Immunopathology
2013-2014

This is concerned with the pathological changes that occur in the tissues as a result of improper immune response. Body immune responses are normal defense mechanisms designed to combat the effect of invasion by various environmental factors such as microorganisms & toxic chemicals.

This is concerned with the pathological changes that occur in the tissues as a result of improper immune response. Body immune responses are normal defense mechanisms designed to combat the effect of invasion by various environmental factors such as microorganisms & toxic chemicals. It usually works effectively.

**Immune response:**
- Non-specific host defense mechanisms (**innate immunity**)
- Specific immunity (**adaptive immunity**) i.e., the humoral and cellular

The major components of innate immunity are:
- Physiological barriers (skin & mucous membr.) that block entry of microbes,
- phagocytic cells (mainly neutrophils and macrophages), dendritic cells,
- natural killer (NK) cells,
- complement proteins

The two most important cellular reactions of innate immunity are:
- inflammation, the process in which phagocytic leukocytes are recruited and activated to kill microbes,
- anti-viral defense, mediated by dendritic cells and NK cells

**Cell-mediated immunity.**
Dendritic cells (DCs) capture microbial Ags from epithelia & tissues and transport the Ags to LNs. During this process, the DCs mature, and express high levels of MHC molecules and costimulators.

Naive T cells recognize MHC-associated peptide Ags displayed on DCs. The T cells are activated to proliferate and to differentiate into effector and memory cells, which migrate to sites of infection and serve various functions in cell-mediated immunity.

CD4+ effector T cells of the Th1 subset recognize the antigens of microbes ingested by phagocytes, and activate the phagocytes to kill the microbes. CD4+ T cells also induce inflammation.

CD8+ cytotoxic T lymphocytes (CTLs) kill infected cells harboring microbes in the cytoplasm.

Some activated T cells differentiate into long-lived memory cells

Diseases may result from:
1. Inadequate immune response.
2. Excessive immune response.
3. Inappropriate immune response.

**Inadequate immune responses:**
These can result from immuno-deficiency states. There are two classes of immunodeficiency syndromes:
1. **Primary;** which is present at birth & often the result of a genetic disorder. (Fig. 7-1)
2. **Secondary;** which is much more common than the primary. It can be secondary to
   a. Drugs
   b. Diseases
   
(Fig. 7-2)

**Primary immunodeficiency**

**X-linked agammaglobulinemia (Bruton disease)**
This is one of the more common forms of primary immunodeficiency. It is due to failure of pre-B-cells to differentiate into B-cells that result in the absence of gamma globulin in the blood (agammaglobulinemia). The disease is seen primarily in males. In most cases, there are recurrent bacterial infections. For obscure reasons, auto-immune diseases (such as SLE & dermatomyositis) also occur in up to 20% of patients.

**Isolated IgA-deficiency**
This is the most common of all primary immunodeficiency states. There is marked reduction in the level of serum IgA but other immunoglobulins are normal. In most cases it is asymptomatic & detected accidentally, but some patients have recurrent respiratory infections & diarrhea. There is also a significant, unexplained association with autoimmune diseases.

**Hyper-IgM syndrome**
In normal immune responses to protein antigens, IgM & IgD antibodies are produced first, followed by the sequential elaboration of IgG, IgA, & IgE antibodies. This orderly appearance of antibody types is called isotype switching & is important for generating classes of antibodies that can effectively activate complement &/or opsonize bacterial pathogens. Patients with this syndrome produce normal or even above normal levels of IgM antibodies to antigens but fail to produce other antibody classes (IgG, IgA, or IgE isotypes).

**Thymic hypoplasia (DiGeorge syndrome)**

Affected infants show failure of T-cells to form, with hypoplasia of the thymus gland; the result of failure of development of the third and fourth pharyngeal pouches. The latter structures normally give rise to the thymus, parathyroid glands, & portions of the face & aortic arch. Thus in addition to the thymic & T-cell defects, there may be parathyroid gland hypoplasia resulting in hypocalcaemia and tetany, with facial abnormalities that include cleft lip and palate and congenital cardiac malformations. In 90% of cases there is a deletion affecting chromosome 22q11. Transplantation of thymic tissue has successfully treated some of these infants.

**Severe combined immune deficiency (SCID)**
This condition may be inherited as a recessive disorder either autosomal or an X-linked. The condition is due to failure of development of both B-cell & T-cell precursors from primitive stem cells. Therefore the thymus is small or absent & lymphoid tissues in lymph nodes & gut are also greatly reduced.
Children present early in life with recurrent infections including candidal thrush, pneumonia & diarrhea. There is a very low blood lymphocyte count & low blood immunoglobulin levels.

**Acquired immunodeficiency syndrome (AIDS)**

AIDS is a retroviral disease caused by human immunodeficiency virus (HIV) and characterized by profound immuno-suppression leading to:

1. Opportunistic infections
2. Secondary neoplasms
3. Neurological manifestations.

It is a worldwide disease. About 22 million people have died of AIDS since the epidemic was recognized some 30 years ago; 3 million people died in the year 2000 alone. On the basis of serologic data, an estimated 35 million people are infected with HIV (roughly 1 in every 100), including 1.4 million children & 17 million women. AIDS represents the fifth most common cause of death in adults (25-44 years of age) in USA.

**Epidemiology:**

Transmission of HIV occurs under conditions that help the exchange of blood or body fluids containing the virus or virus-infected cells. Thus, the three major routes are

1. Sexual contact
2. Parenteral inoculation
3. Passage of the virus from infected mothers to their newborns.

**Epidemiologic studies have identified five groups at risk for developing AIDS**

1. Homosexual or bisexual males (46% of reported cases).
2. Intravenous drug abusers (25% of all patients).
3. Heterosexual contacts of members of other high-risk groups (11% of patients).
4. Recipients of blood & blood components (but not hemophiliacs) who received transfusions of HIV-infected whole blood or components (e.g., platelets, plasma) (1% of patients).
5. Hemophiliacs, especially those who received large amounts of factor VIII or IX concentrate (less than 1% of all cases).

The epidemiology of HIV infection & AIDS is different in children (<13 years age). About 1% of all AIDS cases occurs in this population, 90% of them result from transmission of the virus from mother to infant, while the remaining 10% are hemophiliacs & others who have received blood or blood products.

**Sexual Transmission**

Sexual transmission is clearly the predominant mode of infection worldwide. The virus is present in semen, both extra-cellularly & within mononuclear
inflammatory cells, & enters the recipient's body through tears or abrasions in the genital mucosa.

**Parenteral Transmission**
Parenteral transmission of HIV is seen in three groups:
1. Intravenous drug abusers
2. Hemophiliacs receiving factor VIII or IX concentrates
Among intravenous drug abusers, transmission occurs through shared needles and syringes contaminated with HIV-containing blood. This group represents the main line in the transmission of HIV to other adult population through heterosexual activity.

**Mother-to-infant transmission** (vertical transmission)
This is the major cause of pediatric AIDS. Three routes are involved:
1. **In utero** (transplacental spread)
2. **Intra-partum**, (during delivery)
3. **Via ingestion** of HIV-contaminated breast milk.

HIV infection cannot be transmitted by casual personal contact in home, workplace, or school, & there is no convincing evidence for spread by insect bites.

**Etiology**
AIDS is caused by HIV. This is a human retrovirus belonging to the lentivirus family. Two genetically different but antigenically related forms of HIV, called HIV-1 & HIV-2. The virion is spherical & surrounded by a lipid envelope derived from the host cell membrane (Fig. 7-3). The virus core contains:
1. **The major capsid protein** P24.
2. **Nucleocapsid protein** P7/P9.
3. **Two copies of genomic RNA**
4. **The three viral enzymes** (protease, reverse transcriptase & integrase).

P24 is the most readily detectable viral antigen useful in the diagnosis of HIV infection in blood screening. The viral envelope is studded by two viral glycoproteins (gp120 & gp41) critical for HIV infection of cells. The highly effective anti HIV-1 protease inhibitor drugs prevent viral assembly by inhibiting the formation of mature viral proteins. In addition there are other regulatory genes, the products of which are important for HIV pathogenicity, & a number of therapeutic approaches are being developed to block their actions. Molecular analysis of different viral isolates reveals considerable variability in many parts of the HIV genome. Most variations cluster in certain regions of the envelope glycoproteins. Because the immune response against HIV-1 is targeted against its envelope, such extreme variability in antigen structure poses a barrier for vaccine development.

**Pathogenesis**
The two major targets of HIV infection are the immune system & the central nervous system.

**Immunopathogenesis of HIV disease:**
AIDS leads to severe impairment of the cell-mediated immunity system. Infection by HIV leads to destruction of CD$_4$ lymphocytes & a decreased helper/suppressor T-cell ratio in the blood. The virus gains entry to T-cells by attaching to surface CD$_4$ molecules. The CD$_4$ molecule is a high-affinity receptor for HIV. This explains the selective tropism of the virus for CD$_4$+T-cells & its ability to infect other CD$_4$+cells, particularly macrophages & dendritic cells. However binding to CD$_4$ is not sufficient for infection; the HIV envelope gp120 must also bind to other cell surface molecules (co-receptors) to facilitate cell entry (Fig. 7-4). The virus core containing the HIV genome enters the cytoplasm of the cell. The viral genome then undergoes reverse transcription, leading to formation of complementary DNA (cDNA). In the dividing T-cells, the cDNA enters the nucleus & integrates into the host genome. After integration, the provirus may remain non-transcribed for months or years & the infection becomes latent; alternatively, proviral DNA may be transcribed to form complete viral particles that bud from the cell membrane, leading to cell death (Fig. 7-5).

HIV colonizes the lymphoid organs (spleen, lymph nodes, and tonsils). Infected T-cells, macrophages, & dendritic cells represent reservoirs of infection. Initially, the immune system can vigorously proliferate to replace the dying T-cells, thus masking the massive cell death occurring primarily in the lymphoid tissues. Due to loss of CD$_4$+ cells, patients will have an inversion of the CD$_4$ /CD$_8$ ratio in the peripheral blood; normally it is about 2, while in AIDS patients the ratio ≤ 0.5. ADIS patients will also have qualitative defects in T-cell function.

Pathogenesis of central nervous system involvement:
The nervous system is a major target of HIV infection. Macrophages & their equivalents in the CNS; the microglia, are mainly infected with HIV. The virus is mostly carried into the brain by infected monocytes. The mechanism of HIV-induced damage of the brain remains obscure. It is believed that neurologic deficit is caused indirectly by viral products & soluble factors e.g. cytokines produced by macrophages/microglia.

Clinical phases
There are four phases (Fig. 7-6)

1- **Primary infection (sero-conversion)**: after infection, a median time of 2 months elapses before antibodies to HIV are detected in the blood. Rapid viral replication occurs in all organs (P$_{24}$ antigen is detectable in blood), & an immune response develops, with increased number of virus-specific CD$_8$+cytotoxic T-cells. About 50% of patients develop an influenza-like illness, skin rashes or lymphadenopathy, associated with transient fall in CD$_4$+T-cells. This phase represents the early acute phase.

2- **Asymptomatic phase (incubation period)**: it represents a stage of relative containment of the virus. The immune system is largely intact, but there is continued HIV replication. The length of this phase is
uncertain, it can last for years. Patients have antibodies to HIV in blood, are infective, can transmit the disease, & are asymptomatic.

3- **AIDS-related complex**: the proportion of CD4 infected cells increases, their function is partially impaired & their numbers in blood fall to around 400 cells/μliter. It is associated with non-specific general malaise, fever, night sweats, weight loss & diarrhea. Persistent generalized lymphadenopathy is common, with serological & hematological evidence of impaired cell-mediated immunity & reduced CD4+ T-cells. Superficial fungal infections are frequent & infections with pathogens as Salmonella & Haemophilus are sever. Similarly, gynecological infections such as candidiasis & pelvic inflammatory disease are increased. 2 & 3 phases represent the chronic phase (middle phase), that may last 7 to 10 years. However, sometimes rapid progression after 2 to 3 years happens.

4- **AIDS (crisis phase)**: it represents the final phase with fully developed immunodeficiency characterized by fever, fatigue, weight loss, generalized lymphadenopathy & diarrhea; the CD4+ cell count is below 500 cells/μL. The patients develop serious opportunistic infections, secondary neoplasms &/or neurologic manifestations (so called AIDS-defining conditions), & the patient is said to have developed full-blown AIDS. Also any individual with CD4+ cell counts less than or equal to 200/μL is diagnosed as having AIDS.

**Opportunistic infections**

These are responsible for about 80% of deaths in patients with AIDS.
1. Pneumocystis carinii pneumonia is the presenting feature in many cases.
2. Recurrent mucosal candidiasis
3. Disseminated cytomegalovirus infection (particularly enteritis & retinitis)
4. Herpes simplex; especially severe ulcerating oral & perianal infections
5. Mycobacterium tuberculosis & atypical mycobacteria (mycobacterium ovium-intracellular), usually disseminated infections
6. Toxoplasmosis, which is the most common secondary infection of the central nervous system
7. Cryptococcal meningitis is also quite frequent.
8. Cryptosporidium or isospora belli infections are often the cause of the so common persistent diarrhea. However, bacterial pathogens such as Salmonella & Shigella species may also be seen.

**Neoplasms**

The basis of increased risk of malignancy is multifactorial and include
1. Profound defects in T-cell immunity
2. Dysregulated B-cell & monocyte functions
3. Infections with known viruses e.g. Human herpes virus type 8, EBV, human papilloma virus & unknown viruses.

**Patients with AIDS have a high incidence of certain tumors as:**

1- **Kaposi sarcoma (KS)**: this vascular tumor is the most common neoplasm in AIDS patients. It is more common among homosexual and
heterosexual males than in other risk groups. KS in AIDS patients is usually multicentric & tends to be aggressive. It can affect the skin, mucous membranes, GIT, lymph nodes, & lungs. KS is associated with human herpes virus 8 infections in AIDS patients.

2- **Non-Hodgkin lymphomas**: the second most common neoplasm in AIDS patients. These tumors are highly aggressive, & involve many extra-nodal sites, commonly the brain; so primary lymphoma of the brain is considered as an AIDS-defining condition. 30%-40% of these lymphomas are associated with EBV infection.

3- **Cervix uteri carcinoma**: this due to human papilloma virus infection in AIDS patients. This virus is intimately associated with squamous cell carcinoma of the cervix & its precursor lesions (cervical dysplasia & carcinoma in situ); therefore, gynecologic examination should be routinely done for HIV-infected women.

**Central nervous system involvements:**
This is common in AIDS patients. 40%-60% of patients have clinically evident neurologic dysfunction. In addition to opportunistic infection & neoplasms, patients may have a progressive encephalopathy clinically called AIDS-dementia complex.

**Vaccine**
Molecular analyses have revealed an alarming degree of polymorphism in viral isolates from different AIDS patients; this renders vaccine development more difficult. In addition, the nature of the protective immune response is not yet fully understood. Therefore, at present, prevention & effective public health measures remain the mandatory in the fight against AIDS.

**Inappropriate immune response:**
**Transplant rejection:**
Organ transplantation is used increasingly to treat irreversible diseases of the kidney, liver, heart, lung, & bone marrow. Unfortunately, the action of the immune system of the recipient can lead to destruction of the transplanted tissue a process termed "transplant rejection". This is a complex immunologic phenomenon involving both cell- and humoral-mediated hypersensitivity responses of the host, directed against histocompatibility antigens, human leukocytes antigens (HLA) on the donor allograft. The endothelial cells that line the blood vessels of the graft are particularly rich in both HLA & blood group antigens, thus blood vessels are important targets of the host's immune response to a transplanted allograft.

**Patterns of transplant rejection:**
Rejection reactions have been classified as
1. Hyperacute
2. Acute
3. Chronic
The changes are described in the context of renal transplants; however, similar changes are seen in any other vascularized organ transplant.

**Hyperacute rejection:**
This occurs within a very short time from the moment the organ is perfused by the host's blood (minutes to a few hours). In this form there is a widespread intravascular thrombosis in small vessels, with focal necrosis. It is the result of pre-formed humoral host antibodies reacting with antigens in the graft. These preformed antibodies developed due to
1. Previous rejection of a transplant
2. Multiparous women who develop anti-HLA antibodies against paternal antigens shed from the fetus (a rejection in this instance will affect the transplanted organ donated by the husband and offspring)
3. Prior blood transfusions because platelets and WBCs are rich in HLA antigens and donors and recipients are usually not HLA-identical.

It is typically recognized grossly by the surgeon just after the vascular anastomosis is completed. The hyperacutely rejected kidney rapidly becomes cyanotic, mottled, & flaccid & may excrete only a few drops of blood-stained urine. In contrast to a non-rejected kidney graft that regains a normal pink coloration & tissue turgor & promptly excretes urine. Histologically the rejected kidney show acute arteritis & arteriolitis, vessel thrombosis & ischemic necrosis.

**Acute rejection:**
It occurs within days or weeks of transplantation, but may also appear after cessation of immunosuppressive therapy that is given to the recipient to prevent rejection. It is mediated by both humoral & cell-mediated mechanisms. Acute cellular rejection is mediated by T-cells reacting against donor HLA antigens, particularly class II. It is accompanied by signs of renal failure. Histologically there is extensive interstitial CD4+ & CD8+T-cell infiltration. The humoral component of acute rejection is characterized by vasculitis with endothelial necrosis, neutrophils infiltration of vessel walls, & damage to the intima and elastic lamina of the larger arteries in the graft.

**Chronic rejection:**
In recent years, acute rejection has been significantly controlled by immunosuppressive therapy; this has resulted in the emergence of chronic rejection as an important cause of graft failure. Chronic rejection occurs slowly & progressively after transplantation (months to years). It is the result of slow breakdown of the host's tolerance to the graft and may be due to inadequate immune suppression. The condition is manifested by a progressive rise in serum creatinine levels (which is an index of renal dysfunction), over a period of 4 to 6 months. Histologically, there is intimal fibrosis mainly in arteries & arterioles, leading to secondary ischemic damage to the parenchyma manifested by hyalinization and loss of glomeuli, interstitial fibrosis, & tubular atrophy. Chronic rejection does not respond to standard immunosuppressant regimens.

**Complication of renal transplantation:**
1. Thrombosis of vascular graft
2. Recurrence of original renal disease.
3. Transplant rejections, hyperacute, acute or chronic.

from an adult).

**Autoimmune diseases**: Autoimmune diseases are the result of immune reactions against self-antigen. Sometimes the immune response is an antibody response (autoantibody), or it is a cell-mediated immune response. In autoimmune diseases, the normal mechanisms ensuring tolerance for self-antigens have broken down. (Self-tolerance indicates lack of immune responsiveness to one's own tissue antigens). Some autoimmune diseases have a genetic component; e.g. certain diseases are associated with particular HLA histocompatibility types. In other situations, an autoimmune disease can be triggered by a microbial infection.

**Mechanisms of Autoimmunity**: Autoimmunity arises from a combination of the inheritance of 

**susceptibility genes**, which may contribute to the breakdown of self-tolerance, and 

**environmental** triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes. In general, these genetic and environmental influences conspire to create an imbalance between control mechanisms that normally function to prevent self-reactivity and pathways that lead to the generation and activation of pathogenic effector lymphocytes.

**Role of Susceptibility Genes**: Most autoimmune diseases are complex multigenic disorders. Among the genes known to be associated with autoimmunity, the greatest contribution is that of HLA genes. It is postulated that the presence of particular MHC alleles affects the negative selection of T cells in the thymus or the development of regulatory T cells, but there is little proof for either possibility. It should be pointed out that many normal individuals inherit the MHC alleles that are disease-associated in patient populations. Therefore, the presence of particular MHC alleles is not, by itself, the cause of autoimmunity.

**Polymorphisms of other genes may play role like**:
- Polymorphisms in a gene called *PTPN-22*, which encodes a protein tyrosine phosphatase, are associated with rheumatoid arthritis, type 1 diabetes
- Polymorphisms in the gene for *NOD-2* are associated with Crohns disease
- The genes encoding the *IL-2 receptor (CD25)* is associated with multiple sclerosis and other autoimmune diseases

**Role of Infections**: Many autoimmune diseases are associated with infections. Two mechanisms have been postulated to explain the link between infections and autoimmunity.

■ First, infections may up-regulate the expression of costimulators on APCs. If these cells are presenting self-antigens, the result may be a breakdown of anergy and activation of T cells specific for the self-antigens.

■ Second, some microbes may express antigens that have the same amino acid sequences as self-antigens. Immune responses against the microbial antigens may result in the activation of self-reactive lymphocytes. This phenomenon is called **molecular mimicry**. A clear example of such mimicry is rheumatic heart disease, in which antibodies against streptococcal proteins cross-react with myocardial proteins and cause myocarditis. Microbes may induce other abnormalities that promote autoimmune reactions.

■ Some viruses, such as Epstein-Barr virus (EBV) and HIV, cause polyclonal B-cell activation, which may result in production of autoantibodies.
The tissue injury that is common in infections may release self-antigens and structurally alter self-antigens so that they are able to activate T cells that are not tolerant to these new, modified antigens.

**General Features of Autoimmune Diseases**: Diseases caused by autoimmunity have some important general features.

- **Once an autoimmune disease has been induced it tends to be progressive**, sometimes with sporadic relapses and remissions.
  - One reason for this is that the immune system contains many intrinsic amplification loops that allow small numbers of antigen-specific lymphocytes to accomplish their task of eradicating complex infections. When the response is inappropriately directed against self-tissues, the very same amplification mechanisms exacerbate injury.
  - Another reason for the persistence and progression of autoimmune disease is the phenomenon of epitope spreading. Infections, and even the initial autoimmune response, may damage tissues, release self-antigens and expose epitopes of the antigens that are normally concealed from the immune system. The result is continuing activation of lymphocytes that recognize these previously hidden epitopes; since these epitopes were not expressed normally, the lymphocytes did not become tolerant to them. The activation of such autoreactive T cells is referred to as epitope spreading because the immune response “spreads” to epitopes that were initially not recognized.

- The clinical and pathologic manifestations of an autoimmune disease are determined by the nature of the underlying immune response. $T_{H1}$ responses are associated with destructive macrophage-rich inflammation and the production of antibodies that cause tissue damage by activating complement and binding to Fc receptors. $T_{H17}$ responses are believed to underlie inflammatory lesions dominated by neutrophils as well as monocytes.

- **Different autoimmune diseases show substantial clinical, pathologic, and serologic overlaps**. For this reason, precise phenotypic classification of these disorders is often a challenge.

**Autoimmune diseases may be either:**
- **Organ specific** (response directed against a single component of a single tissue).
- **non-organ-specific** autoimmune disease (response directed against a component that present in many tissues & organs throughout the body).

The organ specific autoimmune diseases are listed in following tables:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Disease</th>
<th>Associated autoantibody</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Vitiligo</td>
<td>Antityrosine Ab</td>
<td>Hypopigmentation</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Grave's disease</td>
<td>thyroid-stimulating Ab</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>thyroid growth-stimulating Ab</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Hashimoto's disease</td>
<td>Anti-thyroid specific Ab</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>Addison's disease</td>
<td>Anti-adrenal Ab</td>
<td>Hypoadrenocorticalism</td>
</tr>
<tr>
<td>Stomach</td>
<td>Autoimmune (type A) gastritis</td>
<td>Anti-intrinsic factor &amp; parietal cell Ab</td>
<td>Pernicious anemia</td>
</tr>
</tbody>
</table>
Pancreatic islet cells (insulin-producing)  | Type I diabetes mellitus | Anti-islet B-cell (insulin) Ab | Diabetes mellitus  
Skeletal muscle  | Myasthenia gravis  | Acetylcholine receptors Ab | Muscle fatigue

Multi-organ involvement is frequently caused by secondary damage due to circulating immune complex. This group of disorders is often collectively called the "connective tissue diseases" or "collagen vascular diseases".

<table>
<thead>
<tr>
<th>Disease</th>
<th>Main organ involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Skin, kidney, joints, heart, lung</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>Skin, gut, lung</td>
</tr>
<tr>
<td>Polymyositis-dermatomyositis</td>
<td>Skeletal muscle, skin</td>
</tr>
<tr>
<td>Rheumatoid disease</td>
<td>Joints, lungs, systemic vessels</td>
</tr>
</tbody>
</table>

**Systemic lupus erythematosus (SLE):** SLE is an autoimmune disease and one of the "connective tissue disorders". SLE is a complex disorder of multifactorial origin resulting from interactions among genetic, immunological, and environmental factors that act in concert to cause activation of helper T cells and B cells and result in the production of several species of pathogenic autoantibodies. Etiology & pathogenesis: SLE is a complex disease of multifactorial origin including genetic, hormonal, & environmental factors leading to the apoptosis of cells. Inadequate clearance of the nuclei of these cells results in a large burden of nuclear antigens. An underlying abnormality in B and T lymphocytes is responsible for defective tolerance, because of which self-reactive lymphocytes survive and remain functional. These lymphocytes are stimulated by self-nuclear antigens, and antibodies are produced against these antigens ANA (antinuclear antibodies). The net result is a cycle of antigen release and immune activation resulting in the production of high-affinity autoantibodies. test for ANAs is sensitive because it is positive in virtually every patient with SLE, but it is not specific because patients with other autoimmune diseases also frequently score positive. Antibodies to double-stranded DNA and the so-called Smith (Sm) antigen are virtually diagnostic of SLE. - antiphospholipid Abs (Abs that react with proteins in complex with phospholipids (phospholipid–prothrombin complex, phospholipid–β2-glycoprotein complex)) have venous and arterial thromboses, which may be associated with recurrent spontaneous miscarriages and focal cerebral or ocular ischemia. This constellation of clinical features, in association with lupus, is referred to as the secondary antiphospholipid antibody syndrome. The association of SLE with HLA-II (HLA-DQ locus have been linked to the production of anti-double-stranded DNA, anti-Sm, and antiphospholipid antibodies)

**Mechanisms of Tissue Injury:** Regardless of the exact mechanisms by which autoantibodies are formed, they are clearly the mediators of tissue injury. ■Most of the visceral lesions are caused by immune complexes (type III hypersensitivity).
Autoantibodies specific for red cells, white cells, and platelets opsonize these cells and promote their phagocytosis and lysis.

**Malar skin rash:** direct immunofluorescence microscopy reveals deposition of immunoglobulins (IgG, IgM) & complement at the dermo-epidermal junction. Histologically: there is characteristic liquefactive degeneration of the basal layer of epidermis, edema at the dermo-epidermal junction & mononuclear infiltrates around blood vessels & skin appendages.

**Renal disorder:** The basis of the glomerular damage is the deposition of immune complexes within glomeruli.

Involvement of the heart showing mainly pericarditis, myocarditis & vascular lesions called **Libman-Sacks endocarditis**, which represent a nonbacterial verrucous endocarditis.

**Rheumatoid Disease (Rheumatoid Arthritis) (RA):** RA is a multi-system connective tissue disease in which the dominant effects are on the joints. It is characterized by the presence of a circulating autoantibody, "**Rheumatoid Factors**".

**Pathogenesis:** Although much remains uncertain, it is currently believed that rheumatoid arthritis is triggered by exposure of a genetically susceptible host to an **arthritogenic antigen** resulting in a breakdown of immunological self-tolerance and a chronic inflammatory reaction. In this manner, an acute arthritis is initiated, but it is the continuing autoimmune reaction, the activation of CD4+ helper T cells, and the local release of inflammatory mediators and cytokines that ultimately destroys the joint.

About 80% of the patients have **rheumatoid factors (RF)** in their serum & synovial fluid. RF represents an autoantibody mainly of IgM class directed against the Fc portion of IgG. RF & IgG form immune complex that fix complement, attract neutrophils, & lead to injury by a type III hypersensitivity reaction.

**Genetic susceptibility** major contributor to the pathogenesis of rheumatoid arthritis.

1-HLA-**DRB1** alleles
2-**PTPN22:** it encodes a protein tyrosine phosphatase, which participates in activation and control of inflammatory cells, including T cells.

**Environmental arthritogen:** The environmental arthritogen thought to be the **initiator of the disease** remains uncertain.

1-Microbial agents including Epstein-Barr virus, retroviruses, parvoviruses, mycobacteria, **Borrelia, Proteus mirabilis**, and **Mycoplasma**

2-Recently, **citrullinated proteins** (proteins modified by the enzymatic conversion of arginine to citrulline, many of which are fibrins) formed in the body (especially in the lungs of smokers) have been implicated in the pathogenesis of rheumatoid arthritis.

**Pathologic changes:** In the early stage there will be rheumatoid synovitis. The synovium is swollen with prominent villous pattern. There is a great increase in chronic inflammatory cells mainly lymphocytes, plasma cells & macrophages with formation of lymphoid follicles. There is marked synovial hypertrophy & hyperplasia, often with increased vascularity due to angiogenesis. There is often fibrinous effusion in the joint space; the fibrin gets deposited on the synovial surfaces.

With time there is articular cartilage destruction with replacement by vascular granulation tissue (pannus). The latter grows across the surface of the articular cartilage from the edge of the joint. The inflammatory pannus causes focal destruction of the subjacent bone; this is manifested as "erosions" on radiographs. Following
destruction of the articular cartilage & erosion of the subarticular bone, the pannus fills the joints space. Subsequent fibrosis & classification may cause permanent ankylosis of the affected joint.

**Systemic sclerosis (SS):**
It is one of the connective tissue diseases, & affects many systems & organs. It is three times more common in women than in men, & occurs mainly in middle-aged or elderly individuals. The main abnormality is an excess formation of fibrous tissue, which leads to rigidity of the affected organ. Vessel wall thickening & perivascular fibrosis are characteristic features in SS, & are responsible for slowly progressive ischemic damage in a wide range of tissues. The skin is the most commonly affected organ (scleroderma), but the alimentary tract, lung, kidney & heart may also be involved. There is usually affection of the skin of the fingers & distal regions of the upper extremities. Extending to the upper arms, shoulders, neck & face may occur. There is dermal thickening due to fibrous replacement of the normal dermal structures.

**Mixed connective tissue disease:**
Patients present with multiple features suggestive of SLE, polymyositis, & systemic sclerosis. They also have high titer of antibodies to ribonucleoprotein antigen. Two distinctive features of this disease
1. The kidneys are rarely involved
2. An extremely good response to corticosteroids.

**Amyloidosis**
Amyloid is the generic term for a variety of proteinaceous materials that are abnormally deposited in tissue interstitium causing clinical disorders. A protein is described as being amyloid if, due to an alteration in its secondary structure, it takes on a particular aggregated insoluble form, similar to the beta-pleated sheet. Symptoms vary widely depending upon where in the body amyloid deposits accumulate. Amyloidosis may be inherited or acquired.
Proteins are at risk of mis-folding as they are synthesized, to make a bad protein. The cellular enzymes, called proteases, cause proteolysis of these bad proteins. The problem occurs when the proteins do not dissolve in proteolysis. When the fragments do not dissolve, they get spit out of proteolysis and they aggregate to form oligomers. The oligomers can aggregate together and further stabilize to make amyloid fibrils.
The modern classification of amyloid disease tends to use an abbreviation of the protein that makes the majority of deposits, as an example, overproduction of immunoglobulin light chains in multiple myeloma (termed AL amyloidosis)

The diagnosis depends on identification by light microscopy of the material in biopsy. H & E stain shows amyloid as an amorphous, eosinophilic hyaline extracellular substance.
It also takes up certain special stains; the most widely known of these is congo red stain, which gives pink to red color under ordinary light microscopy but characteristically green birefringence under polarizing microscopy. (Fig. 7-10)

Electron microscopy of amyloid shows that it is composed of fibrils in a β-pleated sheet. (Fig. 7-11)

Effects
Progressive accumulation causes pressure atrophy at adjacent cells.

Chemical nature of amyloid:
1. AL (amyloid light chain) derived from plasma cell & contains Ig light chain. It is encountered with some forms of monoclonal B-cell proliferation.
2. AA (amyloid-associated): derived from serum precursor protein synthesized by the liver (serum amyloid associated) (SAA). It is non-immunoglobulin protein and deposited in the setting of chronic inflammatory states.
3. Aβ: found in the cerebral lesions of Alzheimer disease.
4. Transthyretin (TTR), this is a normal serum protein that binds & transports thyroxin & retinol. It is deposited in the heart of aged patients. A mutant form of TTR is deposited in some genetic disorders and is called familial amyloid polyneuropathies.
5. β2 – microglobulin, this is a component of the MHC class I molecules & a normal serum protein.

Amyloidosis may be systemic (generalized) or may be localized to a single organ. Systemic amyloidosis may be
1. Primary which is associated with immunocyte dyscrasia
2. Secondary as a complication at chronic diseases.

Primary amyloidosis
1. AL type, usually systemic. Examples include amyloidosis which is associated with multiple myeloma (a malignant neoplasm of plasma cells). In this neoplasm two forms of AL are synthesized
   a. Abnormal amount of specific immunoglobulin producing M (myeloma) protein spike on serum electrophoresis.
   b. λ & κ light chains known as Bence Jones protein which is excreted in urine.
2. Reactive systemic amyloidosis (AA) : the distribution of the amyloid deposition in this pattern is systemic. Previously this from was considered to be secondary because it is associated with chronic infectious diseases like TB, bronchiectasis, chronic osteomyelitis. With the use of antibiotics to control such infections, currently it tends to be
associated with chronic inflammation caused by autoimmune states such as rheumatoid arthritis and inflammatory bowel disease.

3. **Localized amyloidosis** (AL) limited to one organ or tissue that may produce detectable nodular masses or be evident only through microscope examination.

4. **Endocrine amyloid** (TTR) this form is found in medullary carcinoma of the thyroid, islet cell tumor of pancreas and pheochromocytoma.

5. **Amyloid of aging** (TTR) usually occurs in the age group 70-80 years and is called **senile systemic amyloidosis**. The heart is predominantly involved.

**Pathogenesis:**
Long standing tissue injury & inflammation cause macrophage activation & lead to elevated SAA levels through the influence of cytokines (IL$_1$, IL$_6$) on liver cells. Elevation of SAA levels alone does not lead to amyloidosis. It is believed that SAA is normally degraded to soluble end products by action of monocyte-derived enzymes. So individuals who develop amyloidosis have an enzyme defect that results in the incomplete breakdown of SAA, thus generating insoluble AA molecules.

**Morphological effects on various organs**

**Kidneys** become large, pale, gray and firm. Amyloid is deposited in the glomeruli, peritubular tissue and in the wall of blood vessels. *(Fig. 7-12)*

**Spleen** becomes firm, enlarged, pale and waxy on cut section (Sago spleen).

**Liver** is enlarged, pale and waxy. The deposition occurs in the space of Disse and surrounding blood vessels.