IMMUNOPATHOLOGY

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, but 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. 6-1)
2. Secondary; which is much more common than the primary. It can be secondary to
   a. Drugs
   b. Diseases
   (Fig. 6-2)

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 results 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) & is characterized by
1. Profound immuno-suppression leading to 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
20 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 concentrates (less than
1% of all cases).
The epidemiology of HIV infection & AIDS is different in children (<13 years age). About 1% off 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, have been isolated from patients. HIV-1 is the more common type in USA, Europe & central Africa, whereas HIV-2 is commoner in West Africa. HIV-1 virion is spherical & contains a cone-shaped core surrounded by a lipid envelope derived from the host cell membrane (Fig. 6-3). The virus core contains:

1. The major capsid protein P24.
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 core is surrounded by a matrix protein called P17. 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 CD4 lymphocytes & a decreased helper-suppressor T-cell ratio in the blood. The virus gains entry to T-cells by attaching to surface CD4 molecules. It takes over cellular metabolism to synthesize new virus. The CD4 molecule is a high-affinity receptor for HIV. This explains the selective tropism of the virus for CD4+T-cells & its ability to infect other CD4+cells, particularly macrophages & dendritic cells. However binding to CD4 is not sufficient for infection; the HIV envelope gp120 must also bind to other cell surface molecules (co-receptors) to facilitate cell entry (Fig. 6-4). 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. 6-5).

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 CD4+ cells, patients will have an inversion of the CD4+/CD8 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. 6-6)
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 (P24 antigen is detectable in blood), & an immune response develops, with increased number of virus-specific CD8+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 $CD_4$ 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 $CD_4^+T$-cells. Superficial fungal infections are frequent & infections with pathogens as Salmonella & Haemophilus are severe. 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 represent the final phase with fully developed immunodeficiency characterized by fever, fatigue, weight loss, generalized lymphadenopathy & diarrhea; the $CD_4^+$ 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 $CD_4^+$ cell counts less than or equal to 200/µL is diagnosed as having ADIS.

**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 intravenous drug abusers or 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. **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.

2. **Cervix uteri carcinoma:** this due to human papilloma virus infection in ADIS 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 -& 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.
Since testing recipients for the presence of antibodies to donor lymphocytes become a routine practice, hyperacute rejection occurs in less than 0.4% of transplants. 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 glomeruli, 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.

Transplantation of other solid organs
Beside the most frequent kidney transplantation, transplantations of liver, heart, lungs, & pancreas are also commonly performed. All these organs transplantation, unlike that of the kidney, can be performed with a disregard to histocompatibility typing. In transplantation of these organs instead we consider
1. ABO blood group typing
2. Absence of preformed circulating antibody
3. Body habitus (e.g. a child cannot receive a heart transplant from an adult).

Autoimmune diseases
Autoimmune diseases are the result of immune reactions against self-antigens i.e. against body tissue or individual tissue components. 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 involved in the pathogenesis of autoimmune diseases
There are regulatory mechanisms that present normally to prevent the occurrence of autoimmune diseases. Failure of such mechanisms is responsible for the occurrence of such diseases in some 3% of the population that suffer from such diseases. These will be discussed under the heading of immunological tolerance and its breakdown.

Immunological tolerance
Both T- and B-cells bear self-reactive molecules (receptors) that can recognized self-antigens and react with them to produce eventually tissue damage and this is the essence in the production of various autoimmune diseases. To avoid such incidents T- and B-cells bearing such molecules (receptors) must be either eliminated or down-regulated so that the immune system is made specifically non-reactive i.e. tolerant to self antigens. Since T-cells and in particular CD4+ T-cells, have a central role in controlling all immune responses, the process of T-cell tolerance is much more important than B-cell tolerance in the avoidance of autoimmunity. This is because not only T-cells may produce tissue damage directly but also self-reacting-B-cells will not be able to produce auto-antibodies unless they receive appropriate T-cell help.
Processes that induce specific tolerance arise inside the thymus (thymic tolerance) or outside the thymus (peripheral tolerance).

Thymic tolerance is achieved through eliminating all T-cells capable of recognizing self-proteins. This is not, however, induced to many tissue-specific proteins.

Peripheral tolerance this involves several mechanisms
1. Immunological ignorance: the self-antigens are invisible to the immune system either because of sequestration of the antigen e.g. within the vitreous humour of the eye or because the self antigens are presented to the CD4+ cells in low levels that is not enough to activate such cells. To prevent large amounts of self-antigen from gaining access to antigen-presenting cells a slow gradual tissue breakdown is achieved through apoptosis.
2. **Anergy**: CD4+ T-cells requires two signals to become activated and initiate an immune response: an antigen-specific signal through the T-cell antigen receptor and a second, nonspecific signal through interaction of CD4+ cells with antigen-presenting dendritic cells. Such an interaction is only likely to occur in secondary lymphoid tissues such as lymph nodes i.e. the encounter of both cells is very restricted. If no second signal is available then stimulation through T-cell receptor alone leads to apoptosis or a state of longstanding unresponsiveness called anergy.

3. **Suppression**: self-reactive T-cells may be actively suppressed by inhibitory T-cells, which recognize the same antigen (suppressor T-cells; CD8+). This is achieved through cytokines produced by the suppressor T-cells to inhibit nearby helper (CD4+) T-cells.

4. **B-cell tolerance**: this is less complete than T-cell tolerance. The production of self-reactive antibodies by these B-cells is limited mainly by the lack of T-cell help for cell antigens.

**Breakdown of tolerance**

For autoimmune diseases to occur, the above mechanisms of immunological tolerance must be broken down.

1. **Overcoming peripheral tolerance**: resulting from excessive access of self-antigens to antigen presenting cells, excessive nonspecific signaling, or alterations in which self-antigens are presented to the immune system. All these are likely to happen when inflammation or tissue damage is present. The structures of the self-antigen’s peptides (self-peptides) may be altered by viruses, free radicals or ionizing radiation. With such structural changes the previously established tolerance is bypassed. Tissue damage may release antigens that are already sequestered from the immune system e.g. spermatozoa & ocular antigens. Post-traumatic uveitis & orchitis (after vasectomy) probably result from immune responses against antigens normally sequestered in the eye & the testis.

2. **Molecular mimicry**: structural similarity between self-antigens and microbial antigens may trigger an immune response. In systemic infection, this cross reactivity will cause expansion of the responsive T-cell population recognizing the self-peptide if local conditions allow. The process is known as molecular mimicry. For example, rheumatic heart disease sometimes follows Streptococcal infection because antibodies to Streptococcal M protein cross-react with cardiac glycoproteins.

Once tolerance has broken down, the resulting immunological mediated inflammation and tissue damage may allow presentation of further peptides. The immune response broadens and local tissue damage accelerates. This domino-like process is known as **epitope spreading**.

*(Domino effect: by which one event triggers a succession of other, often similar, events, like a falling domino at the beginning of a line of up-ended dominoes).*

**Etiology of autoimmune diseases**

The interaction between genetic and environmental factors is important in the pathogenesis of autoimmune diseases.

**Genetic factors**

Family studies have confirmed a genetic contribution in all autoimmune diseases. This is supported by the findings that

1. Different autoimmune diseases may cluster within the same family (such as SLE, autoimmune hemolytic anemia, & autoimmune thyroiditis).
2. Subclinical autoimmunity is common among family members.

The genetic contribution to autoimmune disease usually involves multiple genes. The strongest associations between genetic factors and autoimmunity involve alleles of the major histocompatibility complexes (MHC). This is because of central role of the products of many of these genes in the

1. T-cell function
2. Control of immunity and inflammation.

It is likely that the MHC class II alleles influence the presentation of autoantigenic peptides to T-cells.

An example of such a connection is the well-known strong association of HLA-B27 with ankylosing spondylitis.

**Genetic factors in autoimmunity:**
Genetic factors play a significant role in the predisposition to autoimmune diseases. This is supported by the following:

1- There is familial clustering of several human autoimmune diseases. Linkage of several autoimmune diseases with HLA, especially class II antigens.

**Environmental factors**
These may trigger autoimmune diseases and include:

1. Hormones
2. Infections
3. Drugs
4. UV radiation

**Hormones**
The contribution of hormones in the pathogenesis of autoimmune diseases is supported by the following:

1. Most autoimmune diseases affect females much more commonly than males; hormonal factors, besides genetics, must play a major role in this gender difference.
2. The peak age of onset of most autoimmune diseases is within the reproductive years. Evidences implicate estrogens as triggering factors.
3. In animal models removal of the ovaries inhibits the occurrence of autoimmune diseases (e.g. SLE), while estrogen administration accelerates the onset of the disease.

**Infections**
The relationship between infection and autoimmunity is clearest in the situation of molecular mimicry. Autoimmune diseases tend to be less common in parts of the world with high incidence of parasitic diseases and other infections. This inverse relationship between the occurrence of autoimmune diseases and the incidence of various infections is supported by experiments on animal models.

**Drugs**
Drug-induced autoimmunity may involve mechanisms comparable to molecular mimicry, whereby the drug or drug-self molecule complex has a structural similarity to self that allows bypassing tolerance. Drug-mediated autoimmunity affects only a small proportion of those treated and is probably genetically determined. For example, HLA-DR2 is associated with penicillamine-induced myasthenia gravis, whereas DR3 is associated with penicillamine-induced nephritis. Genetic variation in drug metabolism is also important. Individuals who are slow metabolizers of the offending drug are more prone to develop the disease (for e.g. drug-induced SLE) than rapid metabolizers. Slow metabolism of the offending drug may give more time for the formation of immunogenic conjugates between the drug and self-molecule.

**4. Ultraviolet radiation**
Exposure to UV radiation, usually in the form of sunlight is a known trigger for skin eruptions (photosensitivity skin eruption) and sometimes systemic involvement in patients with SLE. UV radiation acts in this context through two possible mechanisms:

a. modifying self-antigens to become immunogenic
b. enhancing apoptosis (cell death) of the cells, which lead to cell surface expression of auto-antigens that are usually hidden within the cell. Such exposure of the antigens leads to Ag-Ab reaction that triggers tissue damage.

Autoimmune diseases may be either organ specific (response directed against a single component of a single tissue) or more often, a 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 thyroid growth-stimulating Ab</td>
<td>Hyperthyroidism</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>
<tr>
<td>Pancreatic islet cells (insulin-producing)</td>
<td>Type I diabetes mellitus</td>
<td>Anti-islet B-cell (insulin) Ab</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptors Ab</td>
<td>Muscle fatigue</td>
</tr>
</tbody>
</table>

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". It is a fairly common disease, with a prevalence of 1:2500 persons. Like most autoimmune diseases, there is a strong female predominance (9:1) and is particularly common in young & middle-aged individuals. Clinically, the disease is characterized by remissions & relapses, with an acute or insidious onset that may involve any organ in the body. Acute flare-ups are usually controlled by steroids or other immunosuppressive drugs. Renal failure, intercurrent infections, & diffuse central nervous system involvement are the major causes of death.

**Etiology & pathogenesis:**
SLE is a complex disease of multifactorial origin including genetic, hormonal, & environmental factors, resulting in a T-cell & B-cell activation that leads to the production of several autoantibodies. The main defect in SLE is a failure to maintain self-tolerance. Many types of autoantibodies can be identified in SLE patient particularly antinuclear antibodies (ANAs), which are directed against several nuclear antigens. ANAs can be identified using the indirect immunofluorescence test, which is positive in virtually every patient with SLE, so that the test is quite sensitive. However, it is not specific. However, the presence of autoantibodies against double stranded DNA is diagnostic to SLE. Antibodies against blood cells, including red cells, platelets, & lymphocytes, are found in many patients. Antiphospholipid antibodies are found in 40% to 50% of SLE patients. Because phospholipids are required for blood clotting, SLE patients with antiphospholipid antibody tend to have venous and arterial thrombosis, thrombocytopenia & recurrent spontaneous miscarriages (antiphospholipid syndrome).
**Genetic factors:**
There is much evidence supporting the genetic predisposition for SLE:
1. There is a higher rate of concordance in monozygotic twins (25%) than in dizygotic twins (1%-3%).
2. Family members have an increased risk of developing SLE, & up to 20% of clinically unaffected first-degree relatives may have autoantibodies.
3. There is a positive association between SLE & class II HLA genes.
4. About 6% of SLE patients have inherited deficiencies of complement components. Lack of complement may impair removal of immune complexes from the circulation & favor tissue deposition, resulting in tissue injury.

**Nongenetic factors:**
1. The clearest example of environmental factors in initiating SLE is the occurrence of a lupus-like syndrome in patients receiving certain drugs, including procainamide & hydralazine. Thus, most patients treated with procainamide for more than 6 months develop ANAs, with clinical features of SLE appearing in 15%-20% of them.
2. Sex hormones; the female predominance of SLE, reflects the important influence of sex hormones in the development of the disease, due to the helpful effects of estrogens on antibody synthesis.
3. Exposure to ultraviolet light exacerbates the disease in many individuals. Ultraviolet light may damage DNA & promote cell injury that will release cellular contents & augment the formation of DNA/antiDNA immune complexes.

**Mechanism of tissue injury:**
Most of the visceral lesions are caused by immune complexes (type III hypersensitivity). For example, DNA/anti-DNA complexes can be detected in the glomeruli. In addition, autoantibodies against red cells, white cells, & platelets causing effect by type II hypersensitivity. The denaturated nucleus of an injured cell will be engulfed by a neutrophil or macrophage producing the LE cell. LE cell test is positive in about 70% of patients with SLE.

**Clinical manifestations:**
The clinical presentation of SLE is so variable & with similarities to other autoimmune connective tissue diseases (rheumatoid arthritis, polymyositis & others) so that it has been necessary to develop diagnostic criteria. If a patient has four or more of the criteria, serially or simultaneously, during any interval of observation, the diagnosis of SLE is established. The range of features that can occur in SLE is shown by the American Rheumatism Association List of Diagnostic Criteria for SLE
1. Discoid skin rash.
2. Malar rash.
3. Photosensitivity.
5. Arthritis.
7. Renal disorder.
8. Neurologic disorder.
10. Immunologic disorder.
Skin rashes of various types occur in about 80% of all patients with SLE. One of the most common tissues affected in SLE is the skin. The most common patterns of skin rash are:
1. Chronic discoid LE: round (discoid), red scaly telangiectatic plaques, usually on the face & scalp,
2. Malar skin rash: a symmetrical, slightly raised red erythematous rash on the cheeks & across the bridge of the nose (butterfly rash). This is seen in 50% of the patients.
3. Photosensitivity reactions: exposure to sunlight (ultraviolet light) exacerbates the erythema, & the rash will be seen on the face & sun-exposed areas mainly. 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. (Fig. 6-7)

4. An acute necrotizing vasculitis: clinically, producing slightly raised erythematous patches.

5. Oral mucosal lesions in SLE produce superficial erosions & ulcers.

6. Musculoskeletal symptoms may be the earliest presenting feature of SLE. Joint pain and swelling occurs in about 90% of patients.

7. Serositis: the pericardium & pleura are usually affected. In the acute phase they may lead to serous effusion.

8. Renal disorder: kidney involvement in SLE is common, & is an important cause of morbidity & mortality. The severity of involvement can vary from minor abnormalities (such as asymptomatic albuminuria) to sever glomerular disease leading to renal failure. The basis of the glomerular damage is the deposition of immune complexes within glomeruli. (Fig. 6-8)

9. Neurological & psychiatric disorders are common in SLE.

10. Hematological abnormalities are common in SLE, some having an unknown cause, & others having an autoimmune mechanism:
   a. Normocytic, hypochromic anemia.
   b. Autoimmune hemolytic anemia
   c. Leucopenia usually due to disproportionate reduction of lymphocytes (lymphopenia).
   d. Thrombocytopenia

The spleen may be moderately enlarged. Involvement of the heart showing mainly pericarditis, myocarditis & vascular lesions called Libman-Sacks endocarditis, which represent a nonbacterial verrucous endocarditis. (Fig. 6-9)

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.

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" (seropositive arthritis). RA is a very common condition, with a prevalence of about 1%. It is three to five times more common in women than in men, & the usual age of onset is between 35 to 45 years. The disease is not limited to joints but also affects, among others, the skin, lungs, blood vessels, eyes & the hemopoietic system.

Pathologic changes:
RA typically presents as symmetric polyarthritis, mainly affecting the small joints of the hands & feet. However, larger joints may also be involved e.g. ankles, knees, wrists, elbows & shoulders. Classically, the proximal interphalangeal & metacarpophalangeal joints are affected. The affected joints become swollen, painful & warm, often with redness of the overlying skin. There are three main pathological changes
1. 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.
2. 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.
3. 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. The loss of articular cartilage can lead to secondary osteoarthritis (a degenerative joint disease), especially in the weight-bearing joints such as the knee. Destruction of tendons, ligaments, & joint capsules produces deformities of the joints; that of the hand are characteristic, which include radial deviation of the wrist, ulnar deviation of the fingers, & flexion-hyperextension abnormalities of the fingers (swan-neck deformity).

Rheumatoid subcutaneous nodules develop in about 25% of the patients. They occur along the extensor surface of the forearm or other areas subjected to mechanical pressure. Rheumatoid nodules are firm, nontender, oval or rounded masses up to 2 cm in diameter. Microscopically there is central focus of fibrinoid necrosis surrounded by a palisade of macrophages which is rimmed by granulation tissue.

Pulmonary involvement in RA takes the form of interstitial pneumonitis & fibrosing alveolitis, which leads eventually to a pattern of interstitial fibrosis called "honeycomb lung". The latter is also caused by other diseases such as systemic sclerosis.

Anemia is very common in rheumatoid disease as is increased susceptibility to infections, & sepsis, which are important & common causes of death.

Pathogenesis of RA:
There is a genetic predisposition to RA which is suggested by
1. The increased frequency of this disease among first-degree relatives.
2. The strong association of the disease with HLA-DR4 &/or HLA-DR1.

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.

It is proposed that the disease is initiated in a genetically predisposed individual, by activation of helper T-cells possibly by microbial agent, the activated CD4+cells produce cytokines that will:

- Activate macrophages & other cells in joint space to release degrading (proteolytic) enzymes & other factors that initiate inflammation and cause tissue destruction.
- Activate B-cells, which produce RF (autoantibody). These will form immune complexes with IgG that often get deposited on the synovial membrane with subsequent joint injury.
- It has been found that activated T-cells will also induce osteoclast cell differentiation & activation that leads to bone resorption.

Juvenile rheumatoid arthritis (JRA):
It is a chronic idiopathic arthritis that occurs in children. Like the adult form of (RA) it is a destructive arthritis but differs from it by the following points
1. It affects large joints
2. There is absence of RF
3. There are no rheumatoid nodules.
4. Some cases of JRA are associated with HLA-B27.

Sjögren syndrome:
This autoimmune disease is characterized by dry eyes (keratoconjunctivitis sicca) & dry mouth (xerostomia) resulting from immune-mediated destruction of the lacrimal & salivary glands. It occurs in two forms a primary form i.e. an isolated disorder, and as a secondary form associated with other autoimmune disorder such as, RA, SLE, polymyositis, systemic sclerosis, vasculitis and thyroiditis.

Inflammatory myopathies:
These are heterogeneous group of rare disorders characterized by immune mediated muscle injury & inflammation. Under this heading are three disorders

1. Polymyositis
2. Dermatomyositis
3. Inclusion body myositis.
They may occur alone or with other autoimmune disease as systemic sclerosis.
Clinically, they present with symmetric muscle weakness initially affecting large muscles of the trunk, neck & limbs, with difficulty in getting up from a chair. In dermatomyositis, there is associated skin rash that involves the upper eyelids together with & periorbital edema. Histologically, there is infiltration of lymphocytes with degeneration of muscle fibers.

**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.

**Polyarteritis nodosa (PAN):**
It is a systemic disease characterized by inflammatory necrosis of the wall of small- & medium-sized arteries. The clinical effects are the result of vessel occlusion leading to small areas of infarction. The tissues most seriously affected are the kidneys, heart, alimentary tract, liver, CNS, peripheral nerves, skeletal muscle & skin. The cause of the disease is unknown, but it is likely to be immune-complex-mediated. There is an association with chronic hepatitis B virus antigenemia.

**AMYLOIDOSIS**
Amyloid is the generic term for a variety of proteinaceous materials that are abnormally deposited in tissue interstitium causing clinical disorders.

**Morphology**
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. 6-10)

**Effects**
Progressive accumulation causes pressure atrophy at adjacent cells.

**Composition**
Amyloid is not a single chemical entity, thee major & several minor biochemical forms could be found.

**Physical nature of amyloid**
95% of amyloid component is nonbranching fibrils, 7.5-10 nm in width, with characteristic crossed β-pleated sheet conformation.
The minor component is a nonfibrillar pentagonal glycoprotein (P-component) & proteoglycans, which form the remaining 5%.

**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. Heredofamilial amyloidosis (AA)
   Examples include familial Mediterranean fever, which is an autosomal recessive febrile illness of unknown cause, associated with serosal inflammation such as the peritoneum, pleura & synovium.
4. Localized amyloidosis (AL) limited to one organ or tissue that may produce detectable nodular masses or be evident only through microscope examination.
5. Endocrine amyloid (TTR) this form is found in medullary carcinoma of the thyroid, islet cell tumor of pancreas and pheochromocytoma.
6. 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 (IL₁, IL₆) 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. 6-12)
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.
Clinical correlation
S &S depend on site, amount & duration of the deposition.
Weakness, fatigue, & weight loss are the most common initial symptoms. Later the manifestations may be present as renal disease (nephrotic syndrome) which is often the major cause of symptoms in reactive systemic amyloidosis. Liver involvement is associated with hepatomegaly. Heart involvement may lead to cardiomyopathy that is associated with arrhythmias.