Academic lectures for general medicine students – 3rd Year
2004-2015

GENERAL PATHOPHYSIOLOGY

IMMUNOLOGY
CLINICAL PATHOLOGY 2

R. A. Benacka, MD, PhD
Department of Pathophysiology
Faculty of Medicine, UPJS

Immunological disorders - immunopathology

Classical subdivision:

1. Hypersensitive reactions (allergy) (hypersensitivity)
2. Autoimmune disorders
3. Immunodeficiencies

„Immunological disorders“ is a chapter not any different from „Inflammation“. It is not another world, other mechanisms involved. It is about ***inflammation which got out of the control and became useless.***

Hypersensitivity and autoimmunity are exaggerated and prolonged inflmmations to normal/ expected stimuli or abnormal inflammations to minimal/ non-existing or virtual enemies. In either way body is harmed.

Rational subdivision:

Hyperergic immune status (excessive or autoagressive reactions; inflammation)

→ Hypersensitivity = external foreign antigens

→ Autoimmunity = internal self antigens

Both may share similar mechanisms Coombs & Cell immunopathology

Hypoergic immune status (insufficient reactions), insuficient inflammation

→ Immunodeficiencies

Clinical immunology **2**

Hypersensitivities

Coombs and Gell immunopathological reactions

Type	Alternative names	Antigen	Disorders		Mediators
I	Immediate; Allergy Anaphylactic,	External	Anaphylaxis, Asthma. Atopic eczema Food allergy, Peanut, Tree nut, Seafood, Soy, Whea, Penicillin allergy		Secretory IgE /IgG4
		Autoantigen	None		
II	Cytotoxic, Antibody-dependent, ADCC	External	Erythroblastosis fetalis (Rh), Blood incompatibility, Thrombocytopenia		Membrane bound IgM / IgG (Complement activation)
		Autoantigen	Cytotoxic	Autoimmune hemolytic anemia, Pemphigus vulgaris Goodpasture's syndrome, Membranous nephropathy, Bullous pemphigoid, Idiopathic thrombocytopenic purpura Rheumatic fever, Vasculitis caused by ANCA	
			Receptoric subtype V	Graves' disease, Myasthenia Gravis. Pernicious anemia	
III	Immune complex disease	External	Henoch–Schönlein purpura, Hypersensitivity vasculitis, Arthus reaction Reactive arthritis, Farmer's lung, Post-streptococcal glomerulonephritis, Serum sickness, Extrinsic allergic alveolitis (Hypersensitivity pneumonitis)		Secretory IgG – complex (Complement)
		Autoantigen	Lupus Nephritis, Subacute bacterial endocarditis Systemic lupus erythematosus (SLE) Rheumatoid arthritis		
IV	Delayed-type hypersensitivity cell-mediated	External	Allergic contact dermatitis, Mantoux test		T-cells
		Autoantigen	Diabetes mellitus type 1, Hashimoto's thyroiditis Guillain–Barré syndrome, Multiple sclerosis		
		GVHR	Coeliac disease, Giant-cell arteritis, Chronic transplant rejection		
VII	Undefined	External	Hypersensitivity pneumonitis, Transplant rejection, Allergic bronchopulmonary aspergillosis, Latex allergy (I+IV)		T- cells, IgG, IgM
		Autoantigen	Sjögren's syndrome, Autoimmune hepatitis Autoimmune polyendocrine syndrome, APS1APS2 Autoimmune adrenalitis, Systemic autoimmune diseas		

Modern views on hypersensitivity

- **Hypersensitivity** is basically **aberrant and/or excessive acute or chronic inflammatory reaction** to **foreign antigens**, including pathogenic and non pathogenic prokaryotes, eukaryotes, remnants of the cells, spores, proteins, i.e. compounds which are able to evoke immune reponse. **These reactions are useless, unimportant event. no more wanted and therefore harmfull.**
- Hypersensitive inflammations **always and principally include specific adaptive immunity suite (T & B-lymphocytes)**, although.
- Damage is mediated by **the same attack mechanisms that mediate normal immune responses** to pathogen; **not different from inflammation**; **reactions may be damaging, uncomfortable, or occasionally fatal**
- Generally at least **one prior contact with the offending agent**; antigen is a protein or is capable of complexing with protein (hapten)
- Reactions occur only in sensitized individuals; **pre-sensitized (immune) state of the host**; when ad how sensitization happens is unknown; limited number of people
- **Sensitization** = maintaining preparatory state of immune aggressivity; can be long lived in the absence of re-exposure (>10 years) due to immunologic memory
- **Tolerance** = opposite to sensitization; attenuation of immune reactivity to unimportant things

Hypersensitivity disorders according to the location

HYPERSENSITIVITIES

Organ-specific (focal)

1. Respiratory airways

- Allergic rhinitis (type I)
- Asthma extrinsic (type I, III, IV)
- Hypersensitivity pneumonia

2. Ocular

- Allergic conjuctivitis(type I)
- Atopic keratoconjuctivitis (type I)
- Venereal keratoconjuctivitis (type I)
- Giant cell papillary conjuctivitis
- Contact allergy

3. Skin

- Urticaria (type I)
- Angioedema (type III)
  - hereditary,
  - acquired
- Eczema
- Atopic dermatitis
- Allergic contact dermatitis
- Erythema multiforme
- Stevens –Johnson syndrome

Generalized

- Anaphylactic reaction
- Anaphylactic shock
- Serum sickness
- Generalized drug reactions
- Insect venom allergy
- Systemic food allergy
- Mastocytosis

Hypersensitivity type I (immediate, anaphylactic)

Type	Alternative names	Antigen	Disorders		Mediators
I	Immediate; Allergy Anaphylactic,	External	Anaphylaxis, Asthma. Atopic eczema, Urticaria, Hives, (food allergy (e.g. peanuts, seafood,soy, whea), drugs)		Secretory IgE /IgG4
		Autoantigen	None		
II	Cytotoxic, Antibody-dependent, ADCC	External	Erythroblastosis fetalis (Rh), Blood incompatibility, Thrombocytopenia		Membrane bound IgM / IgG (Complement activation)
		Autoantigen	Cytotoxic	Autoimmune hemolytic anemia, Pemphigus vulgaris Goodpasture's syndrome, Membranous nephropathy, Bullous pemphigoid, Idiopathic thrombocytopenic purpura Rheumatic fever, Vasculitis caused by ANCA	
			Receptoric subtype V	Graves' disease, Myasthenia Gravis. Pernicious anemia	
III	Immune complex disease	External	Henoch–Schönlein purpura, Hypersensitivity vasculitis Arthus reaction Reactive arthritis, Farmer's lung, Post-streptococcal glomerulonephritis, Serum sickness, Extrinsic allergic alveolitis (Hypersensitivity pneumonitis)		Secretory IgG – complex (Complement)
		Autoantigen	Lupus Nephritis, Subacute bacterial endocarditis Systemic lupus erythematosus (SLE) Rheumatoid arthritis		
IV	Delayed-type hypersensitivity cell-mediated	External	Allergic contact dermatitis, Mantoux test		T-cells
		Autoantigen	Diabetes mellitus type 1, Hashimoto's thyroiditis Guillain–Barré syndrome, Multiple sclerosis		
		GVHR	Coeliac disease, Giant-cell arteritis, Chronic transplant rejection		
VII	Undefined	External	Hypersensitivity pneumonitis, Transplant rejection, Allergic bronchopulmonary aspergillosis, Latex allergy (I+IV)		T- cells, IgG, IgM
		Autoantigen	Sjögren's syndrome, Autoimmune hepatitis Autoimmune polyendocrine syndrome, APS1APS2 Autoimmune adrenalitis, Systemic autoimmune diseas		

Type I hypersensitivity = real hypersensitivity

- **Sensitization**
  - Antigen contact, typically low-dose via mucous membranes (respiratory, GI) ⌫ IgE production
  - These antigens are not harmful
- **Elicitation (Re-exposure)**
  - Pre-formed IgE (allergen-specific) triggers mast cell activation ⌫ mediator release
- **Reactions**
  - Can occur within seconds-minutes of exposure
  - Severity ranges from irritating to fatal

System cannot answer this simple question

Dangerous **Innoculous**

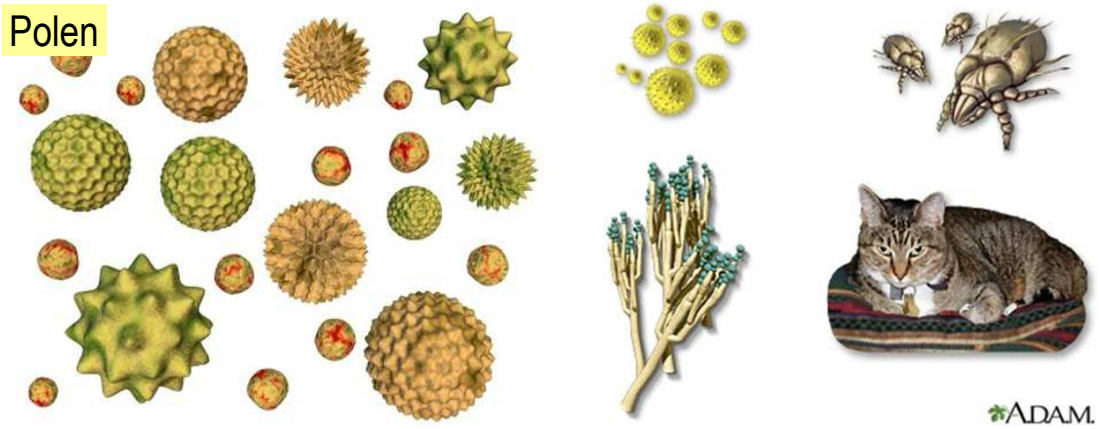
Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immediate (type I) hypersensitivity	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation	Anaphylaxis; allergies; bronchial asthma (atopic forms)
Antibody-mediated (type II) hypersensitivity	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	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury	Autoimmune hemolytic anemia; Goodpasture syndrome
Immune complex–mediated (type III) hypersensitivity	Deposition of antigen–antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction
Cell-mediated (type IV) hypersensitivity	Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction	Contact dermatitis; multiple sclerosis; type I diabetes; tuberculosis

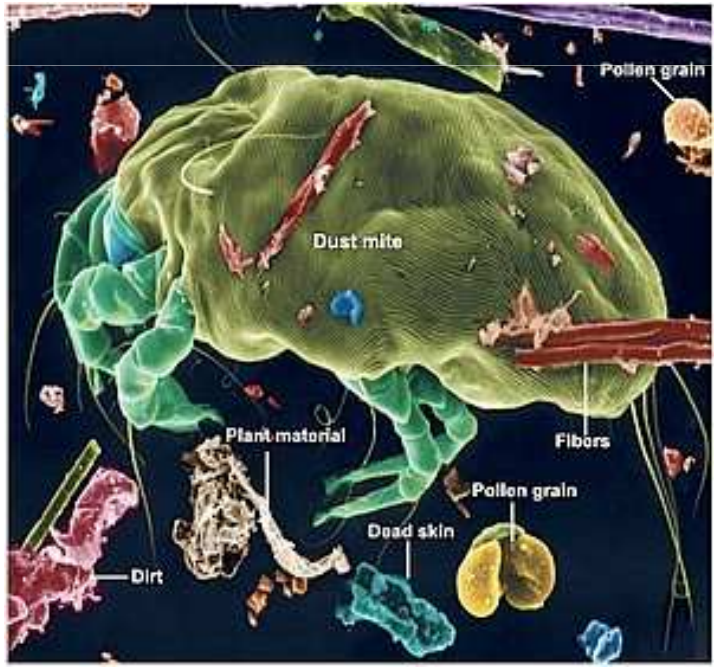
IgE, IgG, IgM, immunoglobulins E, G, M.

Allergens

Food – nuts, soy,shellfish, mustard, fish eggs, sulfits, fish,

Polen





Type I. Allergy (anaphylatoxic)

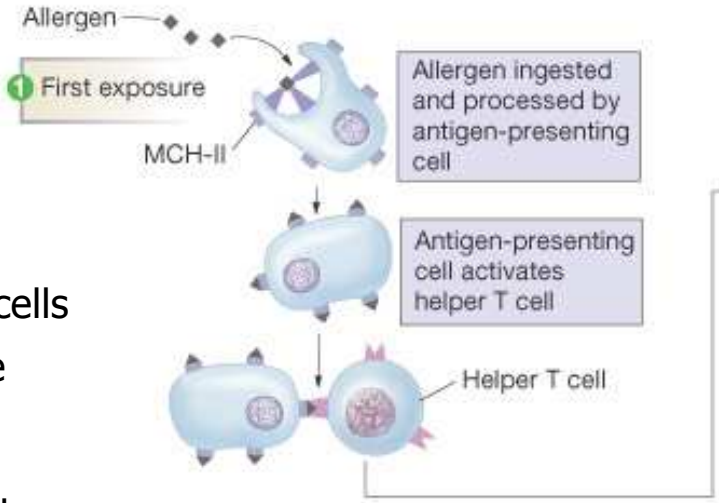
1. In **predisposed individuals,** initial exposure(s) of professional antigen-presenting cells (APCs) to allergen leads mainly **to the activation of allergen-specific T helper 2 (TH2) cells** and IgE synthesis, which is known **as allergic sensitization.**
2. Subsequent exposures to allergen cause inflammatory-cell recruitment and activation and mediator release. In the **early allergic response,** within minutes of contact with allergen**, IgE-sensitized mast cells degranulate:** pre-formed and newly synthesized mediators. histamine, cysteinyl leukotrienes and cytokines, which promote vascular permeability, smooth-muscle contraction and mucus production.

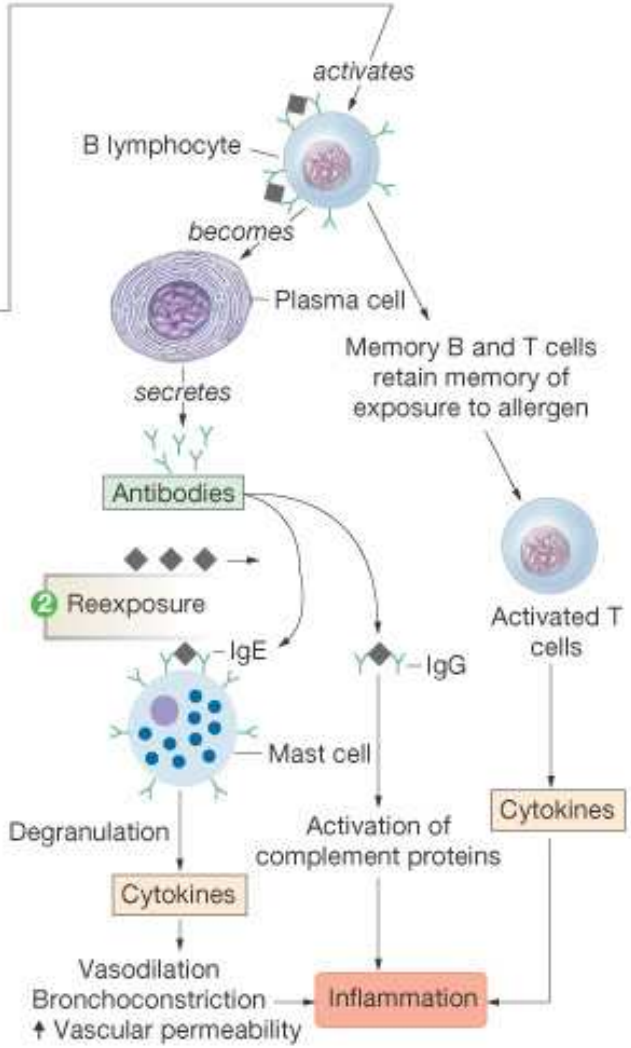
2. Chemokines from mast cells and other cell types recruitment of inflammatory cells that contribute to the **late allergic response**, which is characterized by an influx of **eosinophils and TH2 cells.**
Eosinophils release a large number of pro-inflammatory mediators, including cysteinyl leukotrienes and basic proteins (cationic proteins, eosinophil peroxidase, major basic protein and eosinophil-derived neurotoxin), and they might be an important source of pro-inflammatory cytokines such as interleukin-3 (IL-3), IL-5 and IL-13.

TH1-cell responses- responsible for some of the pathogenic features in patients suffering from chronic forms of atopy, including epithelial apoptosis and smooth-muscle-cell activation.
Regulatory T (TReg) subset of CD4+ T cells suppression of TH2-cell responses in humans involving the inhibitory cytokines IL-10 and transforming growth factor-beta (TGFbeta).
TH17 cells CD4+ T-cell subset - secretion of IL-17A and IL-17F, specifically associated with the neutrophilic inflammatory events that occur during disease exacerbation and in tissue remodelling.

Type I. allergy (anaphylatoxic)

- **First exposure: sensitization**
  - APC to T-helper presentation
  - T-helper activates B cells
  - B-cell clones produce antibodies (IgE,IgG) distributed in blood
  - Memory B- and T cells are formed as normally





- **Re- exposure:**
  - **in normal individuals adequate response to pathogens or little response to non-pathogens**
  - **in disease state exagerrated response to particular antigens**

Many antibodies

Activated T-lymphocytes

- Inflammation

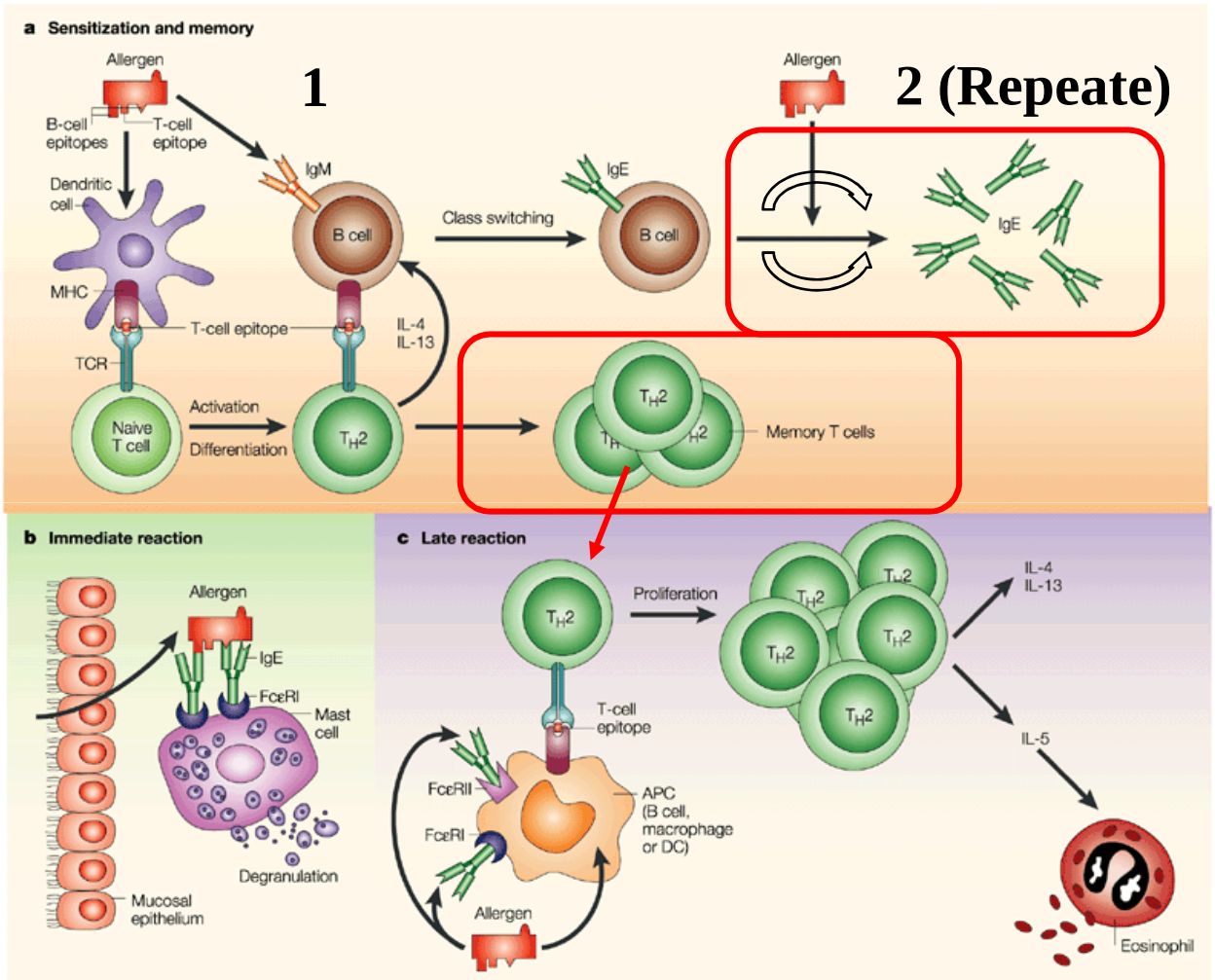
Mechanism of sensitisation, immediate and late response

- **Sensitisation.** soluble allergen at mucosal surface (respiratory tract) is uptaken by antigen-presenting cells (dendritic cells) and/or immunoglobulin-mediated capture by specific B cells to activate T helper 2 (Th2)

Th2 cell produce IL-4 and IL-13 that favour immunoglobulin-class switching of specific B cells to IgE and creation of IgE+ memory B cells and allergen-specific memory T cells. (**this is sensitization**).

Repeated allergen contact will boost IgE+ memory B cells to produce increased levels of allergen-specific IgE antibodies. These are loaded by means of specific receptors (FcaltεRI, high-affinity IgE receptor; FcaltεRII, low-affinity IgE receptor) onto mast cells, basophils, monocytes, dendritic cells and B cells.

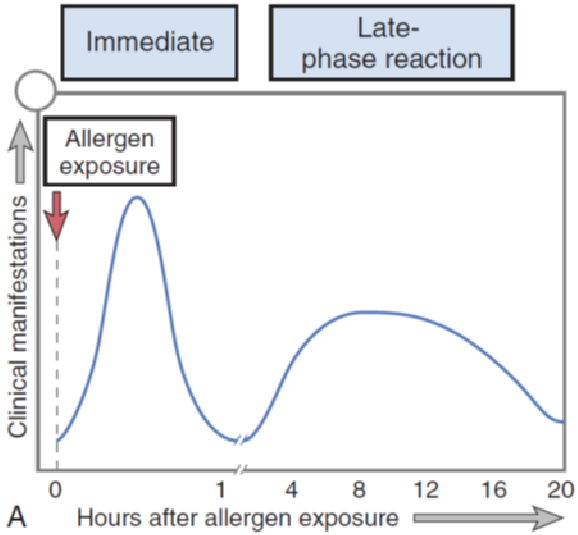
- **Immediate reaction.** The crosslinking of effector-cell-bound IgE by allergens leads to degranulation of mediators (e.g. histamine, leukotrienes) responsible for immediate symptoms of allergy. .

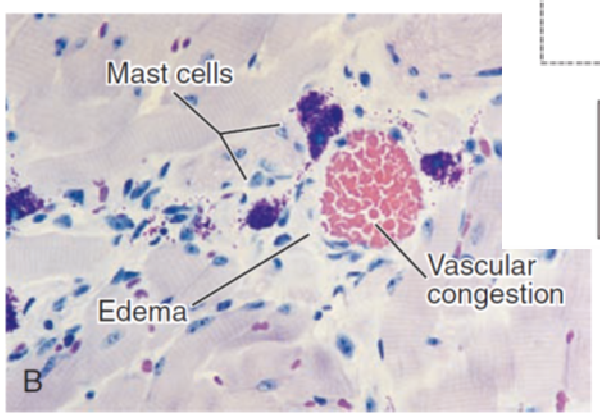


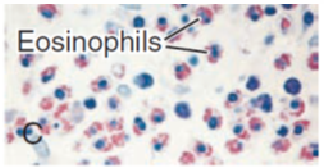
- **Late reaction.** Presentation of allergens to allergen-specific memory T cells, release proinflammatory cytokines (for example, IL-4, IL-5 and IL-13). This process might be enhanced by the IgE-mediated presentation of allergens to T cells. Th2 cytokines (for example, IL-5) induce tissue eosinophilia and the release of inflammatory mediators from **eosinophils.**

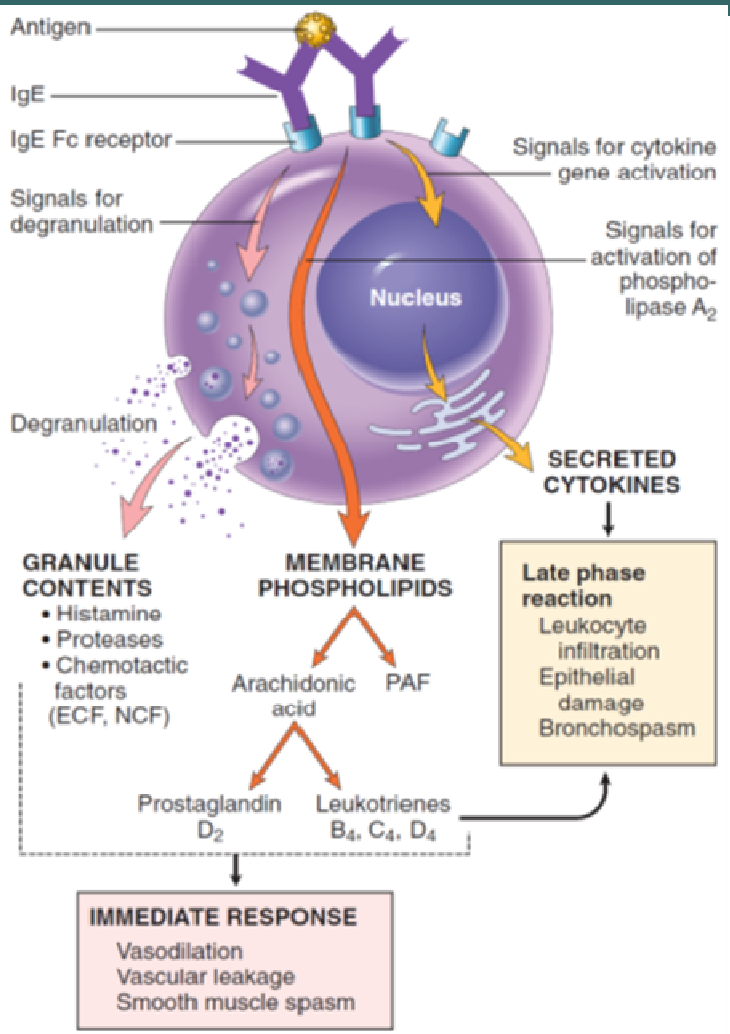
Immediate-phase and late-phase type I. response

Vasodilation and increased permeability	Histamine PAF Leukotriene C4, D4 and E4 Prostaglandin D2 Neutral proteases
Smooth muscle spasm	Histamine PAF Leukotriene C4, D4 and E4 Prostaglandin
Leukocyte extravasation	Leukocyte extravasation

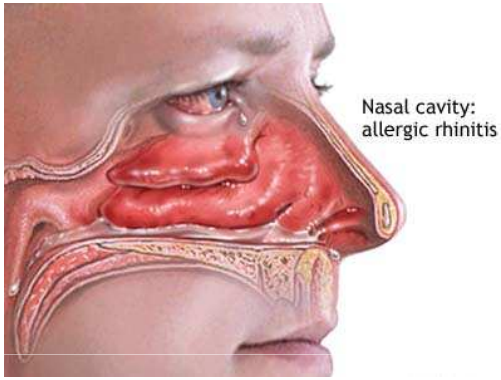






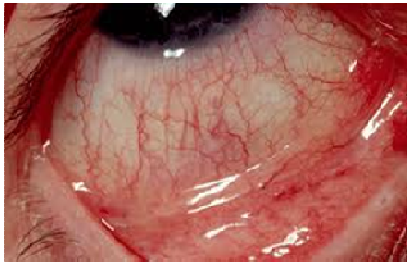


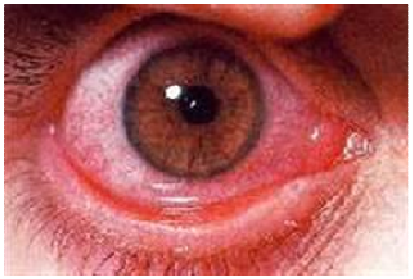
Maniestations of Type I allergy

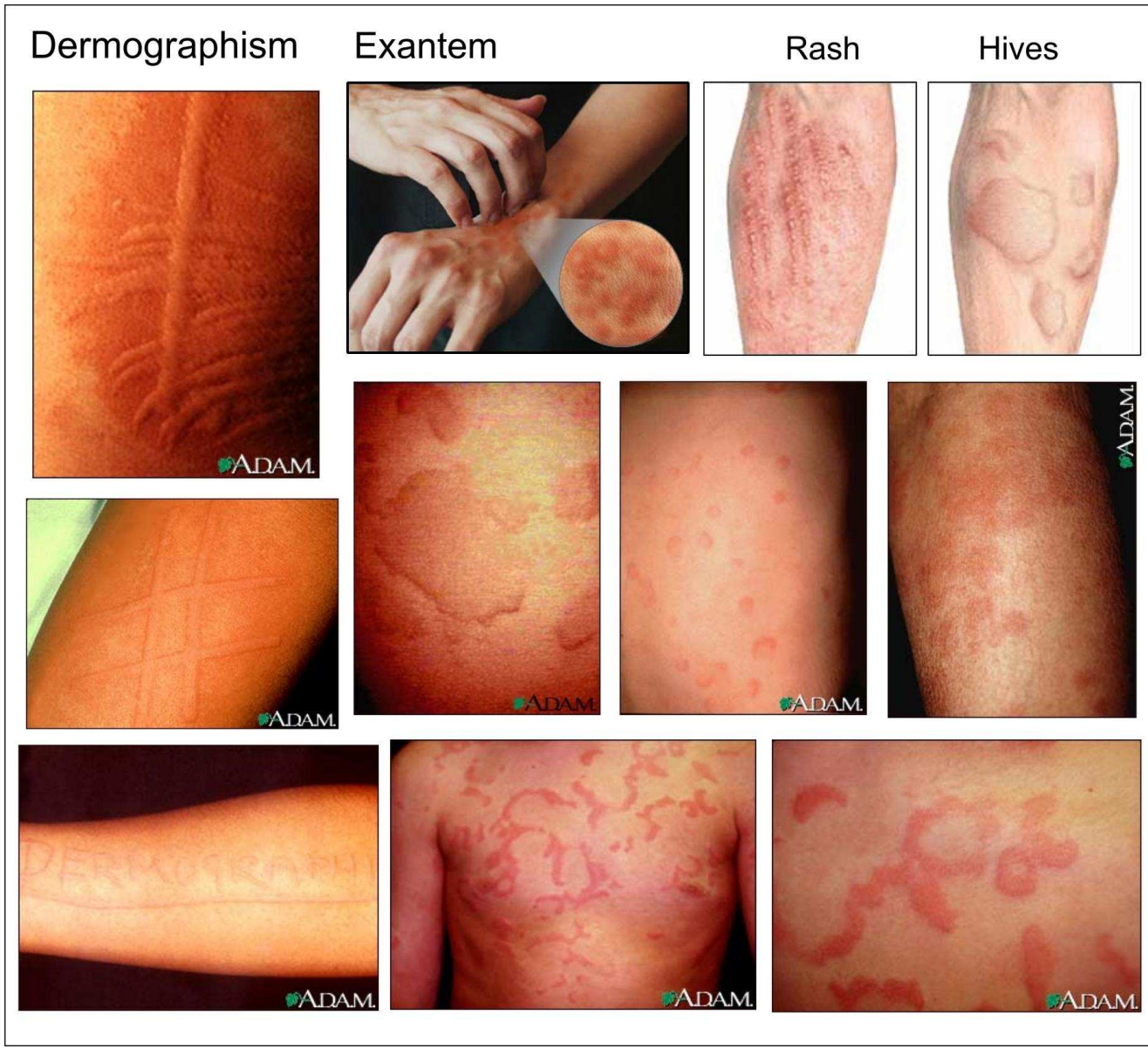


Allergic Rhinitis
Hay Fever; Rose Fever

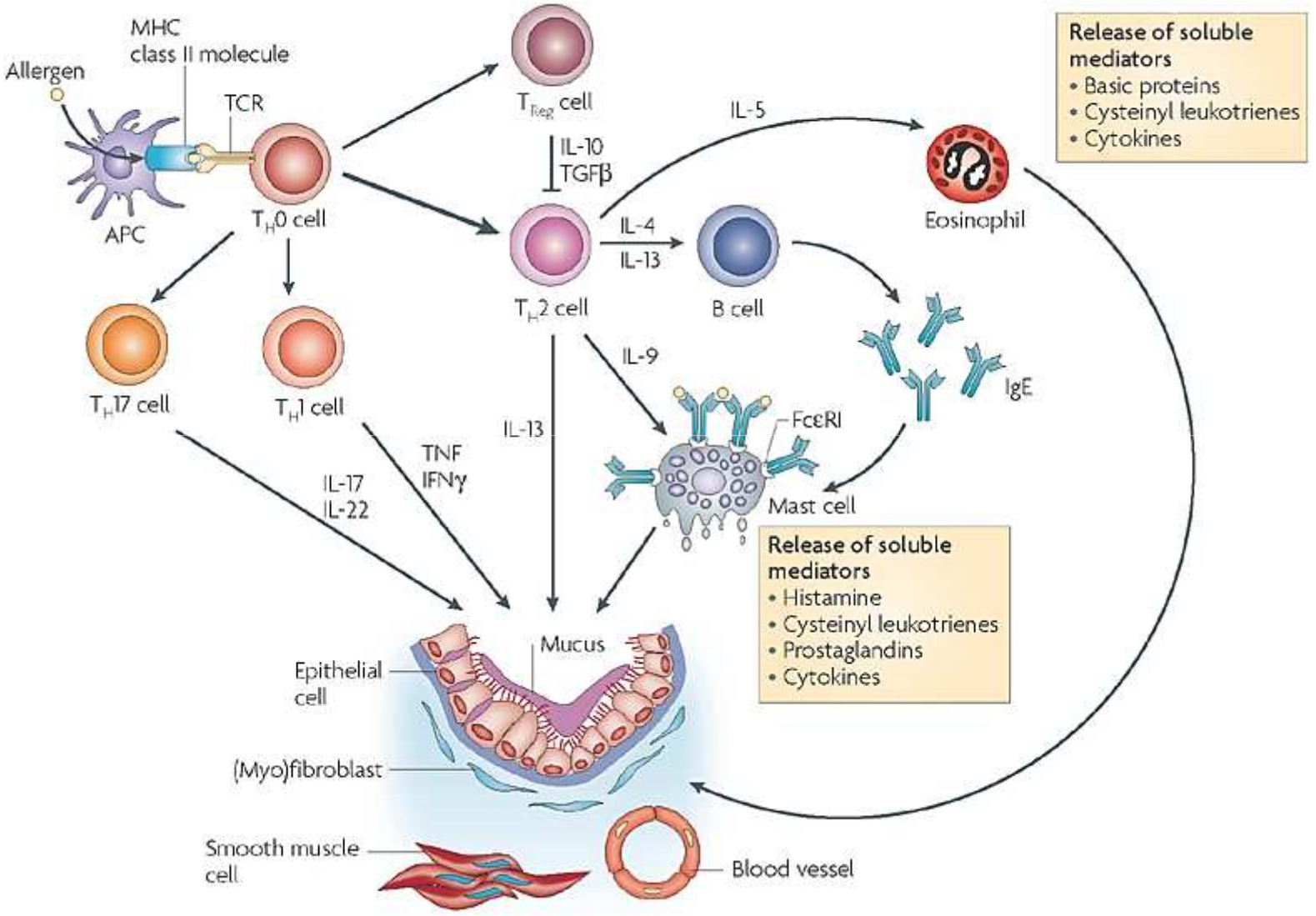
Allergic conjuctivitis





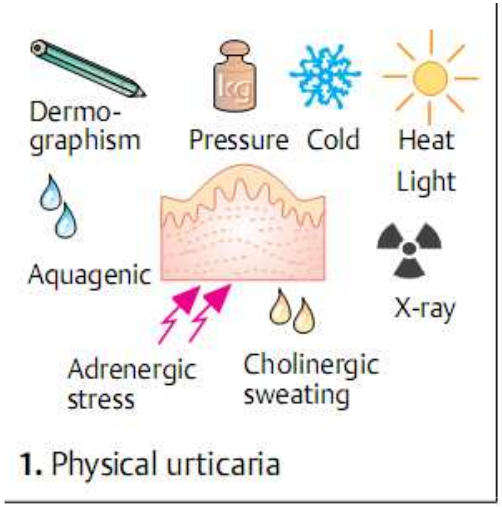


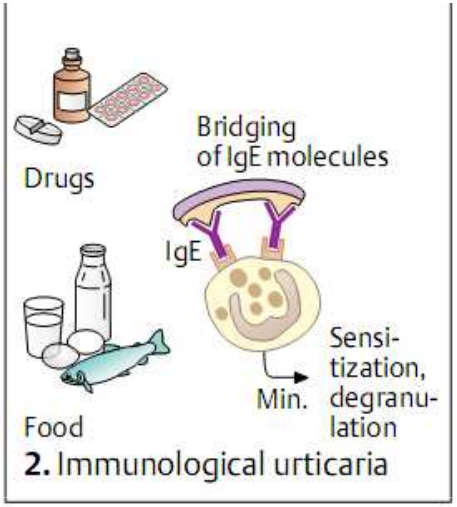
Type I. Allergy (anaphylatoxic)

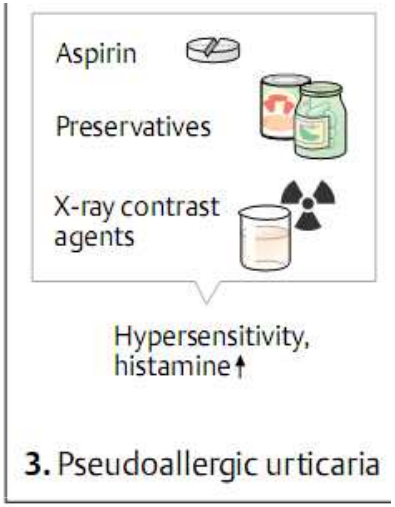


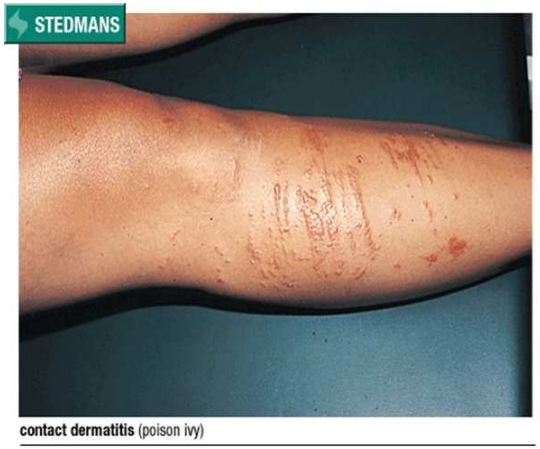
Treatment strategies for allergy and asthma Stephen T. Holgate & Riccardo Polosa Nature Reviews Immunology 8, 218-230 (March 2008)
FceRI, high-affinity receptor for IgE; IFNgamma, interferon-gamma; TCR, T-cell receptor; TNF, tumour-necrosis factor.

Allergic Response:
Inflammatory Reaction to Non-pathogen

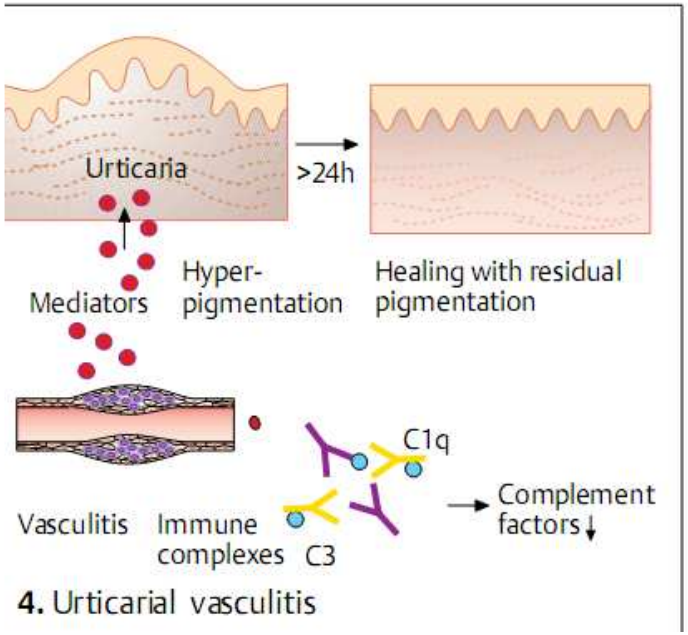


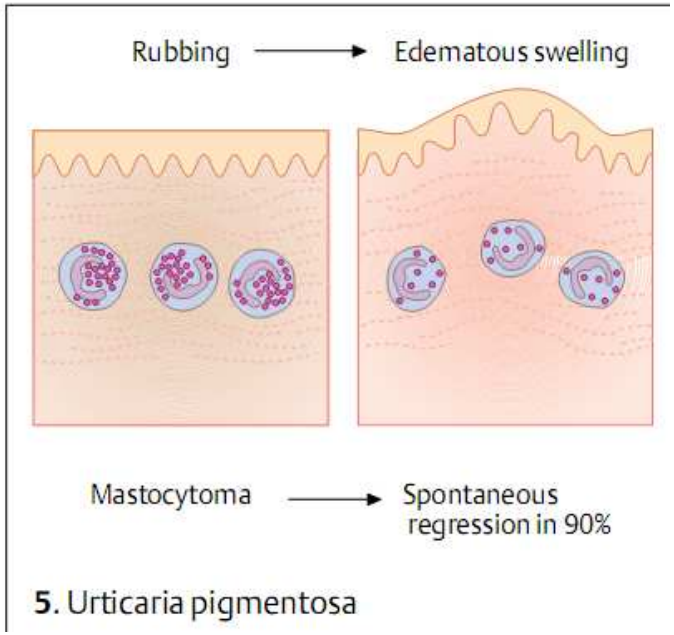


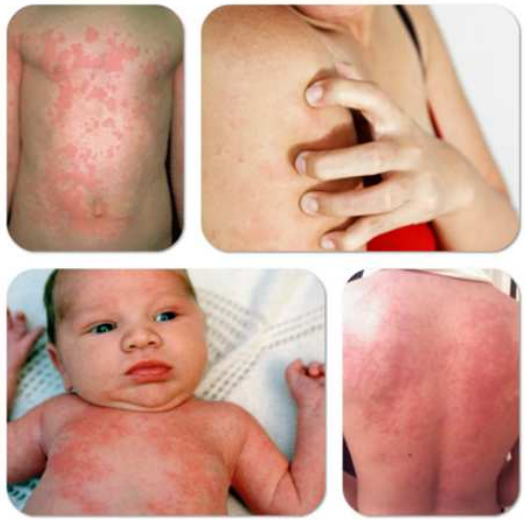




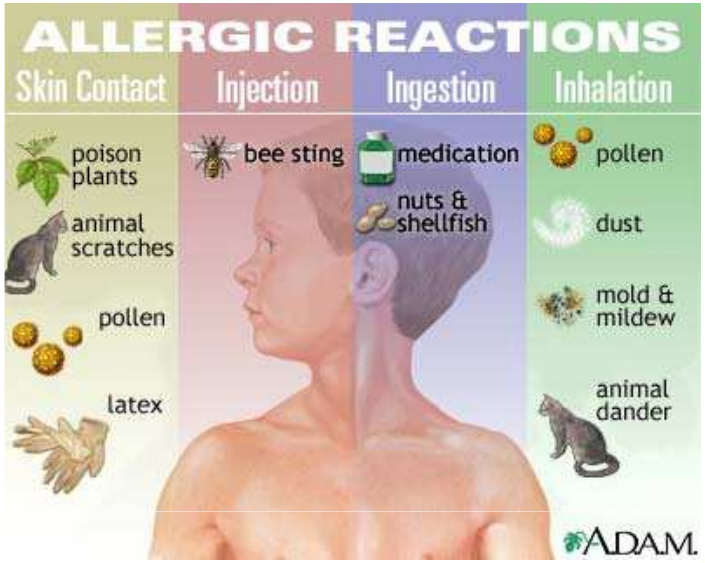
contact dermatitis (poison ivy)

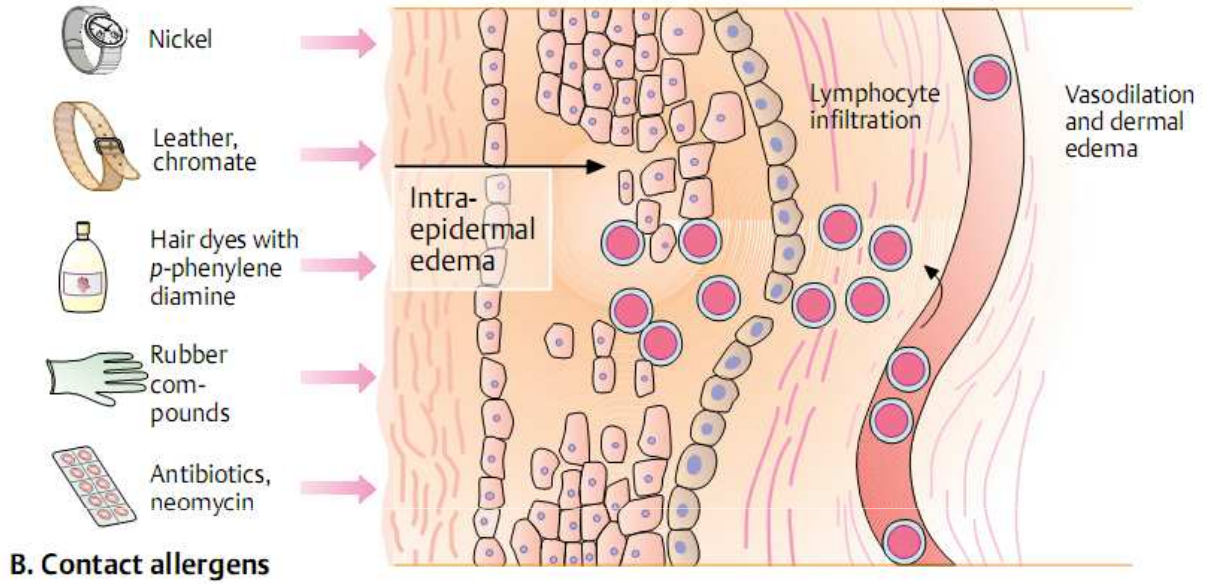




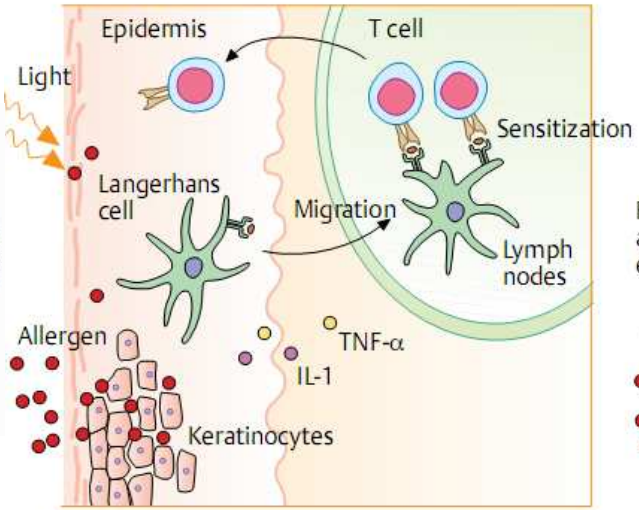


Ekzema

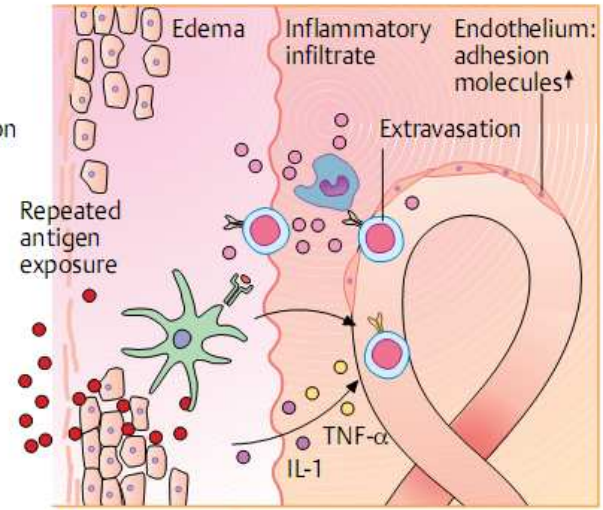




B. Contact allergens



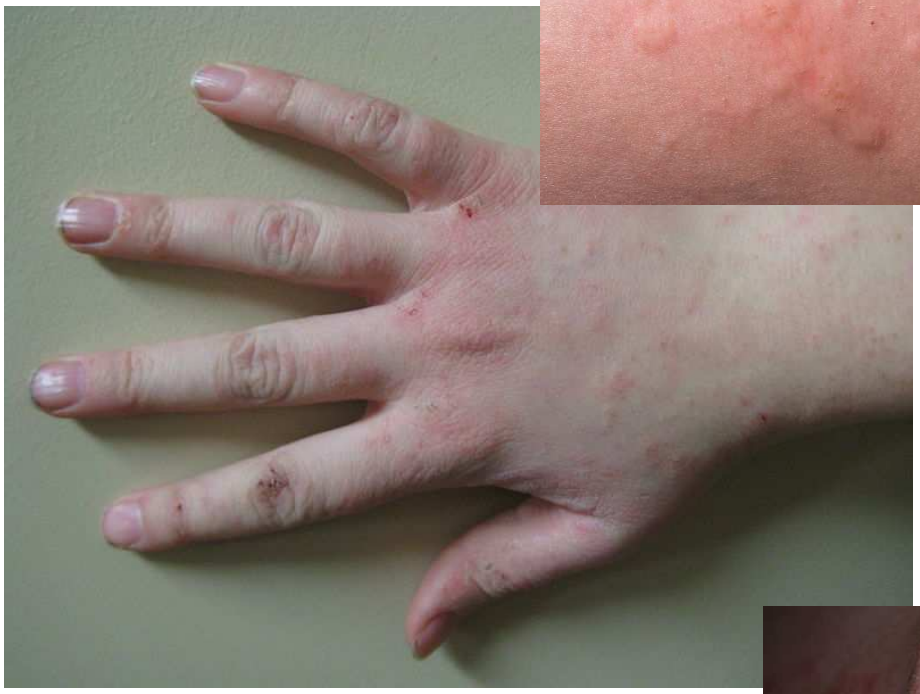
a) Sensitization

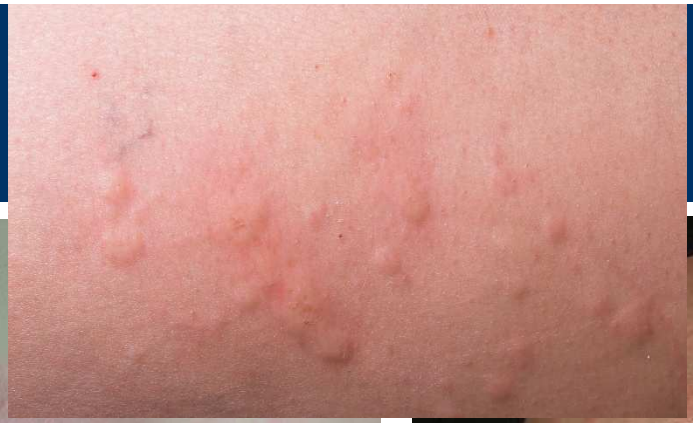


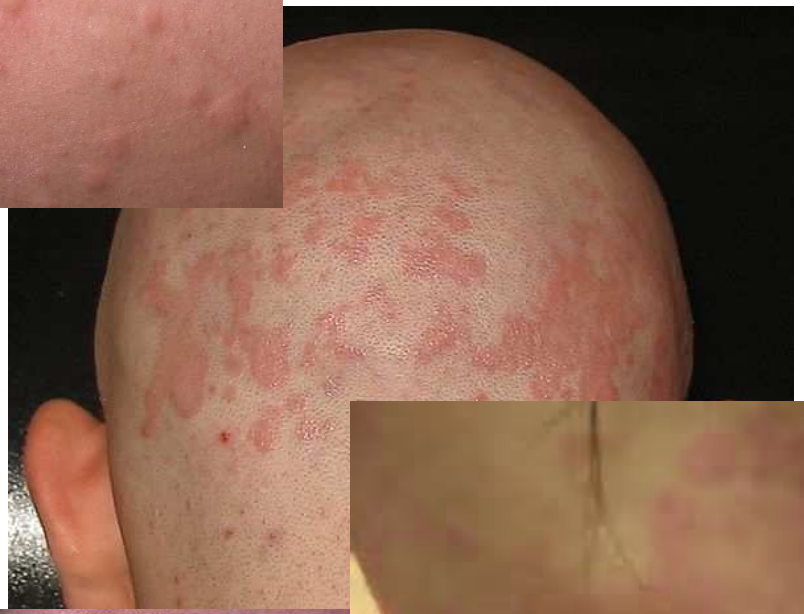
b) Induction of eczema

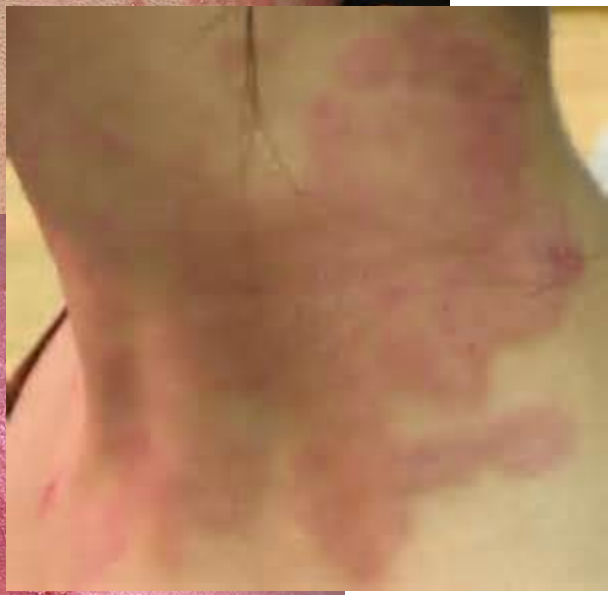
C. Pathogenesis

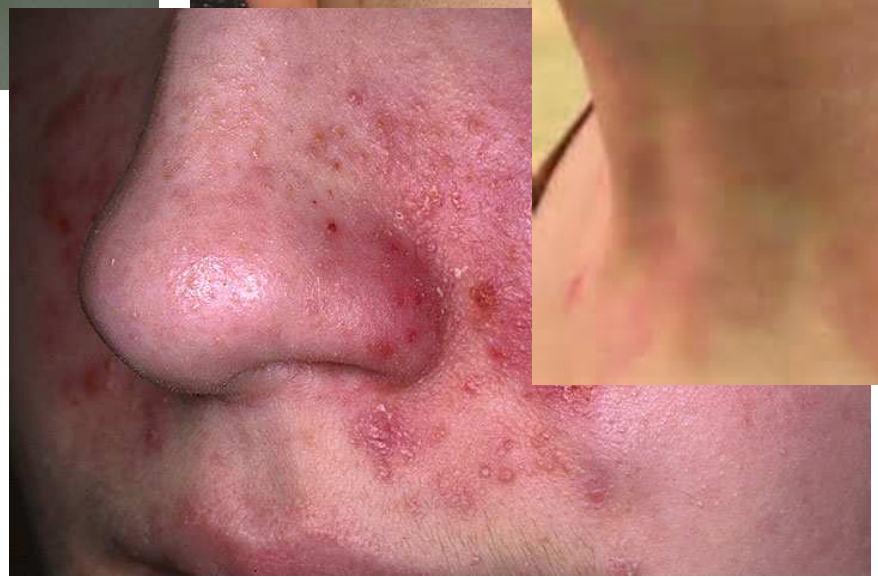
Eczema

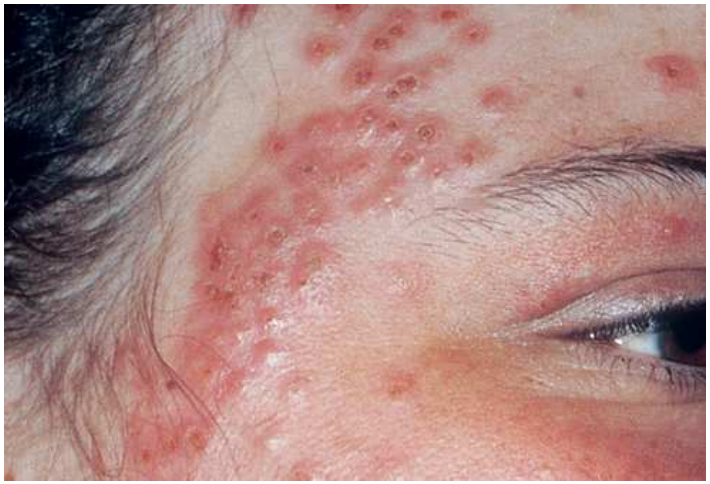




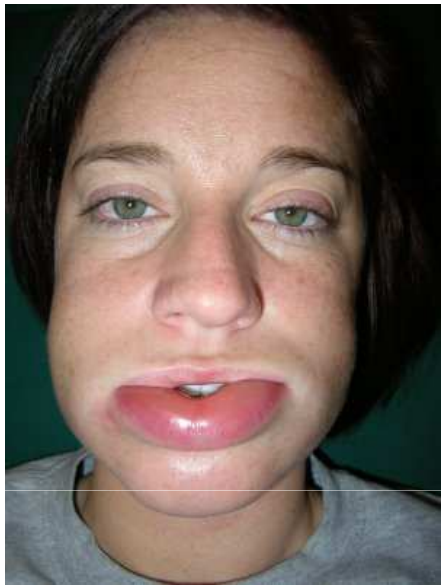
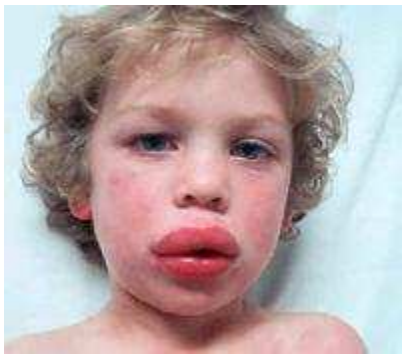
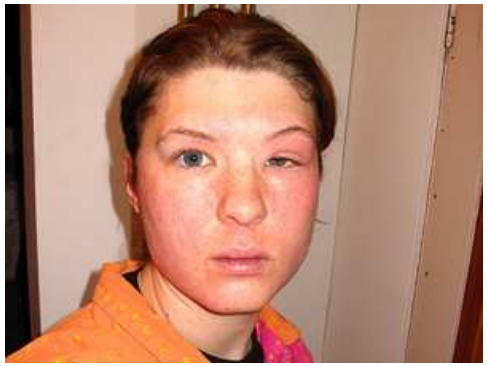
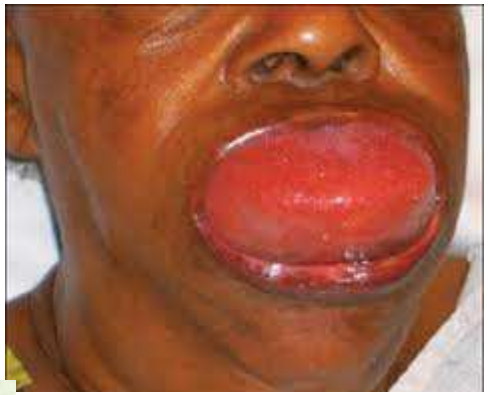
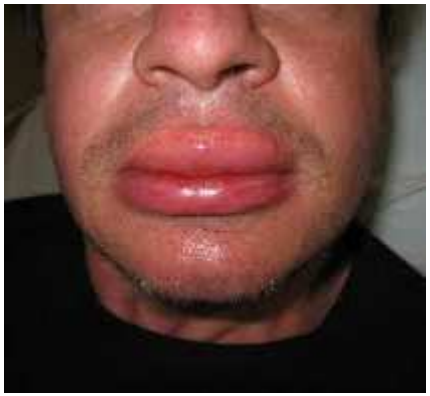
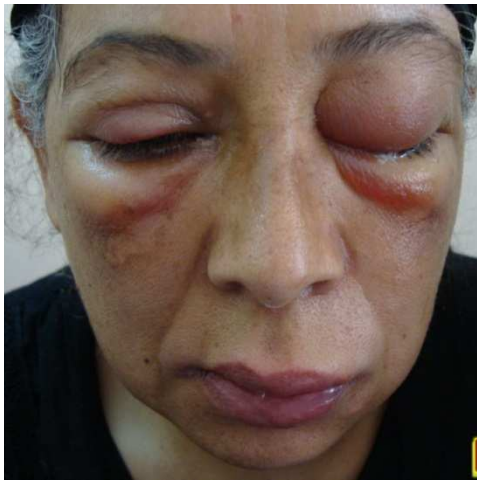
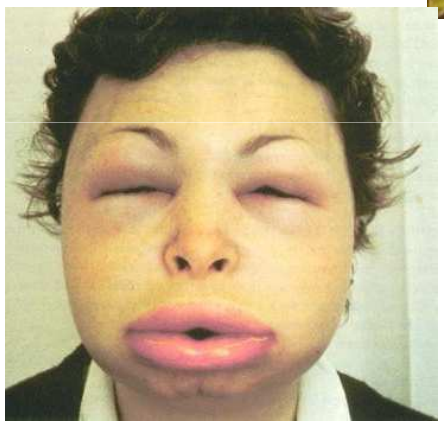
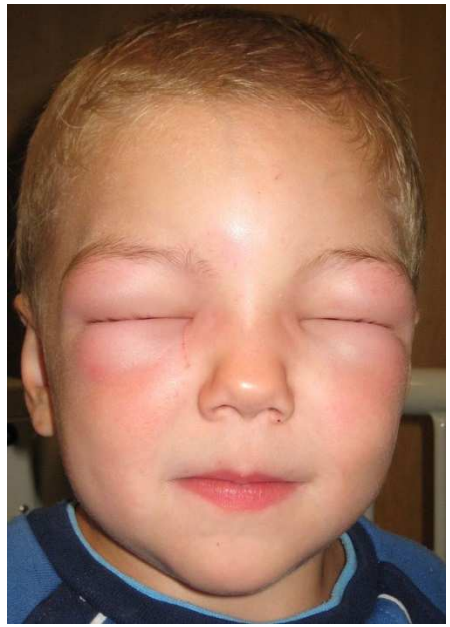








Allergic angioedema (Quicke edema)

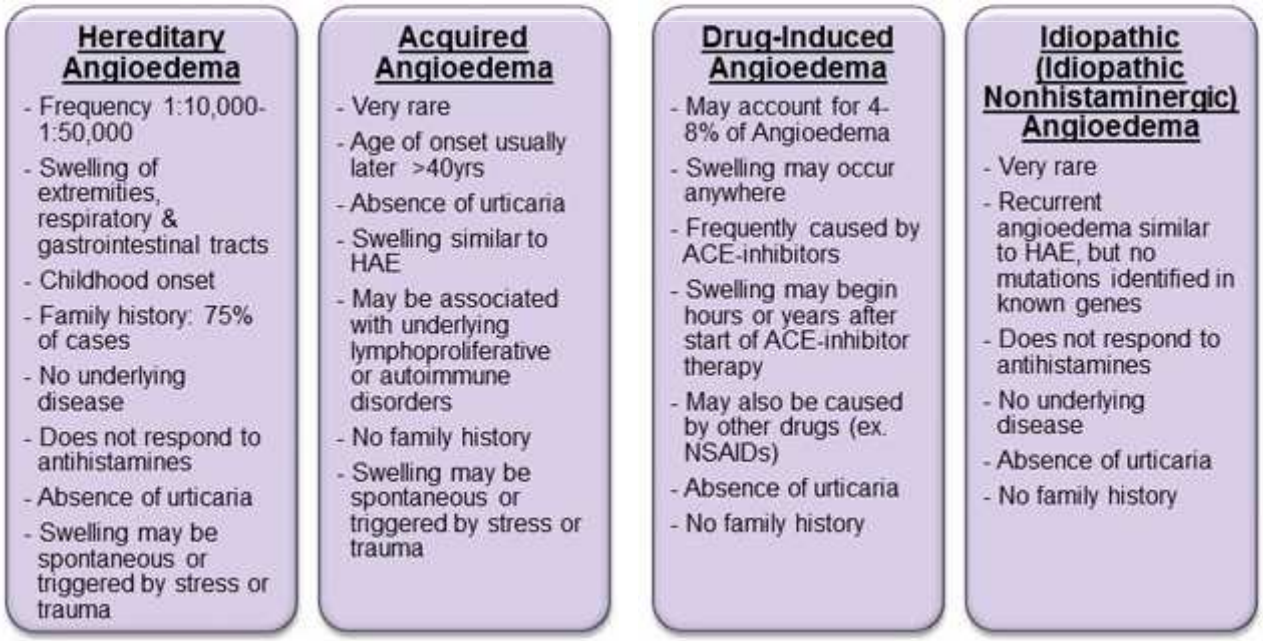









- Angioedema: increased bradykinin (made by kallikrein from HMW - kininogen) -> vascular dilatation; capillary permeability; exudate leakage, pain ; unresponsive to histamine
- Face: ocular, lips, Mouth:, tongue, larynx, Bowels

Disfiguring Angioedema
Didier G. Ebo, and Chris H. Bridts
N Engl J Med 2012; 367:1539

Hereditary & acquired angioedema

- **Drugs associated with angioedema:**
  - Angiotensin-converting enzyme (ACE) inhibitors: to control high blood pressure;
  - Non-steroidal anti-inflammatory drugs (NSAIDs): aspirin, pain-killers
  - Radiocontrast agents: CT scans;
  - Opiates: this include morphine, oxycodone and generally used as strong pain-killers;
- **Allergic angioedema:** postinfectional; insect stings; food : fish, nuts, eggs, milk, chocolate, etc; meat (animal proteins).



Hypersensitivity type II

Type	Alternative names	Antigen	Disorders		Mediators
I	Immediate; Allergy Anaphylactic,	External	Anaphylaxis, Asthma. Atopic eczema Food allergy, Peanut, Tree nut, Seafood, Soy, Whea, Penicillin allergy		Secretory IgE /IgG4
		Autoantigen	None		
II	Cytotoxic, Antibody-dependent, ADCC	External	Erythroblastosis fetalis (Rh), Blood incompatibility, Thrombocytopenia		Membrane bound IgM / IgG (Complement activation)
		Autoantigen	Cytotoxic	Autoimmune hemolytic anemia, Pemphigus vulgaris Goodpasture's syndrome, Membranous nephropathy, Bullous pemphigoid, Idiopathic thrombocytopenic purpura Acute rheumatic fever, Vasculitis caused by ANCA	
			Receptoric subtype V	Graves' disease, Myasthenia Gravis. Pernicious anemia, Diabetes mellitus (anti insuilin receptor)	
III	Immune complex disease	External	Henoch–Schönlein purpura, Hypersensitivity vasculitis, Arthus reaction Reactive arthritis, Farmer's lung, Post-streptococcal glomerulonephritis, Serum sickness, Extrinsic allergic alveolitis (Hypersensitivity pneumonitis)		Secretory IgG – complex (Complement)
		Autoantigen	Lupus Nephritis, Subacute bacterial endocarditis Systemic lupus erythematosus (SLE) Rheumatoid arthritis		
IV	Delayed-type hypersensitivity cell-mediated	External	Allergic contact dermatitis, Mantoux test		T-cells
		Autoantigen	Diabetes mellitus type 1, Hashimoto's thyroiditis Guillain–Barré syndrome, Multiple sclerosis		
		GVHR	Coeliac disease, Giant-cell arteritis, Chronic transplant rejection		
VII	Undefined	External	Hypersensitivity pneumonitis, Transplant rejection, Allergic bronchopulmonary aspergillosis, Latex allergy (I+IV)		T- cells, IgG, IgM
		Autoantigen	Sjögren's syndrome, Autoimmune hepatitis Autoimmune polyendocrine syndrome, APS1APS2 Autoimmune adrenalitis, Systemic autoimmune diseas		

Antibody mediated hypersensitivity type II

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Red cell membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (GpIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal desmoglein)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein (NC1) in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, downmodulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal myelopoiesis, anemia

*Except of **newborn icterus from blood incompatibility** all disease unites in the frame of „type II hypersensivitiy“ are all autoimmune disorders*

Three various mechanisms of type II response

- **Complement –dependent**

Complement and antibodies opsonize the target

Target is destroyed by fagocytosis or Complement drilling complex (C6-C9)

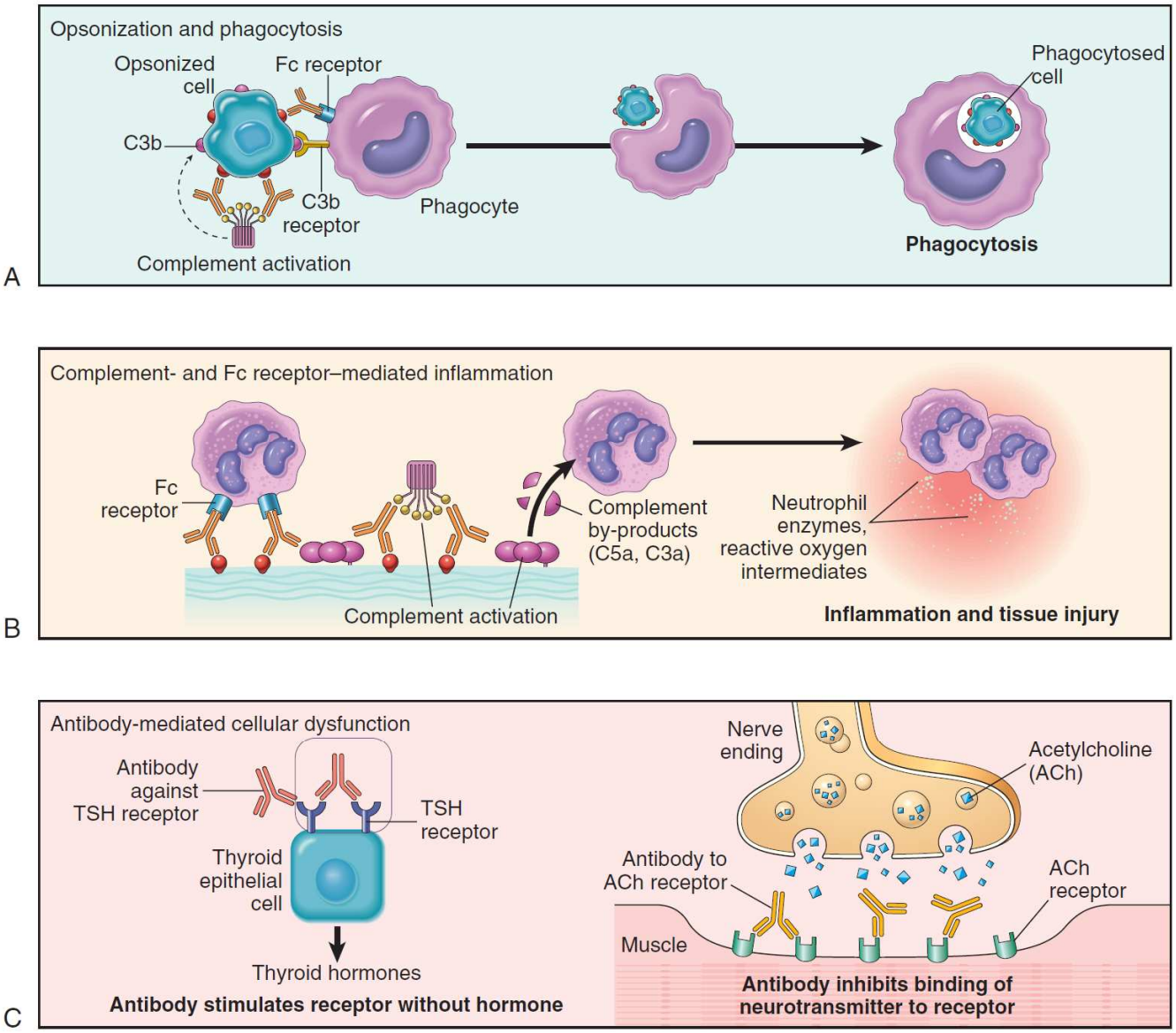
- **ADCC**

Antibody and complement opsonize the target

Target is destroyed by NK or granulocyte attack

- **Receptor- mediated antibodies**

Antibiodies are produced to target the receptors (cause destruction of receptors /or not opposite = ligand-receptor effects)



Erytroblastosis fetalis

Hemolytic disease of the newborn (of the fetus and newborn, HDN, HDFN) IgG+ IgM from mother pass through the placenta

Mechanisms:

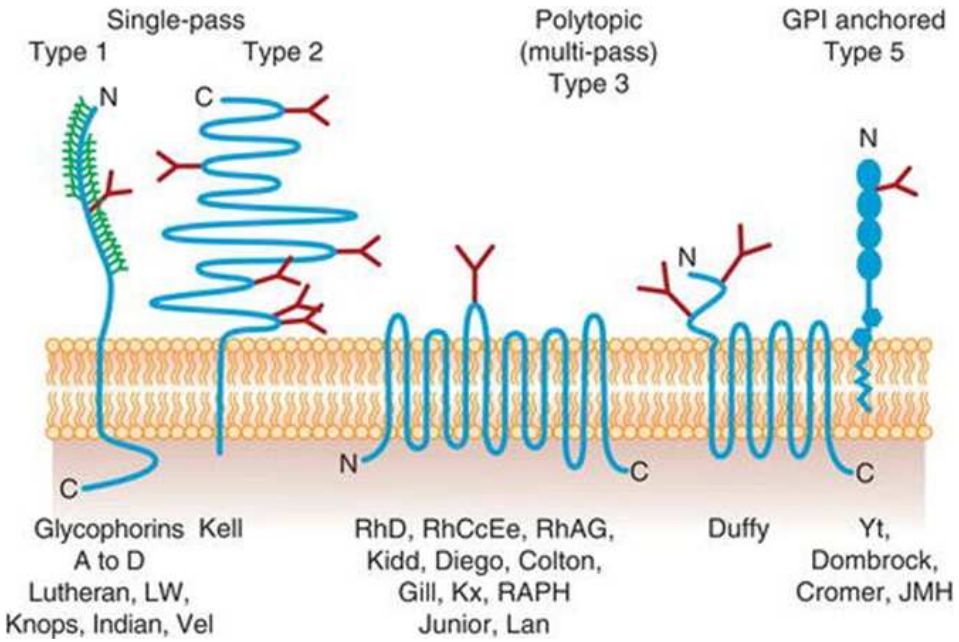
- Fetal-maternal hemorrhage - abortion, childbirth, ruptures in the placenta during pregnancy
- Blood transfusion (incompatible in Kell group)
- ABO sensitisation Ab made by O-mother against A, B, or AB child (15% of pregnancies)

Manifestations:

- Hemolysis - **hyperbilirubinemia, neonatal jaundice** within 24 hours after birth.
- Profound anemia can cause **high-output heart failure** (pallor, enlarged liver and/or spleen, generalized swelling, and respiratory distress.
- Prenatal manifestations - **hydrops fetalis;** petechiae and purpura.
- Complications: kernicterus, hepatosplenomegaly, inspissated bile syndrome and/or greenish staining of the teeth, hemolytic anemia and damage to the liver due to excess bilirubin.

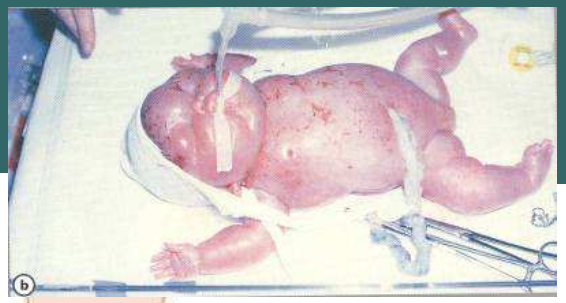
Antibodies to blood groups; Kell and Rh are most frequentl.

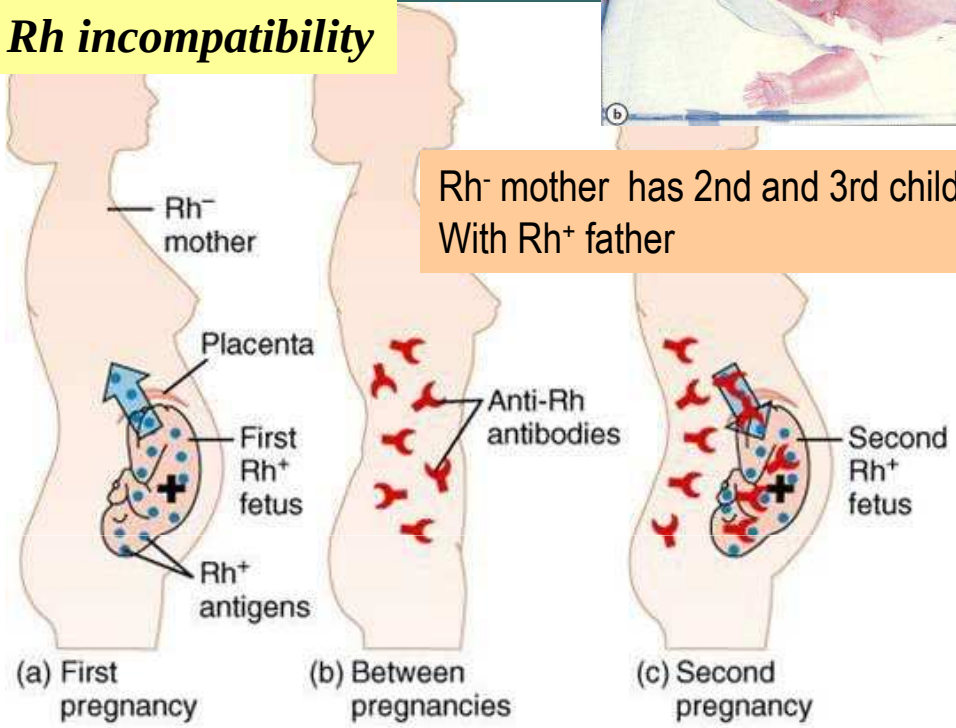
- **ABO hemolytic disease** (mild; anti-A antibodies anti-B antibodies
- **Rhesus D hemolytic disease** the most common; mild to severe HDN.
- **Rhesus E hemolytic disease** rare, mild condition
- **Rhesus c hemolytic disease** mild to severe; 3 most common form of severe HDN
- **Rhesus e hemolytic disease** – rare
- **Rhesus C hemolytic disease** - rare
- **anti-Rhc and anti-RhE antibodies** together) - can be severe
- **Kell hemolytic disease** anti-K 1 antibodies



Blood groups

Rh incompatibility



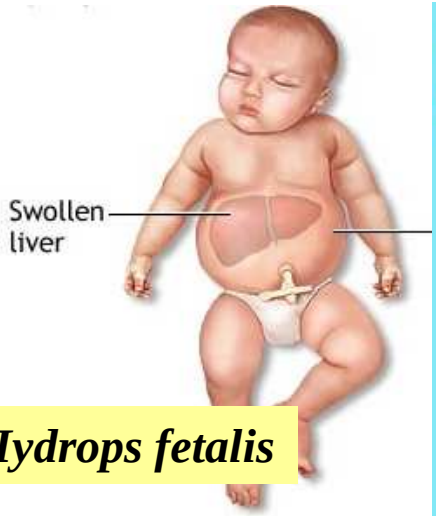


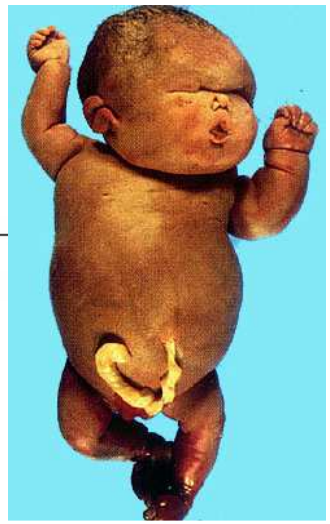
Rh⁻ mother has 2nd and 3rd child
With Rh⁺ father

ABO system

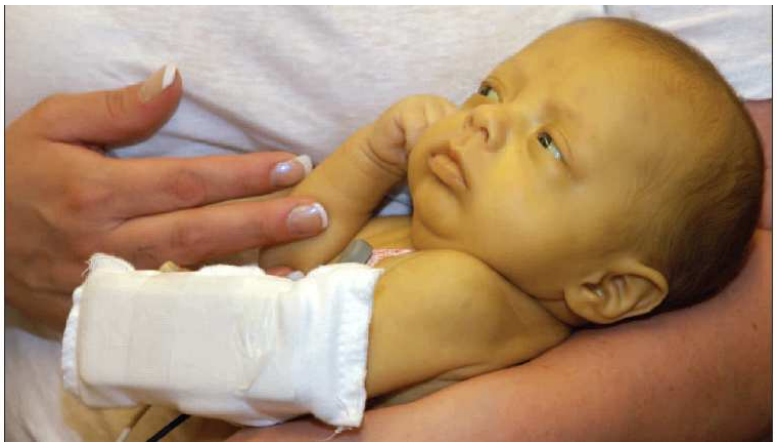
	red blood cell	Antibodies in plasma
O	RBC No A or B antigens	"Anti-A" and "anti-B"
A	A antigens	"Anti-B"
B	B antigens	"Anti-A"
AB	A and B antigens	None to A or B

Multipara with O group over time rise up Ab against A and B babies





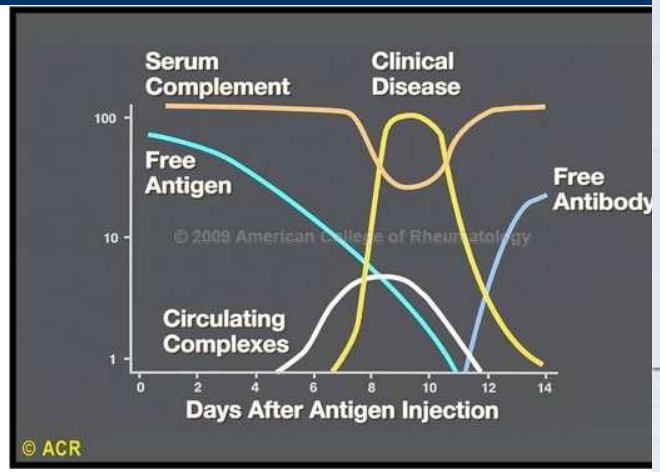
Hydrops fetalis

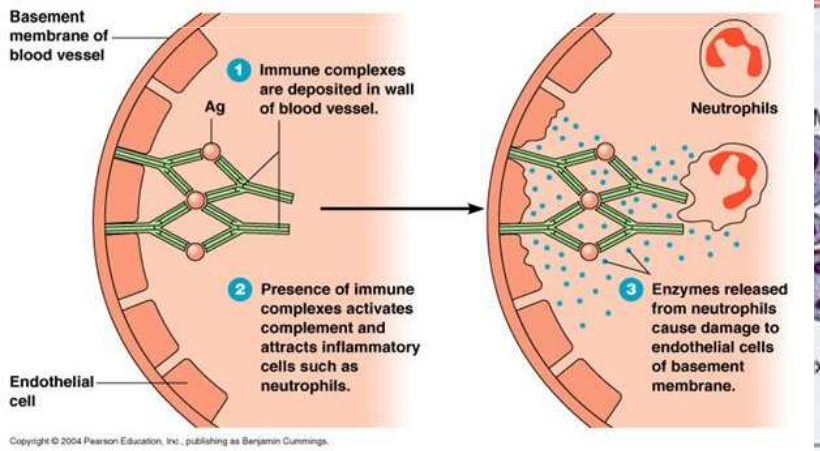


Hypersensitivity type III (immune complex type)

Type	Alternative names	Antigen	Disorders		Mediators
I	Immediate; Allergy Anaphylactic,	External	Anaphylaxis, Asthma. Atopic eczema Food allergy, Peanut, Tree nut, Seafood, Soy, Whea, Penicillin allergy		Secretory IgE /IgG4
		Autoantigen	None		
II	Cytotoxic, Antibody-dependent, ADCC	External	Erythroblastosis fetalis (Rh), Blood incompatibility, Thrombocytopenia		Membrane bound IgM / IgG (Complement activation)
		Autoantigen	Cytotoxic	Autoimmune hemolytic anemia, Pemphigus vulgaris Goodpasture's syndrome, Membranous nephropathy, Bullous pemphigoid, Idiopathic thrombocytopenic purpura Acute rheumatic fever, Vasculitis caused by ANCA	
			Receptoric subtype V	Graves' disease, Myasthenia Gravis. Pernicious anemia, Diabetes mellitus (anti insuilin receptor)	
III	Immune complex disease	External	Henoch–Schönlein purpura, Hypersensitivity vasculitis, Arthus reaction Reactive arthritis, Farmer's lung, Post-streptococcal glomerulonephritis, Serum sickness, Extrinsic allergic alveolitis (Hypersensitivity pneumonitis)		Secretory IgG – complex (Complement)
		Autoantigen	Lupus Nephritis, Subacute bacterial endocarditis Systemic lupus erythematosus (SLE), Rheumatoid arthritis		
IV	Delayed-type hypersensitivity cell-mediated	External	Allergic contact dermatitis, Mantoux test		T-cells
		Autoantigen	Diabetes mellitus type 1, Hashimoto's thyroiditis Guillain–Barré syndrome, Multiple sclerosis		
		GVHR	Coeliac disease, Giant-cell arteritis, Chronic transplant rejection		
VII	Undefined	External	Hypersensitivity pneumonitis, Transplant rejection, Allergic bronchopulmonary aspergillosis, Latex allergy (I+IV)		T- cells, IgG, IgM
		Autoantigen	Sjögren's syndrome, Autoimmune hepatitis Autoimmune polyendocrine syndrome, APS1APS2 Autoimmune adrenalitis, Systemic autoimmune diseas		

Type III





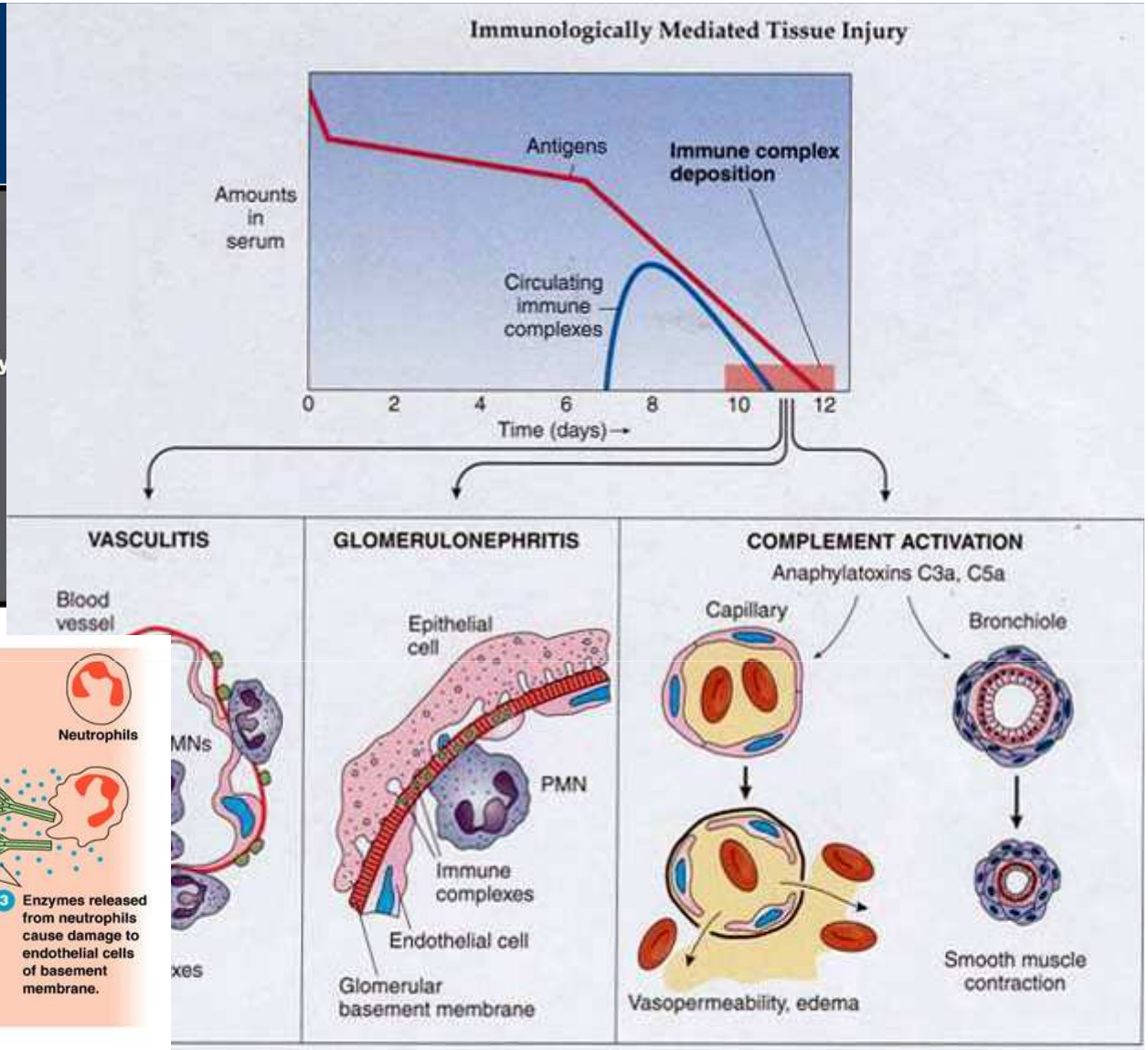


FIGURE 4-9
Type III hypersensitivity. In the serum sickness model of immune complex tissue injury, antibody is produced against a circulating antigen, and immune complexes form in the blood. These complexes deposit in tissues such as blood vessels and glomeruli and, augmented by complement activation, induce tissue injury or dysfunctional responses.

Serum sickness [ICD-10 T80.6]

- **Serum sickness** = immune complex hypersensitivity (type III) reaction to proteins in antiserum derived from a non-human animal source, occurring 4–10 days after exposure.; first identified: C.von Pirquet and B. Schick (1906)
- **Serum sickness-like reaction (SSLR)** refer to similar illnesses that arise from the introduction of certain non-protein substances.
- Etiopathogenesis: Igs interact with antiges into complexes → enter blood vessels wall → activate complement → inflammatory response and (consuming much of the available C3|).
  - **Animal antisera,** e.g. antitoxins other administered to prevent or treat an infection or envenomation, poisoning; equine antitoxins, snake and spider antivenins, antilymphocyte globulins, and streptokinase
  - **Application (s.c, i.c, i.m.) of extracts** of allergens , hormones and vaccines against bacterias or viruses used in diagnostics or therapy; **infliximab and rituximab**, which are therapeutic proteins using recombinant DNA technology and used to treat disorders such as Crohn's disease, rheumatoid arthritis, and psoriasis
  - **Drugs:** sulfonamides, penicillins, cephalosporins, allopurinol, barbiturates, captopril, griseofulvin, phenytoin procainamide, quinidine, streptokinase, rituximab, ibuprofen; The drug traditionally linked to SSLR in children is **cefaclor**, an oral second-generation cephalosporin
  - **Vaccines** hepatitis B, haemophilus influenzae type b, rabies, inactivated influenza vaccine
  - **viral infections,** most commonly hepatitis B and C

Serum sickness a SSLR

- Signs/symptoms: as long as after 1-3 weaks (7-21 days) after exposure to non – human proteins; similar to those in real infection / intoxication :
  - skin rashes (morbilliform, urticarial or purpuric), itching, arthralgia (finger, toe joints)
  - malaise, fever (39-41°C) appears before rash, lymphadenopathy (near the site of injection)
  - hypotension (decreased blood pressure), shock
  - splenomegaly (enlarged spleen) lymphadenopathy,
  - glomerulonephritis, proteinuria, hematuria
  - a self-limited disease, generally lasting 5-30 days with slow regress

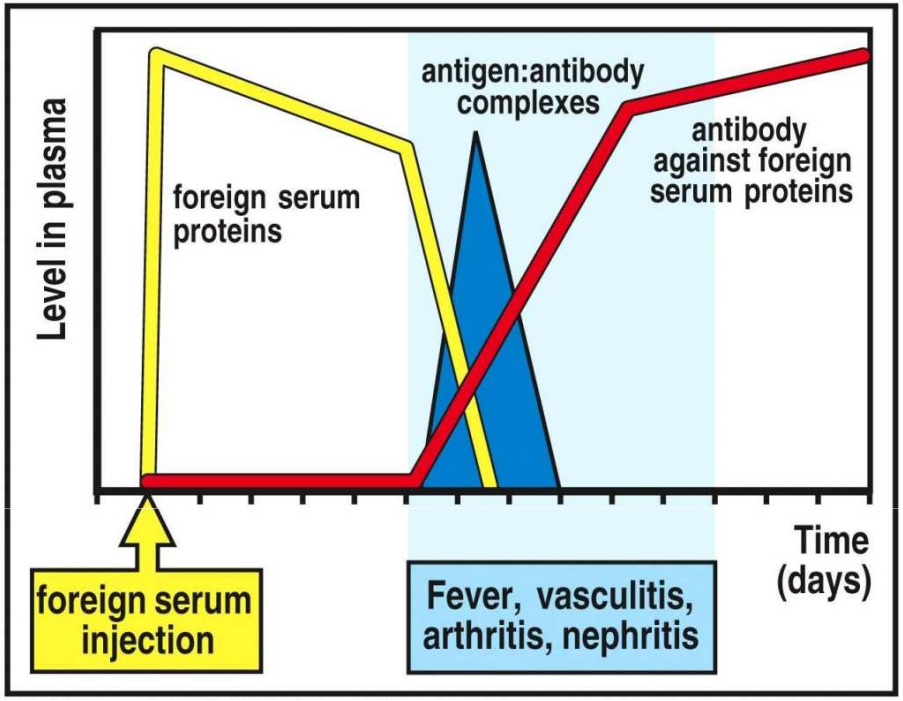


Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

Serum sickness-like reaction (SSLR)

- similar clinical presentation with **fever, rash (resemble urticaria, "purple-urticaria"), pruritus, and arthralgias with periarticular swelling** (hips, knees, wrists, and ankles), but occurs most classically **1-3 weeks following exposure to certain drugs.** Often resolves spontaneously over 2-3 weeks after discontinuation of the offending medication
- Lymphadenopathy and eosinophilia are occasionally present.
- SSLR typically **lacks the circulating immune complexes so characteristic of serum sickness**, as well as the hypocomplementemia, vasculitis, and proteinuria.[2,3] In general, SSLR is less common and less severe than true serum sickness.

Serum sickness-like reaction (SSLR)

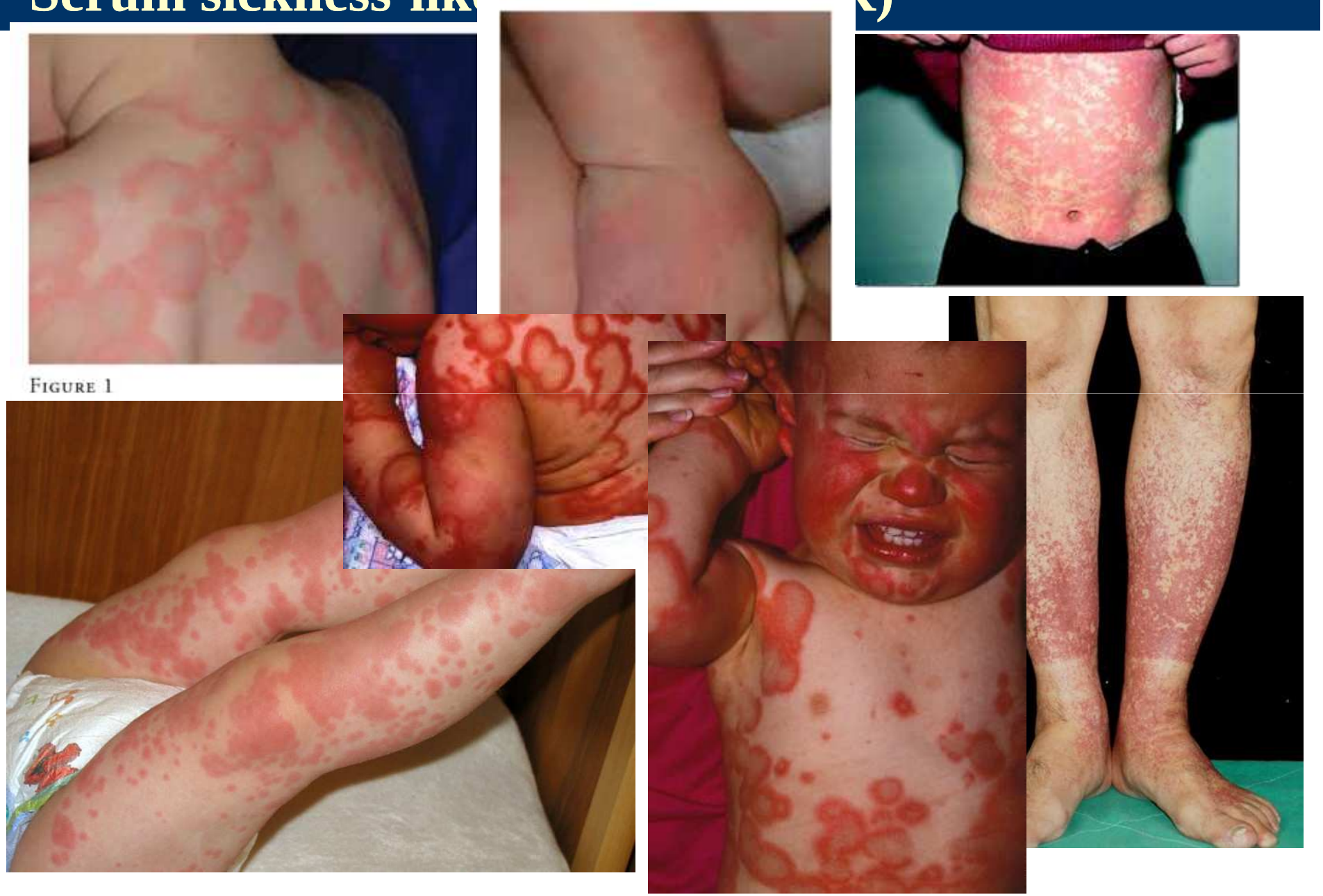
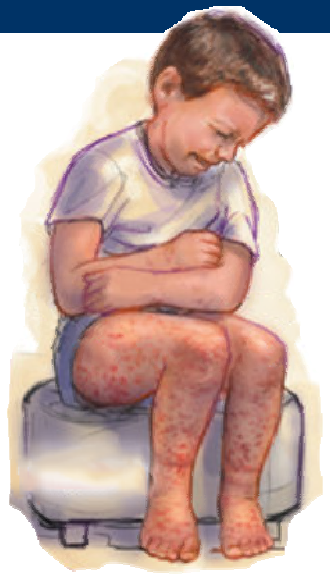
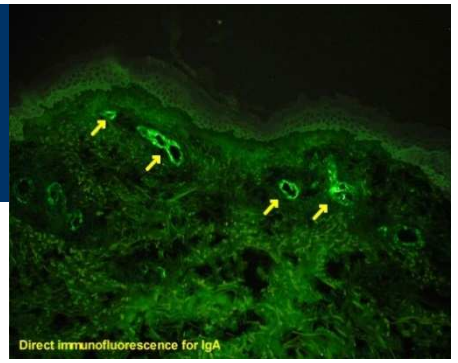


FIGURE 1

Henoch–Schönlein Purpura (HSP)

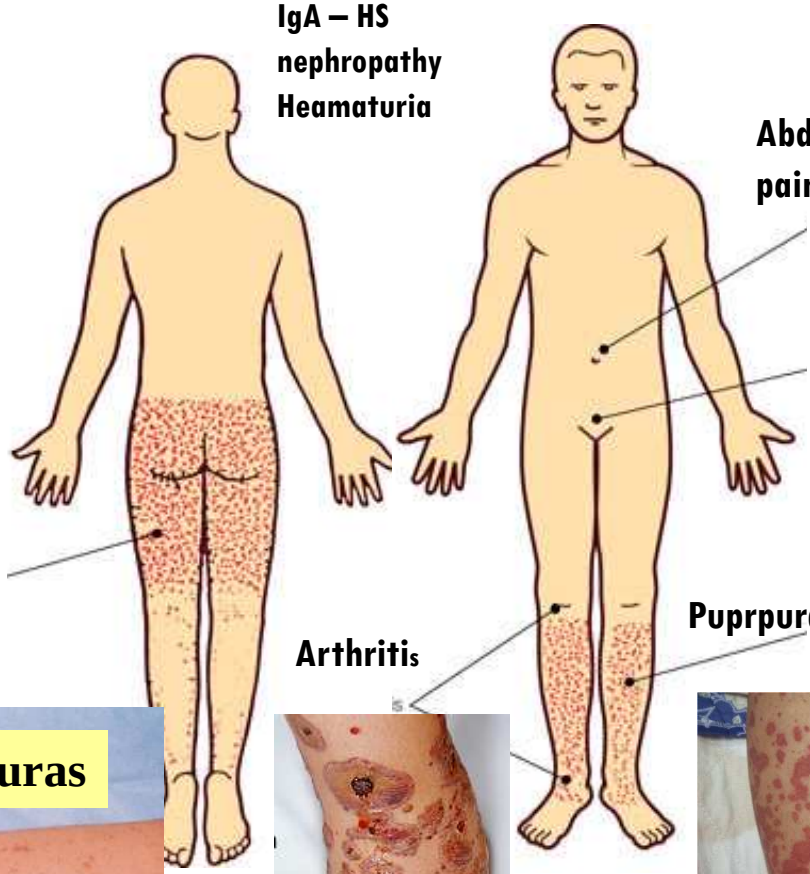




IgA – HS nephropathy
Heamaturia

Abdominal pain

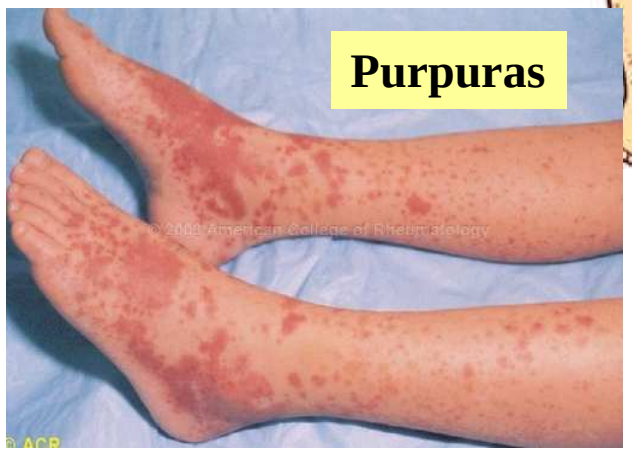
Reddish-puple spots bruised areas on buttocks, legs, feet

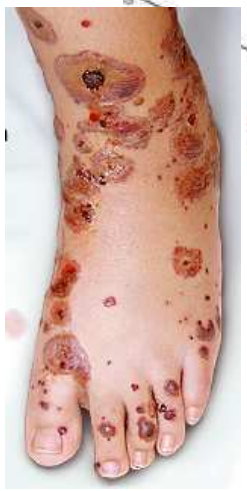


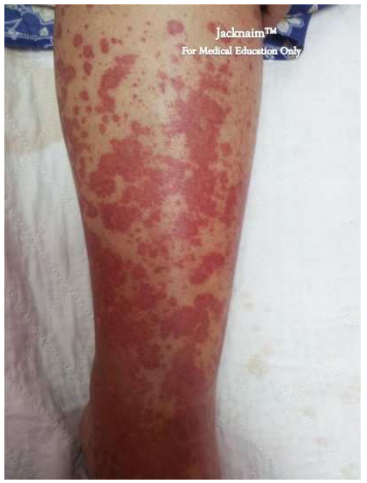
Arthritis

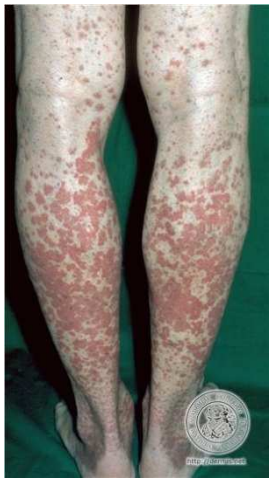
Puprpura sites

Uncommonly purpuras are seen in trunck, palms, arms, Reddish-puple spots (bruised areas on buttocks, legs, feet

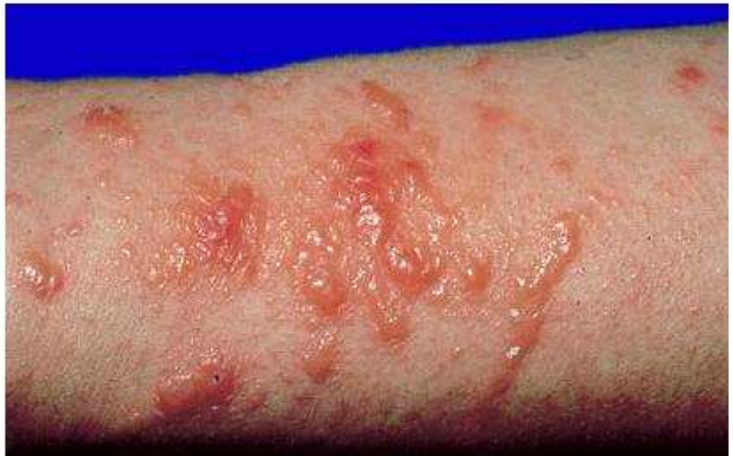


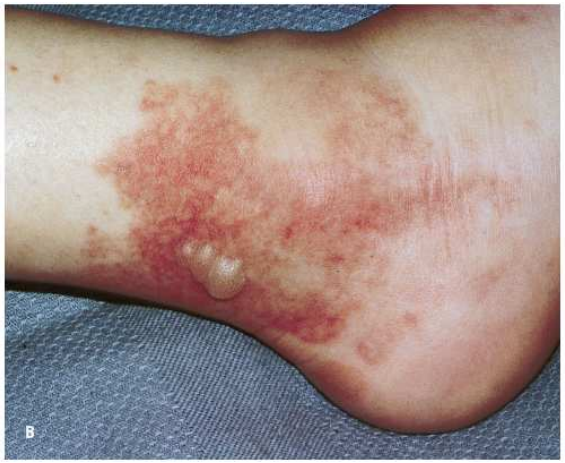






Arthus reaction (phenomenon)





Nicolas Maurice Arthus (1903): horse serum inj. subcut. into rabbits. After 4 inj. wound evolves from an edema into gangrene.

- Definition: local type III hypersensitivity reaction following subcutaneous/ intradermal injection of some antigens (across-species) in animal/patient that was previously sensitized (has circulating antibody; deposition of antigen/antibody complexes mainly in the vascular walls, serosa (pleura, pericardium, synovium), and glomeruli.
- Etiology: vaccinations: diphtheria (Corynebacterium); tetanus (Clostridium), recombinant hepatitis B virus vaccine (1992)
- Pathomechnism: formation of IgG-based immune complexes → deposition in dermal blood vessels → activation of C5a and C3a, → recruitment of PMNs (leucocytosis) and local mast cell degranulation
- Signs/synmptoms: **local vasculitis** (**redness, infiltrations, edema, induration**), later **fibrinoid / haemorrhagic necrosis** (due to ischemia-aggravating thrombosis in the tissue vessel walls);**, sterile abscesses, and in severe cases, gangrene**

Arthus reaction

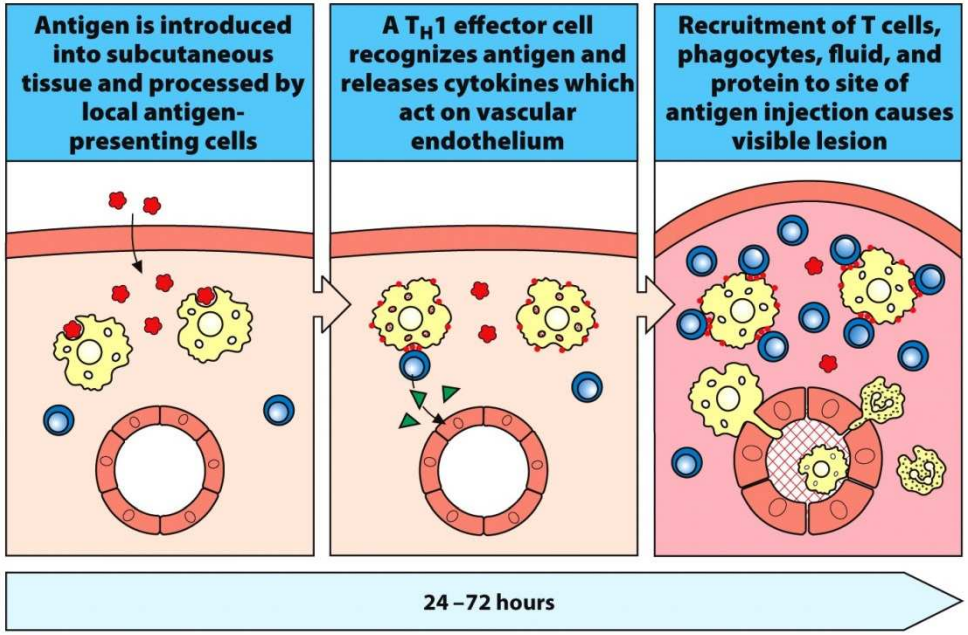


Figure 12.36 The Immune System, 3ed. (© Garland Science 2009)

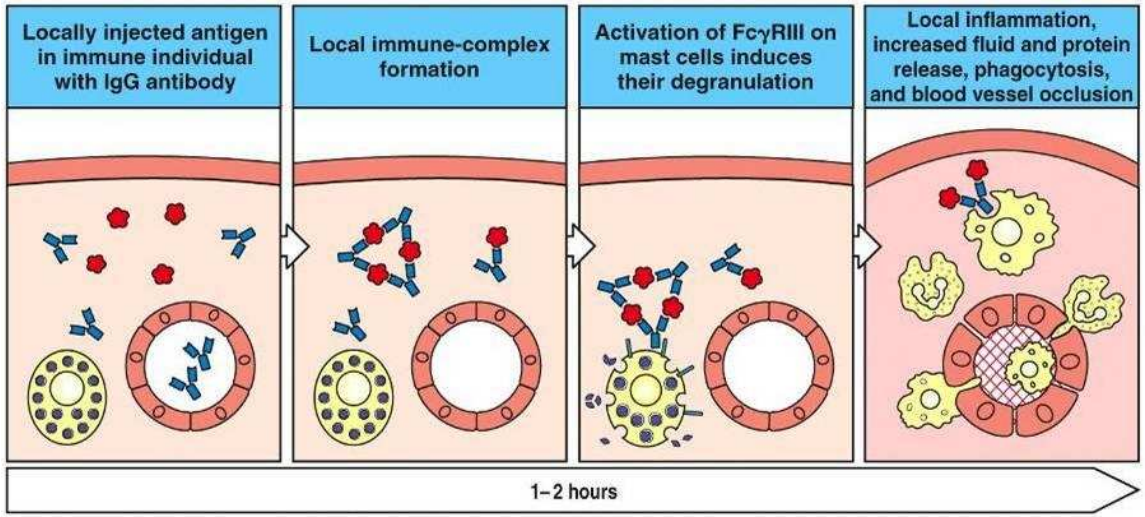


Figure 12-22 Immunobiology, 6/e. (© Garland Science 2005)

Clinical immunology **3**

Autoimmnune diseases

Autoimmune disorders according to the location

AUTOIMMUNE DISORDERS

Organ-specific (focal)

1. Neuromuscular

Myasthenia gravis, Stiff-man sy.
Eaton-Lambert myasthenic sy.
Acute disseminated encephalitis
Multiple sclerosis,
Guillain-Barré sy.
Chronic inflammatory demyelinating polyradiculoneuropathy
Chronic neuropathy w monocolonal gammopathy
Multifocal motor neuropathy

2. Endocrinne

Graves disease, Hashimoto thyroiditis
Thyroiditis w hyperthyroidism
Autoimmune Addison disease
Diabetes mellitus type I
Autoimmune polyglandular sy., type I
Autoimmune polyglandular sy., type II

Tissue-nonspecific (systemic)

1.Collagenoses
Conective tissue disoders

- Systemic lupus erythermatodes (SLE)
- Sjogren sy.
- Polymyosistis/ Dermatomyositis
- Rheumatoid arthritis
- Systemic sclerosis (sclerodermia)
- Ankylosing spondylitis
- Reactive arthritis
- Mixed connective tissue disorder (MCTD)
- Bechcet sy.
- Psoriasis

2. Vasculititis
Vasculitic syndromes

- Systemic necrotising vasculitis
  - Classic polyarteritis nodosa
  - Churg-Strauss disease
  - Polyangiitis overlap sy.
- Wegener granulomatosis
- Temporal arteritis
- Takayasu arteritis
- Kawasaki disorder
- Isolated vasculitis of central nervous sy.
- Thrombangiitis obliterans
- Miscellanous vasculitis

3. Others

- Sarcoidosis
- Graft-host disease
- Cryopathies

Autoimmune disorders by location (cont')

AUTOIMMUNE DISORDERS

Organ-specific (focal)

3. Cutaneous
- Pemphigus vulgaris
- Pemphigus foliaceus
- Paraneoplastic pemphigus
- Bullous pemphigoid
- Gestational pemphigoid
- Cicatricial pemphigoid
- Dermatitis herpetiformis
- Epidermolysis bullosa acquir.
- Autoimmune alopecia
- Erythema nodosum
- Linear IgA disease
- Chronic bullous disease of childhood

4. Hematogenic
- Autoimmune hemolytic anemia
- Autoimmune trombocytopenic purpura
- Autoimmune neutropenia

5. Paraneoplastic
- Opsoclonic – myoclonic epilepsy
- Cerebellar degeneration
- Encephalomyelitis

Tissue-nonspecific (systemic)

6. Gastrointestinal/ hepatobiliary
- Gluten sensitive enteropathy
- Pernicious anemia
- Autoimmune chronic hepatitis
- Primary biliary sclerosis
- Sclerosing cholangitis

7. Gastrointestinal/ hepatobiliary

Auto-antibodies commonly found in disorders

Antibodies	Disorders
Anti-nuclear antibody (ANA):	SLE (>95% sensitivity, negative test virtually excludes SLE; low specificity), RA (30- 50%), Discoid lupus, scleroderma (60%), Drug-induced lupus (100%), Sjogren syndrome (80%), miscellaneous inflammatory disorders. Often used as a screening test - marker of the autoimmune process; positive with a variety of different autoimmune diseases but not specific. Titer does not correlate with disease activity.
Anti-double- stranded-DNA ab (anti-ds-DNA)	SLE (60 - 70% sensitivity, high specificity >90%), Lupus nephritis, RA rarely, CTD usually in low titer. Decreasing titer may correlate with worsening renal disease. Titer generally correlates with disease activity.
Anti-SS-A/Ro antibody (ELISA; positive > 10 U/ml)	Sjogren syndrome (60-70% sensitivity, low), SLE (30-40%), RA (10%), subacute cutaneous lupus, vasculitis. Useful in counseling women of childbearing age with known CTD, because a positive test is associated with a small but real risk of neonatal SLE and congenital heart block.
Anti-centromere antibody	CREST (70- 90%, high specificity), Scleroderma (10-15%), Raynaud disease (10-30%). Predictive value of a positive test is >95% for scleroderma or related disease (CREST, Raynaud). Diagnosis of CREST is made clinically
Anti-Smith antib. (anti-Sm)	SLE specific. positive test increases probability of SLE(ELISA; positive > 25 U/ml)
Anti-ribonucleoprotein antibody (RNP) (ELISA; positive > 25 U/ml)	MCTD (95-100% sensitivity, low specificity), Scleroderma (20-30%, low), SLE (30%), Sjo¶gren syndrome, RA (10%), Discoid lupus (20 - 30%). A negative test essentially excludes MCTD; a positive test in high titer, while nonspecific, increases posttest probability of MCTD.
Anti-Jo1 histidine-tRNA ligase	Inflammatory myopathy
Anti-Scl-70 antibody	Scleroderma (15-20%, high specificity >95%)
Anti-topoisomerase antibodies	Type I topoisomerase Systemic sclerosis (anti-Scl-70 antibodies)
Anti-histone antibodies	SLE 50%-70% sensitivity; drug-induced LE (lupus erythematosus) > 95% sensitivity
Rheumatoid factor (RF)	Rheumatoid arthritis (50-90%) Other rheumatic diseases, chronic infections, some malignancies, some healthy individuals, elderly patients. Titer does not correlate with disease activity
Anti-neutrophil cytoplasmic antibody (ANCA)	Wegener granulomatosis (systemic necrotizing vasculitis) (56-96%, high specificity); Crescentic glomerulonephritis or other systemic vasculitis (e.g., polyarteritis nodosa). Ability of this assay to reflect disease activity remains unclear.

Autoimmnune conditions

- organ specific

- Endocrine system
- Skin
- Hematologic system
- Neuromuscular system
- Hepatobiliary system
- Gastrointestinal system
- Renal system
- Paraneoplastic neurologic disorders

Some of organ-specific autoimmune Diseases

ENDOCRINE

- Diabetes mellitus I.type → β- cells
- Graves disease → thyroid TSH receptors
- Addison disease →supraren
- Type I polyglandular syndrome
- Type II polyglandular syndrome
- Immune- mediated infertility →sperma

NEUROMUSCULAR

- Myasthenia gravis → ACh-receptors
- Eaton – Lambert myotonic) sy.
- Stiff- man syndrome
- Acute disseminated encephalomyelitis
- Multiple sclerosis
- Guillain – Barré syndrome
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy with conduction block
- Chronic neuropathy with monoclonal gamopathy

SKIN & INTEGUMENTA

- Pemphigus and pemphigoid
  - Pemphigus vulgaris , foliaceus, paraneoplastic
  - Pemphigoid bullus
  - Pemphigoid cicatricial, gestationis
- Bullous disorders
  - Epidermolysis bullosa
  - Chronic bullus disease of childhood
- Erythema nodosum
- Autoimmune alopecia
- Dematitis herpetiformis
- Linear IgA disease

HEMATOLOGICAL

- Pernicious anemia
- Autoimmune hemotytic anemias
- Autoimmune trombocytopenia

Autoimmnune conditions

- organ non-specific

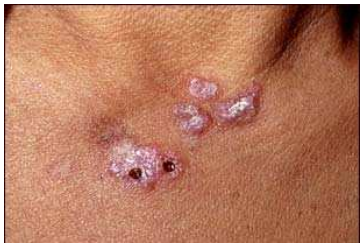
- Collagenoses (Connective tissue diseases)
- Vasculitis (vascular & perivascular diseases)

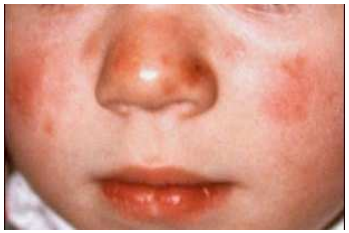
Systemic Lupus Erythematosus

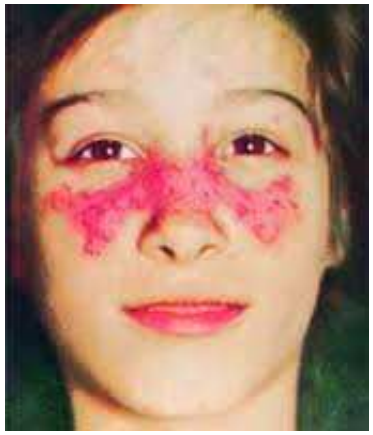
- **D:** chronic autoimmune disease affecting any organ system (skin, joints, kidneys, serosal membr., and heart), major rheumatic disease, and > 90% of persons with the disease have polyarthralgias.
- **EP:** common disease; more common in African Americans, Hispanics, and Asians than whites; prevalence 1: 2000 person; peak incidence 15-40 years; female-to-male 9:1 (30:1 during the childbearing years).
- **ET:** ? multifactorial :
  - **genetic** (familial cases, identical twins; association with class II HLA genes, HLA-DQ locus),
  - **hormonal** (estrogens favor the development, androgens protect against),
  - **immunologic, infections**
  - **environmental factors** (UVB light - exposure to the sun or unshielded fluorescent bulbs, may trigger exacerbations),
  - **drugs** (hydralazine, procainamide, quinidine, methyldopa, isoniazid, and phenytoin),
- **Manifestations:**
  - 90% Arthritis, painful and swollen jointsjoints (mimick rheumatic arthritis)
  - 80% Fever, fatigue; feeling tired, 70% Vasculitis,
  - 50% Butterfly erythema (hallmark), 50% Pleural effusions, chest pain, pleuropericarditis,
  - 50% Lupus glomerulonephritis (progressive), Raynauld fingers, swollen lymph nodes,
  - hair loss, mouth ulcers,
  - Often there are periods of illness, **flares,** and periods of **remission** with few symptoms

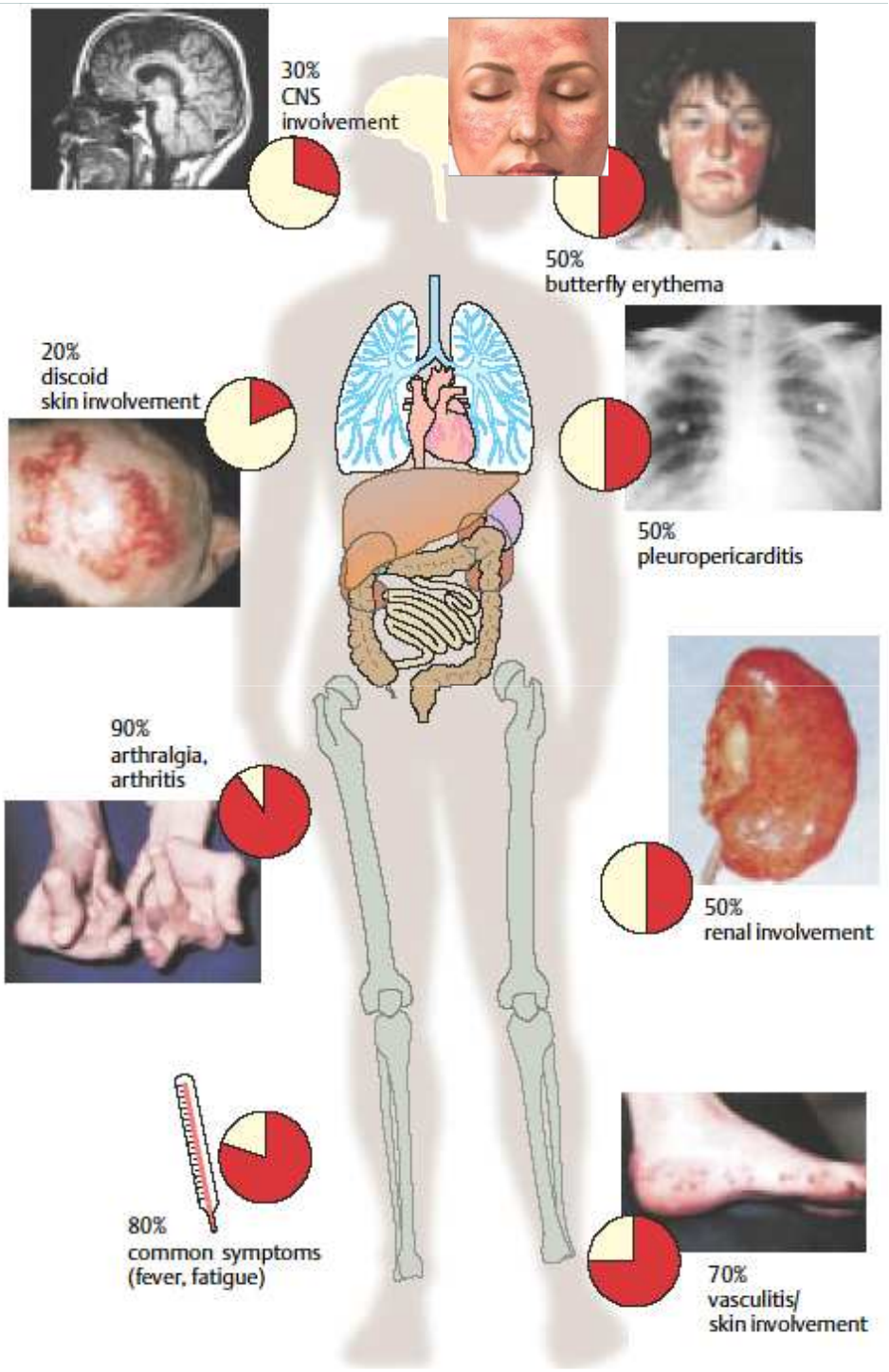
Systemic lupus erythemato

- SLE is a chronic inflammatory disease believed to be a type III immunopathology reaction
- Sensitized B-lymphocyte cells show **polyclonal B-cell activation shift towards immature B cells**; produce antibodies targetting DNA, histones, and other proteins,
- Antibodies clump into **antibody-protein complexes** which stick to surfaces and damage blood vessels in critical areas of the body, such as the glomeruli of the kidney.
- Typical in SLE are also **abnormalities in apoptosis** : increased in monocytes and keratinocytes

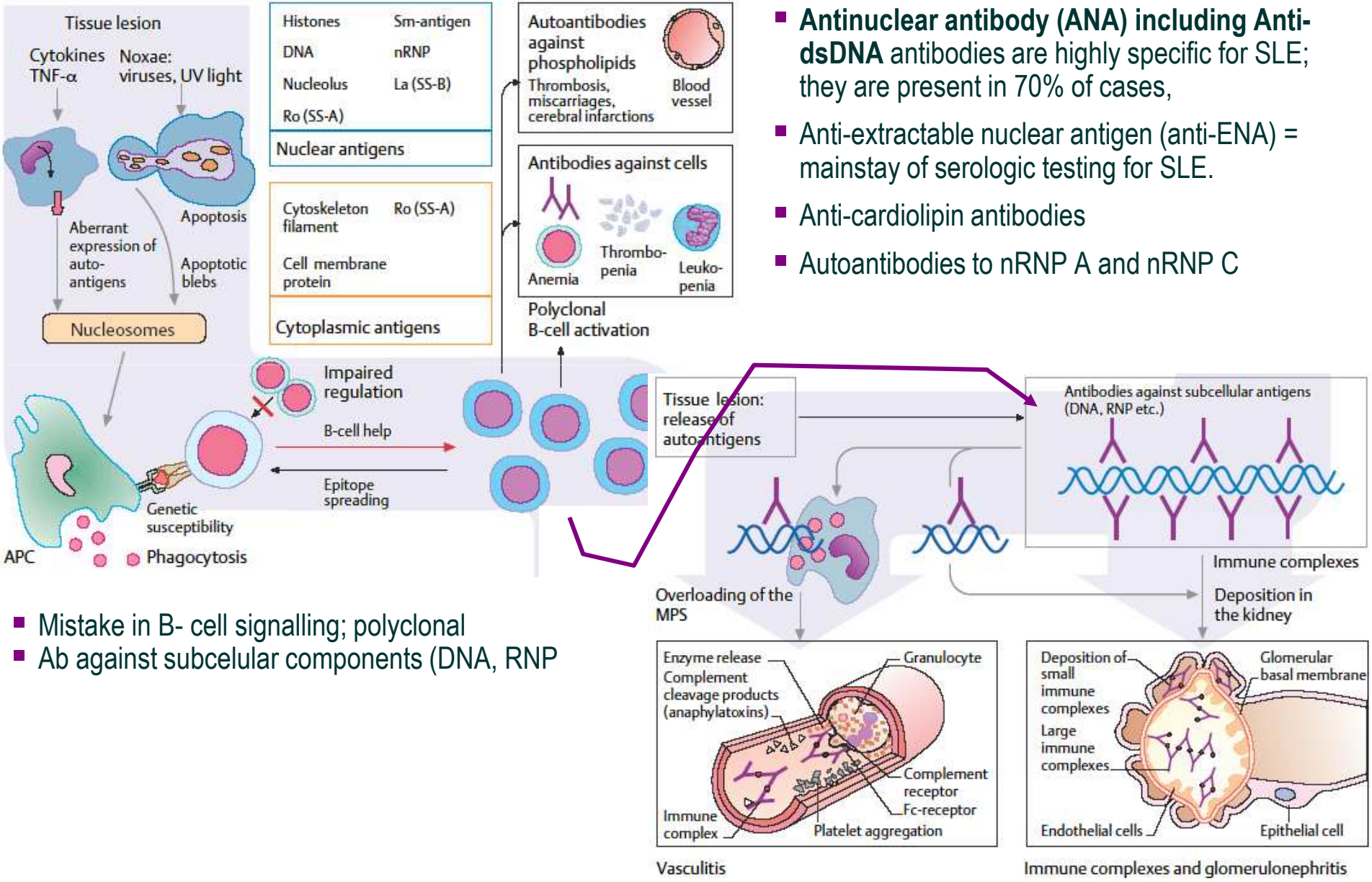








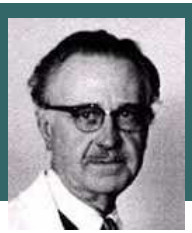
SLE pathogenesis



- **Antinuclear antibody (ANA) including Anti-dsDNA** antibodies are highly specific for SLE; they are present in 70% of cases,
- Anti-extractable nuclear antigen (anti-ENA) = mainstay of serologic testing for SLE.
- Anti-cardiolipin antibodies
- Autoantibodies to nRNP A and nRNP C

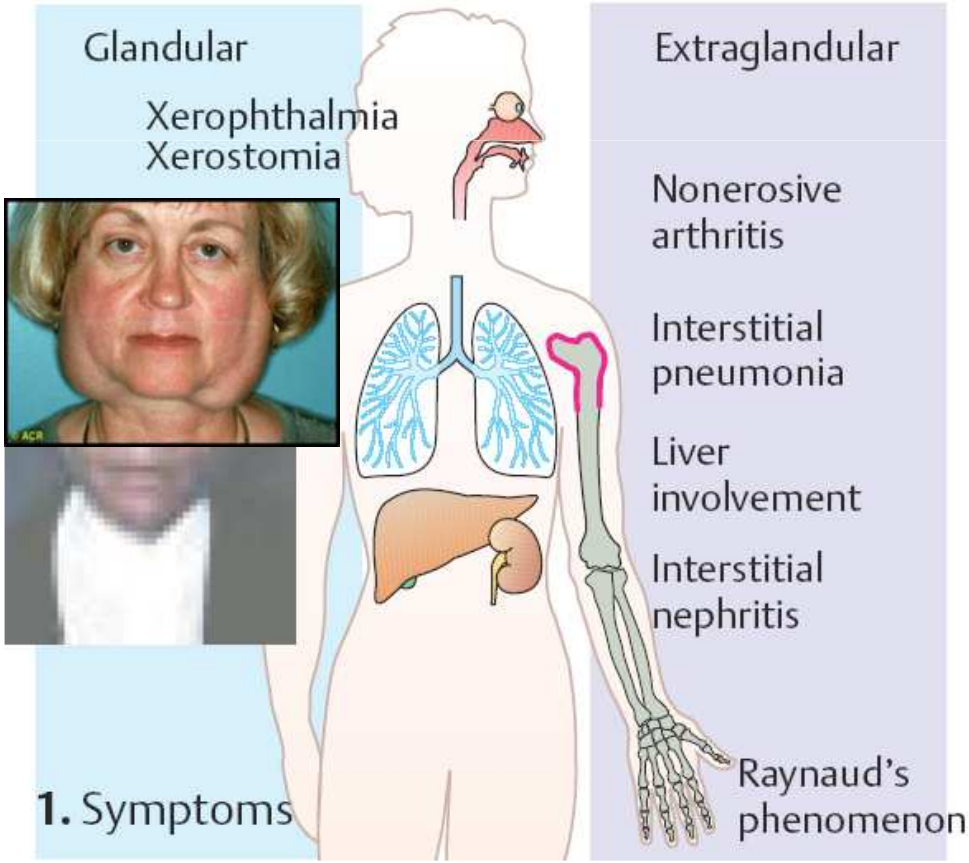
- Mistake in B- cell signalling; polyclonal
- Ab against subcelular components (DNA, RNP

Sjögren's syndrome

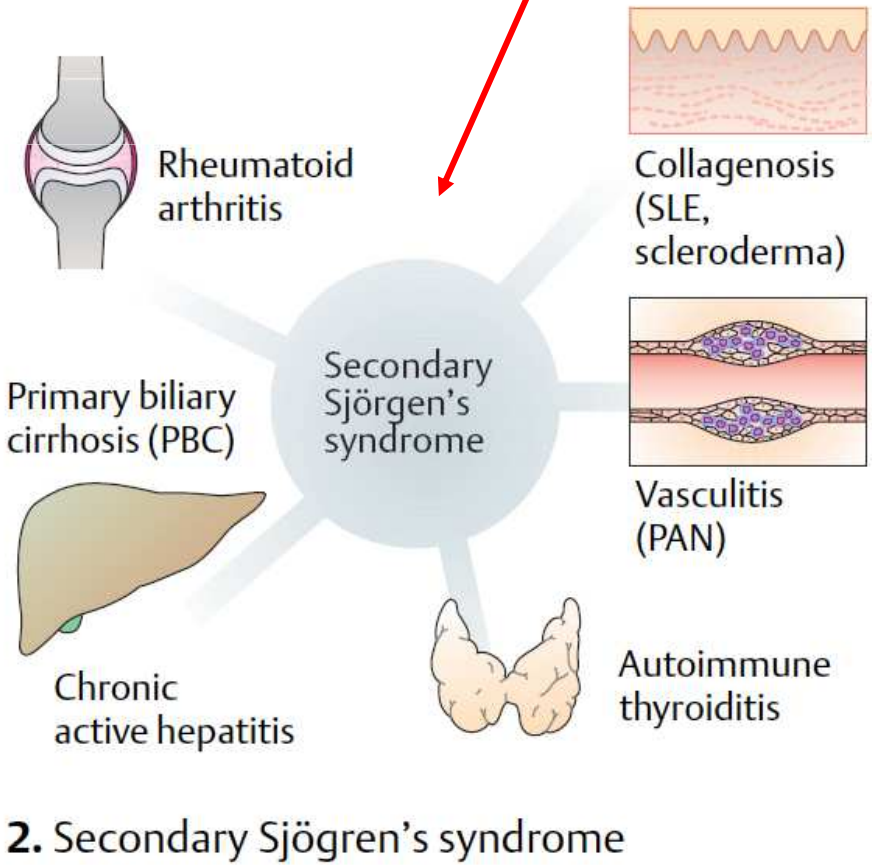


Et: unknown; Henrik S.C. Sjogren (1933)
Sy: generalized dryness (sicca symptoms) lymphocytic infiltration into skin glands; skin, nose, kidneys, blood vessels, lungs, liver, pancreas, brain; peripheral nervous system (distal axonal sensorimotor neuropathy); keratoconjunctivitis

- Primary (Sicca syndrome) (50%);
- Secondary (50%) all symptoms of SS; accompanies AutoID, mostly RA; slower progress
- Resk of: pseudolymphoma, lymphoprilipherative disorders (10%), Hodgkin lymphoma (1%), Salivary gl. tumours



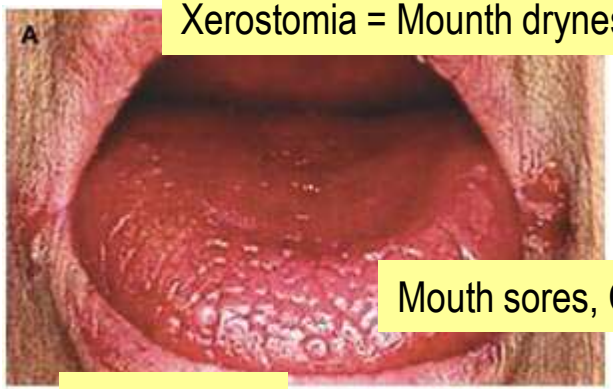
1. Symptoms

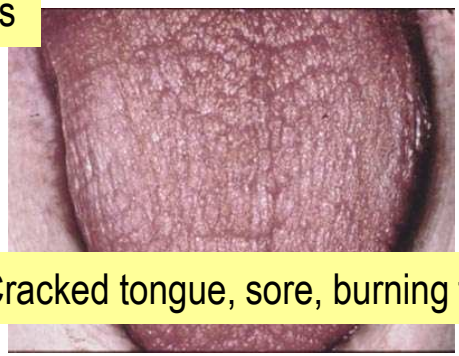


2. Secondary Sjögren's syndrome

Sjögren's syndrome

Xerostomia = Mounth dryness

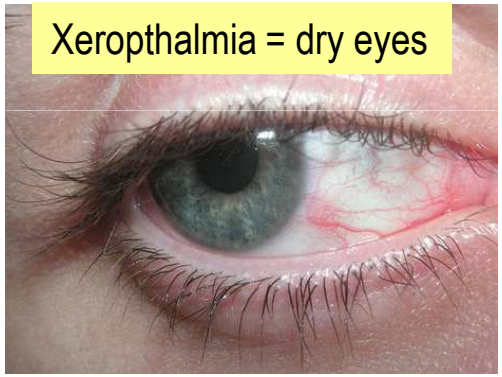




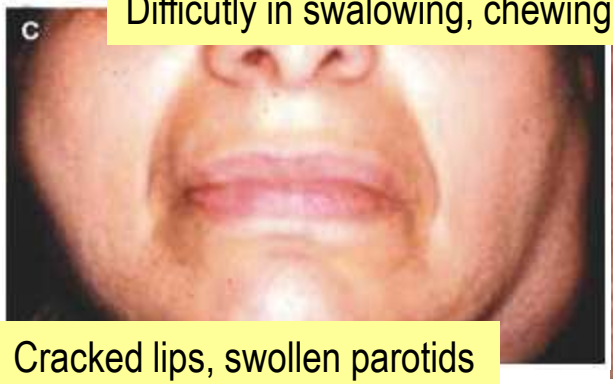
Mouth sores, Cracked tongue, sore, burning th

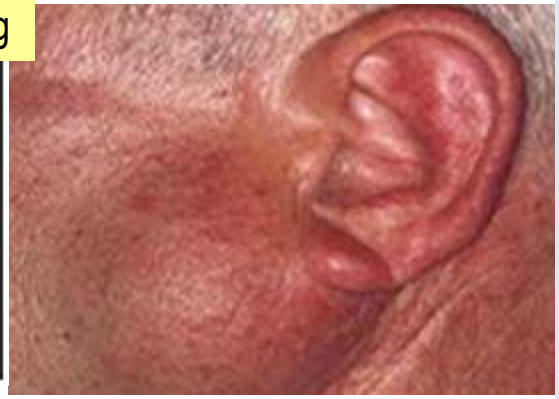
Tooth decay

Xeropthalmia = dry eyes



Difficutly in swalowing, chewing





Cracked lips, swollen parotids

Symptoms of Sjögren's Syndrome

PRIMARY SYMPTOMS

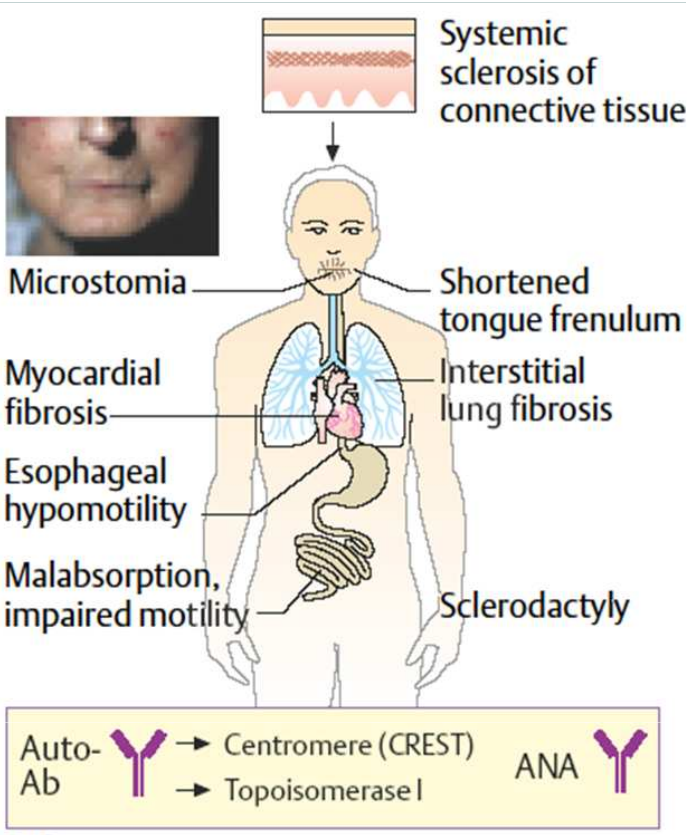
Dry eye
- Gritty, sandy feeling
- Stinging feeling

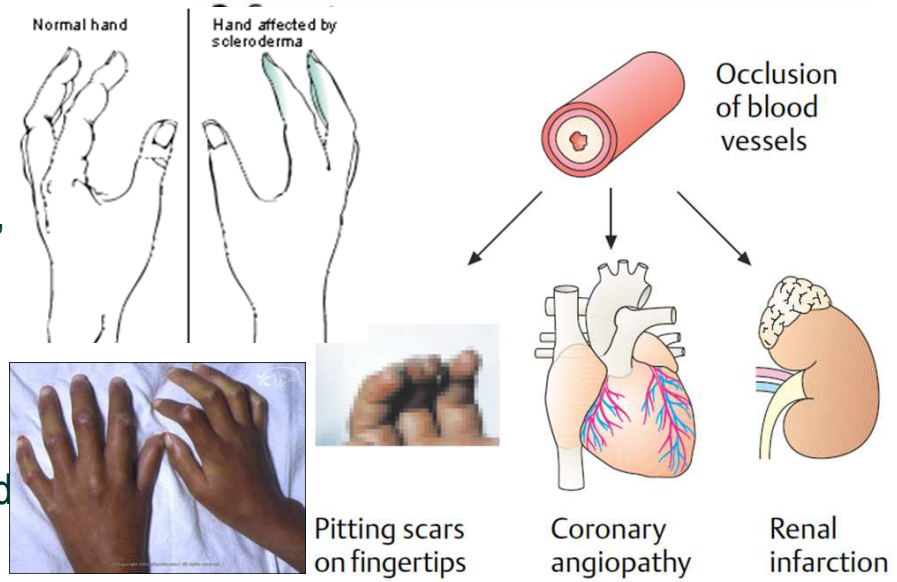
Dry mouth
- Dry, cracked tongue
- Sore throat
- Burning throat
- Difficulty talking
- Difficulty swallowing
- Difficulty chewing dry food
- Change in sense of taste/smell
- Increase in cavities
- Mouth sores
- Cracked lips

OTHER SYMPTOMS
- Swollen parotid glands
- Nausea
- Dry skin
- Joint pain
- Dry nose
- Reflux
- Muscle pain
- Fatigue
- Muscle weakness
- Low-grade fever
- Vaginal dryness
- Neuropathy
- Dizziness

Systemic Sclerosis (scleroderma)

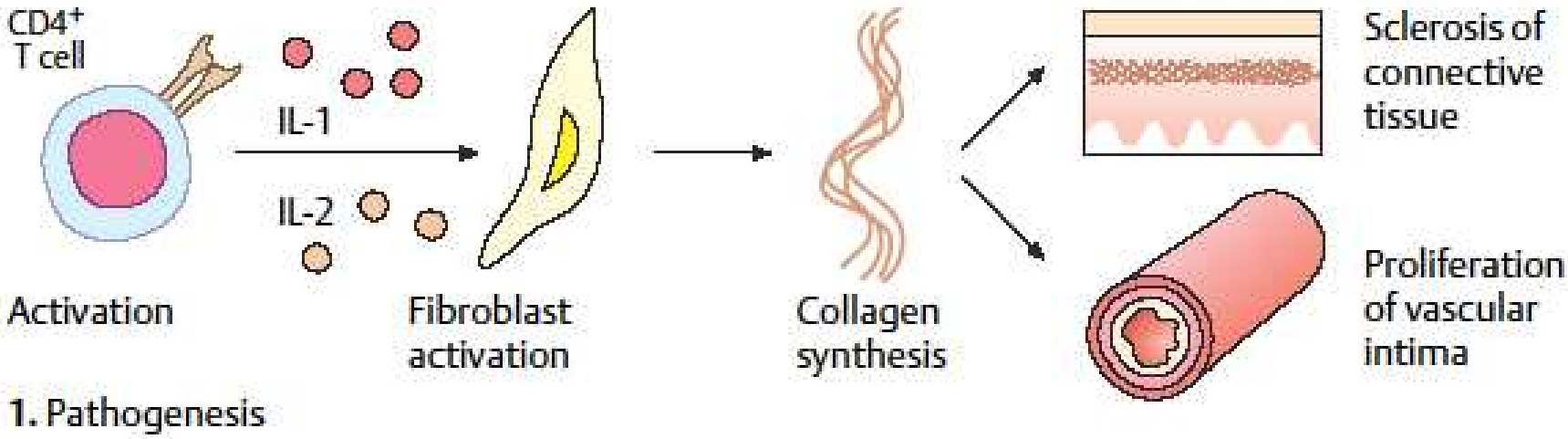
- **ET:** autoimmune disease of connective tissue; humoral and cellular immune system abnormalities
- **PA:** excessive collagen deposition (fibrosis) in the skin and internal organs (lungs, gastrointestinal tract, heart, kidneys), (fixation of subdermal structures, sheaths or fascia covering tendons and muscles)
- **EP:** 4x higher in women, peak incidence (35-50 years), 9-year survival rate is about 40%.
- **SY: 1. Generalized form, 2. CREST syndrome** (limited to the hands and face)
- **Generalized form:** severe and progressive diffuse scleroderma (whole body), early onset of organ involvement
- hardening and thickening of the skin and submucosa
- organs (fibrosis, atrophy) mucosa, submusoca, muscles
- dysphagia (difficulty swallowing) - hardening of esophagus,
- malabsorption - atrophy in the intestine,
- restrictive lung disease - dyspnea, eventually respiratory failure,
- pericarditis, heart block, and myocardial fibrosis
- malignant hypertension, renal insufficiency - renal arteriosclerosis polyarthritis (all persons with scleroderma)
- Raynaud's phenomenon (reversible vasospasm of the arteries supplying the fingers)
- Early heart, lung, or kidney involvement - predictor of shortened survival





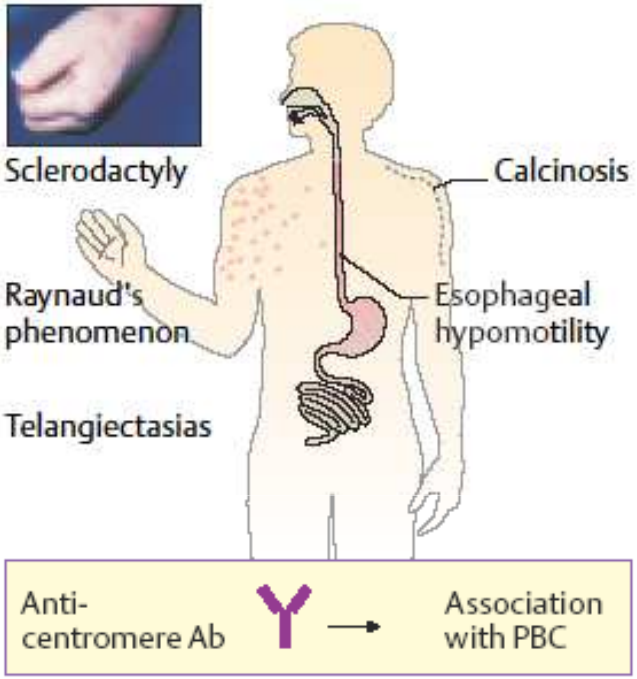
Scleroderma („hard skin“)

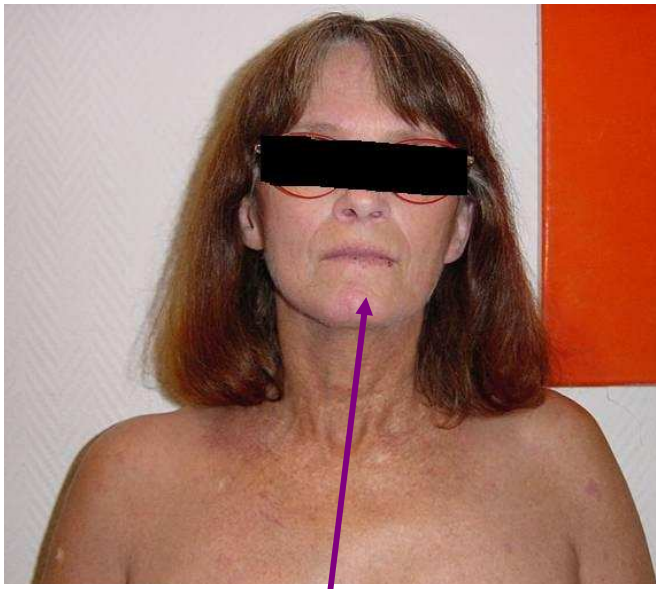
- **Localised scleroderma ('morphoea')** - changes only occur in isolated areas of the skin and the tissues beneath it. It is relatively mild and does not affect internal organs.
- **Systemic sclerosis** - changes may occur in the skin and also in a number of internal organs including blood vessels, joints, the digestive system (oesophagus, stomach and bowel), occasionally the lungs, heart, kidneys and muscles. Changes in the connective tissue may affect the function of any of these organs.
- **Sy:** differs from person to person; it is hard to predict how the disease will develop in each individual
- **PA:** hyperproduction of collagen (scar tissue) thickening and stiffening of tissue
- triggered by some unusual chemical exposure. Scleroderma is probably caused by a combination of different genetic and environmental factors, familiar occurence

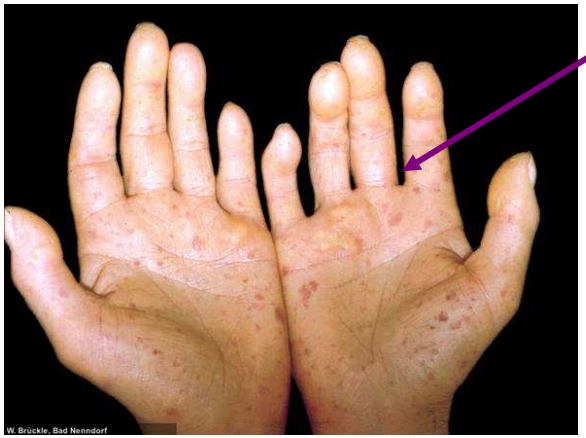


1. Pathogenesis

CREST syndrome







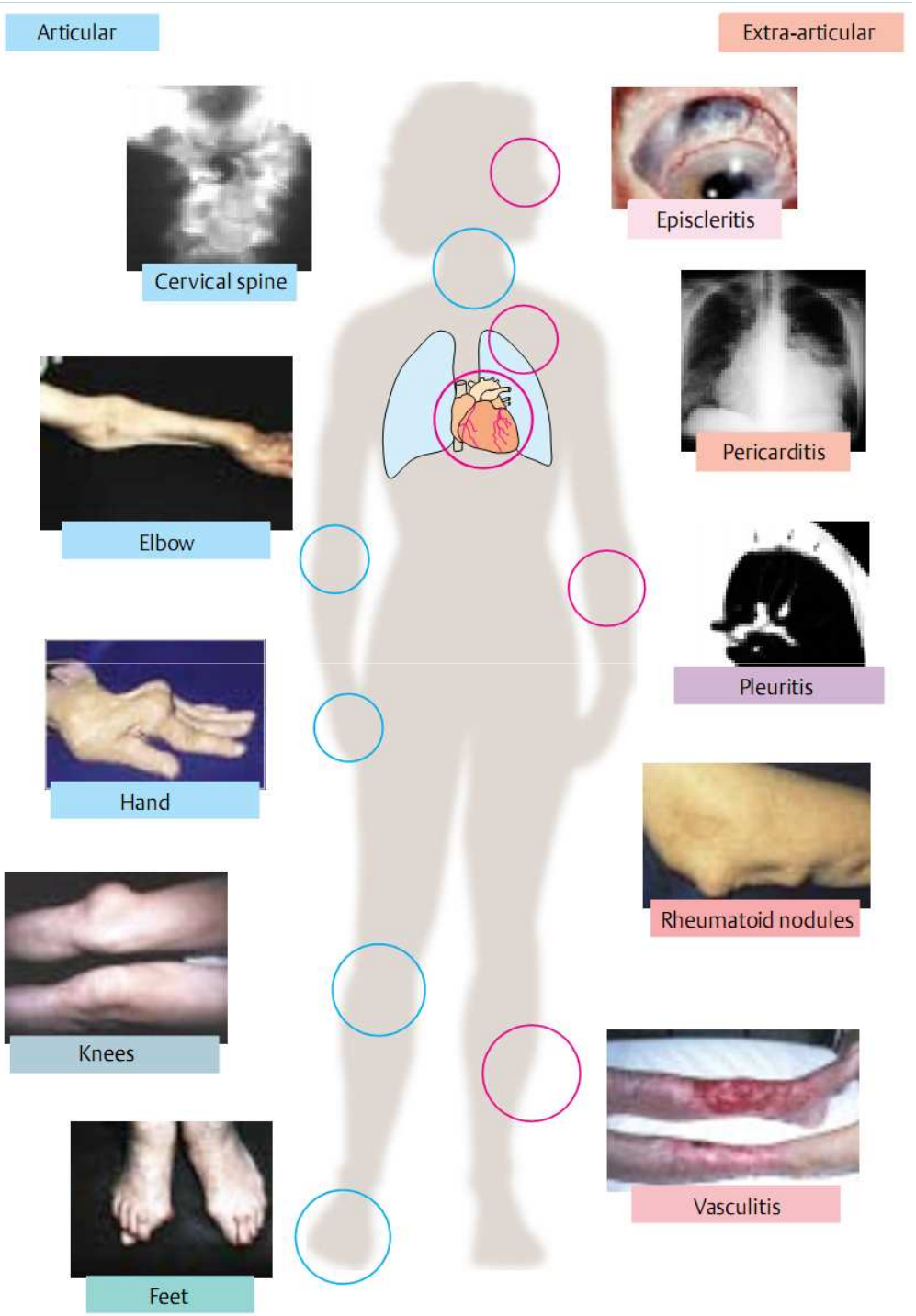
- "*stone facies*" (restricted motion of the mouth),
- sclerodactyly (scleroderma of the fingers),
- calcinosis (calcium deposits in the subcutaneous tissue that erupt through the skin),
- Raynaud's phenomenon, esophageal dysmotility and telangiectasia

Mixed connective tissue disease (MCTD)

Reumatoid arthritis

Lungs: pleuritis, pulmonary fibrosis,
about ¼ of with RA develop rheumatoid lung disease (RLD). Inlcuding
Reumatoid pleurirtis – often pleural effusions
Fibrosis of the lungs (a rare well recognized consequence of therapy with methotrexate and leflunomide).
Caplan's syndrome - lung nodules in RA - patients and additional exposure to coal dust

Joints:
affected symmetrically on both sides; most frequently wrist, hands, elbows, shoulders, knees, ankles

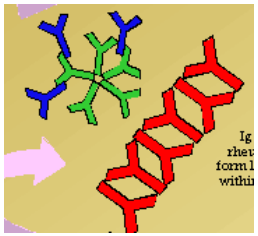


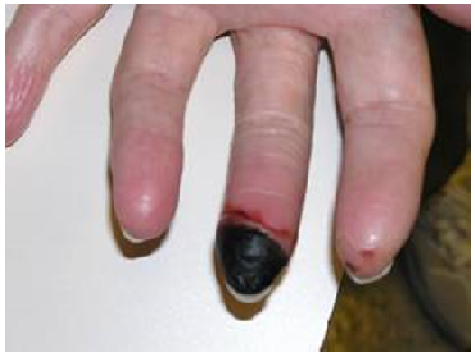
Rheumatoid arthritis

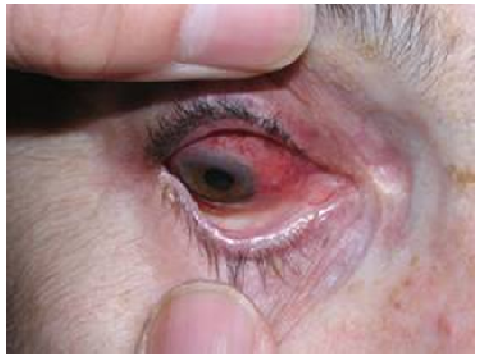
Rheumatoid factor (RF) = autoantibody immunocomplexes that use Fc region bounds of IgG

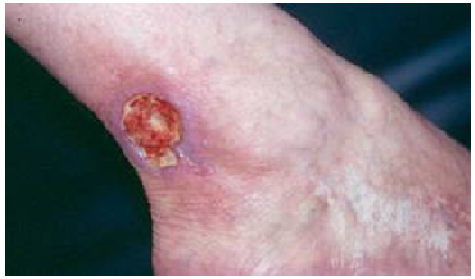
IgM RF- cummulative immuno-complexes formed via binding of IgG autoantibodies (via Fc) to Ig M – rosetts

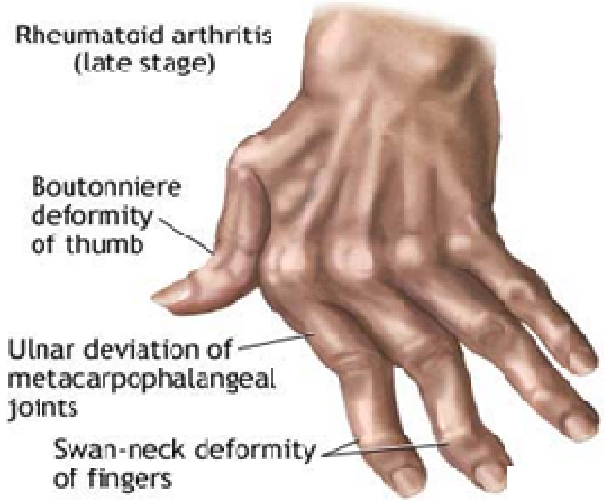
IgG RF – complexes of contraparalel self associated IgG



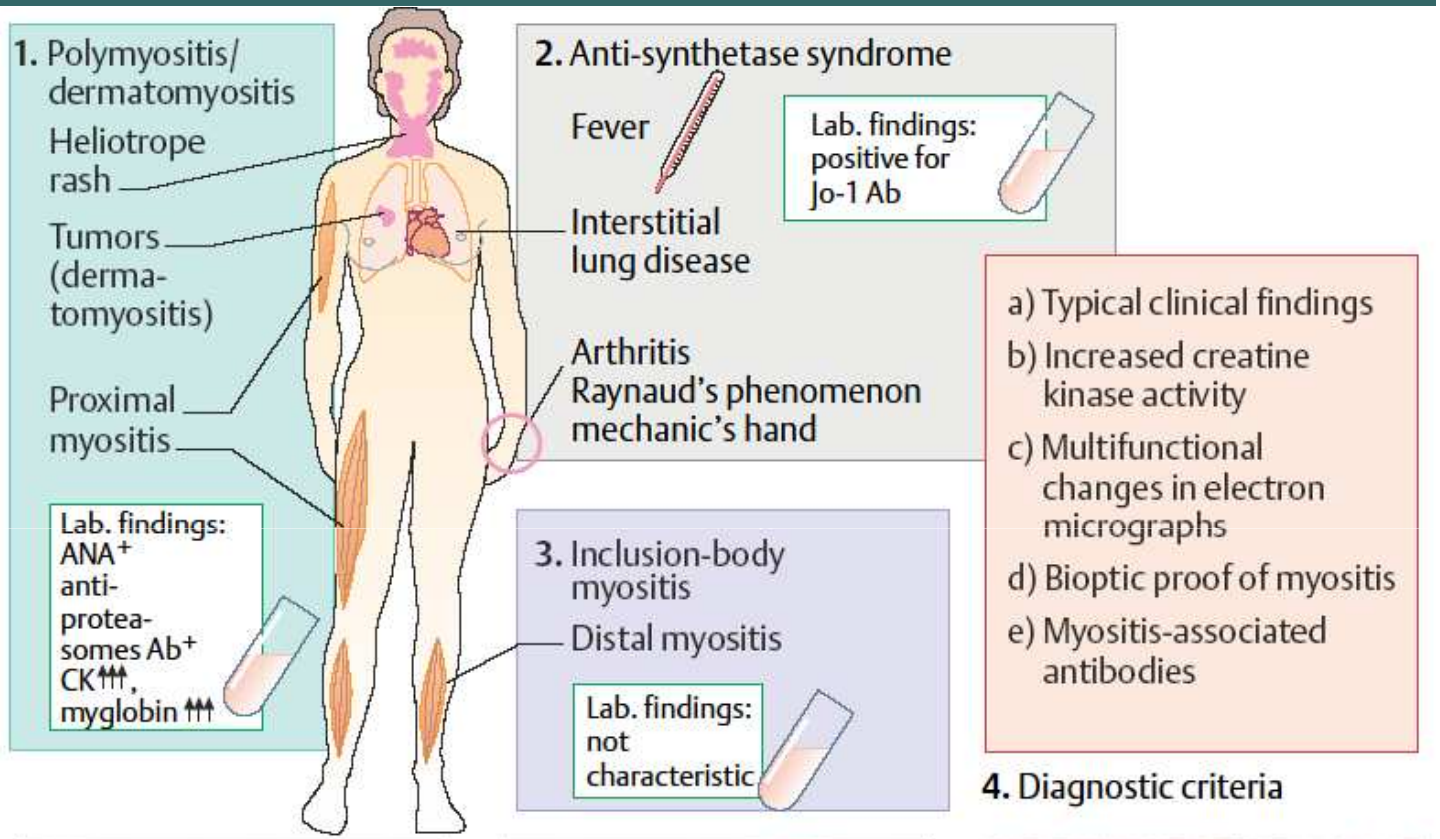






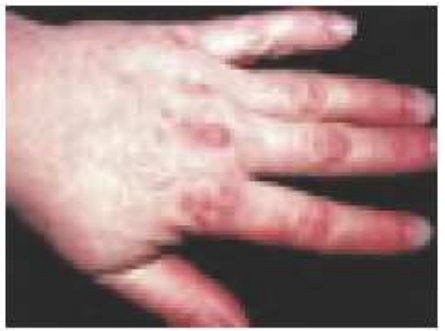


Polymyositis (Dematomyositis)



4. Diagnostic criteria

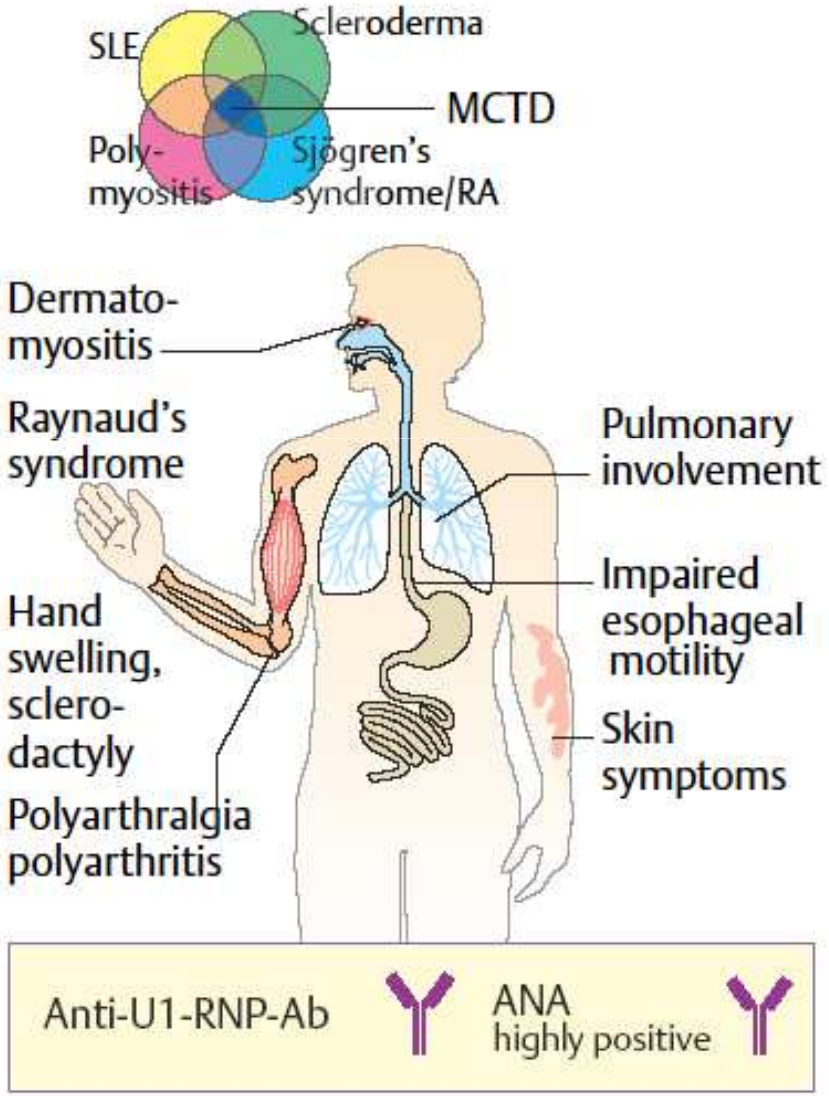
5. Heliotropic exanthema



6. Gottron's sign

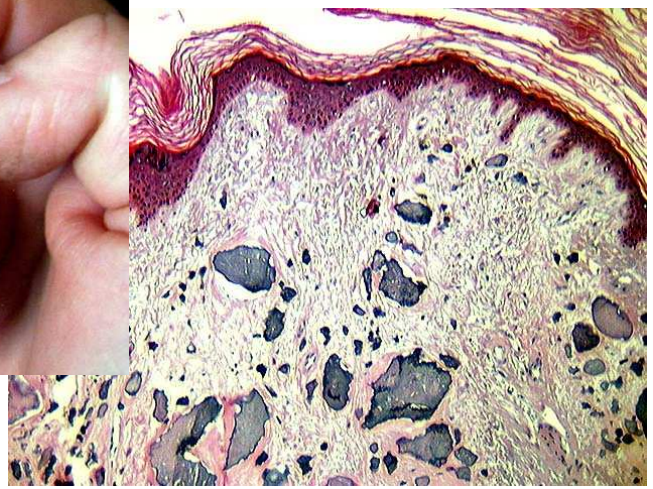
7. Histology of polymyositis

Mixed connective tissue disease (MCTD) - Sharp' overlap syndrome



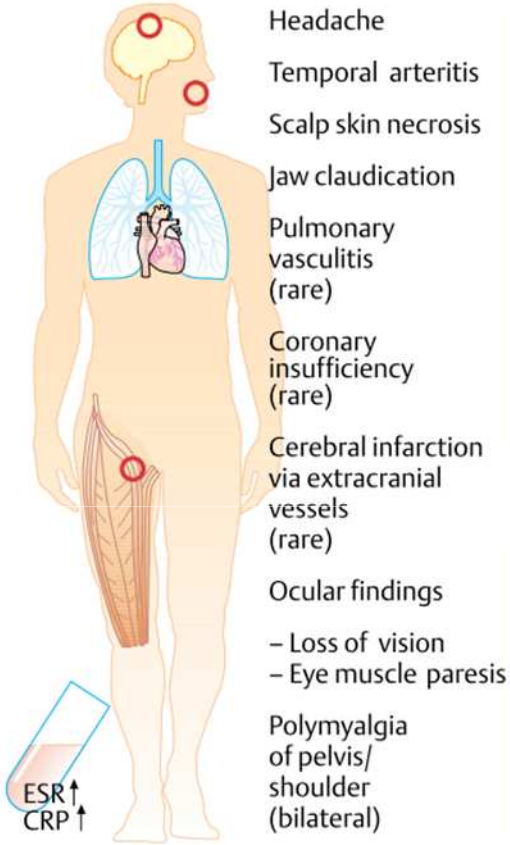
sclerodactyly in late stage of SLE or MCTD

necrosis



Vasculitic syndromes (vasculitis)

- Systemic necrotizing vasculitis
  - Polyarteritis nodosa (classic)
  - Allergic angiitis and granulomatosi (Churg-Strauss disease)
  - Polyangiitis overlap syndrome
- Hypersensitivity vasculitis
- Wegener's granulomatosis
- Temporal arteritis
- Takayasu' arteritis
- Kawasaki's disorder
- Isolated vasculitis of the central nervous system
- Trombangiitis obliterans
- Miscellaneous vasculitis



1. Clinical findings in temporal arteritis/ polymyalgia rheumatica

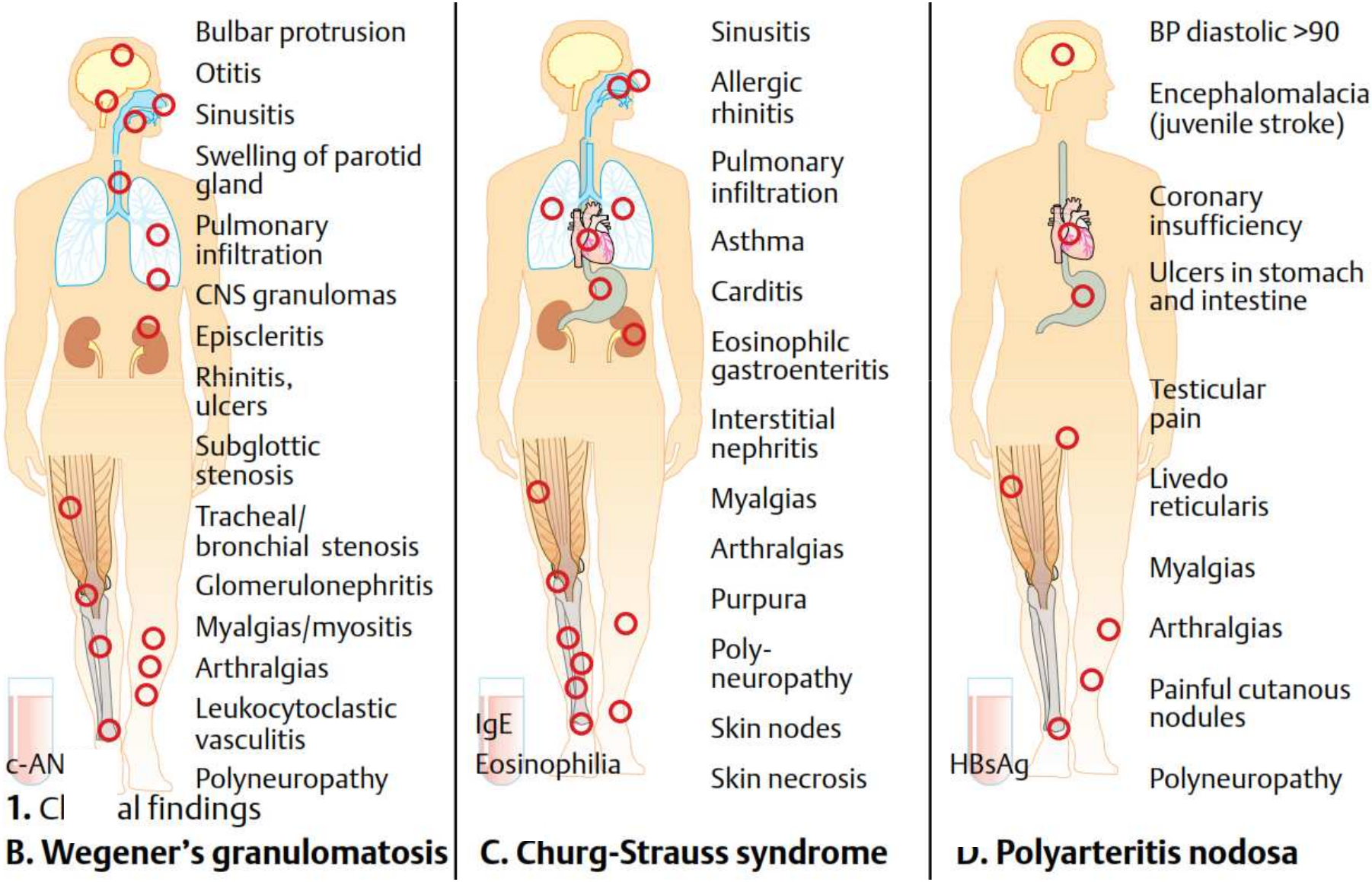
Aching shoulders and/ or bilateral stiffness
Disease onset within 2 weeks
Initial ESR increase of >40 mm in 1 hour
Morning stiffness >1 hour
Age over 65 years
Depression and/or weight loss
Bilateral tenderness on palpation of upper arm

2. Diagnostic criteria of polymyalgia rheumatica

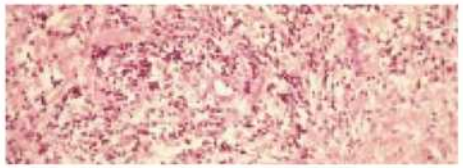
Patient over 50 years at first manifestation
Newly occurrent headache
Clinical findings in temporal arteries:
tenderness on palpation, pulselessness
highly increased ESR
positive arterial biopsy

3. Diagnostic criteria of temporal arteritis

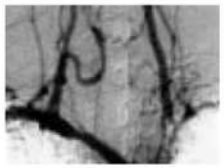
Manifestations of different vasculitis disorders



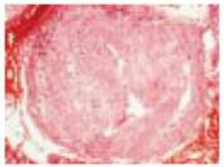
Mechanisms of vasculitis disorders



4. Histology of Takayasu's arteritis

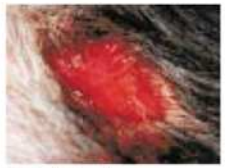


5. Branch stenosis in Takayasu's arteritis



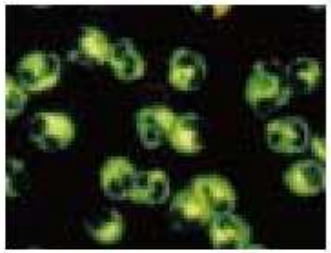
6. Histology of occluded temporal artery

7. Temporal arteritis



8. Head skin ulcer

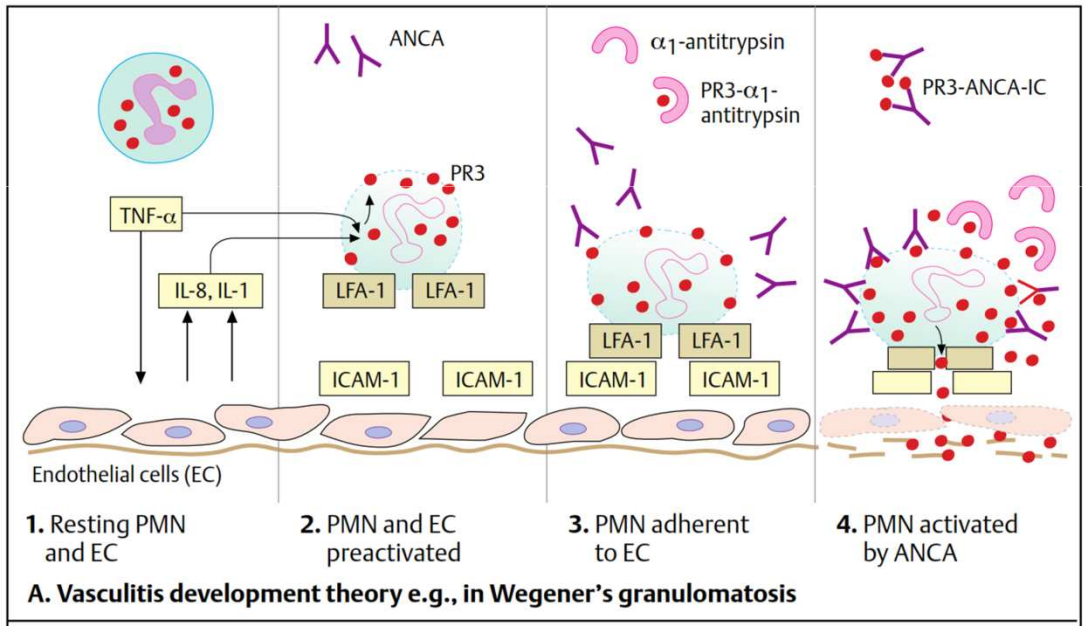
A. Clinical features of giant cell arteritis: Takayasu's and temporal arteritis



2. C-ANCA

3. Saddle nose

4. Vasculitis of the toes



A. Vasculitis development theory e.g., in Wegener's granulomatosis