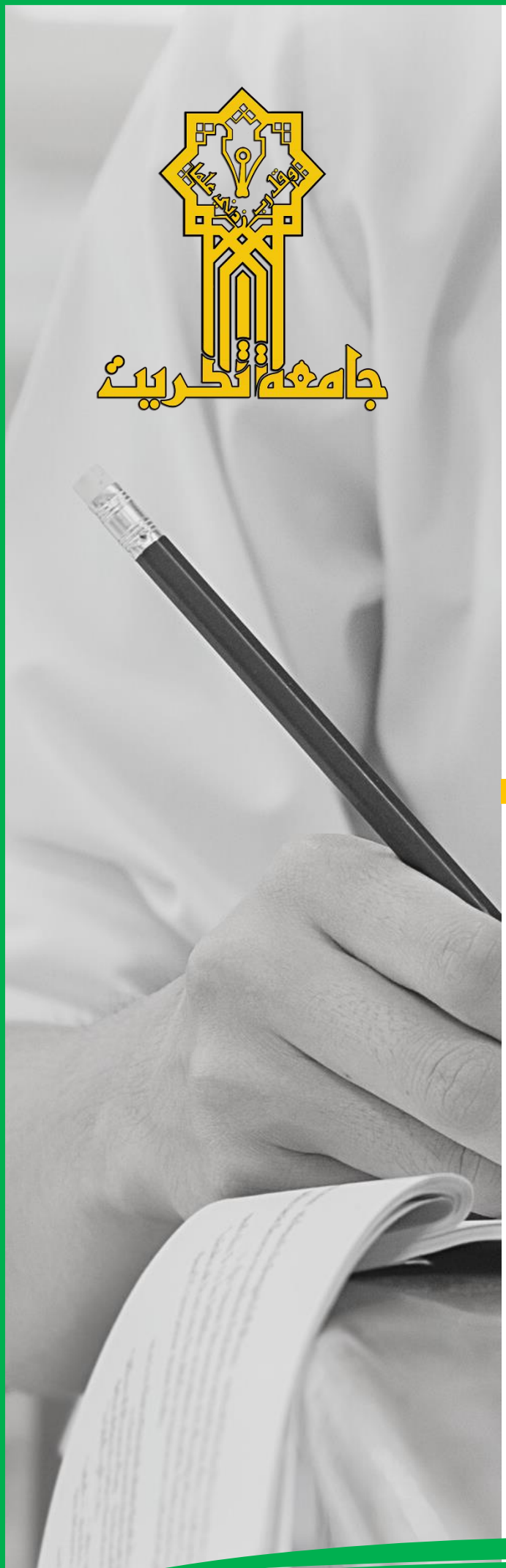

Tikrit University
College of Veterinary Medicine

IMMUNOPATHOLOGY

Subject name: Pathology

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- 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.

Immunologic diseases may result from:

●Inadequate immune response.

●Excessive immune response.

●Inappropriate immune response.

Inadequate immune responses:

These can result from immuno-deficiency states. There are two classes of immunodeficiency syndromes.

Primary: which is present at birth & often the result of a genetic disorder?

Secondary: which is much more common than the primary? It can be secondary to:

●Drugs.

●Diseases:

1. Old age.
2. Chronic malnutrition.
3. Widespread malignancy.
4. Metabolic diseases (diabetes, chronic liver failure, chronic renal failure).
5. Drug therapy (cytotoxic therapy, steroid therapy).
6. Splenectomy (pneumococcal septicemia).
7. AIDS

Hypersensitivity or immunological injury

Immune response is capable of causing tissue injury and disease that are called hypersensitivity disease. This term originated from the idea that individual who mount immune responses against an antigen are said to be "sensitized" to that antigen and therefore, pathologic reaction or excessive reactions are manifestation of hypersensitivity.

Causes of Hypersensitivity diseases

Pathologic immune response may be directed against different types of antigens:

1- Autoimmunity
2- Reaction against microbes
3- Reaction against environmental antigen

Types of Hypersensitivity diseases

1- Type I hyper Hypersensitivity (anaphylaxis)
2- Type II Hypersensitivity (cytotoxicity) (antibody –mediated)
3- Type III Hypersensitivity (arthus reaction)
4- Type IV Hypersensitivity delayed type Hypersensitivity (DTH)

1- Type I hyper Hypersensitivity (anaphylaxis):

This type occur when IgE have receptor on mast cell. The IgE against specific Ag such as penicillin when the person exposed to penicillin to second time , the penicillin react with IgE on the surface of mast cell in this case the mast cell release the following :

1- Preformed mediators e.g histamine, serotonin kinin, and eosinophil chemotactic factor (ECF) neutrophil chemotactic factor(NCF).
2- Granules associated materials include proteinase, lipase and peroxidase.
3- Newly synthesized PGs, leukotrein which lead to inflammation

Time: 10 – 15 min.

Clinical and pathologic manifestation

Systemic reaction(parenteral) administration drugs (e.g. penicillin) may result in systemic anaphylaxis within min. of an exposure in a sensitized host ,itching urticaria and skin erythema appear followed by profound respiratory difficulty cause by pulmonary bronchoconstriction. Or localized like asthma.

2- Type II Hypersensitivity (cytotoxicity) (antibody –mediated):-

This type occurs when the Ab react with Ag is a part of cell mem. Ab directed against antigen on the surface of cell or other tissue components. The Ag may be normal molecules (intrinsic) to cell mem. Or extracellular matrix (endogenous) or may be adsorbed (exogenous) Ag .

e.g. incomplete blood transfusion , auto hemolytic anemia

Time: 1-2 Hrs.

Type of Ab: IgG, IgM.

Mechanisms of Ab- mediated disease:

Ab causing disease by targeting for phagocytosis, by activating complement system, and by interfering with normal cellular function and results in three steps :

A. Opsonization and phagocytosis :when circulating cell ,such as erythrocyte or platelets, are coated (opsonize) with autoantibody ,with or without complement protein ,the cell became target for phagocytosis by neutrophil and macrophages.

B. Complement and Fc receptor mediated inflamm.: auto antibodies bound to cellular or tissue antigen activate the comp. system by classical pathway product of comp. activation recruit neutrophils and monocytes.

C. Antibody- mediated cellular dysfunction: antibody direct against cell surface receptor impair cellular function without causing cell injury or inflamm.
e.g. graves' disease in thyroid

3- Type III Hypersensitivity (arthus reaction):
Antigen-antibody (immune) complex that are formed in circulation may deposit in blood vessels, leading to comp. activation and acute inflamm. The Ag-Ab complex deposit in glomeruli or sarcoplasm of cardiac mm. or in on synovial joint, trigger the comp. to produce comp. component, C3a and C5a**.**

Time: 1-4 hrs.

Localized: to particular organ (kidney , joints, or skin).

Systemic: when complex are formed in the circulation are deposit in several organs, lead to deposition of the immune complex in various tissue, thus initiating an inflamm. Reaction.

4- Type IV Hypersensitivity delayed type Hypersensitivity (DTH):
This type occur when sensitized Tcell react with specifically Ag lead to release of lymphokines such as meth macrophages inhibitory ,TNF, skin reacting factor these lymphokines cause aggregation of lymphocyte, macrophages, few neutrophil and this cell given hydrolytic enzyme causes lysis of the tissue and caseousation.

Time: 24-72 hrs.

A classic example of DTH is the tuberculin reaction ,elicited by Ag challenge in the an individual already sensitized to the tubercle bacillus by a previous infection between 8 and 12 (hrs) after interacutenous injection of tuberculin, a local area of erythema and indurations appear ,reaching a peak (typically 1-2 cm in diameter) in b24 to 72 hrs.

T-Cell-Mediated Cytotoxicity

In this form of T-cell-mediated hypersensitivity, CD8+ CTLs kill antigen-bearing target cells.. The principal mechanism of killing by CTLs is dependent on the perforin-granzyme system. Perforin and granzymes are stored in the granules of CTLs and are rapidly released when CTLs engage their targets (cells bearing the appropriate class I MHC-bound peptides). Perforin binds to the plasma membrane of the target cells and promotes the entry of granzymes, which are proteases that specifically cleave and thereby activate cellular caspases. These enzymes induce apoptotic death of the target cells. CTLs play an important role in the rejection of solid-organ transplants and may contribute to many immunologic diseases, such as type 1 diabetes (in which insulin-producing |3 cells in pancreatic islets are destroyed by an autoimmune T-cell reaction).

REJECTION OF TRANSPLANTS

The major barrier to transplantation of organs from one individual to another of the same species, called ***allografts:*** is immunologic rejection of the transplanted tissue. Rejection is a complex phenomenon involving both cell- and antibody-mediated hypersensitivity reactions directed against histocompatibility molecules on the foreign graft.

Immune Recognition of Allografts :

Rejection of allografts is a response to MHC molecules, which are polymorphic that no two individuals in an outbred population are likely to express exactly the same set of MHC molecules (except, of course, for identical twins). There are two main mechanisms by which the host immune system recognizes and responds to the MHC nolecules on the graft:

Direct recognition: Host T cells directly recognize the allogeneic (foreign) MHC molecules that are expressed on graft cells. Direct recognition of foreign MHC seems o violate the rule of MHC restriction. Because DCs in the graft express high levels of vtHC as well as important costimulatory molecules, they are the most likely APCs in direct recognition. Host CD4+ helper T cells are

triggered into proliferation and cytokine production by recognition of donor class II MHC (HLA-D) molecules and drive the DTH response. CD8+ T cells recognize class I MHC (HLA-A, -B) and differentiate into CTLs, which kill the cells in the graft.

Indirect recognition:. In this instance, host CD4+ T cells recognize donor MHC molecules after these molecules are picked up, processed, and presented by the host's own APCs. This is similar to the physiologic processing and presentation of other foreign (e.g., microbial) antigens. This form of recognition mainly activates DTH pathways; CTLs that develop by indirect recognition cannot directly recognize and kill graft cells. The indirect pathway is also involved in the production of antibodies against graft alloantigens; if these antigens are proteins, they are picked up by host B cells, and peptides are presented to helper T cells, which then stimulate antibody responses.

AUTOIMMUNE DISEASES:

The evidence is compelling that an immune reaction to ***self-antigens*** (i.e., ***autoimmunity)*** is the cause of certain human diseases; a growing number of entities have been attributed to this process

Or called the disease occurs when there is auto Ab released in the body against body cell component, occurs without clinical disease.

Organ-Specific	**Systemic**
Hashimoto thyroiditis	Systemic lupus erythematosus
Autoimmune hemolytic anemia	Rheumatoid arthritis
Autoimmune atrophic gastritis of pernicious anemia	Sjogren syndrome
Multiple sclerosis	Reiter syndrome
Autoimmune orchitis	Inflammatory myopathies*
Goodpasture syndrome	Systemic sclerosis (scleroderma)*
Autoimmune thrombocytopenia	Polyarteritis nodosa*
Insulin-dependent diabetes mellitus	
Myasthenia gravis	
Graves' disease	

Primary biliary cirrhosis*	
Autoimmune (chronic active) hepatitis*	
Ulcerative colitis	

Classification of autoimmune disease :

1- Glandular tissue disease

2- Connective tissue disease

3- Miscellaneous auto immune dis.

4- DTH

1- **Glandular tissue disease:** these include chronic inflammatory destruction of glandular tissue with presence auto Ab against this G.T. component

A- Chronic auto immune thyroditis: this disease characterized by inflame. reaction of thyroid gland by lymphocyte , plasma cell, macrophage and destruction of the thyroid epithelia (focal ,diffuse) such in case of hashimoto disease (hypothyroidism), gravis' disease (hyperthyroidism).

-The auto Ab against thymoglobulin or against cell mem., of thyroid goiter

-hypothyroidism in which reduced the size of thyroid gland, is a result of inflame. reaction and destruction of thyroid gland.

-hyperthyroidism auto Ab against TSH receptor on thyroid epithelia cell have some effect on TSH cause thyroid hyper function.

B- Chronic auto immune gastritis: the type of inflame. Occur when there is auto Ab react with parietal cell of the stomach, block intrinsic factor which is responsible for absorption vit. B12 there is no vit. B12 absorption ,no release of iron which called pernicious anemia and caused atrophic gastritis (atrophy in mucosal layer).

C- Auto immune adrenalitis: the disease characterized by atrophy of adrenal cortex , auto Ab against adrenal cell. So atrophy of adrenal cortex because inflame. reaction (Addison's disease).

D- Hypo parathyroidism : this disease occur when auto Ab against parathyroid cell ,there is inflame. Reaction and reduced in size of parathyroid ,this disease occure with other immune disease such as gastritis and thyroiditis.

E- Insulin dependent type1 D.M.: the mostly common in children and young adult in which there is auto Ab to the cell of islets of langerhans in which auto Ab react with B-cell mem. Or component lead to destruction and atrophy, auto Ab appear in serum of all patient.

2- Connective tissue disease:

A- Systemic Lupus Erythematosus (SLE):

Is one of C.T dis. Charac. By acute and chronic inflame. lesion in many organ and tissue of body which occurrence of plasma antibodies which react with normal constituents of the cell in the body ,the site of lesion include skin, ms, joint, glomeruli, heart , B.V, red cell, platelets auto Abs to DNA antinuclear antibodies (ANAS) is demonstrated in serum by immunofluorescence test, auto Abs to RNA, and to various cellular constituent. The pathological feature of SLE depend on the position of circulating immune complex in the wall of B.VS so the disease activity correlated with ANAS and low level of complement in serum .

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of protean manifestations and variable behavior. Clinically, it is an unpredictable, remitting and relapsing disease of acute or insidious onset that may involve virtually any organ in the body; however, it affects principally the skin, kidneys, serosal membranes, joints, and heart. Immunologically, the disease is associated with an enormous array of auto antibodies, classically including antinuclear antibodies (ANAs). The clinical presentation of SLE is so variable and it has so many overlaps with other autoimmune diseases (rheumatoid arthritis, polymyositis, and others) that it has been necessary to develop diagnostic criteria for SLE. The diagnosis is established if a patient demonstrates four or more of the criteria during any interval of observation.

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

Etiology and Pathogenesis:

The fundamental defect in SLE is a failure to maintain self-tolerance. **There are a large number of autoantibodies is produced that can damage tissues either directly or in the form of immune complex deposits. 1. Antinuclear Antibodies**

ANAs are directed against several nuclear antigens and can be grouped into four categories: (1) antibodies to DNA, (2) antibodies to histones, (3) antibodies to *non-histone proteins bound to RNA and (4) antibodies to nucleolar antigens.*

Genetic Variables: many lines of evidence support a genetic predisposition to SLE Non genetic Variables as LT traviolet (UV) radiation, environmental as receiving certain drugs and Sex hormones.

B- **Rheumatoid arthritis (RH): this disease also important C.T disease in which charact. By auto Abs against C.T and synovial mem. The auto Abs is IgG, IgA there is modification in IgG in crystal region of Abs and then become antigenic, so there is a new set of Abs(IgM) rheumatoid factor, IgM react with IgG and cause rheumatism , the auto Abs against DNA,RNA, ribonucleo protein and cell mem.**

3- Miscellaneous auto immune dis. :

a- Ulcerative colitis : auto Abs against intestinal epithelia and inflammatory reaction lead to destruction and ulceration of epithelia lead to diarrhea mixed with blood and mucous.

b- Primary biliray cirrhosis: auto Abs against bile duct and result to the chronic fibrosis cholangitis and cirrhosis**.**

IMMUNE DEFICIENCY DISEASES

Immune deficiency diseases may be caused by inherited defects affecting immune system development, or they may result from secondary effects of other diseases (e.g., infection, malnutrition, aging, immunosuppression, autoimmunity, or chemotherapy). Clinically, patients with immune deficiency present with increased susceptibility to infections as well as to certain forms of cancer. The type of infections in a given patient depends largely on the component of the immune system that is affected. Patients with defects in Ig, complement, or phagocytic cells typically suffer from recurrent infections with pyogenic bacteria, whereas those with defects in cell-mediated immunity are prone to infections caused by viruses, fungi, and intracellular bacteria.

A. Primary' (Congenital) Immune Deficiency Diseases

Caused by mutations in genes involved in lymphocyte maturation or function, or in innate immunity. Some of the common disorders are:

1- ***XLA (X-Linked agammaglobulinemia):*** *failure of B-cell maturation, absence of antibodies; mutations in BTK gene, which encodes B-cell tyrosine kinase, required for maturation signals from the pre-B cell and B-cell receptors.*
2- ***Common variable immunodeficiency****: defects in antibody production; cause unknown in most cases.*
3- ***Selective IgA deficiency****: failure of IgA production; cause unknown.*
4- **X-SCID (severe combined immunodeficiency):** failure of T-cell and **B-**cell maturation; mutation in the common y chain of a cytokine receptor, leading to failure of IL-7 signaling and defective lymphopoiesis.
5- **Autosomal SCID:** failure of T-cell development, secondary defect in antibody responses; approximately 50% of cases caused by mutation in the gene encoding ADA, leading to accumulation of toxic metabolites during lymphocyte maturation and proliferation
6- **X-linked hyper-IgM syndrome:** failure to produce isotype-switched high-affinity antibodies (IgG, IgA, IgE); mutation in gene encoding CD40L

Clinical presentation: increased susceptibility to infections in early life.

Primary defect in CMI:

All these defect in CMI also acomporied with Ab deficiency production its inheritance

1- DiGeorge anomaly
2- Chronic mucocutoneous (endocrine abnormal)
3- Purine nucleoside phosphorylase : recurrent infection and neurological diseases.
4- Ataxia telongectasia include cerebral ataxia,
5- Wiskott- Aldrich syndrome: thrombocytopenia ,bleeding, eczema,

B. Secondary Immune Deficiencies (Acquired immunodeficiency)

Immune deficiencies secondary to other diseases or theraplcc are much more common than the primary (inherited) disorders. Secondary immune deficiencies may be encountered in patients with malnutrition, infection, cancer, renal disease, or sarcoidosis. However, the most common cases of immune deficiency are therapy-induced suppression of the bone marrow and of lymphocyte function.

1- Malnutrition: impared synthesis of protein lead to decrease in C synthesis
2- Increase protein loss cause hypo gammaglobulinemia through gut protein loosing enteropathy or burns

3- Lymphoproliferative disease: in case of lymphocytic leukemia , hodgkins lymphoma , non hodgkins lymphoma associated with protein production

4- Viral infection AIDS (HIV) human immunodeficiency so this virus destroyed helper cell and plasma cell lead to decrease in Ab

5- By surgery removal of tonsil or spleen

6- Burns

7- Radiation

8- Therapy cyclosporine ,cyclophosphomide and methrotrexate

Nonspecific immune defect.

1- Defect in phagocytosis: defect in neutrophil is few in number "neutropenia" and defect in macrophage are few in number or immature
2- Defect in complement: defect in C1, C2, C3…etc.

HIV Life Cycle and the Pathogenesis of AIDS

Etiology: AIDS is caused by HIV. This is a human retrovirus belonging to the lentivirus family.

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

Virus entry into cells: requires CD4 and co-receptors, which are receptors for chemokines; involves binding of viral glycoprotein (gp) 120 and fusion with the cell mediated by viral gp41 protein; main cellular targets are CD4+ helper T cells, macrophages, and DCs.

Viral replication: provirus genome integrates into host cell DNA; viral gene expression is triggered by stimuli that activate infected cells (e.g., infectious microbes, cytokines produced during normal immune responses) ***Progression of infection:*** acute infection of mucosal T cells and DCs; viremia with dissemination of virus; latent infection of cells in lymphoid tissue; continuing viral replication and progressive loss of CD4+ T cells.

Mechanisms of immune deficiency:

Loss of CD4+ T cells: T-cell death during viral replication and budding (similar to other cytopathic infections); apoptosis as a result of chronic stimulation;

decreased thymic output; functional defects, Defective macrophage and DC functions. Destruction of architecture of lymphoid tissues (late).

Natural History of HIV Infection:

The clinical course of HIV infection can best be understood in terms of interplay between HIV and the immune system. Three phases reflecting the dynamics of virus-host interaction can be recognized:

(1)an early acute phase,

(2)a middle chronic phase, and

(3)a final crisis phase.

In the absence of treatment, most patients with HIV infection develop AIDS after a phase lasting 7 to 10 years. Exceptions to this include rapid progressors and l o n g t e r m non progressors. Li rapid progressors, the middle, chronic phase is telescoped to 2 to 3 years after primary infection.

Non progressors (fewer than 5% of infected persons) are defined as HIV-infected individuals who remain asymptomatic for 10 years or more, with stable CD4+ counts and low levels of plasma viremia; notably, AIDS eventually develops in the majority of these patients, albeit after a much prolonged clinical latency.

Immunological tolerance:

Is unresponsiveness to an antigen that is induced by exposure of specific lymphocytes to that antigen. Self-tolerance refers to a lack of immune responsiveness to one's own tissue antigens. During the generation of billions of antigen receptors in developing T and B lymphocytes, it is not surprising that receptors are produced that can recognize self-antigens. Since these antigens cannot all be concealed from the immune system, there must be means of eliminating or controlling self-reactive lymphocytes.

Tolerance (unresponsiveness) to self-antigens is a fundamental property of the immune system, and breakdown of tolerance is the basis of autoimmune diseases, and there are **two** types of tolerance:

Central tolerance: immature lymphocytes that recognize self-antigens in the central (generative) lymphoid organs are killed by apoptosis; in the B-cell lineage, some of the self-reactive lymphocytes switch to new antigen receptors that are not self-reactive.

Peripheral tolerance: mature lymphocytes that recognize self-antigens in peripheral tissues become functionally inactive (anergic), or are suppressed by regulator}' T lymphocytes, or die by apoptosis.

The variables that lead to a failure **of <u>self-tolerance</u> and the development of autoimmunity include:**

(1) Inheritance of susceptibility genes that may disrupt different tolerance pathways. Autoimmune diseases have a tendency to run in families, and there is a greater incidence of the same disease in monozygotic than in dizygotic twins. Several autoimmune diseases are linked with the *HLA locus,* **especially class II alleles** *(HLA*-DR, -DQ). **The frequency of a disease in an individual with a particular HLA allele, compared to individuals who do not inherit that allele, is called the** relative risk.

(2) Infections and tissue alterations that may expose self-antigens and activate APCs and lymphocytes in the tissues. Viruses and other microbes, particularly certain bacteria such as streptococci organisms, may share cross-reacting epitopes with self-antigens, such that responses to the microbial antigen may attack self-tissues. This phenomenon is called molecular **mimicry. It is the probable cause of a few diseases, the best example being rheumatic heart disease, in which an immune response against streptococci cross-reacts with cardiac antigens.**