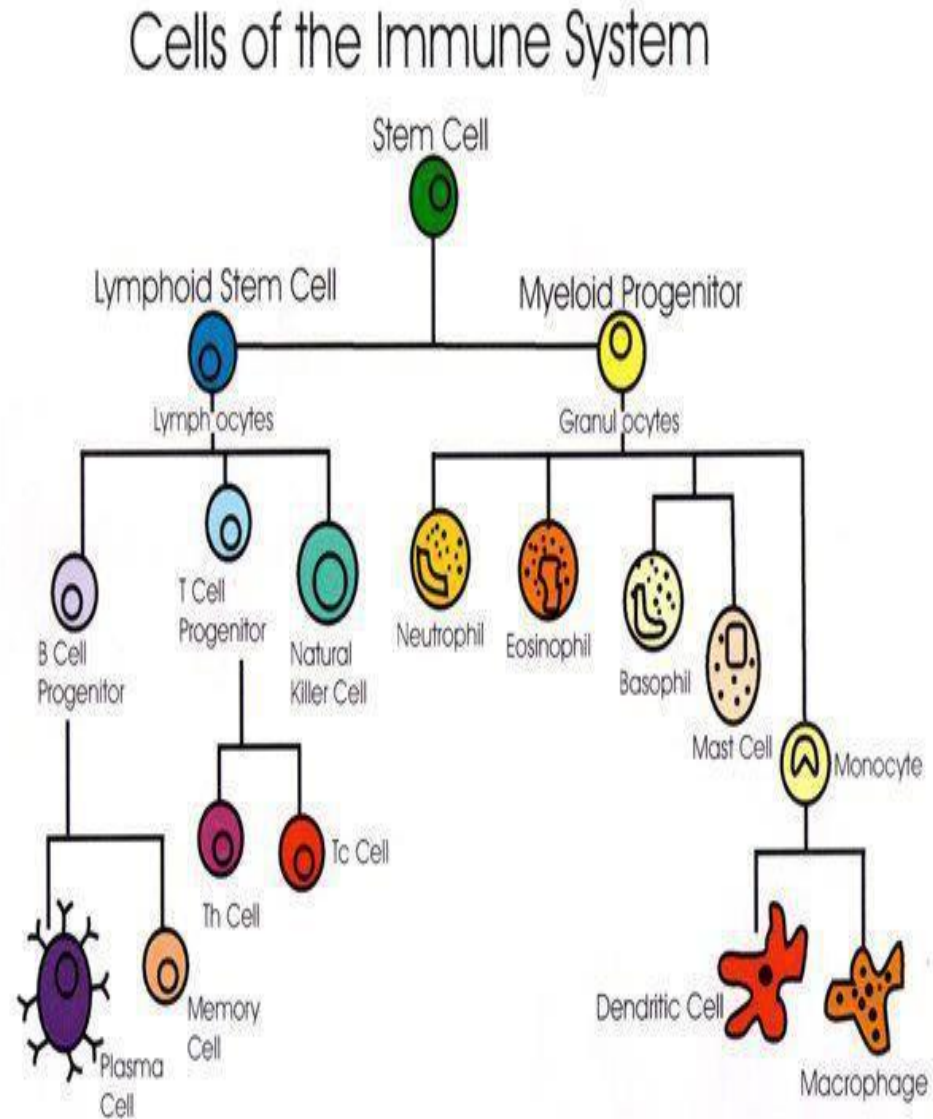
Primary and Secondary Immunodeficiencies Auto immunity & auto immune disorders (e.g., RA,/SLE/MS)

**Paper MHG-203: Immunogenetics
Unit IV, TOPIC 10**

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IMMUNODEFICIENCY

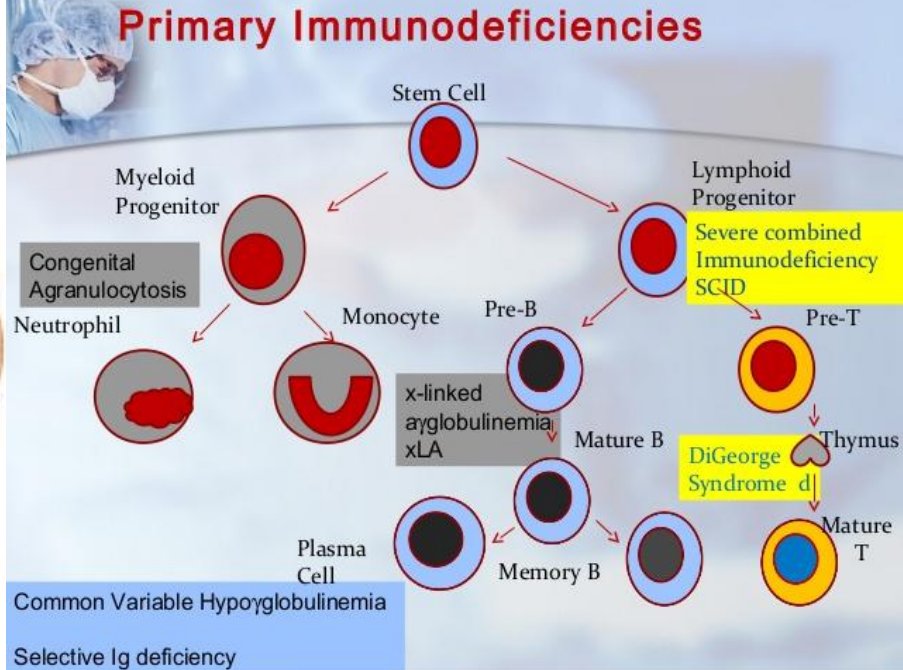
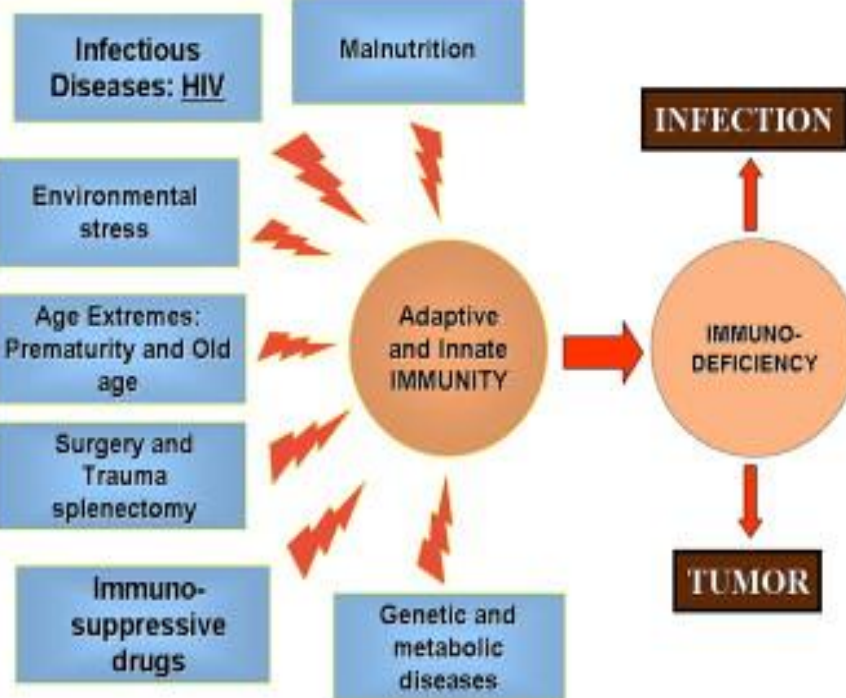
- ❖ The immune system is remarkably versatile defense system that has evolved to protect animals from invading pathogenic microorganisms and cancer. It is able to generate an enormous variety of cells and molecules capable of specifically recognizing and eliminating an apparently limitless variety of foreign invaders. These cells and molecules act together in a dynamic network whose complexity rivals that of the nervous system.
- ❖ Immunodeficiency is a state in which the body's immune system is not able to fight with the infectious conditions.
- ❖ It is also known as immuno-compromise.
- ❖ Immunodeficiency disorders impair the immune system's ability to defend the body against foreign or abnormal cells that invade or attack it (such as bacteria, viruses, fungi, and cancer cells). As a result, unusual bacterial, viral, or fungal infections or lymphomas or other cancers may develop.
- ❖ In an autoimmune disorder, the immune system attacks the body's own tissues. Sometimes the autoimmune disorder develops before the immunodeficiency causes any symptoms.
- ❖ Immunodeficiency also decrease cancer immunosurveillance.



There are two types of immunodeficiency disorders:

- ❖ **Primary:** These disorders are usually present at birth and are genetic disorders that are usually hereditary. They typically become evident during infancy or childhood. However, some primary immunodeficiency disorders (such as common variable immunodeficiency) are not recognized until adulthood. There are more than 100 primary immunodeficiency disorders. All are relatively rare.
- ❑ Primary immunodeficiency disorders are classified by which part of the immune system is affected:
 - ❑ **Humoral immunity**, which involves B cells (lymphocytes), a type of white blood cell that produces antibodies (immunoglobulins)
 - ❑ **Cellular immunity**, which involves T cells (lymphocytes), a type of white blood cell that helps identify and destroy foreign or abnormal cells
 - ❑ Both humoral and cellular immunity (B cells and T cells)
 - ❑ **Phagocytes** (cells that ingest and kill microorganisms)
 - ❑ **Complement proteins** (proteins that help immune cells kill bacteria and identify foreign cells to destroy)
- ❑ The affected component of the immune system may be missing, reduced in number, or abnormal and malfunctioning.
- ❑ Problems with B cells are the most common primary immunodeficiency disorders, accounting for more than half.

- ❖ **Secondary:** These disorders generally develop later in life and often result from use of certain drugs or from another disorder, such as diabetes or human immunodeficiency virus (HIV) infection.
- ❖ They are more common than primary immunodeficiency disorders.
- ❖ Secondary immunodeficiencies, also known as acquired immunodeficiencies, can result from various immunosuppressive agents, for example, malnutrition, aging, particular medications (e.g., chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants, glucocorticoids) and environmental toxins like mercury and other heavy metals, pesticides and petrochemicals like styrene, dichlorobenzene, xylene, and ethylphenol.
- ❖ Immunosuppression generally refers to both beneficial and potential adverse effects of decreasing the function of the immune system. The term immunodeficiency generally refers solely to the adverse effect of increased risk for infection.
- ❖ Various hormonal and metabolic disorders can also result in immune deficiency including anemia, hypothyroidism and hyperglycemia.
- ❖ Chemotherapy and radiation therapy can also suppress the immune system, sometimes leading to immunodeficiency disorders.
- ❖ Smoking, alcoholism and drug abuse also depress immune response.
- ❖ Many types of cancer can cause an immunodeficiency disorder. For example, any cancer that affects the bone marrow (such as leukemia and lymphoma) can prevent the bone marrow from producing normal white blood cells (B cells and T cells), which are part of the immune system.

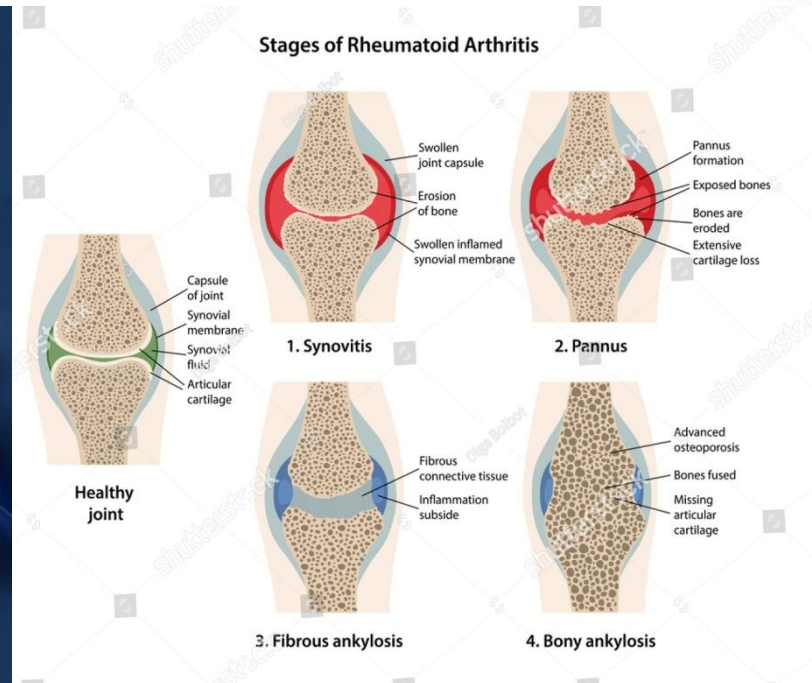
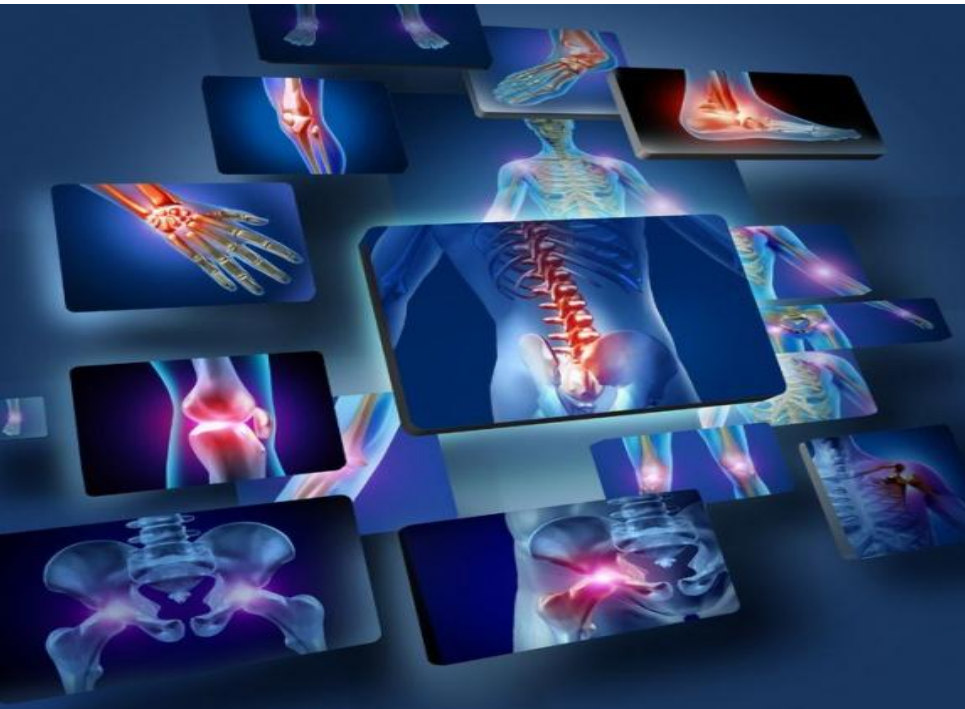


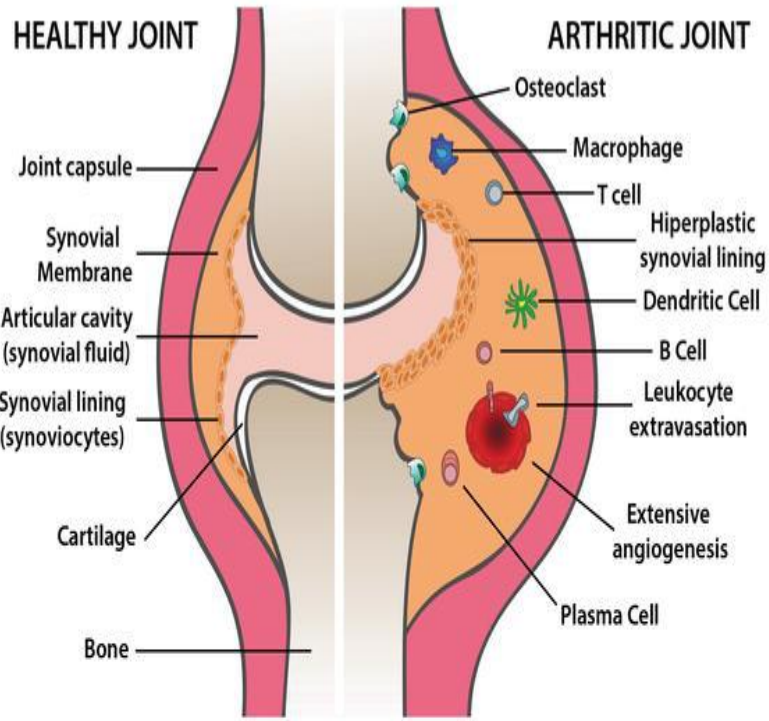
Primary immunodeficiency (Hereditary)	Secondary immunodeficiency (Acquired)
<ul style="list-style-type: none"> ➤ Predominant antibody defect ➤ Combined T and B cell defect ➤ Other cellular immunodeficiency ➤ Complement defect ➤ Phagocytic defect ➤ Diseases of immune dysregulation 	<ul style="list-style-type: none"> ➤ Systemic disorder: Diabetes, HIV infection, Undernutrition, ➤ Immunosuppressive T/t : cytotoxic chemotherapy, Bone marrow transplant, Radiation therapy, Corticosteroids etc) ➤ Prolonged serious illness (critically ill, hospitalized patients)

Immunodeficiency	
B-Cell Deficiencies	T-Cell Deficiencies
<p><i>Recurrent bacterial infections</i></p> <p>Bruton's agammaglobulinemia—defect in B-cell development Common variable—hypogammaglobulinemia—defect in plasma cell differentiation Hyper-IgM syndrome—defect in class switching</p>	<p><i>Severe viral, fungal, and protozoal infections</i></p> <p>Bare lymphocyte syndrome—lack of class II MHC Omenn's syndrome—defect in TCR gene rearrangement DiGeorge syndrome—thymic aplasia</p>
<p>B and T-cell deficiencies</p> <p>Severe combined immunodeficiency</p>	
Phagocytic Cell Deficiencies	Complement Deficiencies
<p><i>Recurrent bacterial infections</i></p> <p>Chronic granulomatous disease—lack of respiratory burst Leukocyte adhesion deficiency—lack of PMN extravasation into tissue Chediak-Higashi syndrome—defect in neutrophil microtubule function and related phagosome/lysosome fusion</p>	<p><i>Recurrent bacterial infections</i></p> <p><i>Defects in immunocomplex clearance</i></p> <p>C1, C2, or C4 deficiency—defects in clearing immunocomplexes C3 or C5 deficiency—block in alternative and classical pathways C6, C7, C8, or C9—defect in MAC assembly and function</p>

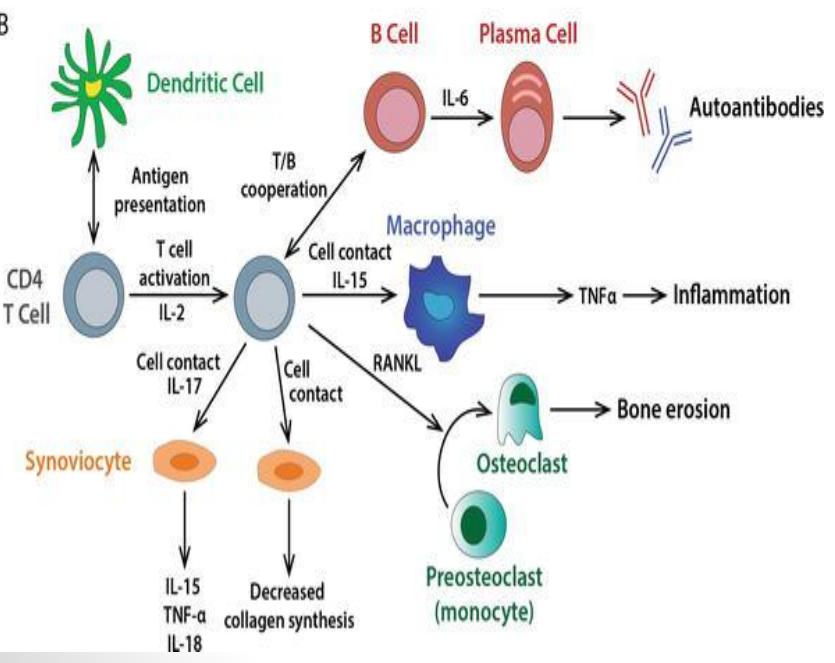
RHEUMATOID ARTHRITIS

- Rheumatoid arthritis is a common autoimmune disorder, most often affecting women from 40 to 60 years old. The major symptom is chronic inflammation of the joints, although the hematologic, cardiovascular, and respiratory systems are also frequently affected.
- Immune Complex-Mediated Hypersensitivity and Chronic Inflammatory Disease.
- Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils
- Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.
- The cytokine based therapy for RA having agent Enbre, which are Chimeric TNF-receptor/IgG constant region for Rheumatoid arthritis





- ❖ Many individuals with rheumatoid arthritis produce a group of auto-antibodies called rheumatoid factors that are reactive with determinants in the Fc region of IgG.
- ❖ The classic rheumatoid factor is an IgM antibody with that reactivity. Such auto-antibodies bind to normal circulating IgG, forming IgM-IgG complexes that are deposited in the joints.
- ❖ These immune complexes can activate the complement cascade, resulting in a type III hypersensitive reaction, which leads to chronic inflammation of the joints.
- ❖ Signs and symptoms of rheumatoid arthritis may include: Tender, warm, swollen joints
- ❖ Joint stiffness that is usually worse in the mornings and after inactivity
- ❖ Fatigue, fever and loss of appetite
- **Risk factors**
- Factors that may increase your risk of rheumatoid arthritis include:
- **Sex.** Women are more likely than men to develop rheumatoid arthritis.
- **Age.** Rheumatoid arthritis can occur at any age, but it most commonly begins in middle age.
- **Family history.** If a member of a family has rheumatoid arthritis, it may have an increased risk of the disease.
- **Smoking.** Increases risk of developing rheumatoid arthritis, particularly with a genetic predisposition for developing the disease. It also appears to be associated with greater disease severity.
- **Environmental exposures.** Although poorly understood, some exposures such as asbestos or silica may increase the risk of developing rheumatoid arthritis. **Obesity.** People especially women age 55 and younger who are overweight or obese appear to be at a somewhat higher risk of developing rheumatoid arthritis.



SYSTEMIC LUPUS ERYTHEMATOSUS

- ❑ One of the best examples of a systemic autoimmune disease is systemic lupus erythematosus (SLE), which typically appears in women between 20 and 40 years of age; the ratio of female to male patients is 10:1.
- ❑ SLE is characterized by fever, weakness, arthritis, skin rashes, pleurisy, and kidney dysfunction.
- ❑ Lupus is more frequent in African-American and Hispanic women than in Caucasians.
- ❑ Affected individuals may produce autoantibodies to a vast array of tissue antigens, such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors; interaction of these auto-antibodies with their specific antigens produces various symptoms.
- ❑ Auto-antibody specific for RBCs and platelets, for example, can lead to complement-mediated lysis, resulting in hemolytic anemia and thrombocytopenia, respectively. When immune complexes of auto-antibodies with various nuclear antigens are deposited along the walls of small blood vessels, a type III hypersensitive reaction develops.
- ❑ The complexes activate the complement system and generate membrane-attack complexes and complement split products that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis. Excessive complement activation in patients with severe SLE produces elevated serum levels of the complement split products C3a and C5a, which may be three to four times higher than normal.
- ❑ C5a induces increased expression of the type 3 complement receptor (CR3) on neutrophils, facilitating neutrophil aggregation and attachment to the vascular endothelium.
- ❑ As neutrophils attach to small blood vessels, the number of circulating neutrophils declines (neutropenia) and various occlusions of the small blood vessels develop (vasculitis).
- ❑ These occlusions can lead to widespread tissue damage. Laboratory diagnosis of SLE focuses on the characteristic antinuclear antibodies, which are directed against double stranded or single-stranded DNA, nucleoprotein, histones, and nucleolar RNA. Indirect immuno-fluorescent staining with serum from SLE patients produces various characteristic nucleus-staining patterns.

Systemic Lupus Erythematosus



BUTTERFLY RASH



ERYTHMATOUS BULLOUS LESIONS



PHOTOSENSITIVE ERYTHEMA



SUBACUTE CUTANEOUS RASH



DISCOID LUPUS



Images :
dermatlas.org

Malar Rash



ALOPECIA



Symptoms

- No two cases of lupus are exactly alike. Signs and symptoms may come on suddenly or develop slowly, may be mild or severe, and may be temporary or permanent. Most people with lupus have mild disease characterized by episodes called flares when signs and symptoms get worse for a while, then improve or even disappear completely for a time.
- The signs and symptoms of lupus will depend on which body systems are affected by the disease. The most common signs and symptoms include:
 - Fatigue
 - Fever
 - Joint pain, stiffness and swelling
 - Butterfly-shaped rash on the face that covers the cheeks and bridge of the nose or rashes elsewhere on the body
 - Skin lesions that appear or worsen with sun exposure (photosensitivity)
 - Fingers and toes that turn white or blue when exposed to cold or during stressful periods (Raynaud's phenomenon)
 - Shortness of breath
 - Chest pain
 - Dry eyes
 - Headaches, confusion and memory loss

Risk factors

- Factors that may increase your risk of lupus include:
 - **Your sex.** Lupus is more common in women.
 - **Age.** Although lupus affects people of all ages, it's most often diagnosed between the ages of 15 and 45.
 - **Race.** Lupus is more common in African-Americans, Hispanics and Asian-Americans.

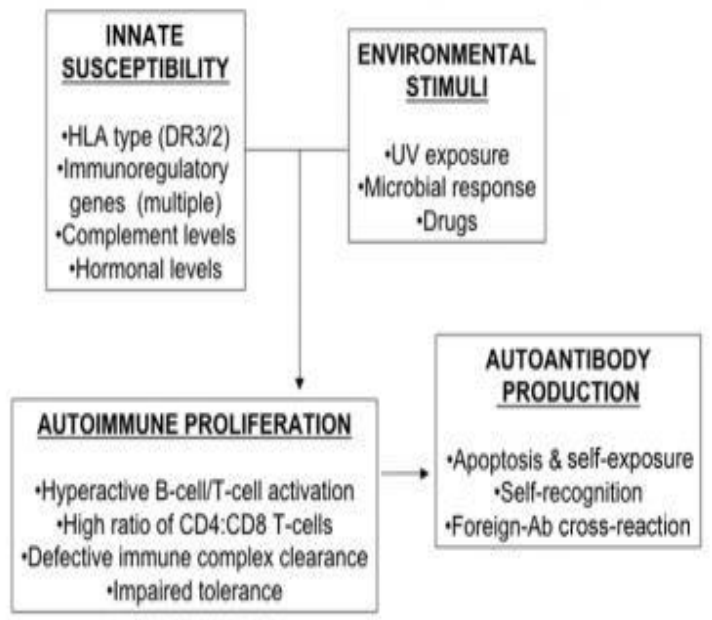
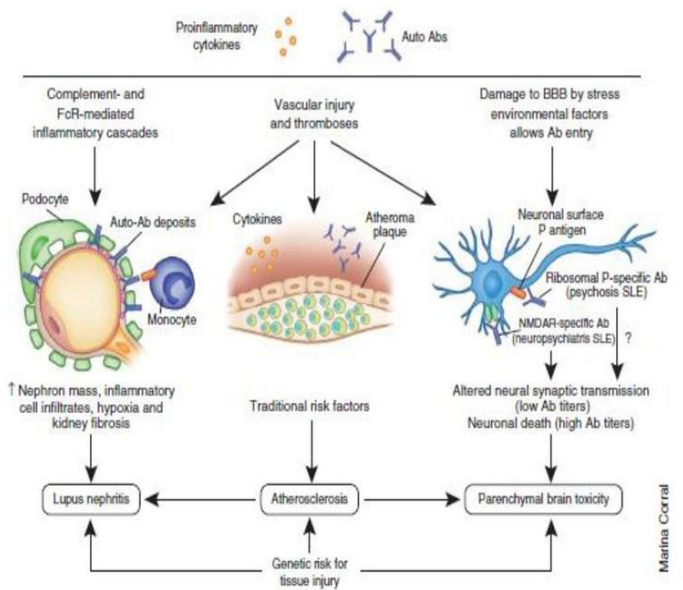
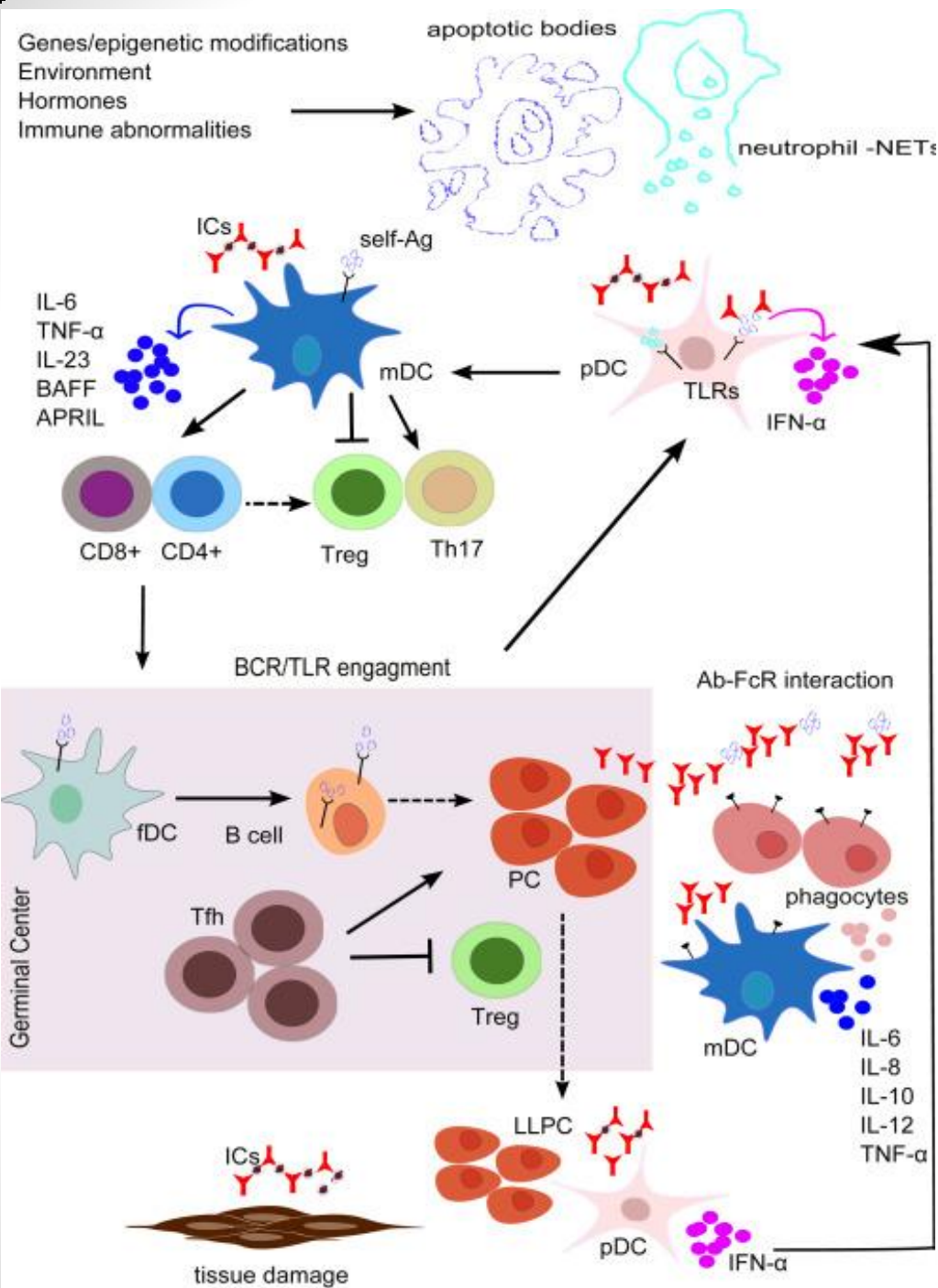
Inheritance pattern

- SLE and other autoimmune disorders tend to run in families, but the inheritance pattern is usually unknown. People may inherit a gene variation that increases or decreases the risk of SLE, but in most cases do not inherit the condition itself. Not all people with SLE have a gene variation that increases the risk, and not all people with such a gene variation will develop the disorder.
- In rare cases, SLE can be inherited in an [autosomal recessive pattern](#), which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Causes

- Normal variations (polymorphisms) in many genes can affect the risk of developing SLE, and in most cases multiple genetic factors are thought to be involved. In rare cases, SLE is caused by mutations in single genes.
- Most of the genes associated with SLE are involved in immune system function, and variations in these genes likely affect proper targeting and control of the immune response.
- Sex hormones and a variety of environmental factors including viral infections, diet, stress, chemical exposures, and sunlight are also thought to play a role in triggering this complex disorder. About 10 percent of SLE cases are thought to be triggered by drug exposure, and more than 80 drugs that may be involved have been identified.
- In people with SLE, cells that have undergone self-destruction ([apoptosis](#)) because they are damaged or no longer needed are not cleared away properly.
- The relationship of this loss of function to the cause or features of SLE is unclear. It is suggested that these dead cells may release substances that cause the immune system to react inappropriately and attack the body's tissues, resulting in the signs and symptoms of SLE.

Mechanisms of organ damage in SLE



MULTIPLE SCLEROSIS

- ✓ Multiple sclerosis (MS) is the most common cause of neurologic disability associated with disease in Western countries. The symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision.
- ✓ Most people with MS are diagnosed between the ages of 20 and 40.
- ✓ Individuals with this disease produce autoreactive T cells that participate in the formation of inflammatory lesions along the myelin sheath of nerve fibers. The cerebrospinal fluid of patients with active MS contains activated T lymphocytes, which infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin.
- ✓ Since myelin functions to insulate the nerve fibers, a breakdown in the myelin sheath leads to numerous neurologic dysfunctions.
- ✓ Epidemiological studies indicate that MS is most common in the Northern hemisphere and, interestingly, in the United States. Populations who live north of the 37th parallel have a prevalence of 110–140 cases per 100,000, while those who live south of the 37th parallel show a prevalence of 57–78 per 100,000. And individuals from south of the 37th parallel who move north assume a new risk if the move occurs before 15 years of age.
- ✓ These provocative data suggest that there is an environmental component of the risk of contracting MS. This is not the entire story, however, since genetic influences also are important. While the average person in the United States has about one chance in 1000 of developing MS, close relatives of people with MS, such as children or siblings, have 1 chance in 50 to 100 of developing MS.
- ✓ The identical twin of a person with MS has a 1 in 3 chance of developing the disease. These data point strongly to the genetic component of the disease. And, as is described in the Clinical Focus of this chapter, MS affects women two to three times more frequently than men.
- ✓ The cause of MS, like most autoimmune diseases, is not well understood. However, there are some suggestions that infection by certain viruses may predispose a person to MS. Certainly some viruses can cause demyelinating diseases, and it is tempting to speculate that virus infection plays a significant role in MS, but at present there is no definitive data implicating a particular virus.

Symptoms

- Multiple sclerosis signs and symptoms may differ greatly from person to person and over the course of the disease depending on the location of affected nerve fibers. Symptoms often affect movement, such as:
- Numbness or weakness in one or more limbs that typically occurs on one side of your body at a time, or the legs and trunk
- Electric-shock sensations that occur with certain neck movements, especially bending the neck forward (Lhermitte sign)
- Tremor, lack of coordination or unsteady gait
- Vision problems are also common, including: Partial or complete loss of vision, usually in one eye at a time, often with pain during eye movement
- Prolonged double vision
- Blurry vision
- Multiple sclerosis symptoms may also include:
- Slurred speech
- Fatigue
- Dizziness
- Tingling or pain in parts of your body
- Problems with sexual, bowel and bladder function
- **Complications:-** People with multiple sclerosis may also develop:
- Muscle stiffness or spasms
- Paralysis, typically in the legs
- Problems with bladder, bowel or sexual function
- Mental changes, such as forgetfulness or mood swings
- Depression
- Epilepsy

Types of multiple sclerosis (MS)

- MS starts in 1 of 2 general ways: with individual relapses (attacks or exacerbations) or with gradual progression.

Relapsing remitting MS

- More than 8 out of every 10 people with MS are diagnosed with the relapsing remitting type.
- Someone with relapsing remitting MS will have episodes of new or worsening symptoms, known as relapses.
- These typically worsen over a few days, last for days to weeks to months, then slowly improve over a similar time period.
- Relapses often occur without warning, but are sometimes associated with a period of illness or stress.
- The symptoms of a relapse may disappear altogether, with or without treatment, although some symptoms often persist, with repeated attacks happening over several years.
- Periods between attacks are known as periods of remission. These can last for years at a time.
- After many years (usually decades), many, but not all, people with relapsing remitting MS go on to develop secondary progressive MS.
- In this type of MS, symptoms gradually worsen over time without obvious attacks. Some people continue to have infrequent relapses during this stage.
- Around half of people with relapsing remitting MS will develop secondary progressive MS within 15 to 20 years, and the risk of this happening increases the longer you have the condition.
- **Primary progressive MS**
- Just over 1 in 10 people with the condition start their MS with a gradual worsening of symptoms.
- In primary progressive MS, symptoms gradually worsen and accumulate over several years, and there are no periods of remission, though people often have periods where their condition appears to stabilise.

MULTIPLE SCLEROSIS

