Diseases of the Immune System

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The Immune system

- Vital for protection and survival
- Diseases:
  - too little immunity or too much immunologic reactivity

The Normal Immune Response

- Mechanisms of protection against infection

I. Innate (natural/native)
   - Present even before infection
   - recognize microbes and protect individuals against infections
   - First line of defense

II. Adaptive (acquired/specific)
   - Referred to as THE “immune response”
   - Stimulated by microbes
   - Recognize mocrobial and nonmicrobial substances
   - Develops after exposure
   - More powerful

Innate Immunity

- major components:
  - epithelial barriers
  - phagocytic cells (mainly neutrophils and macrophages),
  - dendritic cells,
  - natural killer (NK) cells
  - several plasma proteins (e.g. complement system

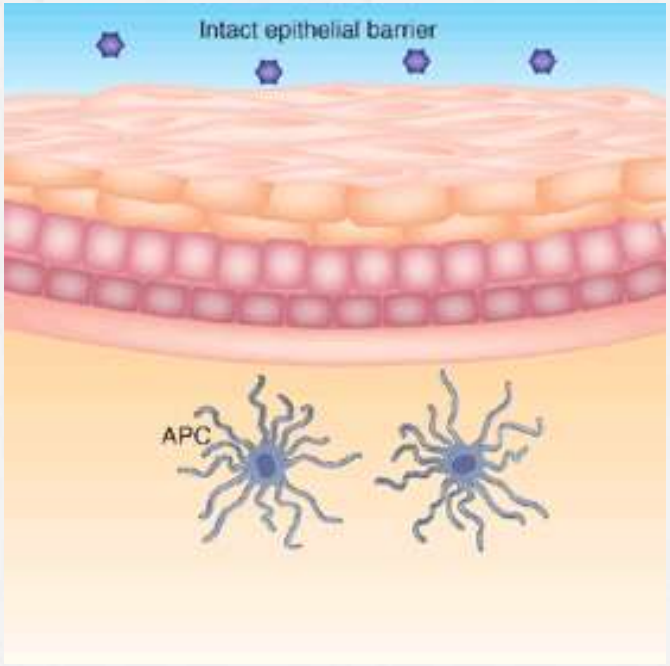
Cellular reactions

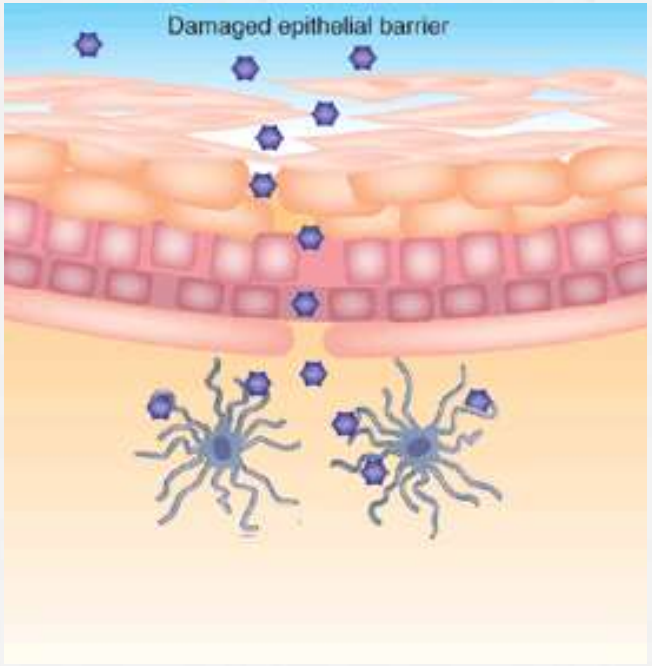
- Inflammation
  - Phagocytic WBCs
- Anti-viral defense
  - Dendritic cells and NK cells

Epithelial barriers

- Epthelia: Skin, GIT & RT
  - mechanical barriers to the entry of microbes from external environment
- Epithelial cells produce anti-microbial molecules: defensins
- lymphocytes in the epithelia combat microbes at these sites. If breached other defense mechanisms are called in

Epithelial barriers





The cells of Innate Immunity

- Monocytes and neutrophils
  - phagocytes in the blood that can rapidly be recruited to any site of infection;
  - monocytes that enter the tissues and mature are called macrophages
- Dendritic cells
  - produce type I interferons, anti-viral cytokines that inhibit viral infection and replication
- Natural killer cells
  - early protection against many viruses and intracellular bacteria

complement system & other proteins

- activated by microbes using the alternative and lectin pathways
- in adaptive immunity it is activated by antibodies using the classical pathway
- Other circulating proteins of innate immunity:
  - mannose-binding lectin & C-reactive protein
  - both coat microbes for phagocytosis.
- Lung surfactant also a component of innate immunity
  - protection against inhaled microbes

Innate Immunity

- The early innate immune response not only provides the initial defense against infections but is also involved in triggering the subsequent, more powerful adaptive immune response

Adaptive Immunity

- Consists of lymphocytes and their products, including antibodies
  - lymphocytes are not inherently specific for microbes
    - capable of recognizing a vast array of foreign substances

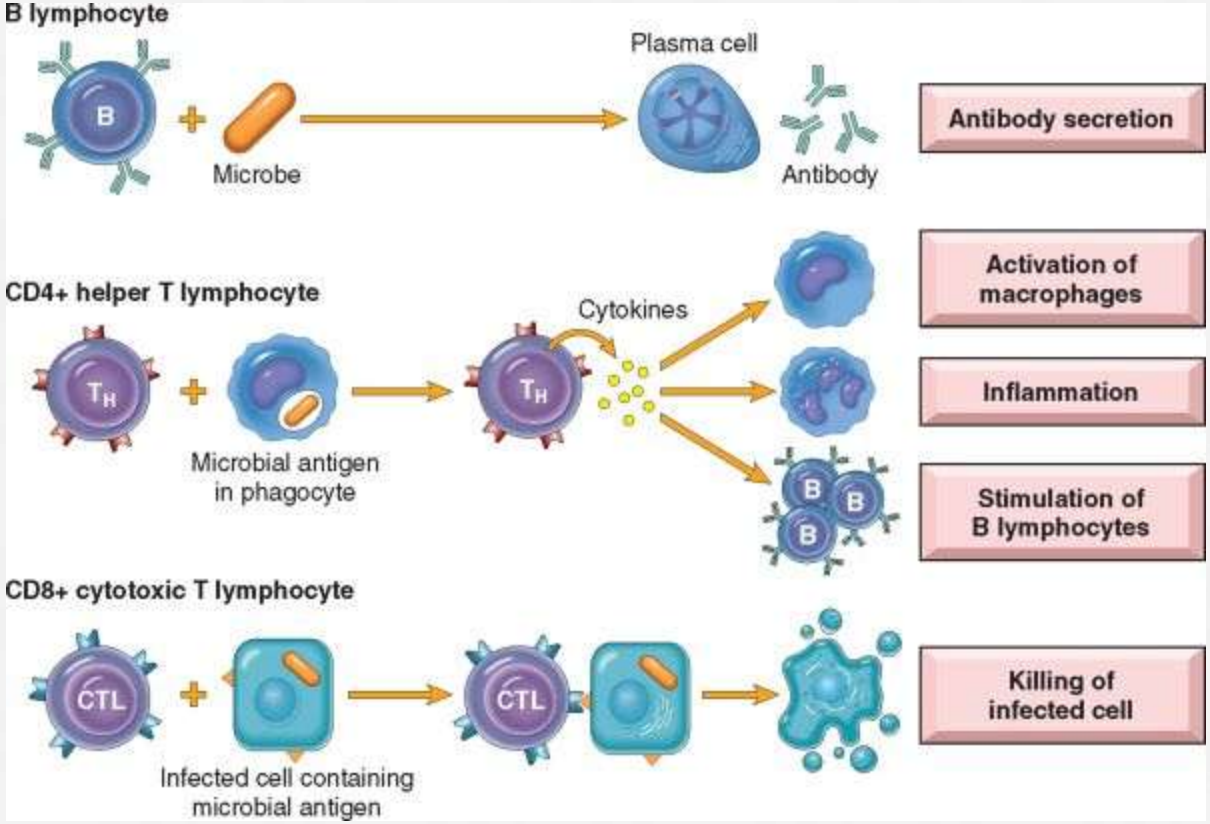
Adaptive Immunity

1. humoral immunity, protects against extracellular microbes and their toxins
    - Humoral immunity, mediated by B-lymphocytes and their secreted antibodies (immunoglobulins)
2. cell-mediated (or cellular) immunity, responsible for defense against intracellular microbes
    - mediated by T-lymphocytes
- Both classes of lymphocytes express highly specific receptors for a wide variety of antigens

COMPONENTS OF THE IMMUNE SYSTEM:

- Cells
- Tissues
- Selected molecules

The lymphocytes



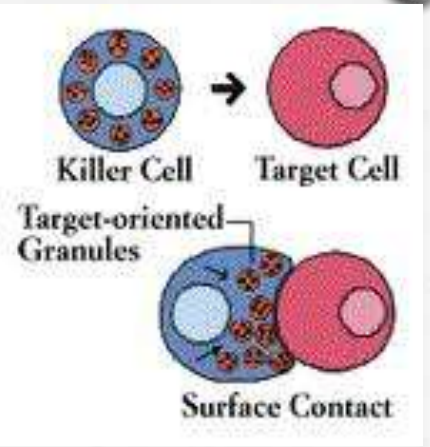
The lymphocytes

- Naive
  - immunologically inexperienced
- Effector cells
  - Activated and differentiated
  - eliminate microbes
- memory cells
  - live in a state of heightened awareness
  - are better able to combat the microbe in case it returns

Macrophages

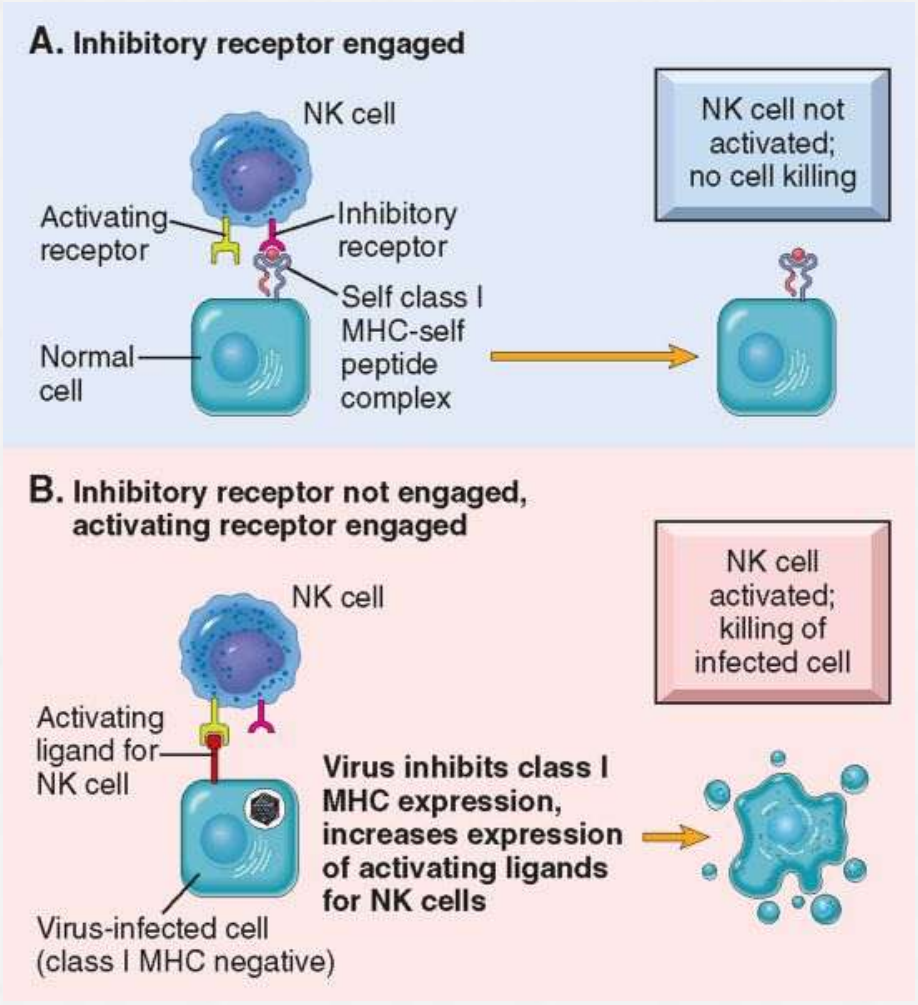
- part of the mononuclear phagocyte system
- functions in the induction and effector phases of adaptive immune responses:
  - function as APCs in T-cell activation.
  - effector cells in certain forms of cell-mediated immunity
    - T cells activate macrophages and enhance their ability to kill ingested microbes
  - efficiently phagocytose and destroy microbes that are opsonized (coated) by IgG or C3b

Natural Killer cells(NK)



- approximately 10% to 15% of peripheral blood lymphocytes
- do not express TCRs or Ig
- larger than small lymphocytes containing abundant azurophilic granules (large granular lymphocytes)
- kill variety of infected and tumor cells, without prior exposure to or activation by these microbes or tumors
- early line of defense against viral infections, some tumors
- surface molecules: CD16 and CD56
- CD16, Fc receptor for IgG: ability to lyse IgG-coated target cells known as antibody-dependent cell-mediated cytotoxicity (ADCC).

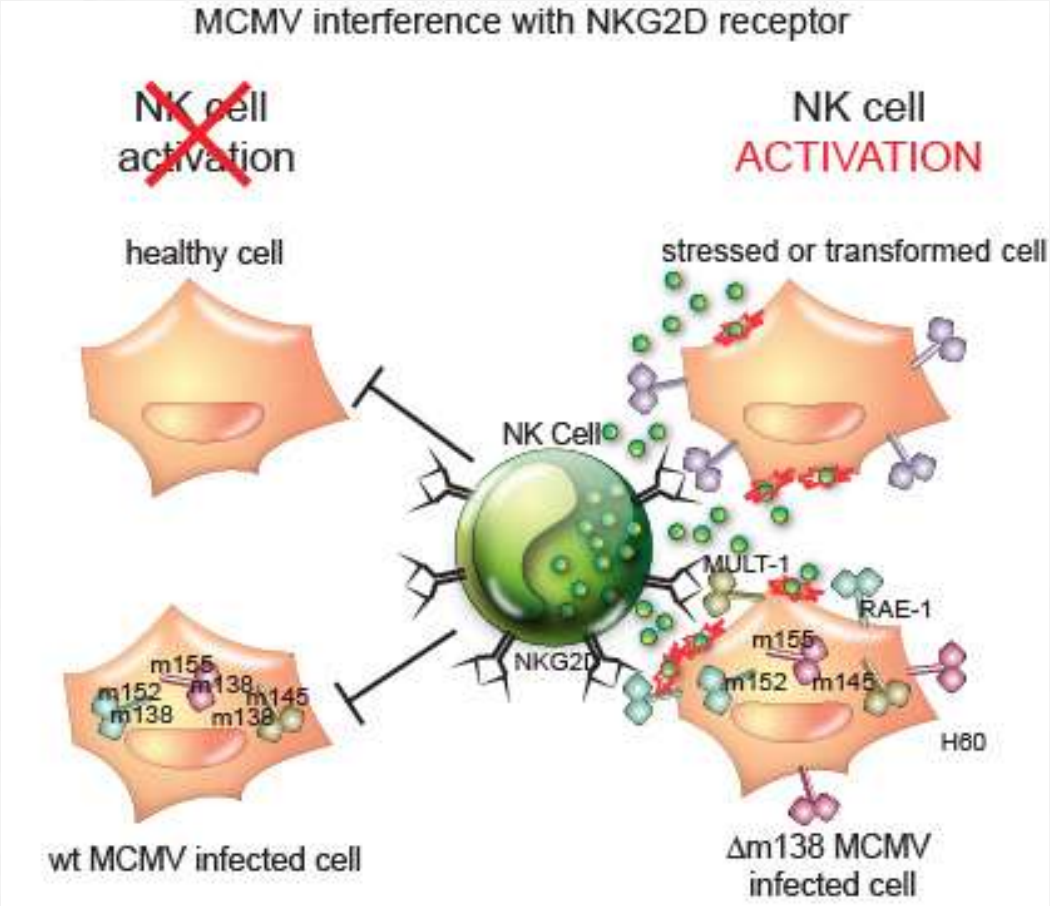
Natural Killer cells(NK)



Natural Killer cells(NK)

- Balance between activating and inhibitory receptors
- Activating: NKG2D family – recognize surface molecules induced by stress: infection&DNA damage
- Inhibitory: recognize self (Class I MHC) expressed on all healthy cells

Natural Killer cells(NK)



Tissue of the Immune System

- generative lymphoid organs (primary, or central) → T and B lymphocytes mature and become competent to respond to antigens
- peripheral (secondary) lymphoid organs
  - Where adaptive immune responses to microbes are initiated

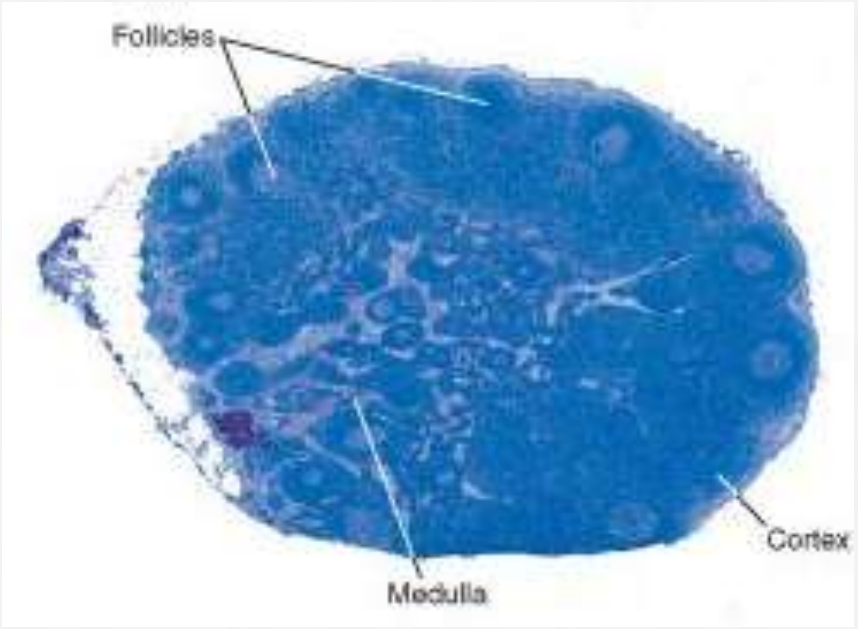
Generative Lymphoid Organs

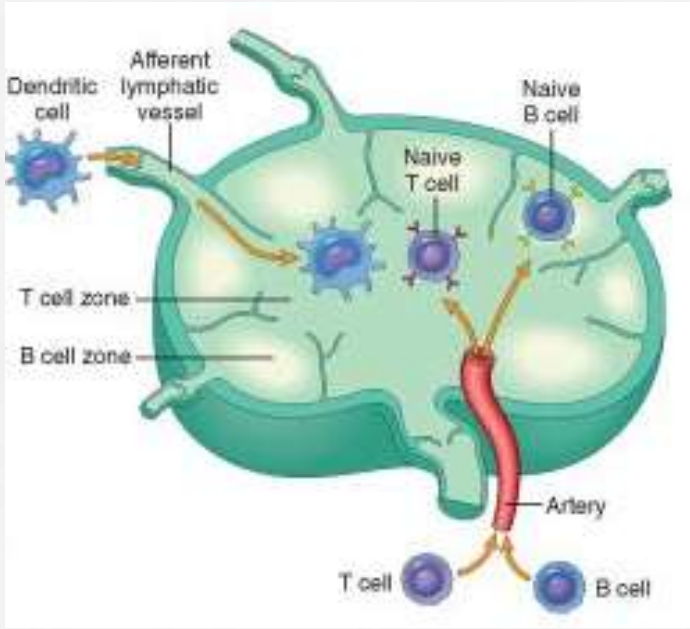
- Thymus - where T cells develop
- bone marrow - site of production of all blood cells and where B lymphocytes mature

Peripheral Lymphoid Organs

- lymph nodes
- Spleen
- mucosal and cutaneous lymphoid tissues
  - organized to concentrate antigens, APCs, and lymphocytes optimizing interactions among these cells and the development of adaptive immune responses

Lymph Nodes


Follicles
Cortex
Medulla


Dendritic cell
Afferent lymphatic vessel
Naive B cell
Naive T cell
T cell zone
B cell zone
Artery
T cell
B cell

Major Histocompatibility Complex (MHC) Molecules: Peptide Display System of Adaptive Immunity

- MHC molecules discovered as products of genes that evoke rejection of transplanted organs
- physiologic function of MHC molecules: to display peptide fragments of proteins for recognition by antigen-specific T cells

Major Histocompatibility Complex (MHC) Molecules: Peptide Display System of Adaptive Immunity

- In humans genes encoding MHC molecules are clustered on a small segment of chromosome 6, the MHC, or the human leukocyte antigen (HLA) complex
  - so named because in humans MHC-encoded proteins were initially detected on leukocytes by the binding of antibodies
- HLA system is highly polymorphic, there are many alleles of each MHC gene in the population
- each individual inherits one set of these alleles that is different from the alleles in most other individuals

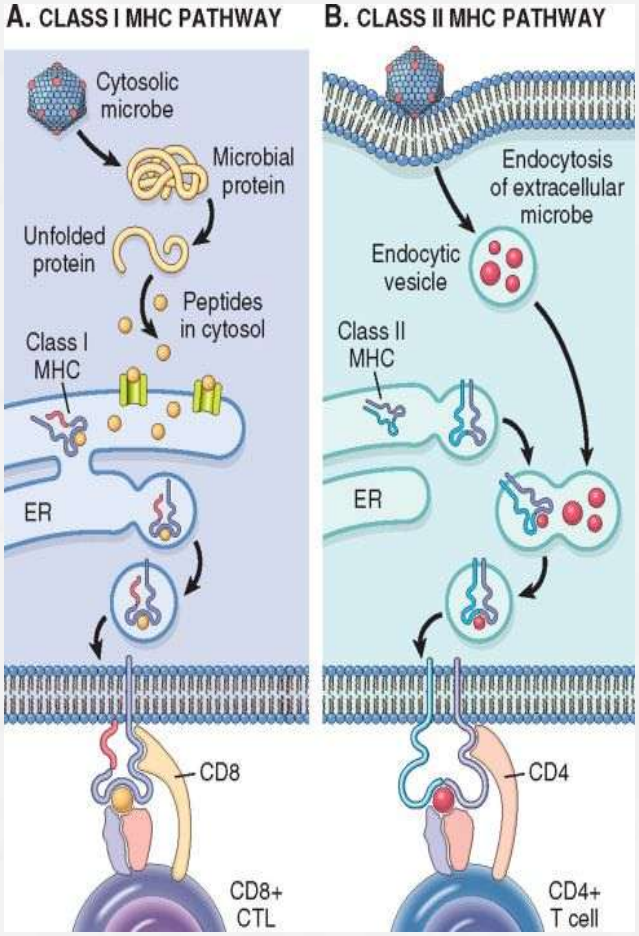
Major Histocompatibility Complex (MHC)

- Classified into three groups:
  - Class I MHC molecules
  - Class II MHC molecules
  - Class III MHC molecules

Class I MHC molecules

- expressed on all nucleated cells and platelets
- encoded by three closely linked loci: HLA-A, HLA-B, and HLA-C
- Each class I MHC molecule, a heterodimer

Major Histocompatibility Complex (MHC)



Class II MHC molecules

- encoded in HLA-D region
- three subregions: HLA-DP, HLA-DQ, and HLA-DR
- Each class II molecule, a heterodimer: noncovalently associated α chain and β chain, both of which are polymorphic

HLA and Disease Association

- Three groups

1. Inflammatory diseases

   - ankylosing spondylitis and several postinfectious arthropathies, all associated with HLA-B27

2. Autoimmune diseases

   - autoimmune endocrinopathies associated mainly with alleles at the DR locus

3. Inherited errors of metabolism

   - 21-hydroxylase deficiency (HLA-BW47)
   - hereditary hemochromatosis (HLA-A)

Association of HLA Alleles and Inflammatory Diseases

Disease	HLA Allele	Relative Risk (%)
Ankylosing spondylitis	*B27*	90–100
Postgonococcal arthritis	*B27*	14
Acute anterior uveitis	*B27*	14
Rheumatoid arthritis	*DR4*	4
Chronic active hepatitis	*DR3*	13
Primary Sjögren syndrome	*DR3*	9
Type 1 diabetes	*DR3*	5
	DR4	6
	DR3/DR4	20

Hypersensitivity

- MECHANISMS OF HYPERSENSITIVITY REACTIONS
  - SENSITIZED -Individuals previously exposed to an antigen
  - HYPERSENSITIVITY - repeat exposures to the same antigen trigger a pathologic reaction
    - implying an excessive response to antigen

Features of Hypersensitivity Reaction

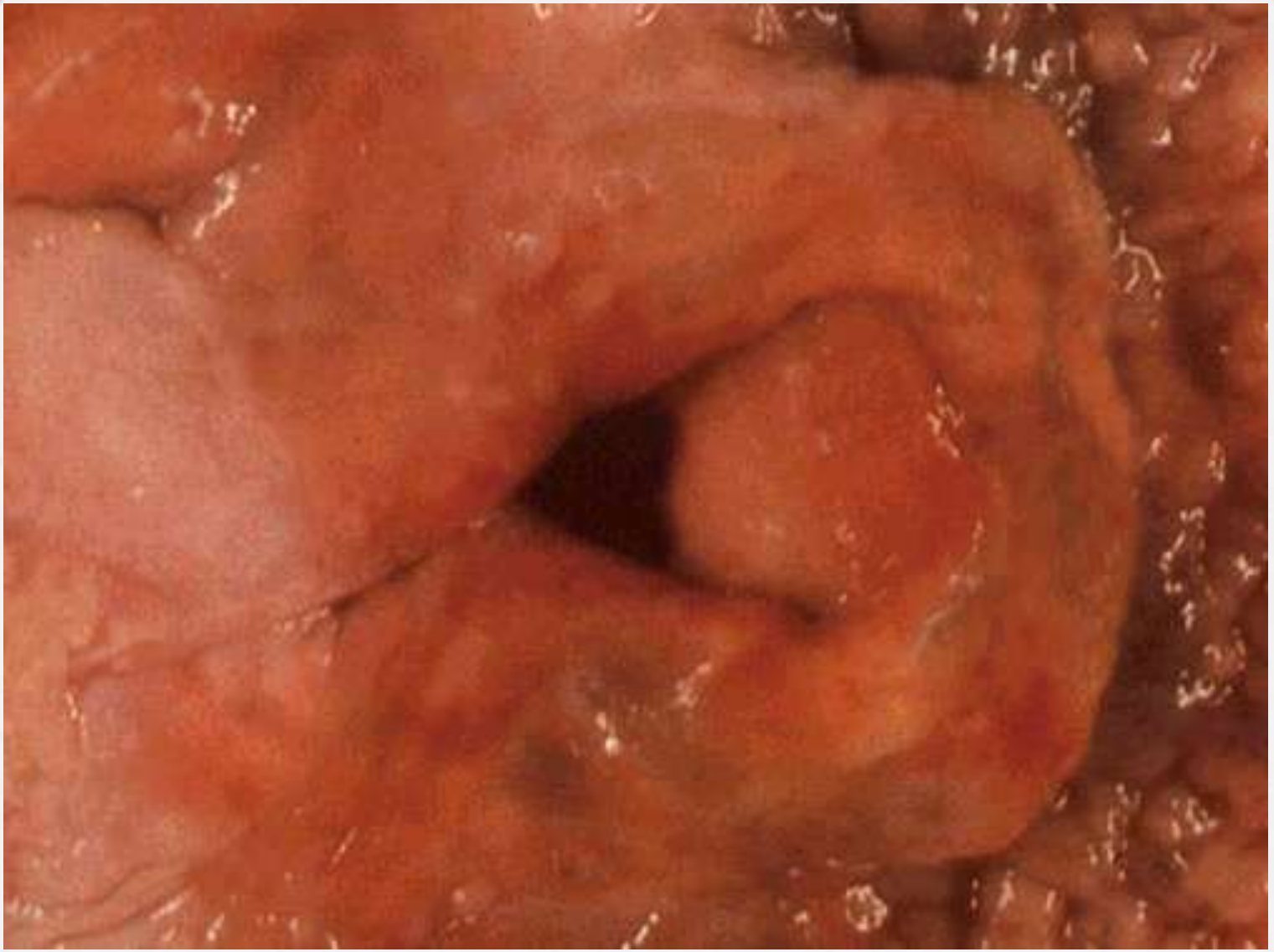
- Both exogenous and endogenous antigens may elicit hypersensitivity reactions
  - Exogenous: dust, pollens, foods, drugs, microbes, chemicals, some blood products
    - response. Vary
      - annoying but trivial discomforts (itching) to potentially fatal diseases, e.g. bronchial asthma & anaphylaxis
  - Endogenous: self, or autologous
    - autoimmune diseases

Features of Hypersensitivity Reaction

- hypersensitivity diseases (allergic and autoimmune disorders)
  - associated with inheritance of particular susceptibility genes: HLA genes & non-HLA genes
- general principle in hypersensitivity: imbalance between effector mechanisms and control mechanisms of immune response

Mechanisms of Immunologically Mediated Diseases

Type	Prototype Disorder	Immune Mechanisms	Pathologic Lesions
Immediate (type I) hypersensitivity	Anaphylaxis; allergies; bronchial asthma (atopic forms)	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; recruitment of inflammatory cells (late-phase reaction)	Vascular dilation, edema, smooth muscle contraction, mucus production, inflammation
Antibody-mediated (type II) hypersensitivity	Autoimmune hemolytic anemia; Goodpasture syndrome	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Cell lysis; inflammation
Immune complex-mediated (type III) hypersensitivity	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Necrotizing vasculitis (fibrinoid necrosis); inflammation
Cell-mediated (type IV) hypersensitivity	Contact dermatitis; multiple sclerosis; type I, diabetes; transplant rejection; tuberculosis	Activated T lymphocytes → i) release of cytokines and macrophage activation; ii) T cell-mediated cytotoxicity	Perivascular cellular infiltrates; edema; cell destruction; granuloma formation



Autoimmune Diseases

Autoimmune Diseases

- immune reactions against self-Antigens

Autoimmune Diseases

3 requirements:

1. presence of immune reaction specific for self-Ag or self-tissue
2. reaction is not secondary to tissue damage
3. absence of another well defined cause of dse.

Autoimmune Diseases

Mechanisms of autoimmunity

-arises from combination of inheritance of susceptibility genes, w/c may contribute to the breakdown of self tolerance, and

-environmental triggers, such as infections & tissue damage, w/c promote the activation of self reactive lymphocytes

Systemic Lupus Erythematosus (SLE)

- prototype of multisystem autoimmune disease
- vast array of autoantibodies, particularly ANAs
- Acute or insidious onset
- chronic, remitting and relapsing
- often febrile illness characterized principally by injury to the skin, joints, kidney, and serosal membranes
  - Every other organ may also be affected

Revised Criteria for Classification of SLE

1997 Revised Criteria for Classification of Systemic Lupus Erythematosus	
Criterion	**Definition**
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or
	Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion

A person is said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

Revised Criteria for Classification of SLE

1997 Revised Criteria for Classification of Systemic Lupus Erythematosus	
Criterion	**Definition**
7. Renal disorder	Persistent proteinuria >0.5 gm/dL or >3 if quantitation not performed or
	Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), or
	Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia—with reticulocytosis, or
	Leukopenia—<4.0 × 10^9 cells/L (4000 cells/mm^3) total on two or more occasions, or
	Lymphopenia—<1.5 × 10^9 cells/L (1500 cells/mm^3) on two or more occasions, or
	Thrombocytopenia—<100 × 10^9 cells/L (100 × 10^3 cells/mm^3) in the absence of offending drugs
10. Immunological disorder	Anti-DNA antibody to native DNA in abnormal titer, or
	Anti-Sm—presence of antibody to Sm nuclear antigen, or
	Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

A person is said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

Systemic Lupus Erythematosus (SLE)

- prevalence: up to 1 in 2500
- predominantly affects women
- 1 in 700, women of childbearing age
  - Female:male (9 : 1)
  - Female:male, (2 : 1) disease developing during childhood or after the age 65
- 2–3 fold higher prevalence in blacks and Hispanics than in whites
- usually arises in the 20s and 30s, may manifest at any age, even in early childhood.

Spectrum of Autoantibodies in SLE

- Antinuclear antibodies (ANAs) are directed against nuclear antigens

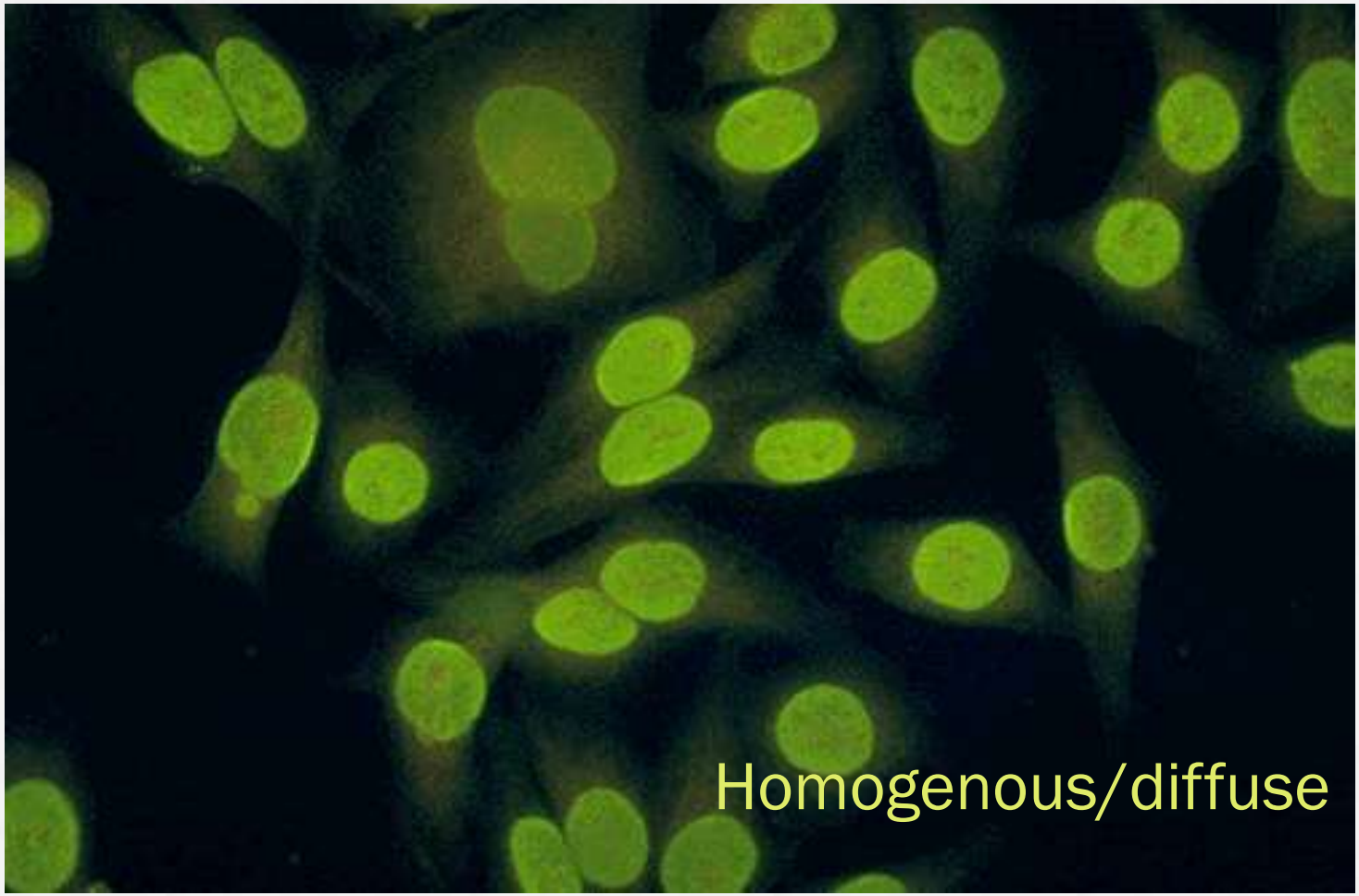
1. antibodies to DNA
2. antibodies to histones
3. antibodies to nonhistone proteins bound to RNA
4. antibodies to nucleolar antigens

- method for detecting ANAs: indirect immunofluorescence

Pattern of nuclear fluorescence

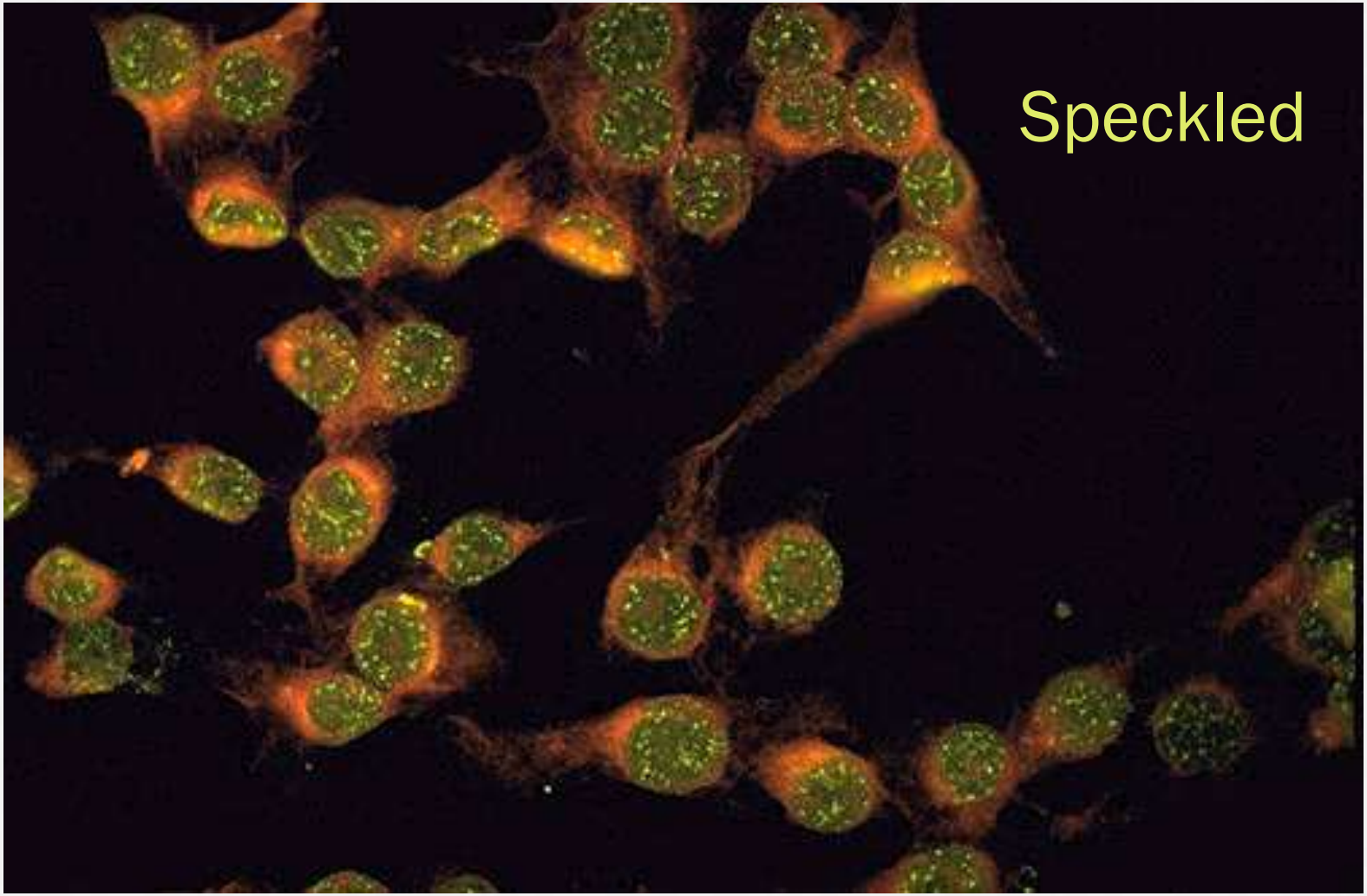
- Homogeneous or diffuse nuclear staining
  - usually antibodies to chromatin, histones, occasionally double-stranded DNA.
- Rim or peripheral staining patterns
  - most often indicative of antibodies to double-stranded DNA.
- Speckled pattern
  - presence of uniform or variable-sized speckles
  - Less specific
  - presence of antibodies to non-DNA nuclear constituents
    - Sm antigen, ribonucleoprotein, SS-A and SS-B reactive
- Nucleolar pattern
  - presence of a few discrete spots of fluorescence within the nucleus
  - represents antibodies to RNA
    - systemic sclerosis.

Antibodies to chromatin, histones, & double stranded DNA

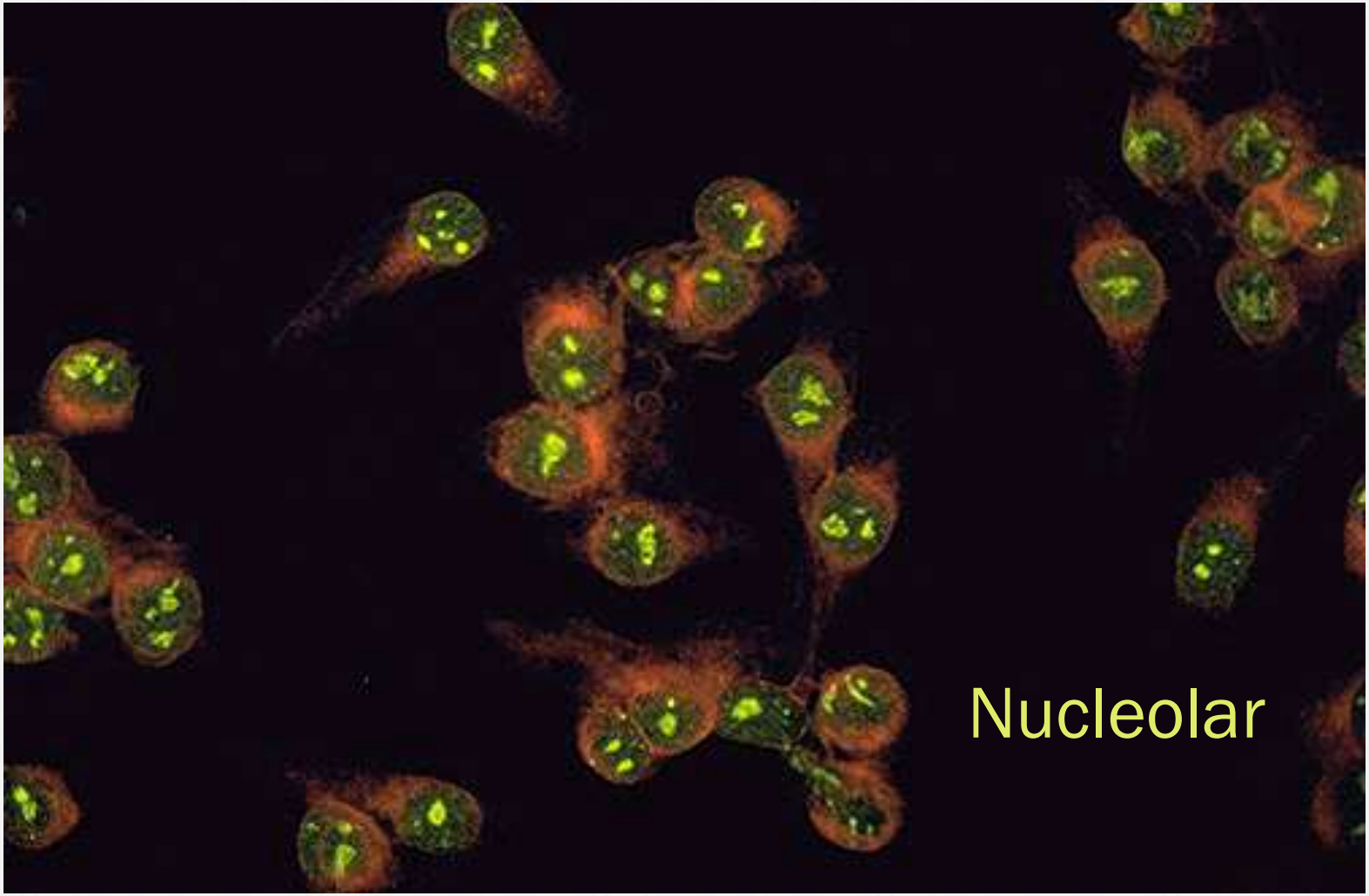


Anti double stranded DNA

Most common, anti Sm, anti ribonulceoprotein, anti SSA, anti-SSB



Anti RNA



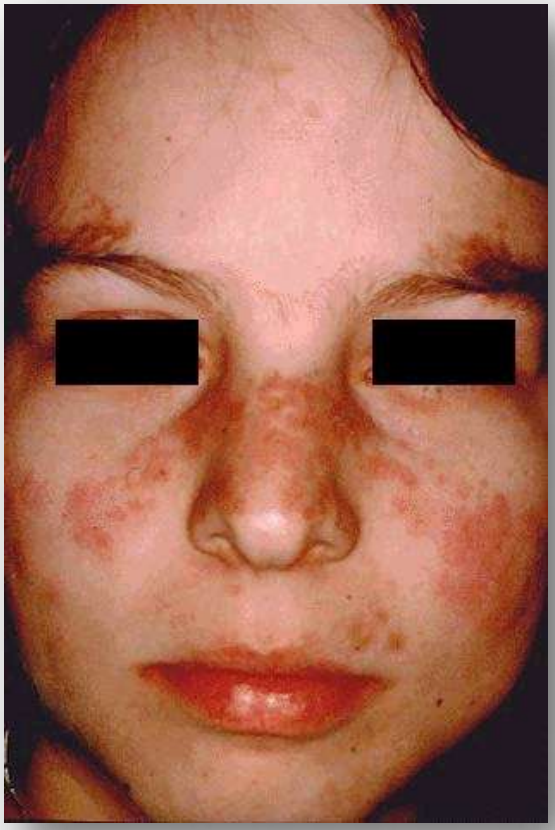
Spectrum of Autoantibodies in SLE

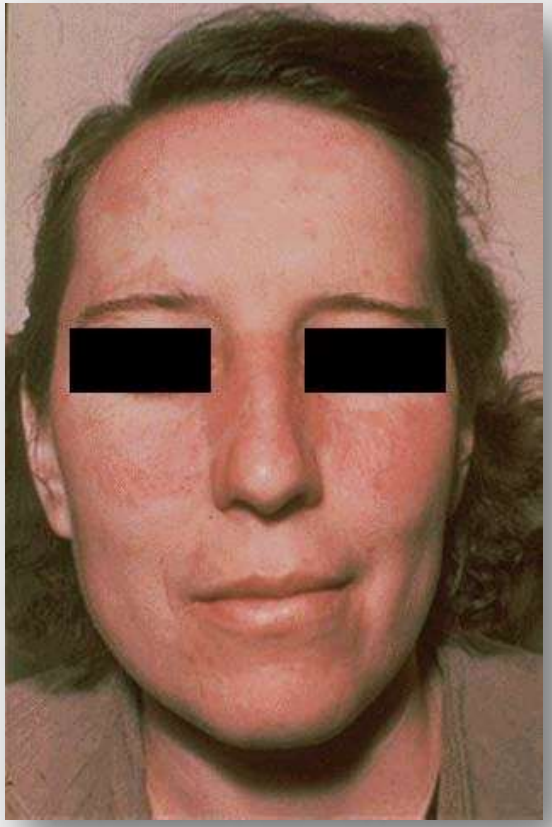
- fluorescence patterns are not absolutely specific for the type of antibody
- *immunofluorescence test for ANAs is sensitive because it is positive in virtually every patient with SLE, but it is not specific because patients with other autoimmune diseases also frequently score positive*
- approximately 5% to 15% of normal individuals have low titers of these antibodies
- *Antibodies to double -stranded DNA and the Smith (Sm) antigen virtually diagnostic of SLE*

SLE

- *Morphology:*
  - Skin – erythema

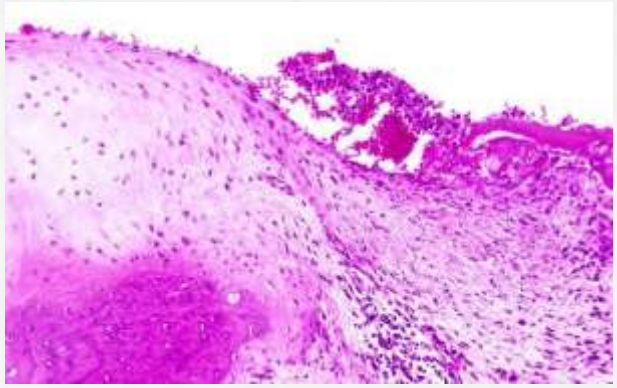
    (malar rash/ butterfly lesion)

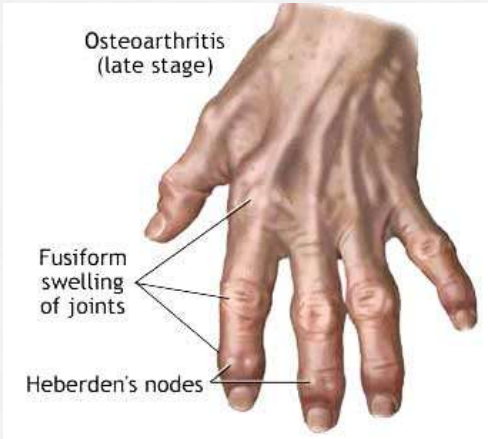




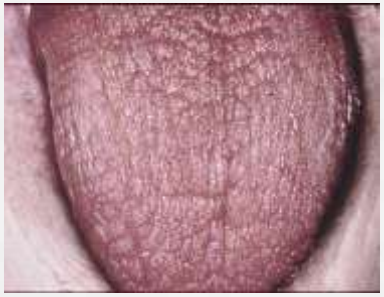
RHEUMATOID ARTHRITIS

- chronic inflammatory disease
  - affects primarily the joints
  - may involve extra-articular tissues: skin, blood vessels, lungs, & heart
- Abundant evidence supports the autoimmune nature of the disease





Sjogren Syndrome



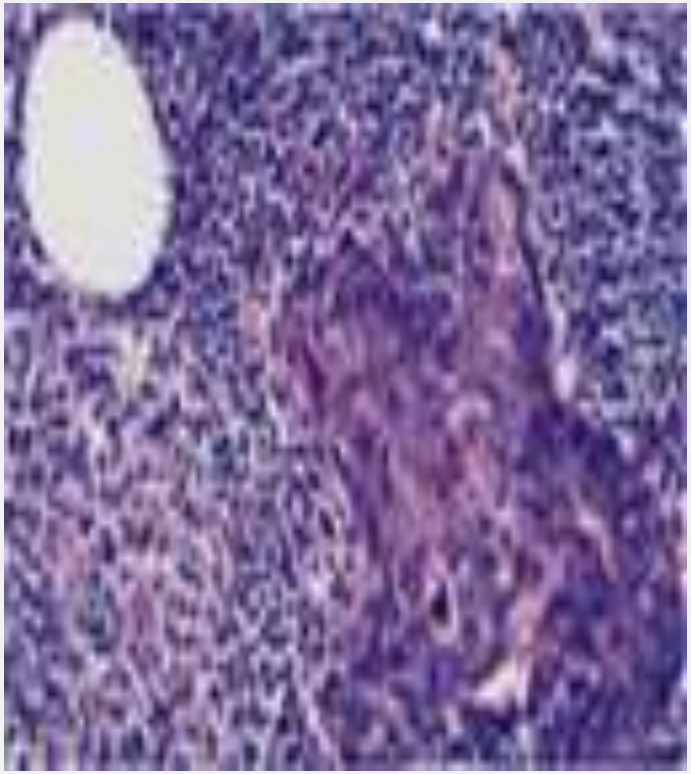
- Chronic disease characterized by Keratoconjunctivitis sicca and Xerostomia
- Immunologic destruction of lacrimal and salivary glands
- Primary form; secondary form (more common)
- Infiltration of CD4+ helper T cells, some B cells
- 75% are (+) RA factor
- 50-80% (+) ANA
- 90% (+) SS-A (Ro); SS-B (La)

Sjogren Syndrome

- Association with HLA – DQA1, DQB1, B8, DR3, DRW52
- Viruses: EBV, HCV, HTLV 1
- Morphology
  - Salivary and Lacrimal – periductal and perivascular lymphocytic infiltratrion
  - Lining of RT, GIT, Vagina
  - Extraglandular tissue involvement in 25%
  - Kidneys – tubulointerstitial nephritis

Sjogren Syndrome

- Salivary gland

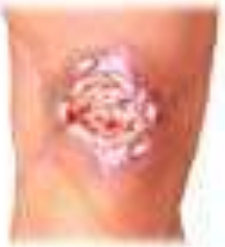


Systemic Sclerosis

- Chronic disease, unknown etiology
- Fibrous tissue accumulation in skin and multiple organs
- 2 categories
  - Diffuse scleroderma
  - Limited scleroderma
    - CREST SYNDROME
    - Calcinosis, Raynauds phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia

The limited symptoms of scleroderma are referred to as CREST

Calcinosis- calcium deposits in the skin



Raynaud's phenomenon- spasm of blood vessels in response to cold or stress

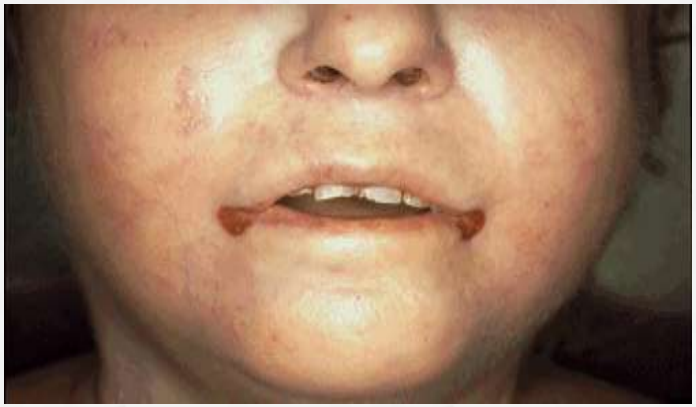
Esophageal dysfunction- acid reflux and decrease in motility of esophagus

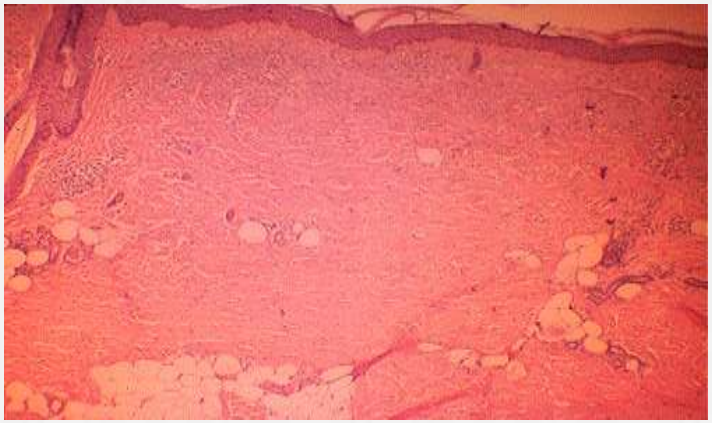
Sclerodactyly- thickening and tightening of the skin on the fingers and hands

Telangiectasias- dilation of capillaries causing red marks on surface of skin

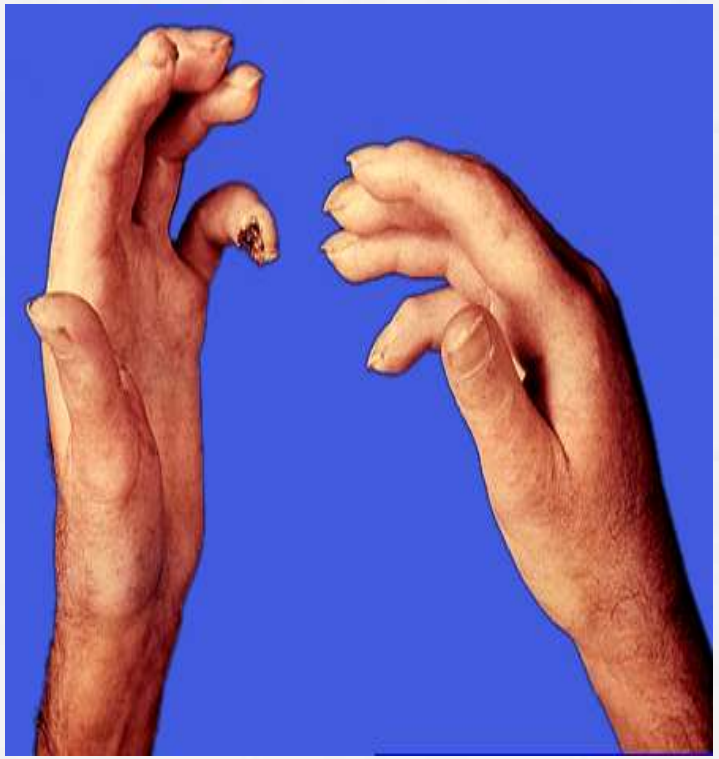
Scleroderma

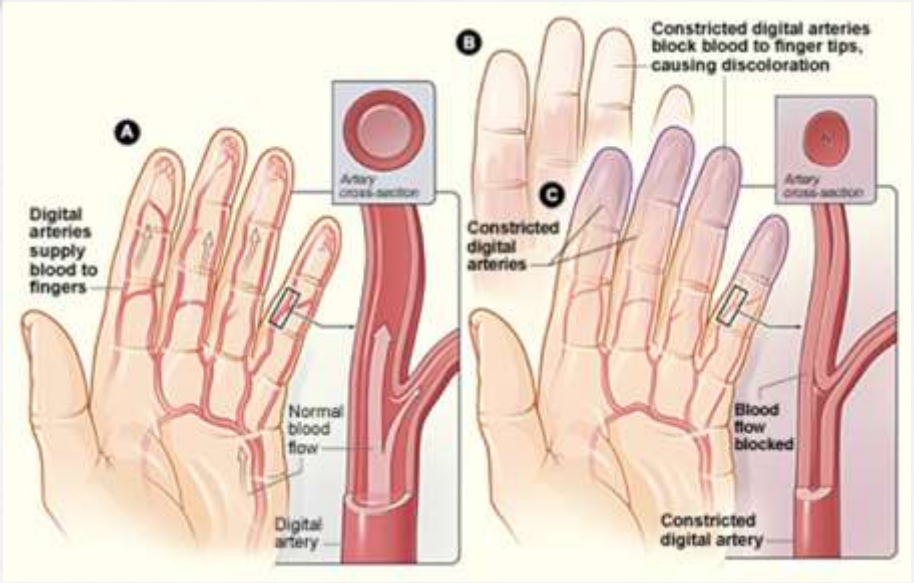
- Skin

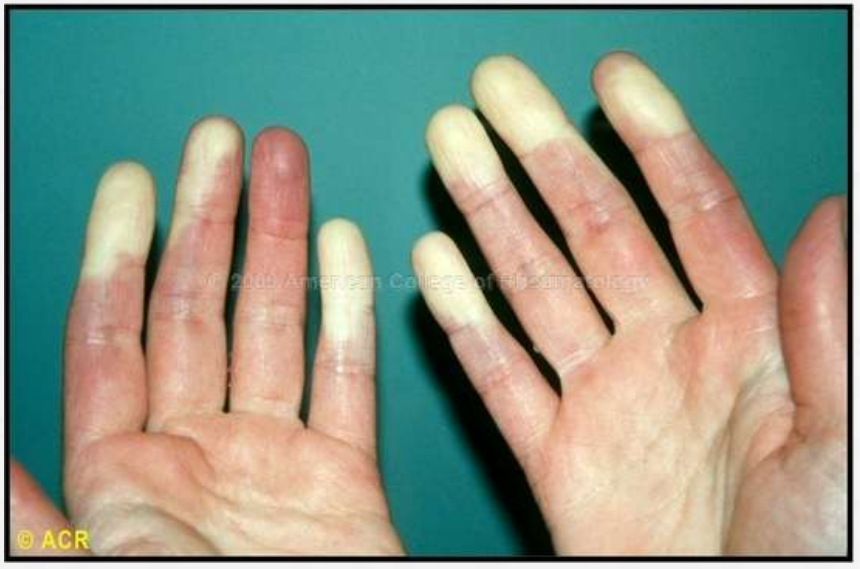




- Hands




A
Digital arteries supply blood to fingers
Artery cross-section
Normal blood flow
Digital artery
B
Constricted digital arteries block blood to finger tips, causing discoloration
C
Constricted digital arteries
Artery cross-section
Blood flow blocked
Constricted digital artery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Others

1. Inflammatory Myopathies
2. Mixed Connective Tissue Disease
   a. High titers of anti U1 RNP
   b. Low incidence of renal disease
   c. Good response to corticosteroids
3. PAN and other vasculitides
   - Noninfectious necrotizing vasculitis

END