

# Auto Immune Diseases

Supachai A. Basit, RMT, PhD

# Auto Immunity

- **Auto or Self antigens**
  - Antigens present in ones own cells
  - Altered by the action of bacteria, viruses, chemicals or drugs as a non-self
- **Auto antibody**
  - Altered cell (Auto Ag) - elicits the productions of Antibody
- **Auto Immunity** (misnomer, alternative= auto allergy)
  - Immune response of auto Ab against self Ag
  - Humoral or cell mediated immune response against the constitute's of the body's own tissues.
  - There are more than 80 different kinds of diseases caused by autoimmunity.

# Autoimmune Diseases

– *Autoimmune diseases is a group of disorders in which tissue injury is caused by humoral (by **auto-antibodies**) or cell mediated immune response (by **auto-reactive T cells**) to self antigens.*

- Normally, the immune system **does not attack the self**. However, there is a large group of **autoimmune** diseases in which the immune system does attack self-cells
- The attack can be directed either against a very **specific** tissue or to a large no. of tissues
- Once started, autoimmune diseases are hard to stop

# Causes of Autoimmune Diseases

## 1. Sequestered or Hidden antigens

- Ag in the secluded places - are not accessible to the immune system.
- E.g. Lens Ag, Sperm Ag & Thyroglobulin.

## 2. Neo antigens

- Altered or Modified Antigens – by physical (irradiation), chemical (drugs) or microbial agents ( intracellular viruses)

## 3. Cessation of Tolerance

- It may result when tolerance to the self-Ag is abrogated.

# Causes of Autoimmune Diseases

## 4. Cross reacting Antigens

- A foreign Ag which resembles self a 2<sup>nd</sup> Ag
- Many species share organ specific Ags.
- E.g. Ag of Human brain & Ag of sheep brain, Streptococcal M protein & Heart muscles, Nephritogenic strains of Streptococci Ags & Renal glomeruli shares similar epitopes.

## 5. Loss of Immunoregulation

- Loss of Self tolerance - caused by over activity or lowered activity of T and B- cells

# Classification of Autoimmune Diseases

- Broadly classified into 3 groups

1. Haemolytic autoimmune diseases

2. Localised & 3. Systemic autoimmune diseases

## 1. Haemolytic autoimmune diseases

- Clinical disorder due to destructions of blood components. Auto Ab are formed against one's own RBCs, Platelets or Leucocytes.
- E.g. Haemolytic anaemia, Leucopenia, Thrombocytopenia, etc.

# Classification of Autoimmune Diseases

## 2. Localised autoimmune diseases or Organ specific autoimmune diseases

- A particular organ is affected due to auto Abs.
- For example:
  - **Thyroiditis** (attacks the thyroid)
  - **Multiple sclerosis** (attacks myelin coating of nerve axons)
  - **Myasthenia gravis** (attacks nerve-muscle junction)
  - **Juvenile diabetes** or Type I DM (attacks insulin-producing cells)

# Classification of Autoimmune Diseases

## 3. Systemic autoimmune diseases or

### Non-organ specific autoimmune diseases

- Immune complexes accumulate in many tissues and cause inflammation and damage.
  - Affects many organs or the whole body
- For example:
- **Systemic Lupus Erythematosus** (anti-nuclear Ab.): Harms kidneys, heart, brain, lungs, skin...
  - **Rheumatoid Arthritis** (anti-IgG antibodies): Joints, hearts, lungs, nervous system...
  - **Rheumatic fever**: cross-reaction between antibodies to streptococcus and auto-antibodies.



# Criteria for AIDs

- AI response is regularly associated with the disease
- Can induce a replica of disease in the animal
- Immunopathologic changes observed in the natural and experimental diseases should be paralleled to each other
- The disease can be transferred via exchange of serum or lymphoid cells

# Genetic Predisposition

- HLA-DR4: RA
- HLA-DR5: thyroiditis
- HLA-DR2: multiple sclerosis
- HLA-DR3: SLE
- HLA-DR3/HLA-B8: Grave's disease

# General Signs

- elevated gamma globulins
- various autoantibodies
- depressed level of serum complement
- immune complex in the serum
- depressed level of Ts cells
- lesions detected in biopsy

# Acute Disseminated Encephalitis

- headache, backache, stiff neck, nausea, low grade fever, weakness and paralysis
- cell mediated allergic response



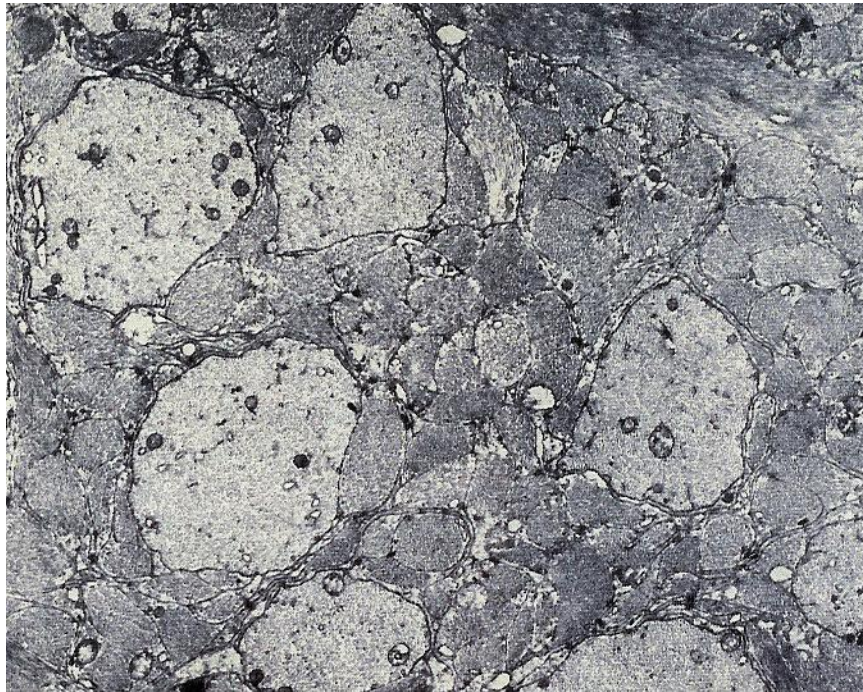
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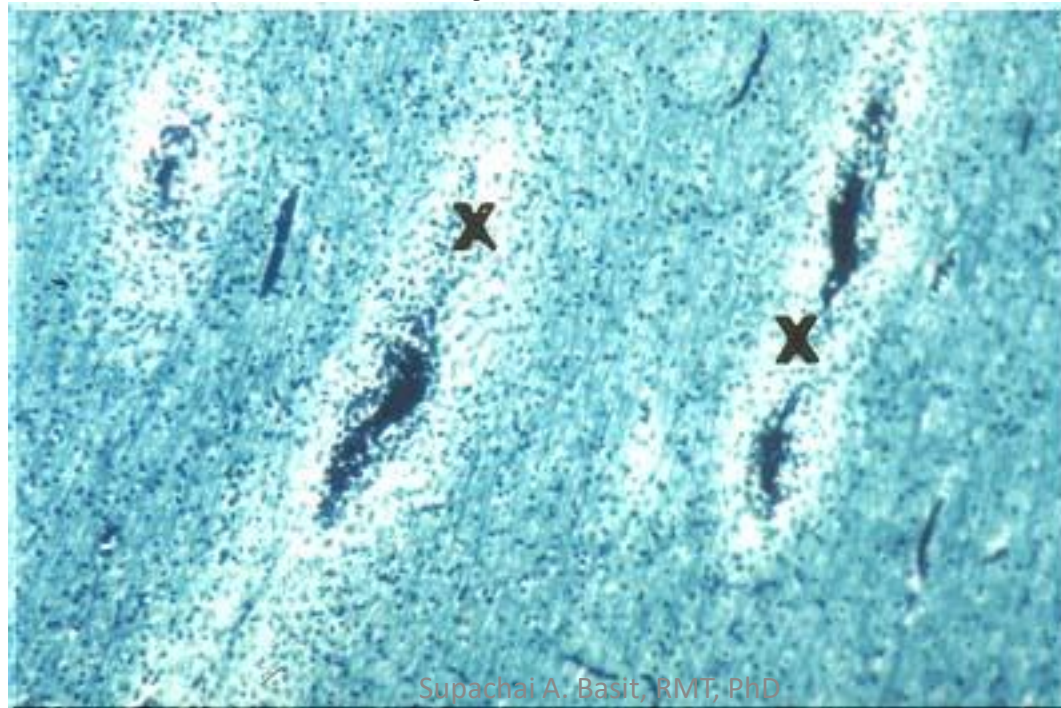
# ADE

- accumulation of macrophages and other WBC at the gray and white matter



# Experimental allergic encephalomyelitis

- occurs 2-3 weeks post sensitization
- perivascular inflammation
- T cells causes demyelination



# Hemolytic Diseases

## Warm AHA

- optimum 37°C

## Cold AHA

- 4° C IgM (anti I or anti-i)

## PCH

- DLA (IgG directed against antigen P)



# ITP

- petechiae, bleeding problems
- platelet  $<100,000$  / $\mu$ L
- IgG against plt (Coomb's test) can be drug induced

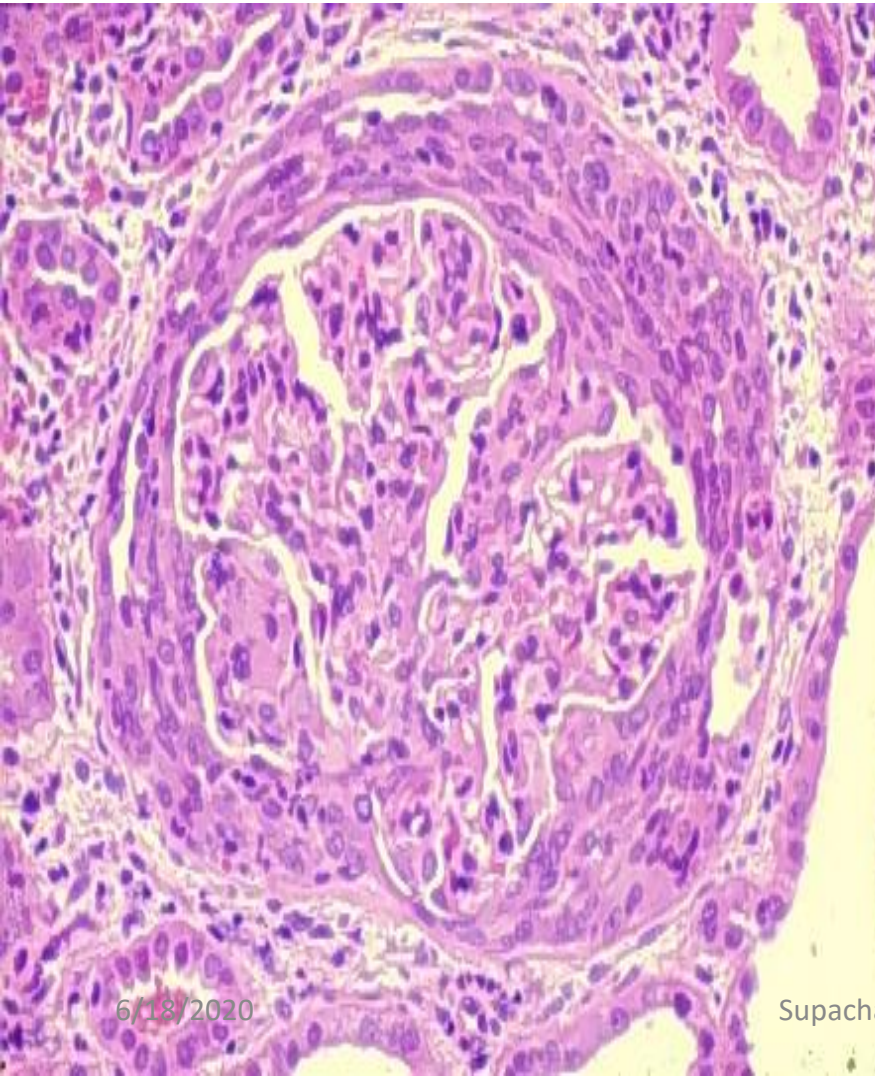




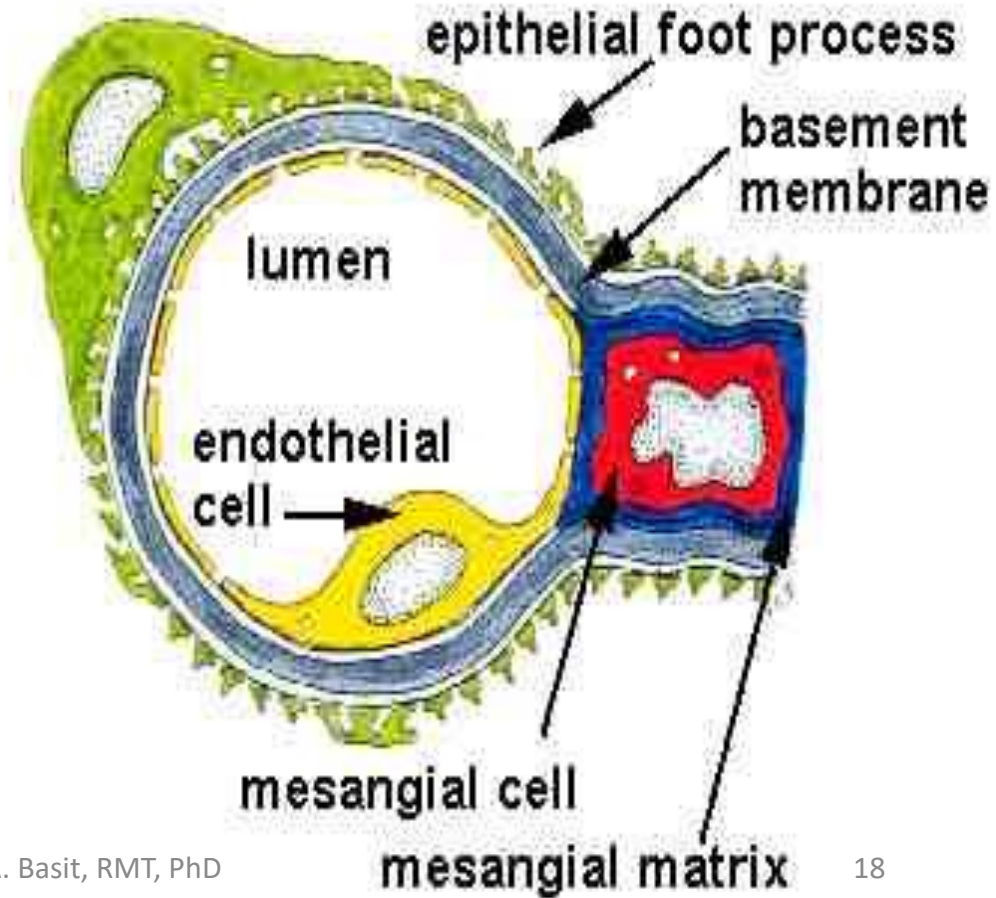
# Goodpasture's syndrome

- pulmonary hemorrhages, hemoptysis, hematuria, AGN
- IgG deposits in alveolar and glomerular basement membrane
- IgG appears to represent an ab specific for an ag shared by kidneys and lungs
- immune complex phenomenon

# Goodpasture (AGN)

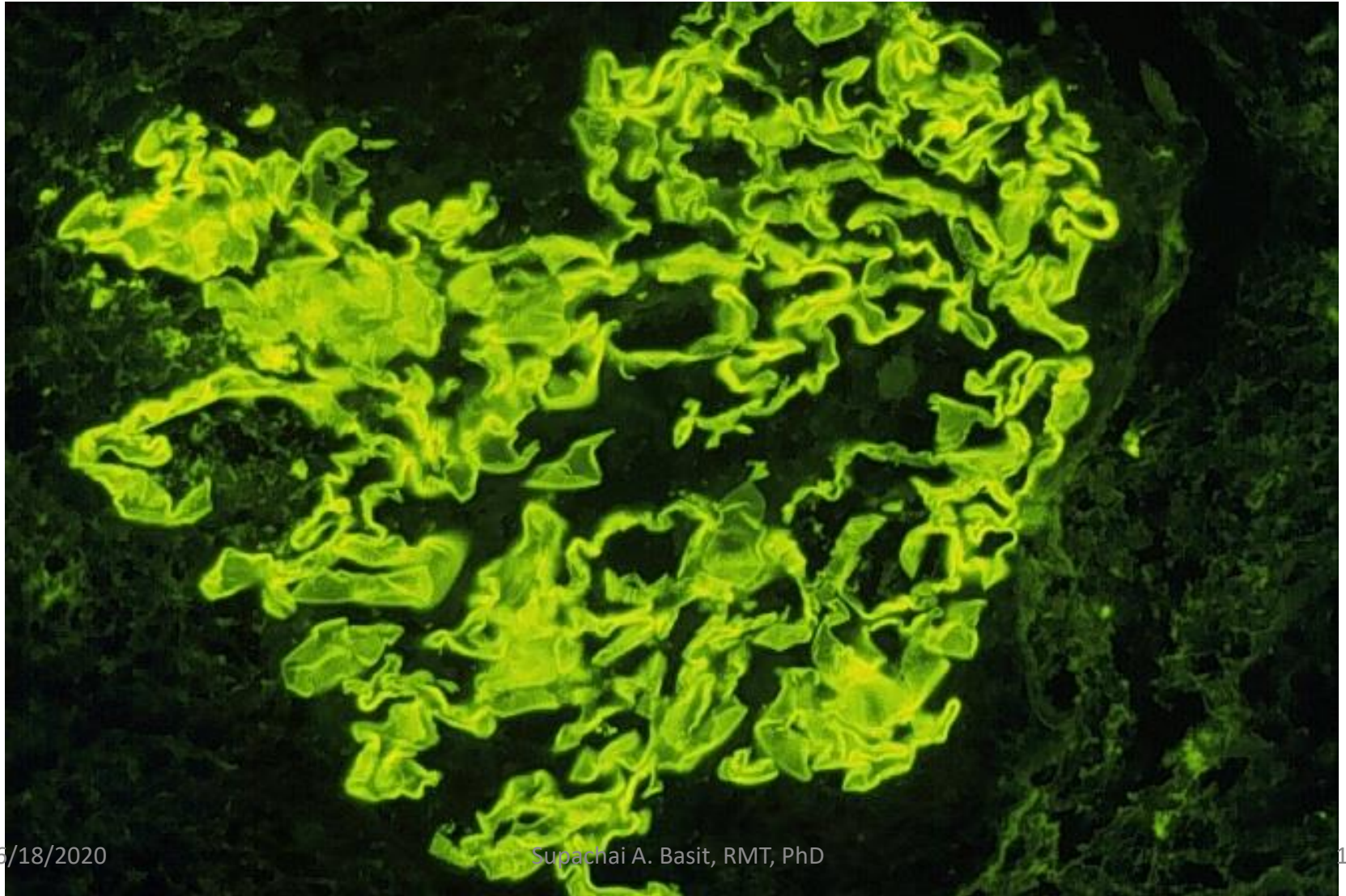


Normal Glomerular Capillary



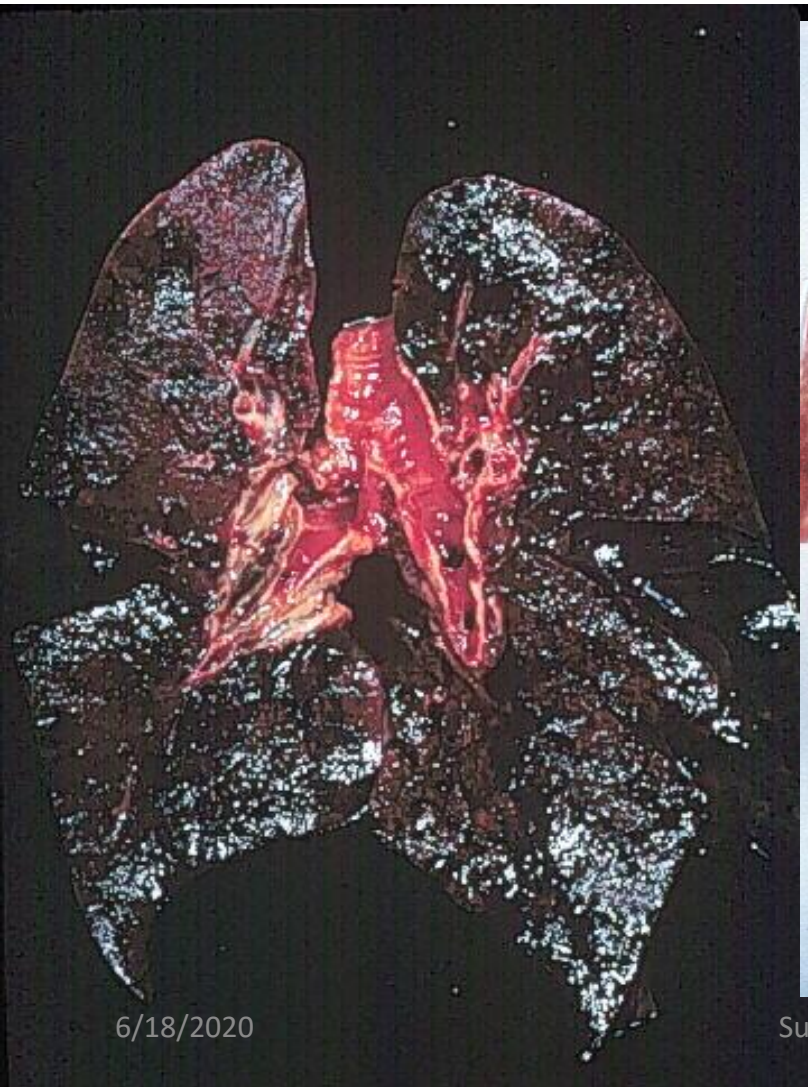


# Immunofluorescence image of linear distribution of IgG on glomerular basement membrane





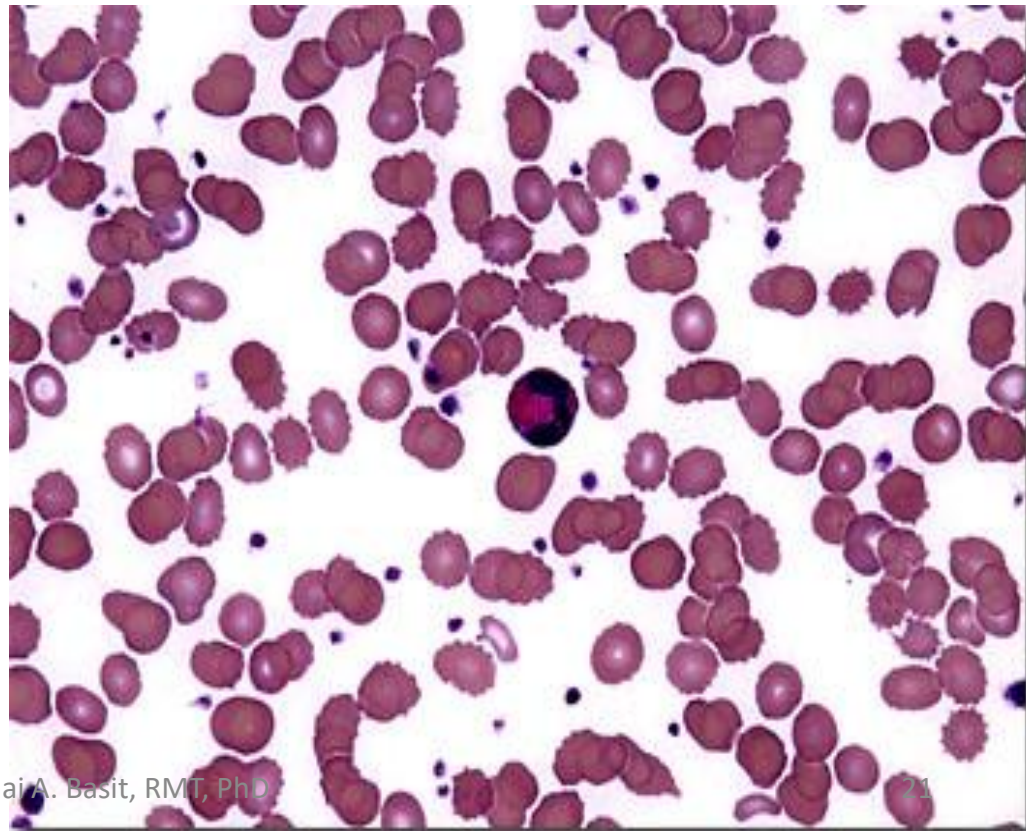
# Pulmonary hemorrhages in Goodpasture syndrome





# Pernicious Anemia

- progressive destruction of stomach glands
- gastric mucosa infiltrated with monocytes and segmenters
- IgG against parietal cell antigen
- abs against intrinsic factors



# Bullous disease

- deposition of IgG in squamous intracellular spaces
- circulating antibasement membrane abs
  1. Pemphigus vulgaris
  2. Bullous pemphigoid

# Pemphigus Vulgaris





# Bullus Pemphigoid



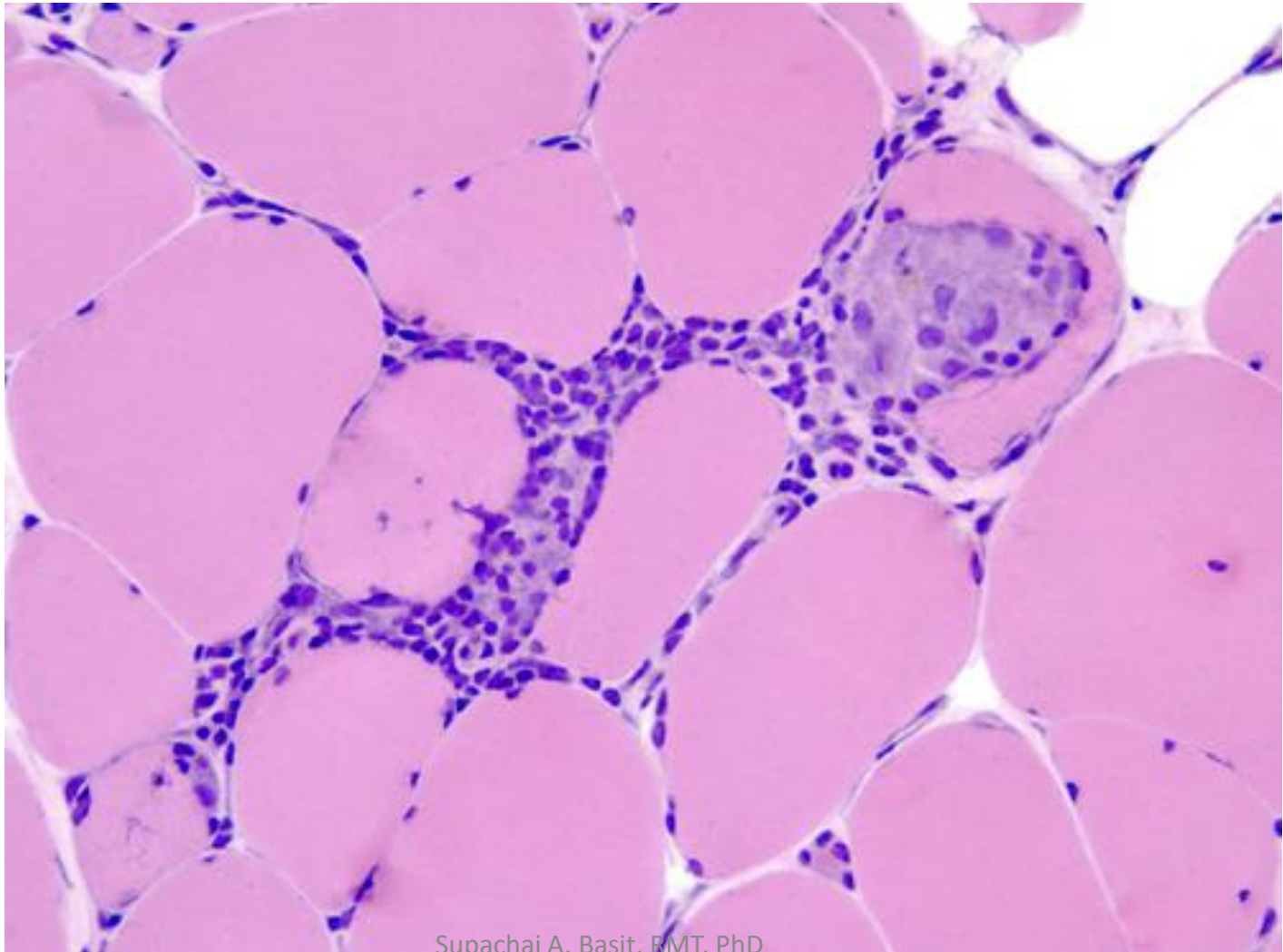


# Polymyositis-dermatomyositis

- weakness of striated muscles with muscle pain and tenderness, skin rash
- hypergammaglobulinemia
- deposition of IgG and complement in the vessel walls of the skin and muscles



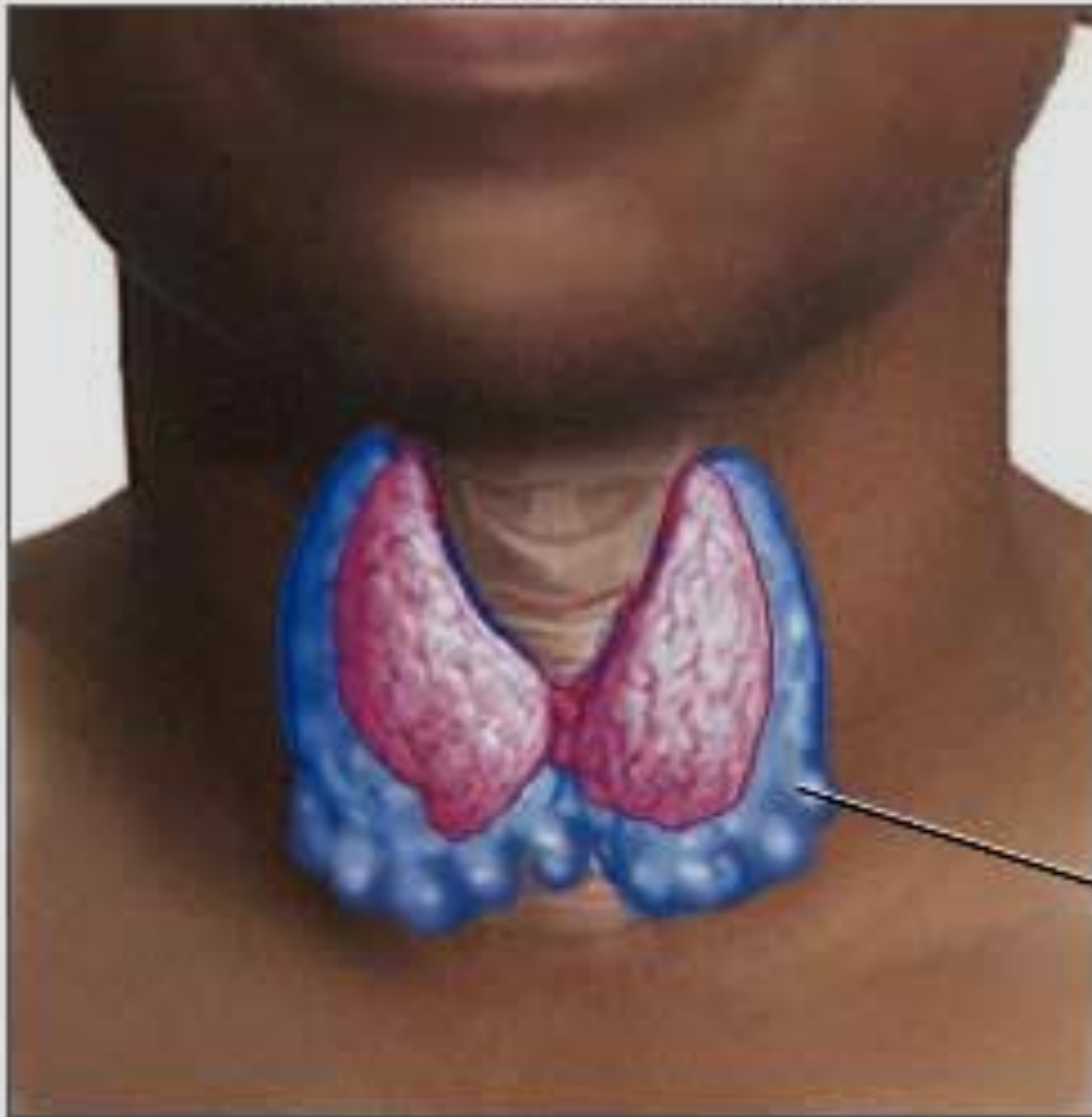
# Polymyositis-dermatomyositis



# Hashimoto's Thyroiditis

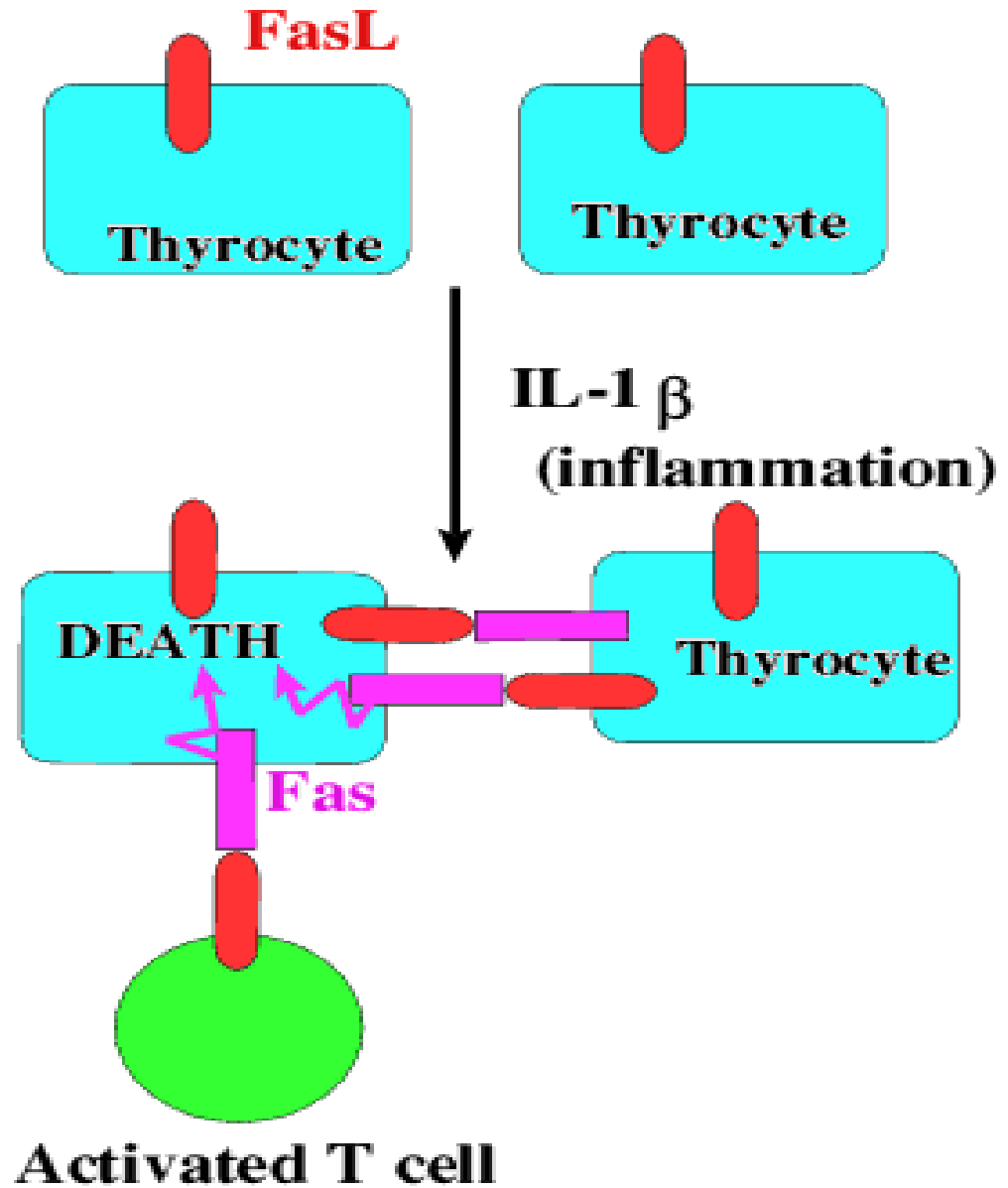
- enlarged thyroid gland
- hypothyroidism
- ab against thyroglobulin
- lesions with experimental animals after administration of Freud adjuvant
- ADCC involvement

# Hashimoto's disease



Enlarged, inflamed  
hypofunctioning  
thyroid (goiter)

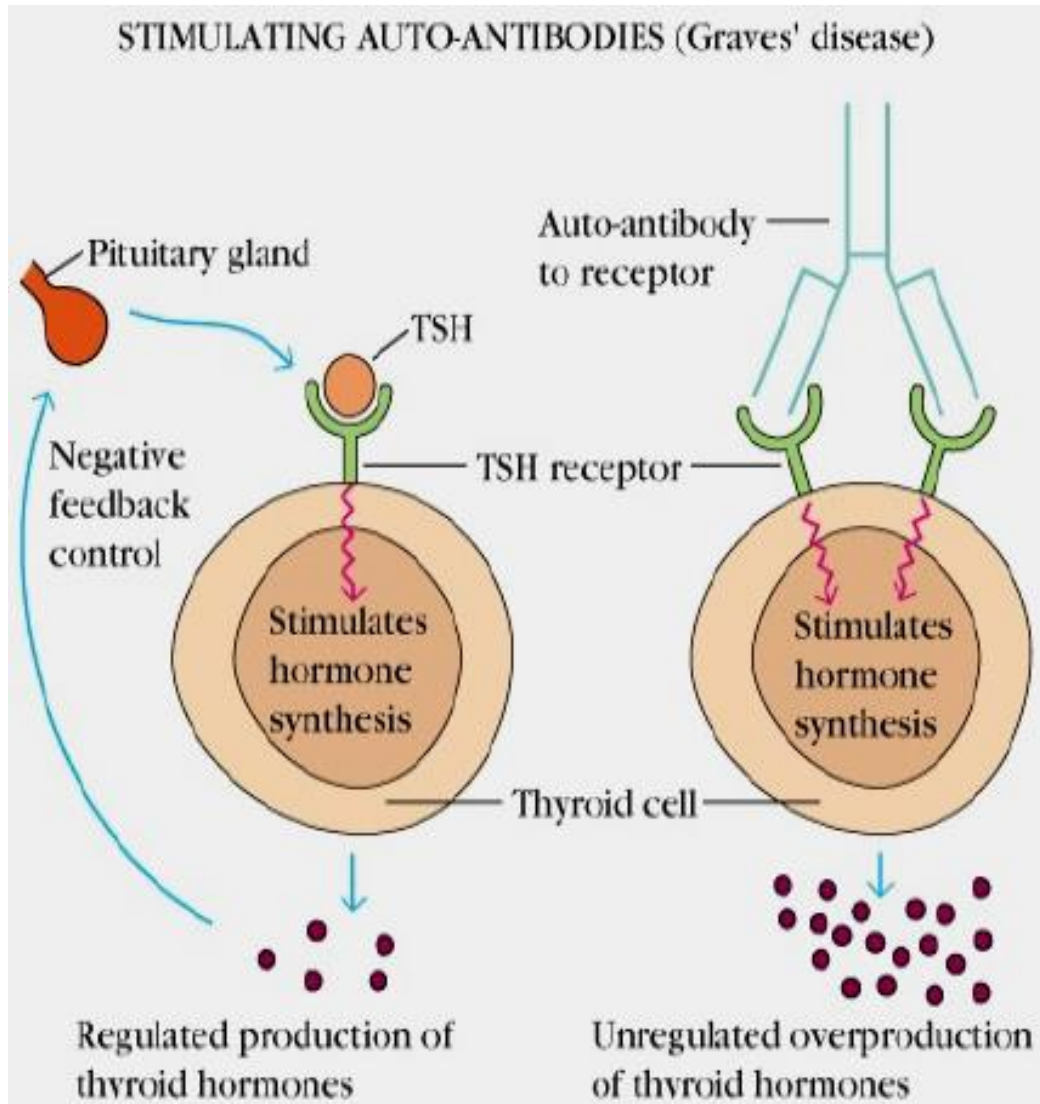
# Mechanisms of Hashimoto



# Graves Disease

- fatigue, nervousness, increased sweating, wt loss, heat intolerance
- inc B cells
- dec Ts cells
- thyroid stimulating abs
- HLA-B8; HLA-D3

# Graves' disease (anti-thyroid stimulating hormone; anti-TSH)

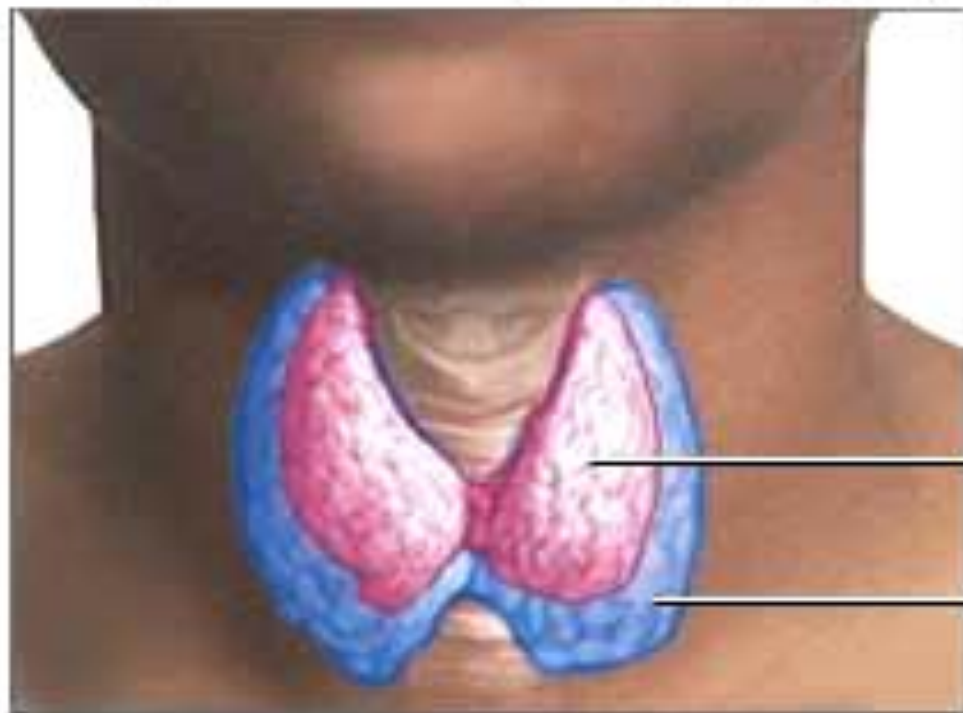


**In Graves' disease, the antibodies do not destroy the thyroid but act as if they are TSH (i.e., they bind and activate the TSH receptor)**





**Exophthalmos (bulging eyes)**



**Normal thyroid**

**Enlarged thyroid**

**Diffuse goiter**

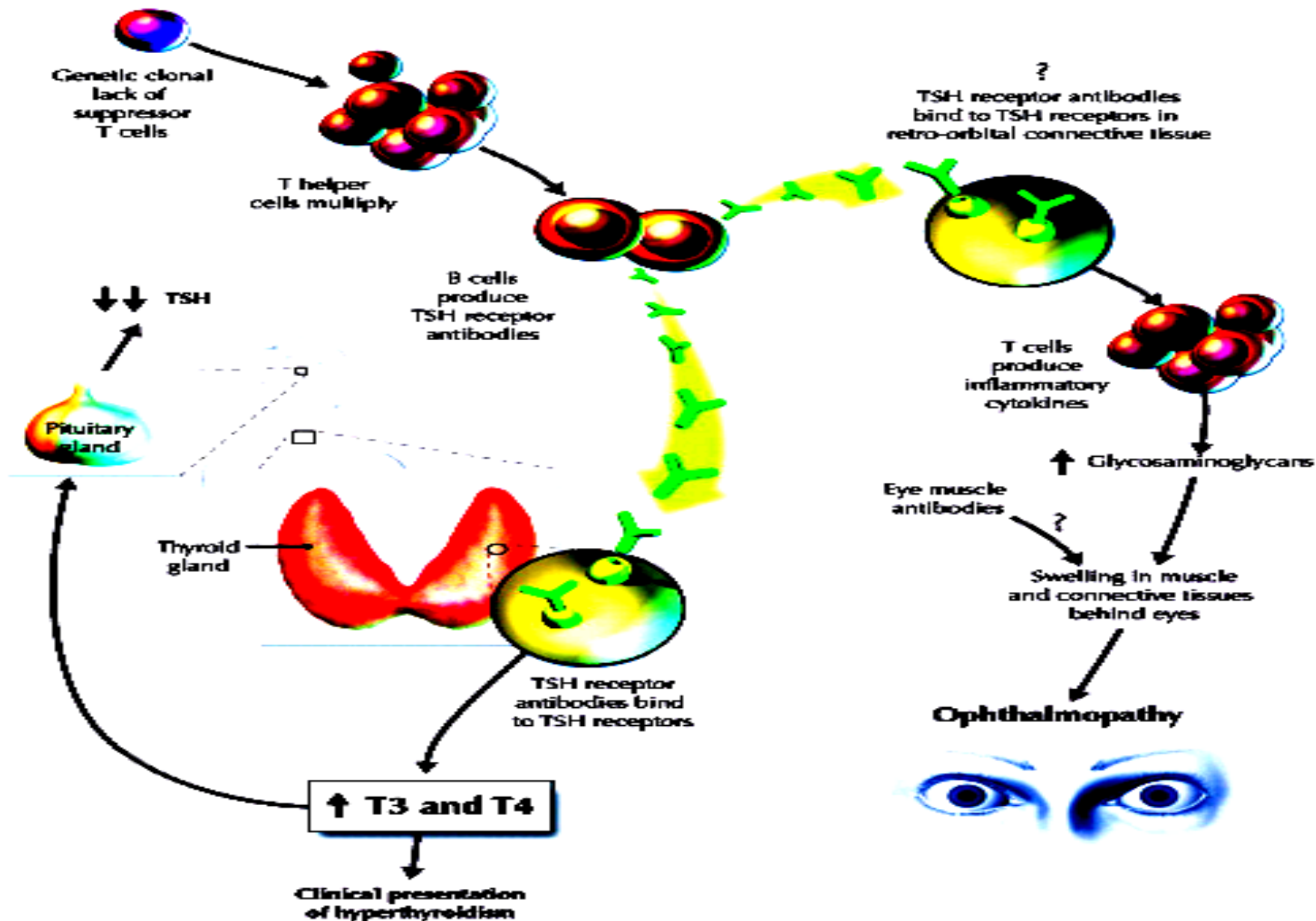
Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety



# Exophthalmia in Graves disease







# Multiple Sclerosis

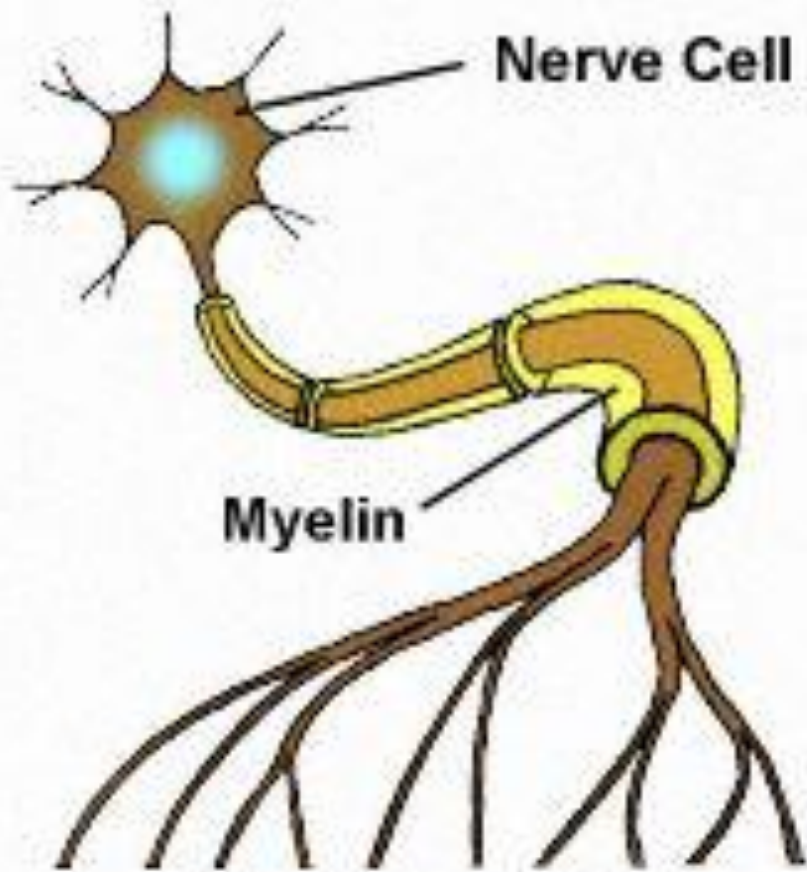
- motor weakness, ataxia, impaired vision, urinary bladder dysfunction
- paresthesia, mental aberrations
- sclerotic plaques
- elevated levels of ab against measles virus in serum/CSF
- inc IgG in CSF
- suppressed T cells/ inc B cells



# Central nervous system (brain and spinal cord)



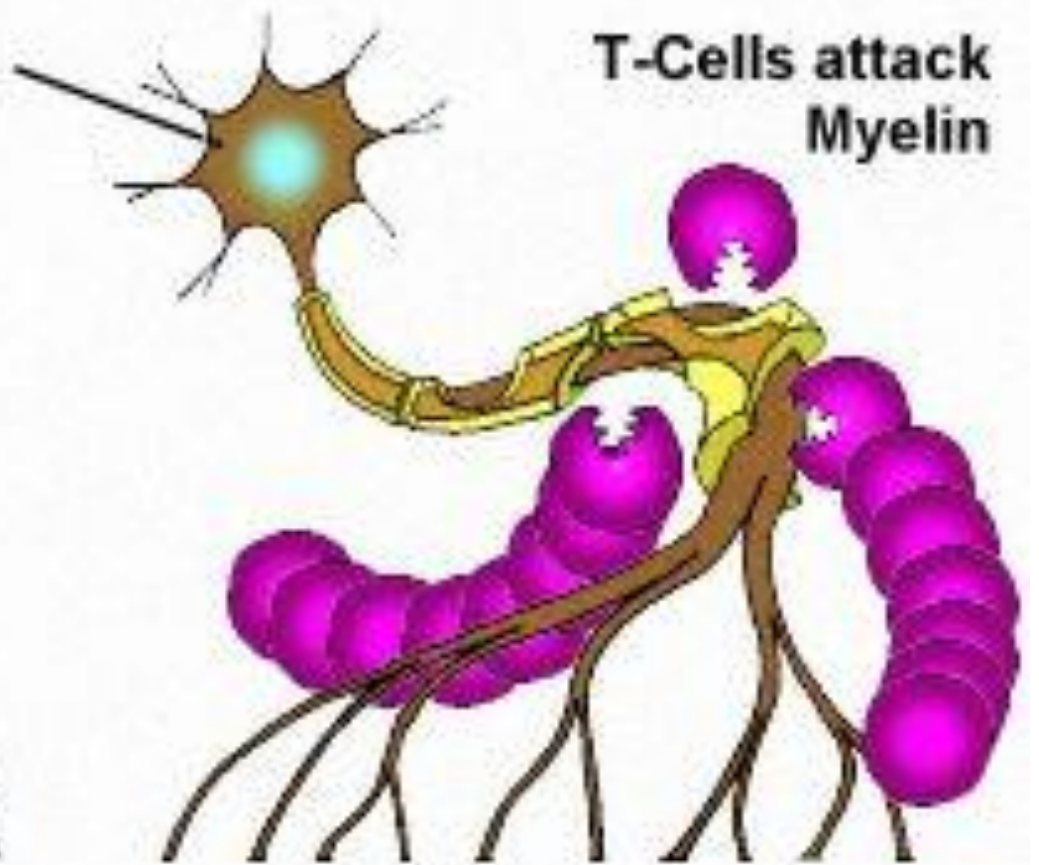
In multiple sclerosis the myelin sheath, which is a single cell whose membrane wraps around the axon, is destroyed with inflammation and scarring



Nerve Cell

Myelin

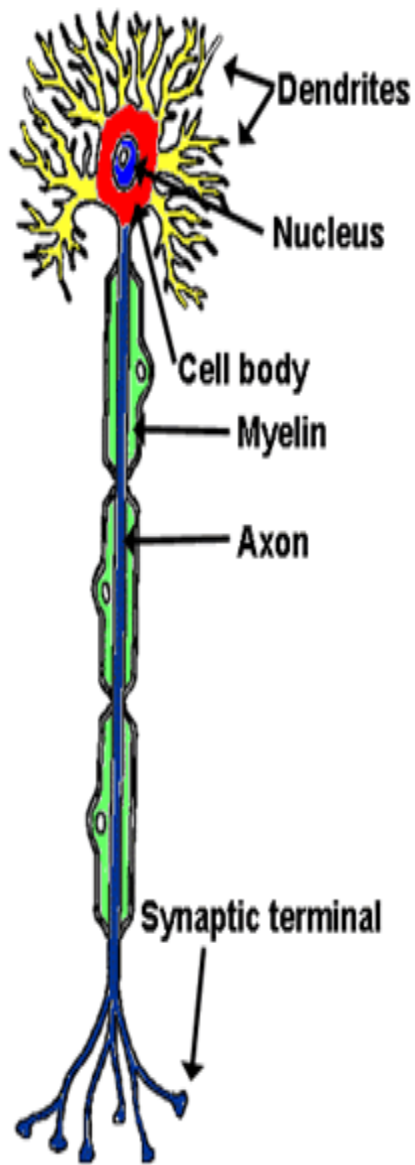
healthy Nerve Cell Fibre



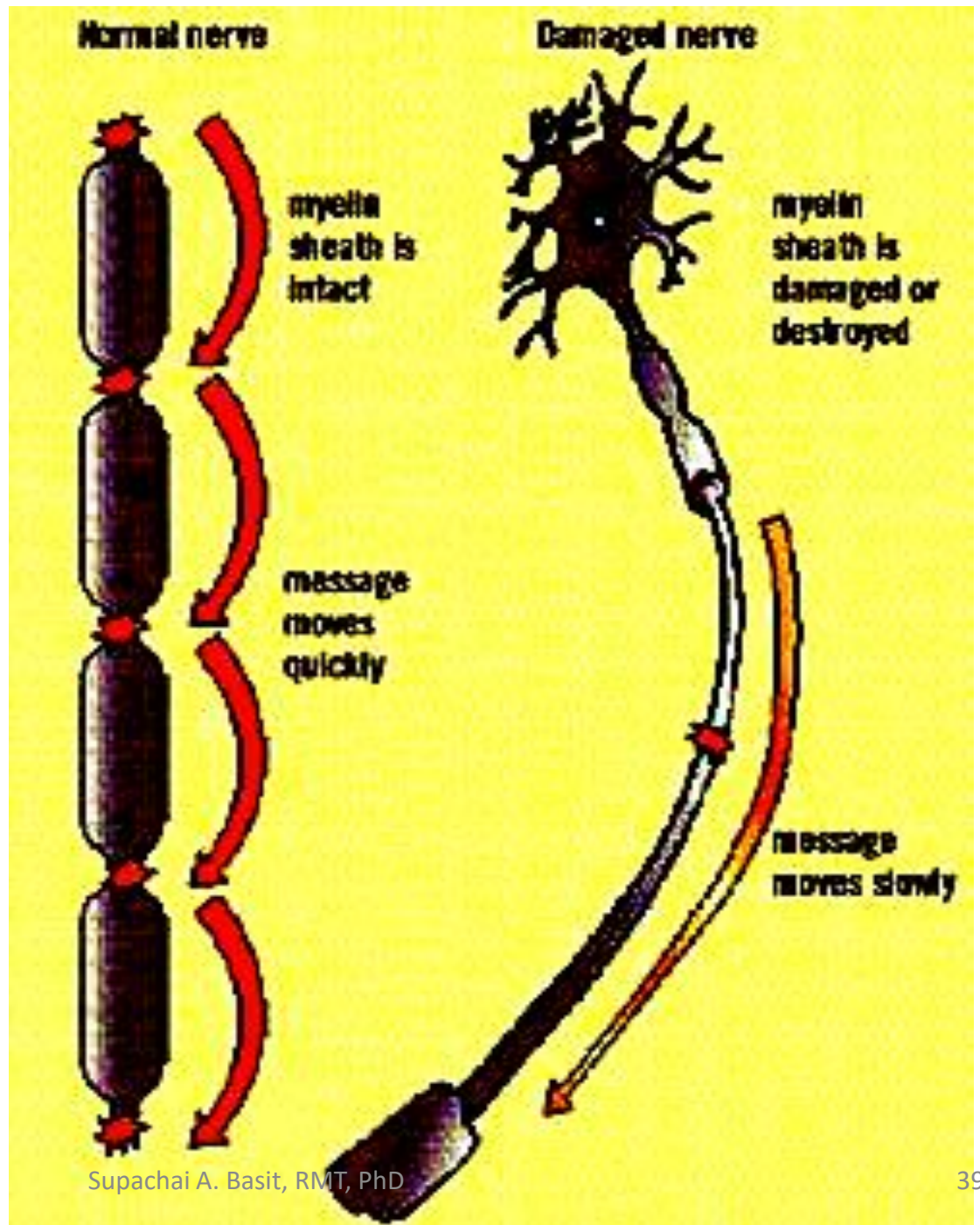
T-Cells attack Myelin

Multiple Sclerosis

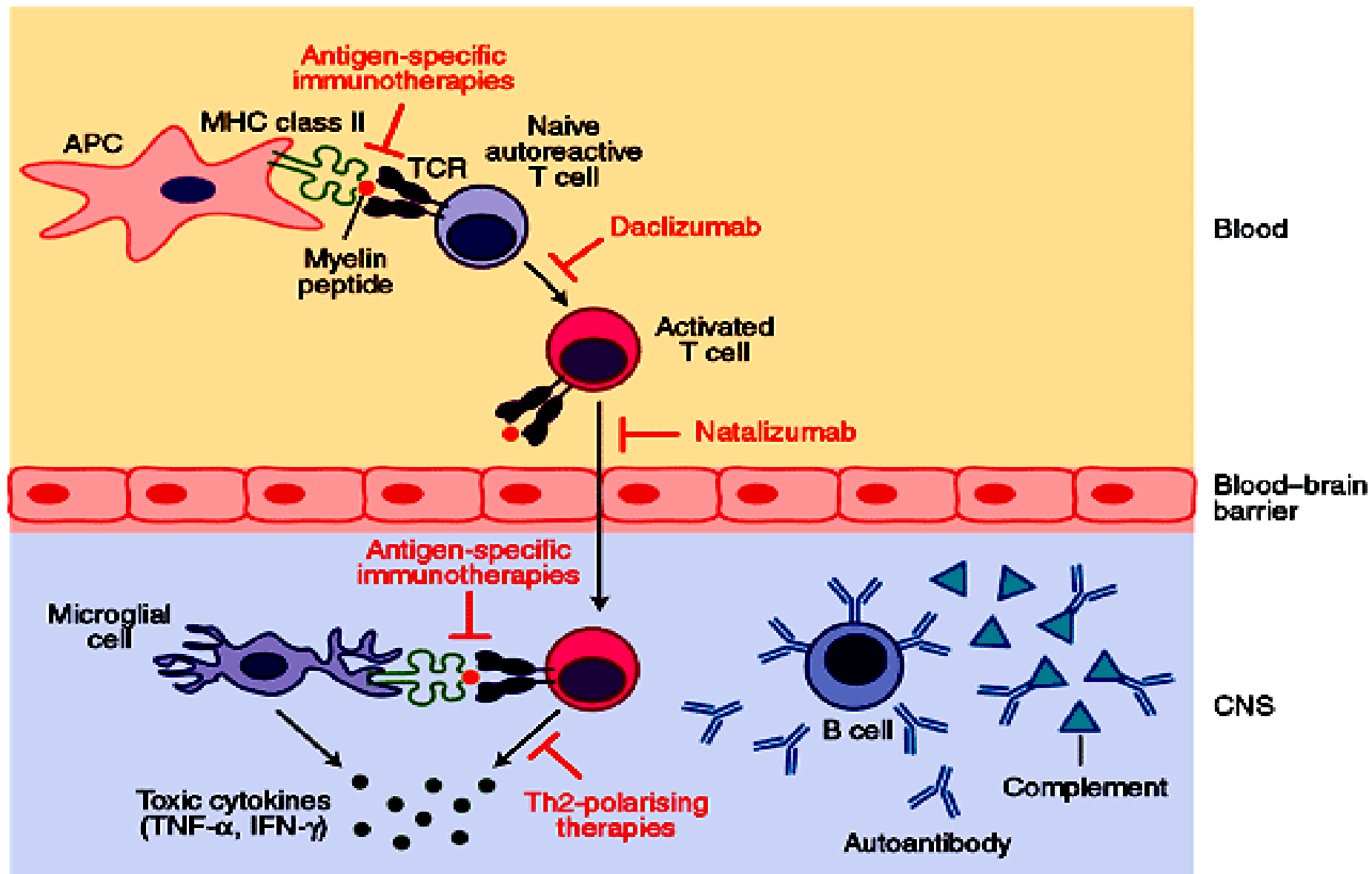




Eric H. Chudler, Neuroscience for Kids, Washington University.

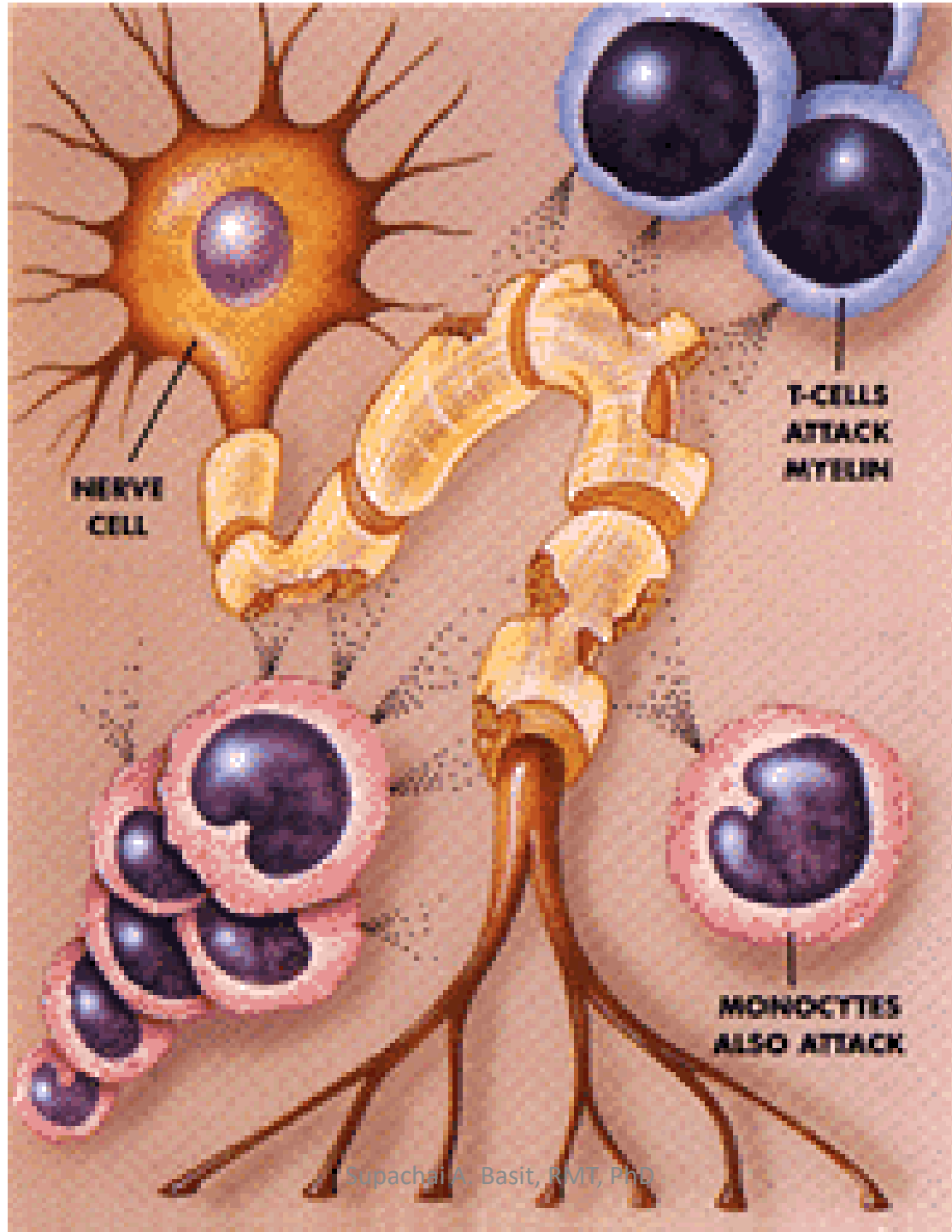


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## The pathogenesis of multiple sclerosis (MS) and points of therapeutic intervention



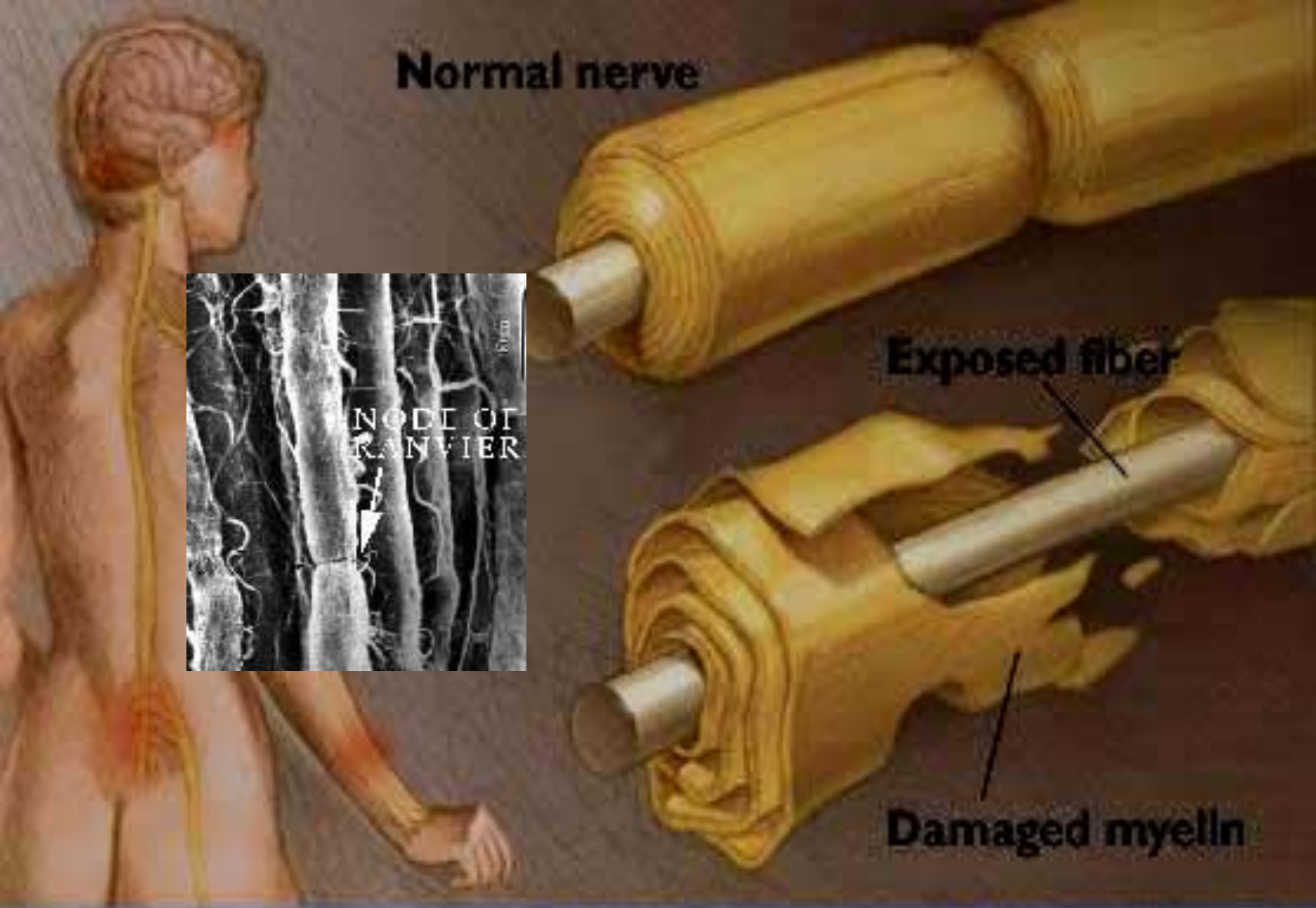


# MS patient



# Guillain Barre Syndrome

- motor weakness, 1<sup>st</sup> of the lower extremities then at the upper extremities, respiratory muscles paralysis and paralysis
- mononuclear cell infiltrate and demyelination
- sensitivity of the lymphocyte to nerve extracts
- anti nerve abs



**Normal nerve**

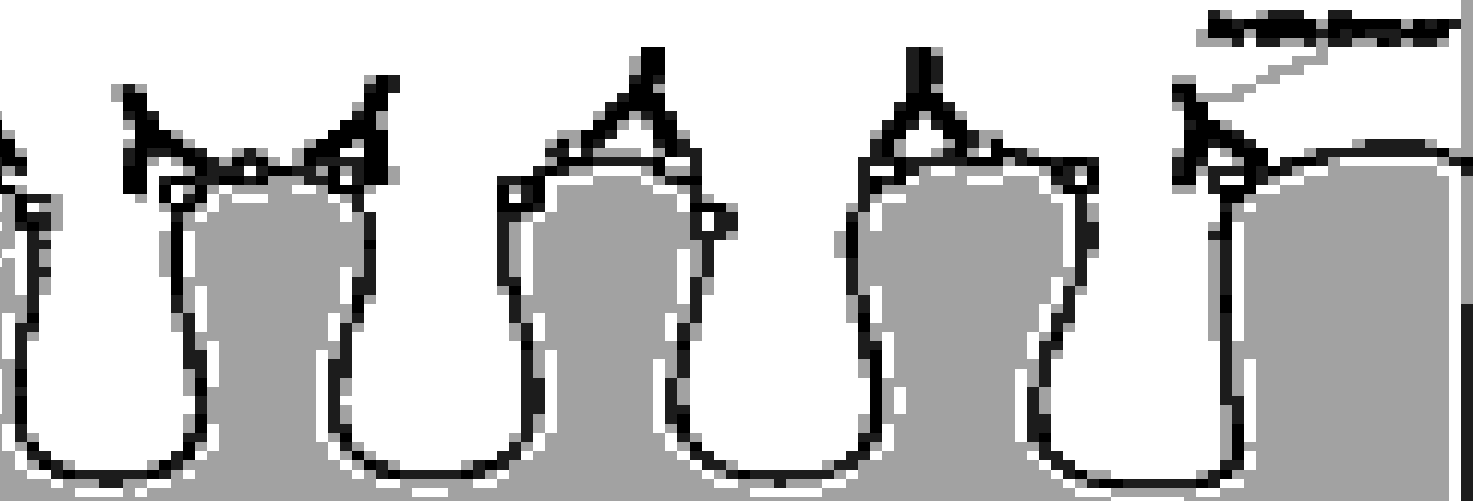
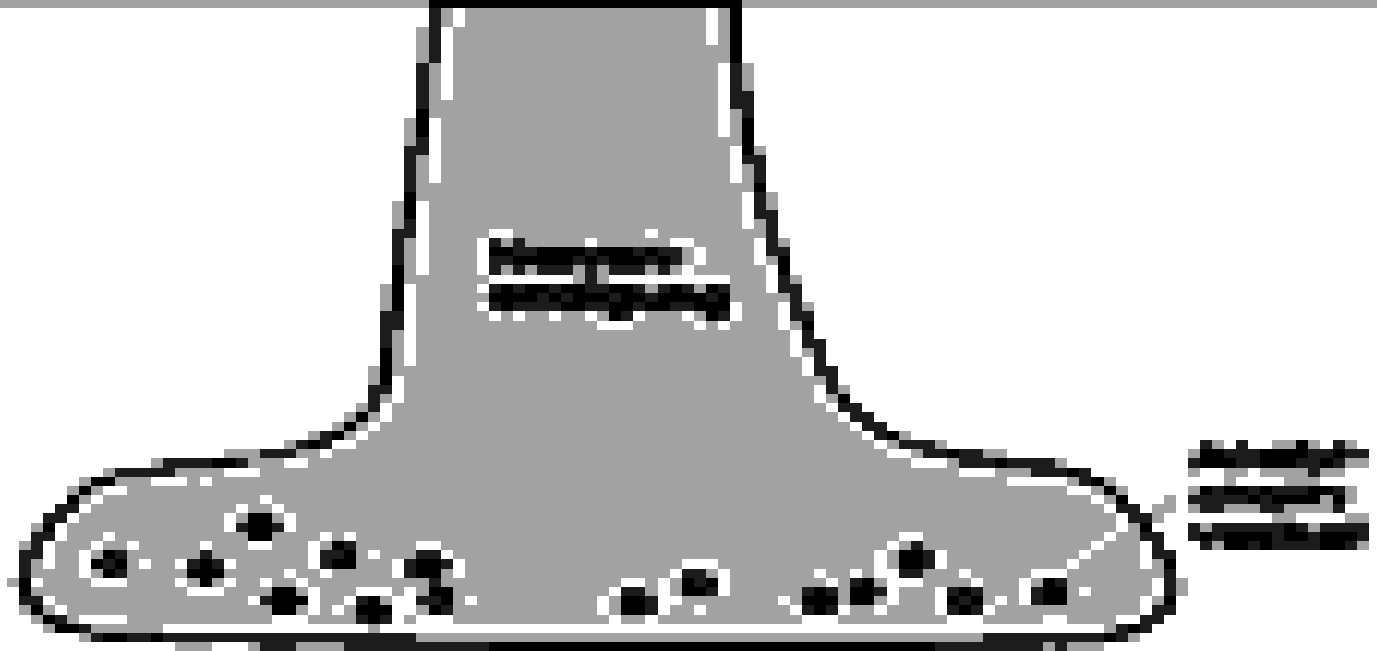
**Exposed fiber**

**Damaged myelin**

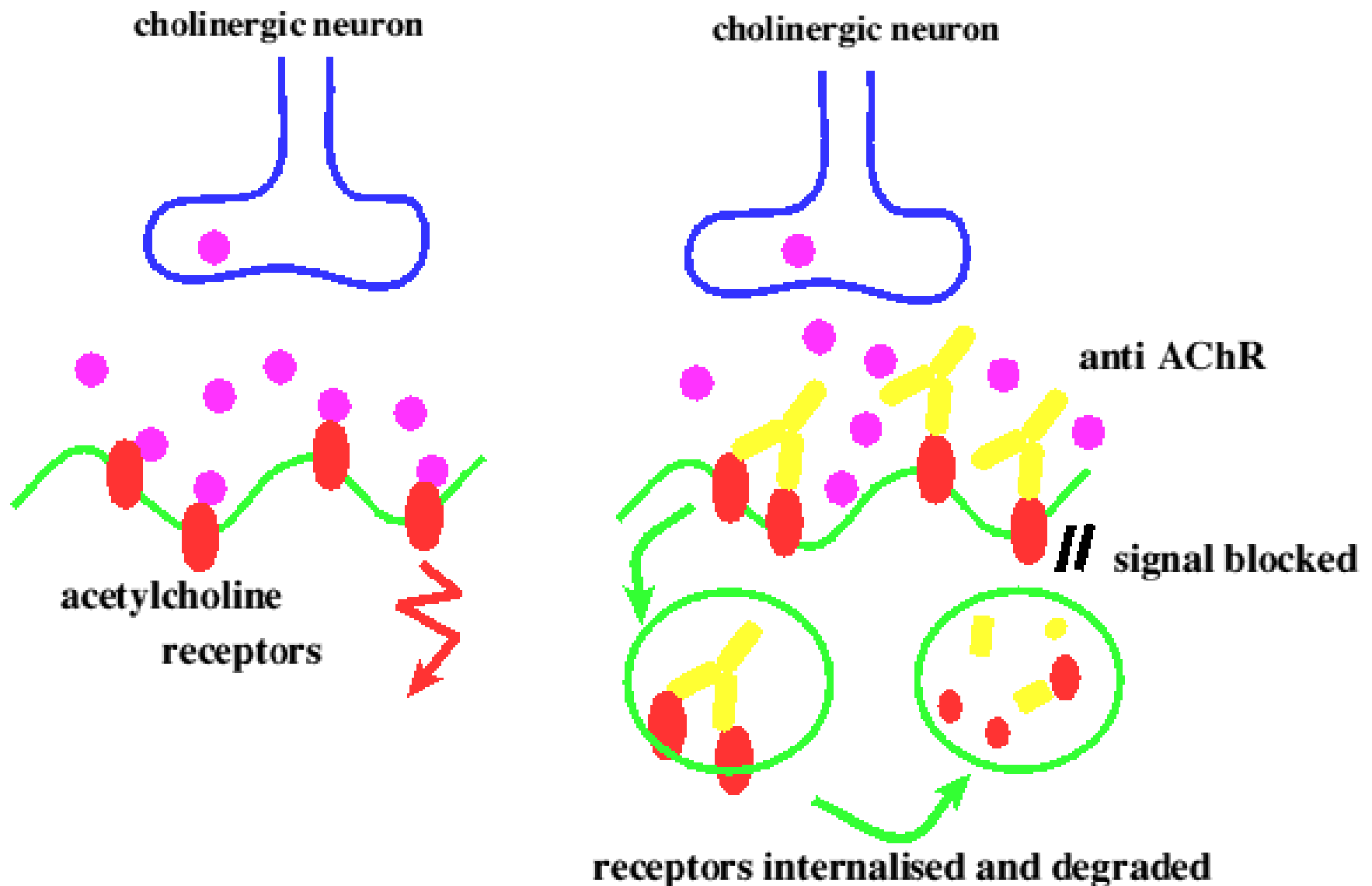
**NODE OF RANVIER**

# Myasthenis Gravis

- muscular weakness and fatigability
- depletion of acetylcholine receptor at myoneural junction
- enlarged thymus and abs against acetylcholine receptor



# Blocking autoantibodies cause Myasthenia Gravis



# Myasthenia Gravis





# Myasthenia Gravis



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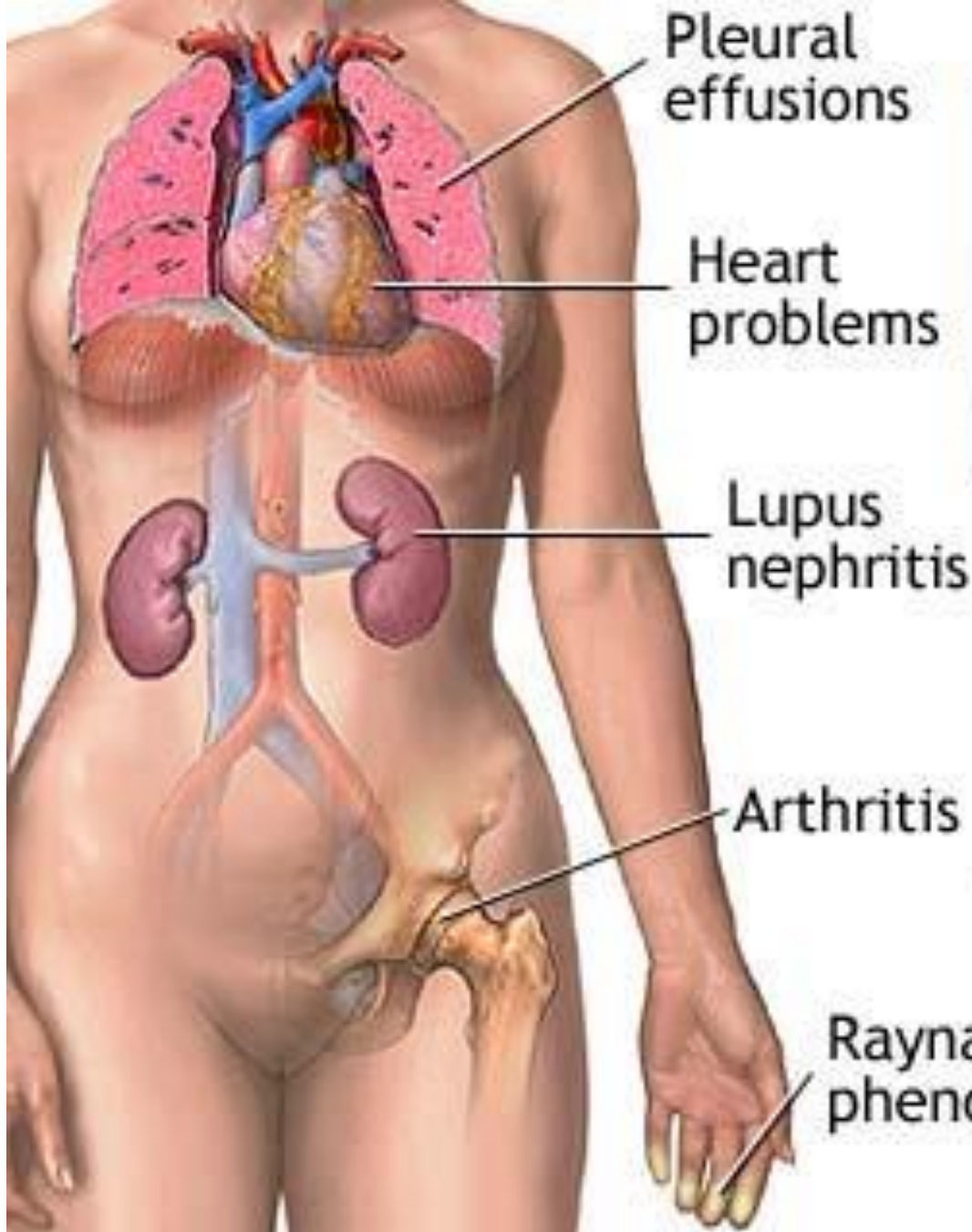
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# SLE

- malaise, fever, lethargy, weight loss
- butterfly rash
- renal involvement
- CNS manifestations
- LE cell phenomenon
- ANA (ss-DNA, ds-DNA or both)
- abs against DNA, RNA, mitochondria, lysosomes, thromboplastin, thrombin
- hypergammaglobulinemia and reduced serum levels of complement



## Butterfly rash



Symptoms of systemic lupus erythematosus may vary widely with the individual



CNS  
Seizures

Skin  
Butterfly rash  
Discoid lupus

Heart  
Endocarditis  
Myocarditis

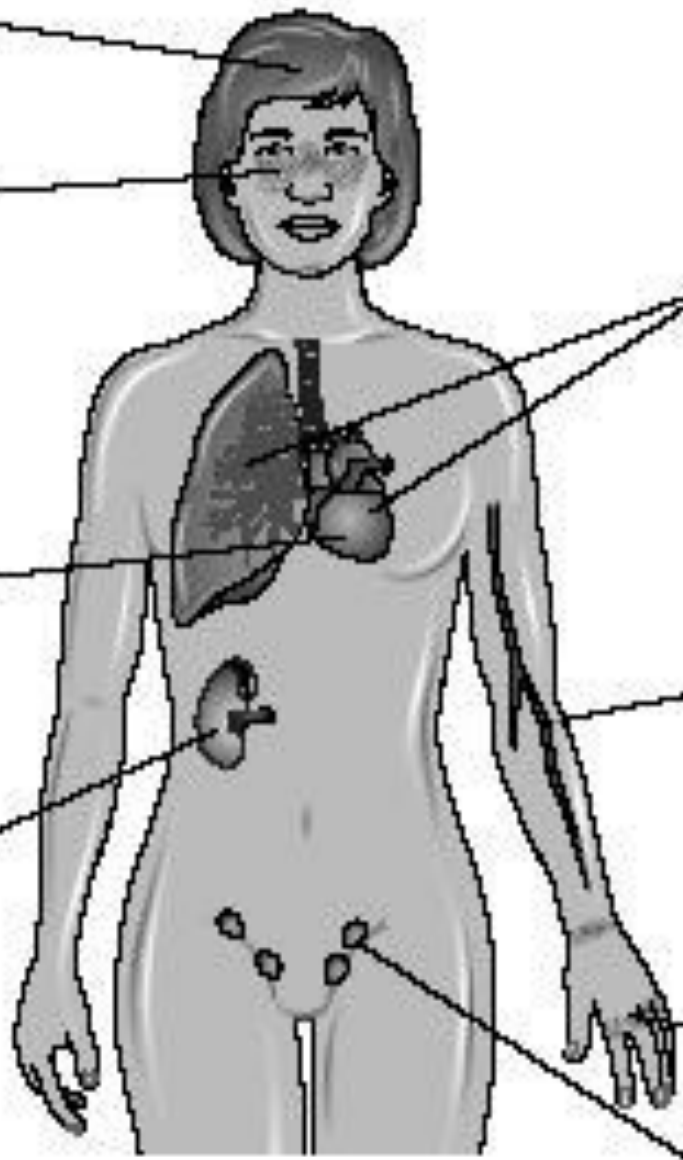
Glomerulonephritis

Serositis  
Pleuritis  
Pericarditis

Hematologic effects  
Hemolytic anemia  
Leukopenia  
Thrombocytopenia

Arthritis

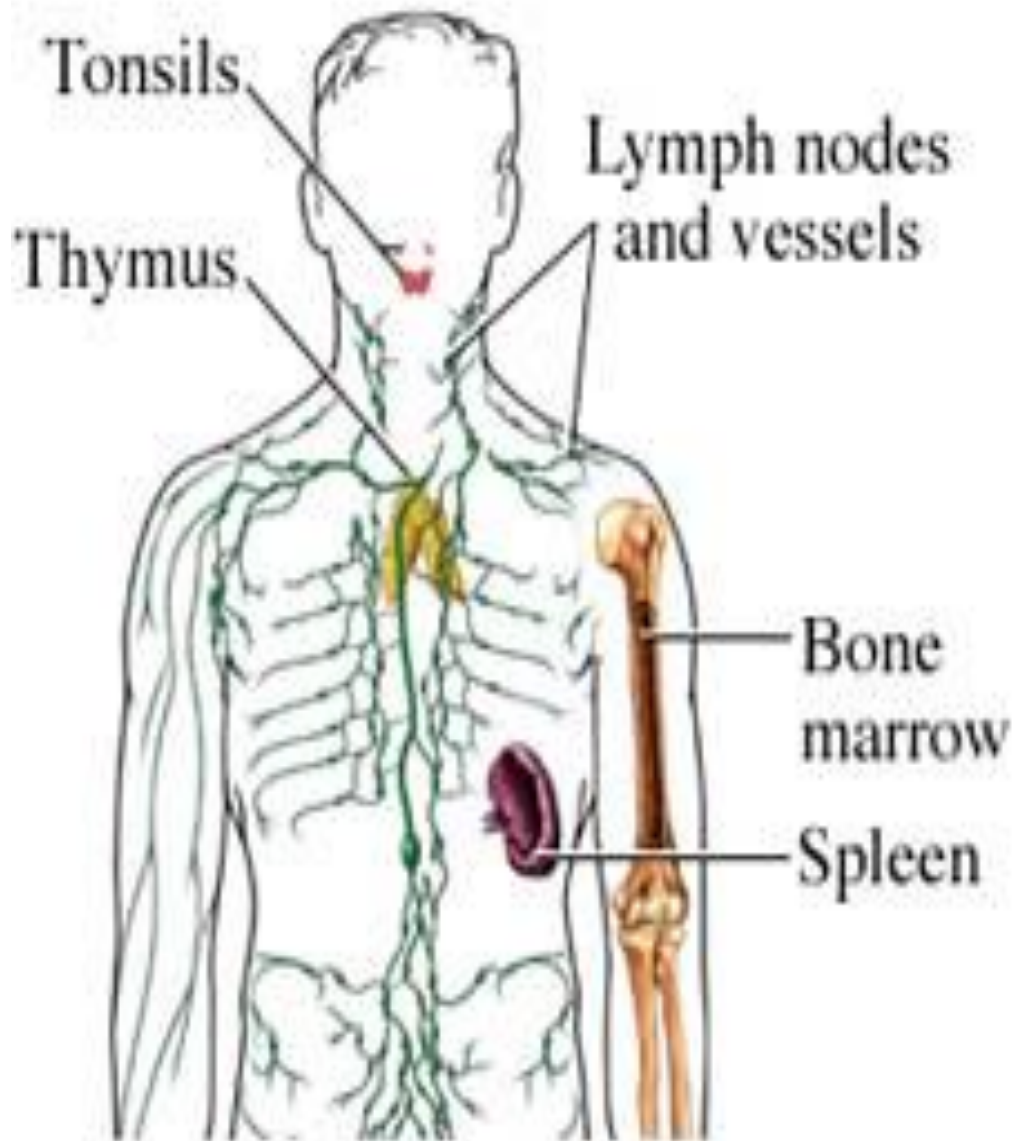
Lymphadenopathy



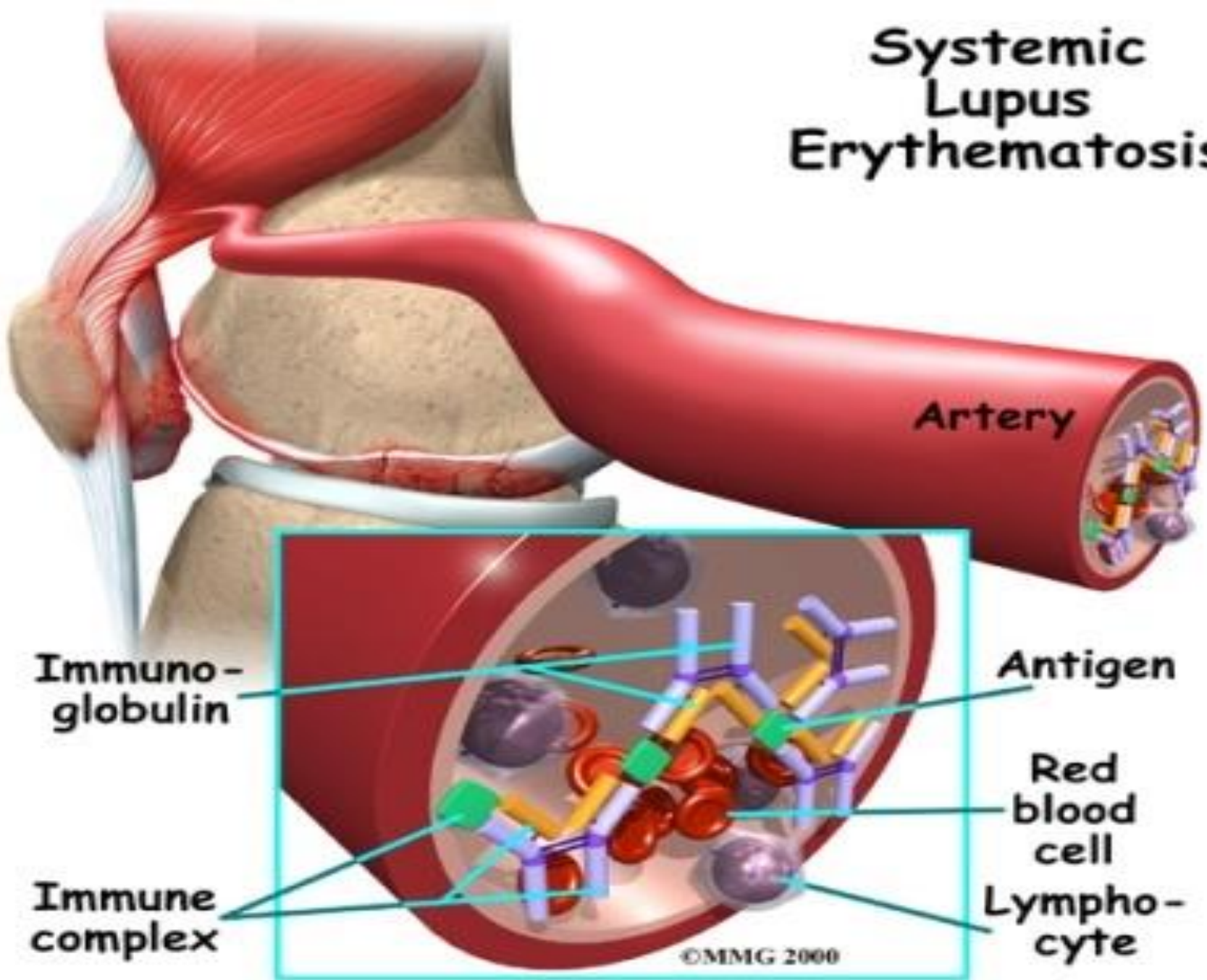






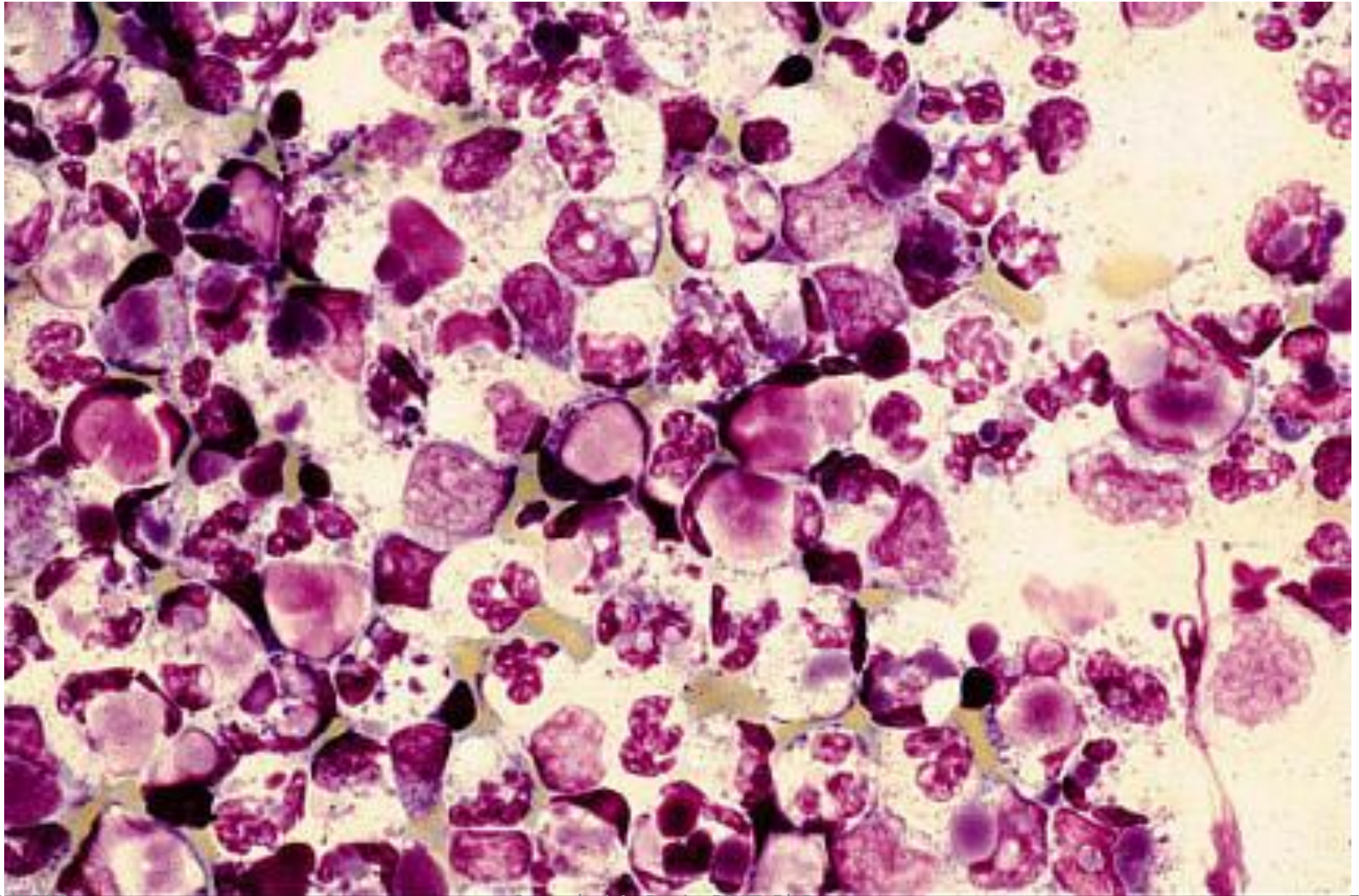


# Systemic Lupus Erythematosus





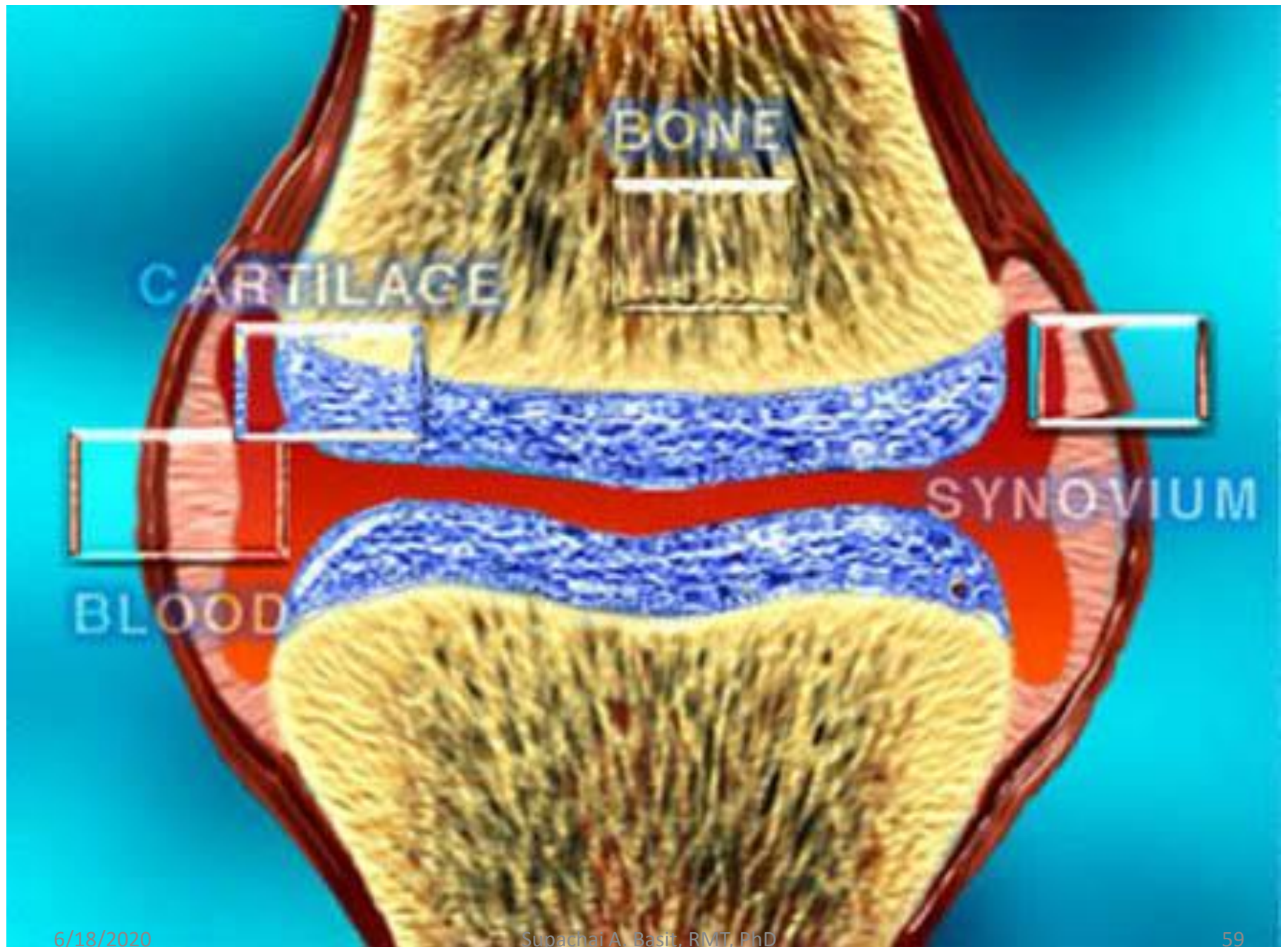
# LE cells



# RA

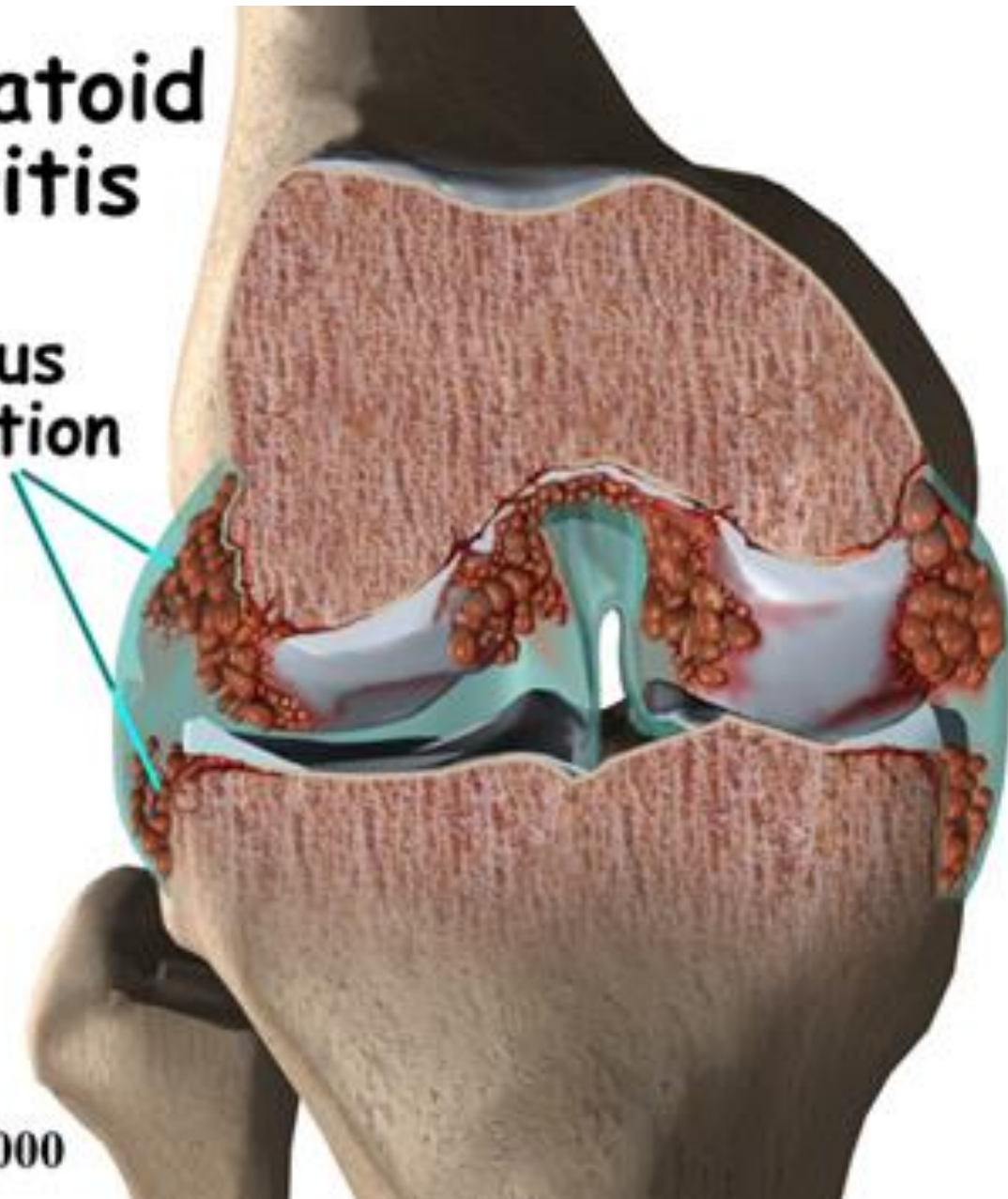
- malaise, wt loss, fever, fatigue, and weakness
- proliferative synovial membrane
- hypergammaglobulinemia and hyperalbuminuria
- Rheumatoid factor in synovial fluid





# Rheumatoid arthritis

Pannus formation



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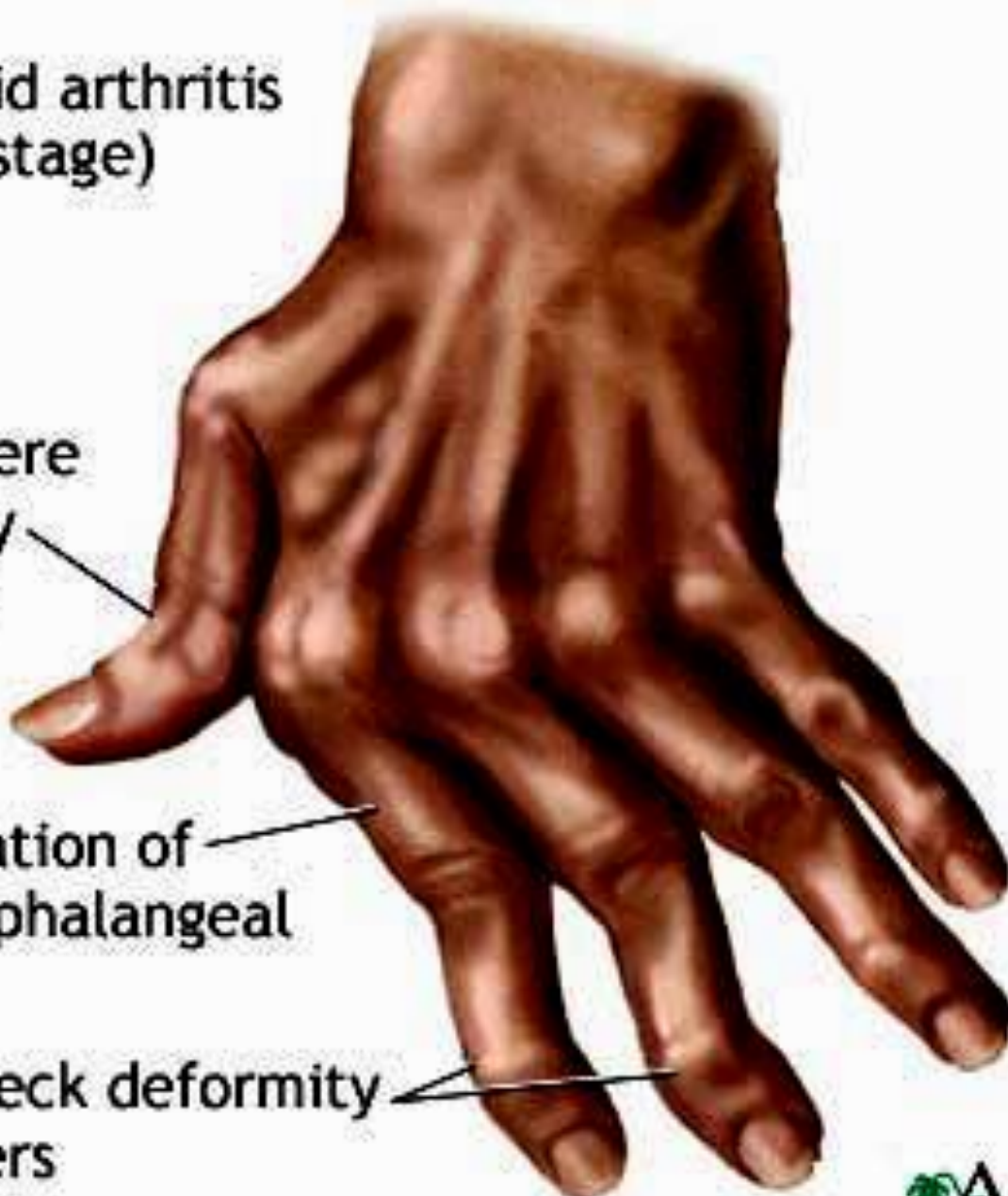


# Rheumatoid arthritis (late stage)

Boutonniere  
deformity  
of thumb

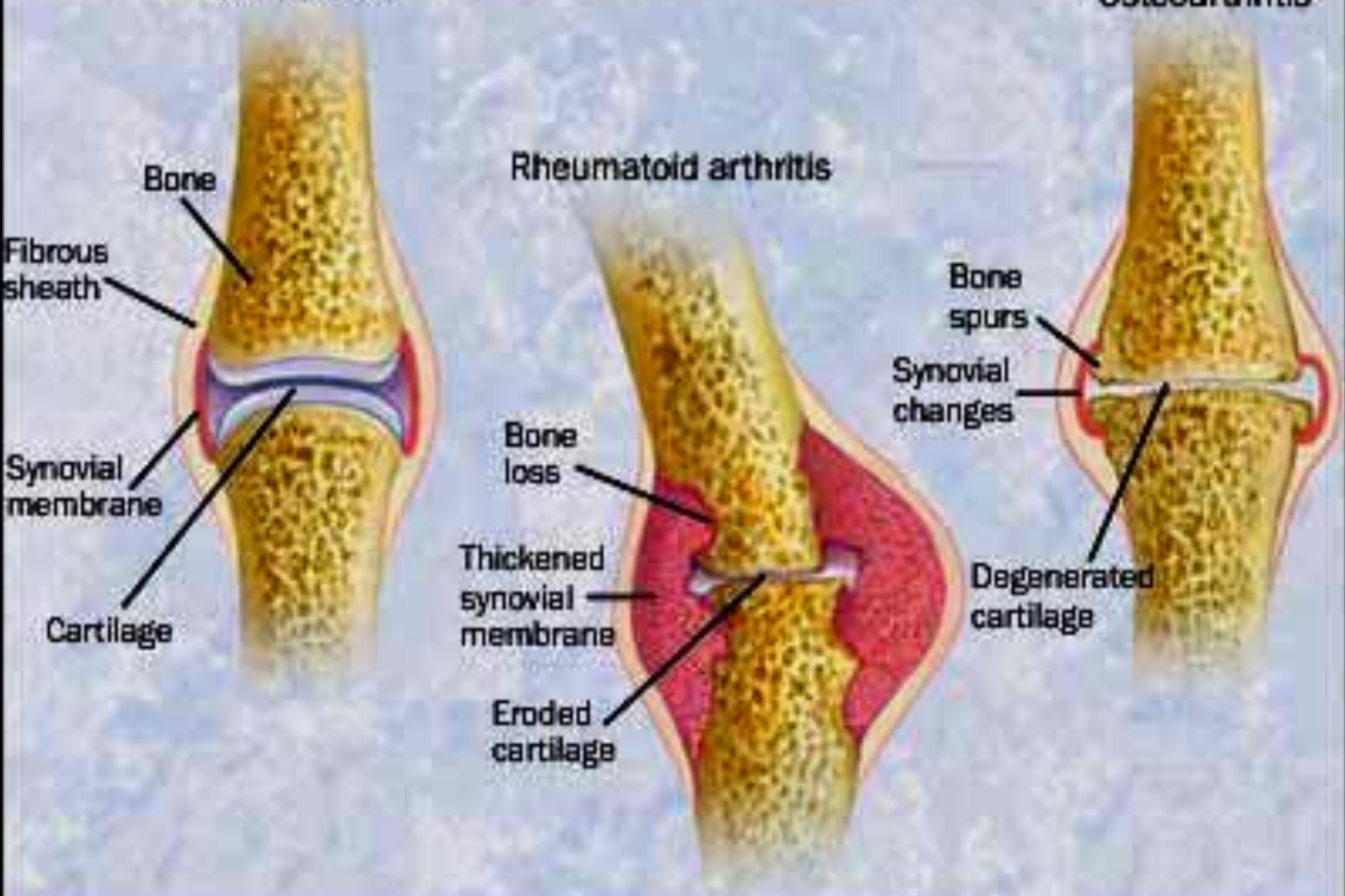
Ulnar deviation of  
metacarpophalangeal  
joints

Swan-neck deformity  
of fingers



# Normal joint

# Osteoarthritis



Bone

Fibrous sheath

Synovial membrane

Cartilage

# Rheumatoid arthritis

Bone loss

Thickened synovial membrane

Eroded cartilage

Bone spurs

Synovial changes

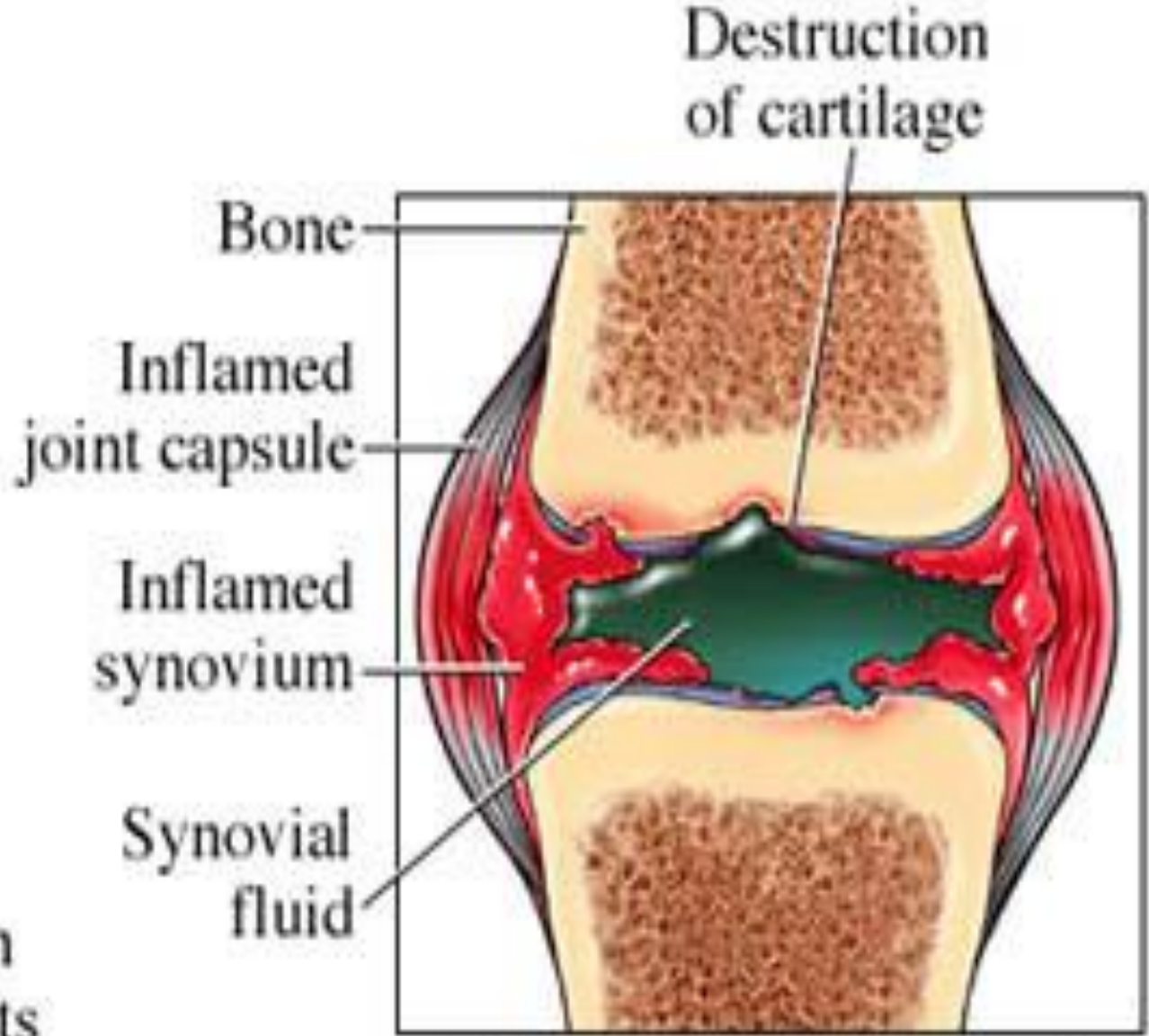
Degenerated cartilage





Joint pain occurring in various joints

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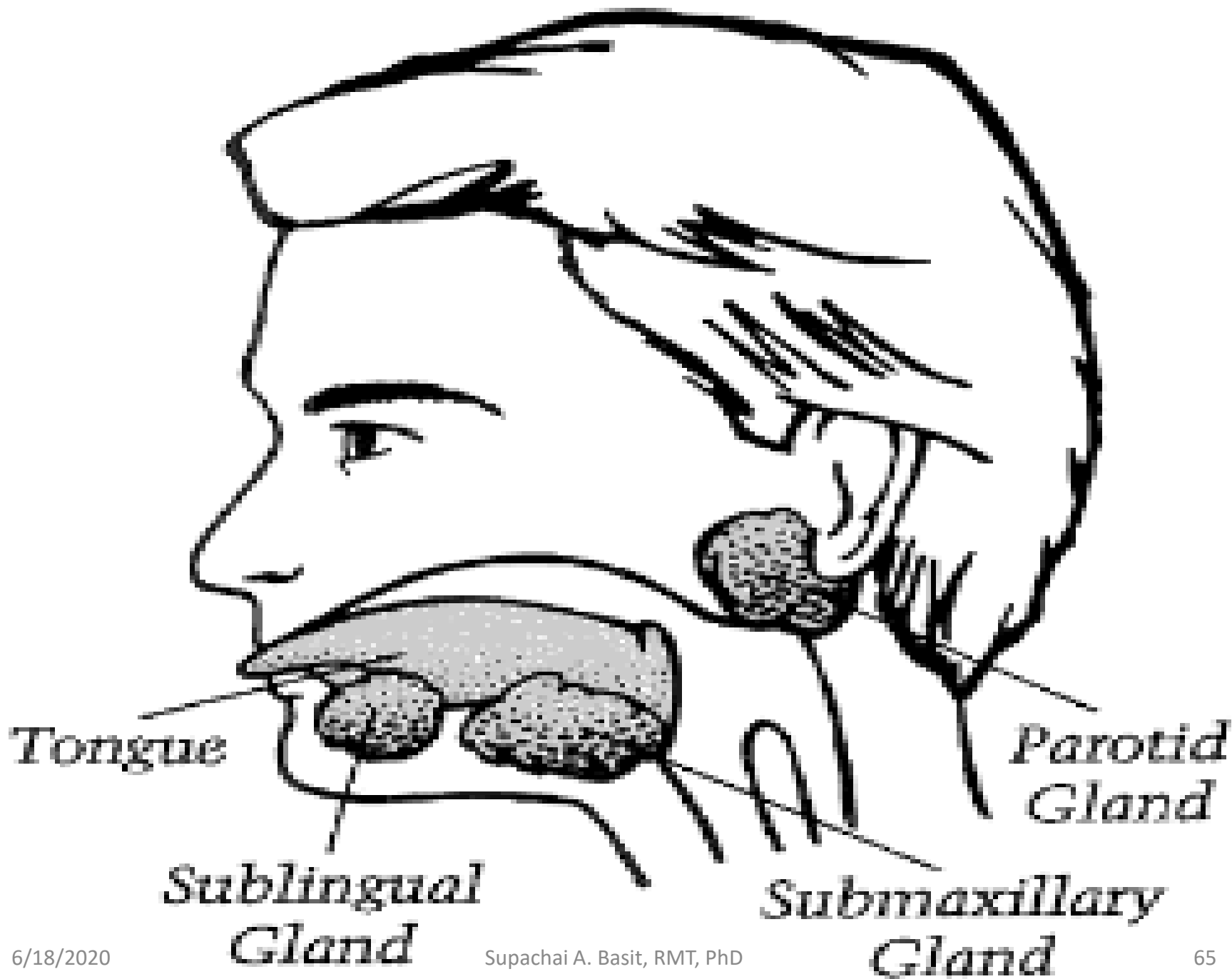
Destruction of cartilage

Enlarged view of a joint



# Sjogren's syndrome

- dry eyes, keratoconjunctivitis, sicca
- dry mouth, xerostomia
- dryness of the nose, larynx, resp tract
- salivary and lacrimal glands infiltrated with plasma cells, B cells and T cells

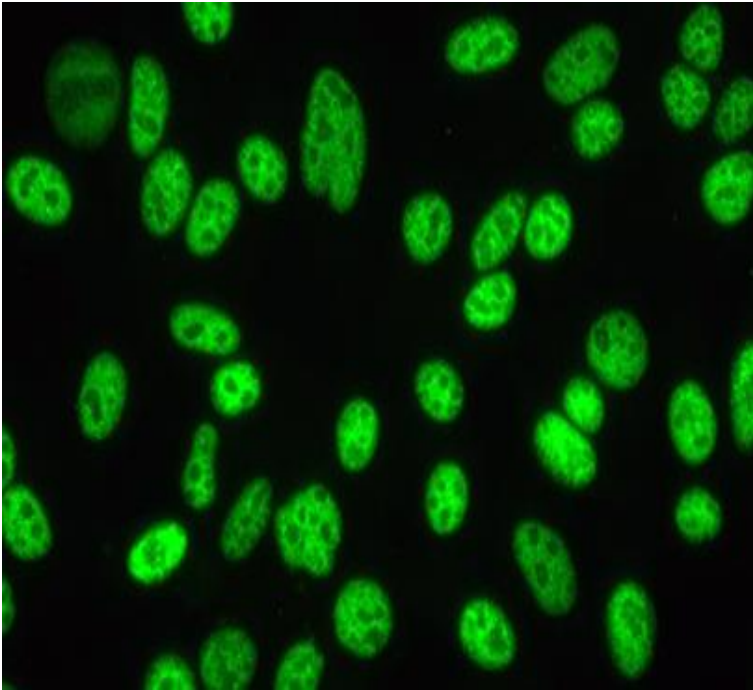




# Diagnosis of Auto immune disease

- Diagnosed by clinical symptoms.
- Confirmed by detecting the auto Ab in the serum of the patients.
- Autoantibodies are demonstrated by immunofluorescent Ab test, haemagglutination, Complement fixation, immunodiffusion, Radio immuno assay, etc.

# ANTINUCLEAR ANTIBODY





# ANTINUCLEAR ANTIBODY

- Anti-nuclear antibodies (ANAs, also known as anti-nuclear factor or ANF) are autoantibodies that bind to contents of the cell nucleus. In normal individuals, the immune system produces antibodies to foreign proteins (antigens) but not to human proteins (autoantigens). In some individuals, antibodies to human antigens are produced

# Subtypes Of ANAs

- ❑ There are many subtypes of ANAs such as,
  - anti-Ro antibodies
  - anti-La antibodies
  - anti-Sm antibodies
  - anti-nRNP antibodies
  - anti-Scl-70 antibodies
  - anti-dsDNA antibodies
  - anti-histone antibodies
  - antibodies to nuclear pore complexes
  - anti-centromere antibodies
  - anti-sp100 antibodies

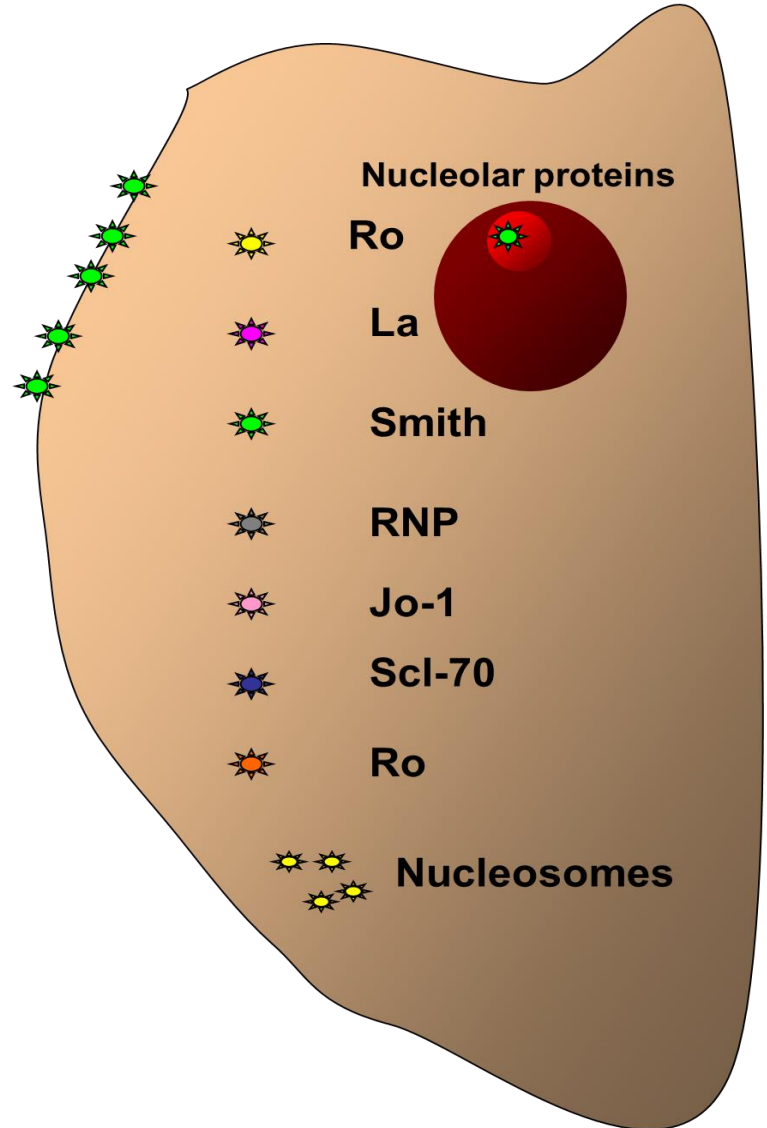
# Subtypes Of ANAs

- Each of these antibody subtypes binds to different proteins or protein complexes within the nucleus. They are found in many disorders including autoimmunity, cancer and infection, with different prevalence of antibodies depending on the condition.

# Nuclear Proteins

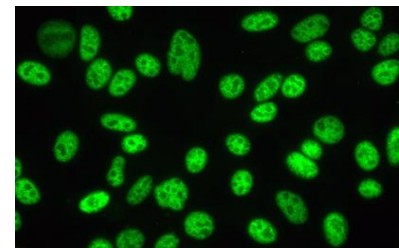
Proteins that have been  
Synthesized in the nucleus  
And thereafter where  
Distributed to their  
respective sites in the cell

dsDNA



# Detection Technique

- **Indirect immunofluorescence is the reference method for screening and titration of circulating autoantibodies in human serum.**
- **Using three different tissues from rat(liver,kidney and stomach) enables autontibodies to be more easily identifying by comparing the results obtained with each tissue.**

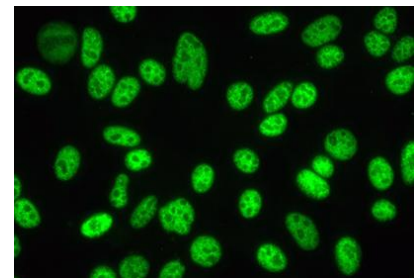




# Types of ANAs

□ There are Three major antibodies detected

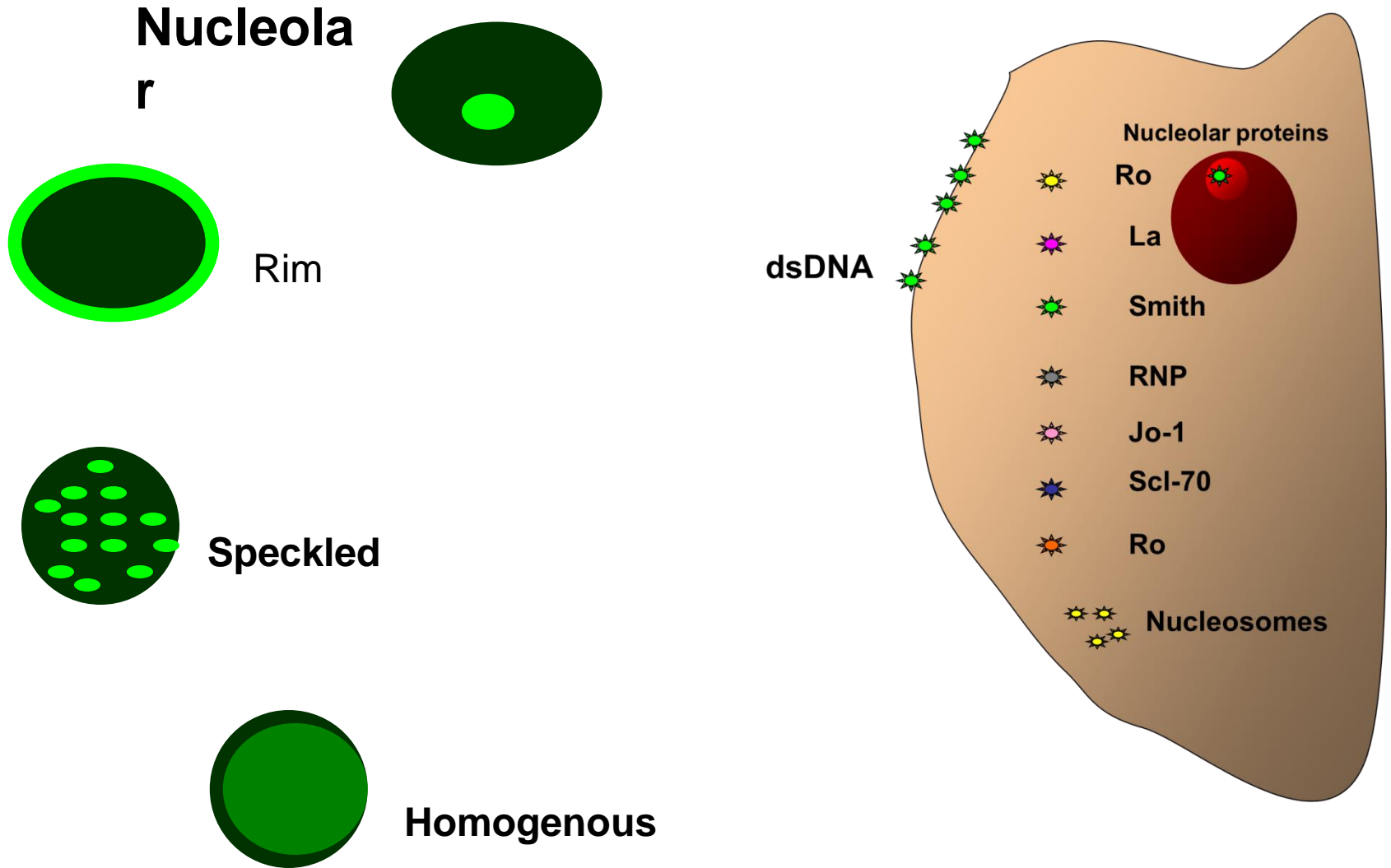
- Antinuclear antibodies (ANA)
- Antimitochondrial antibodies (AMA)
- Antismooth muscle antibodies (ASMA)



# Principle

- An indirect immunofluorescence technique is utilized where patient samples and appropriate controls are incubated with the substrate slides.
- The unreacted antibodies are washed off and an appropriate fluorescence labeled conjugate is applied.
- Unbound conjugate is washed off, and slides are viewed with a fluorescence microscope.
- Positive samples produce apple-green fluorescence.

# PATTERN OF FLUORESCENCE



PATTERN	COMMON ANTIGEN INVOLVED	DISEASE ASSOCIATION
Homogenous	dsDNA,histones	SLE,RA Mixed connective tissue disease,Drug induced lupus
Peripheral (RIM)	Native/dsDNA	SLE
Speckled	Extractable nuclear antigens, Ribonucleoprotein, Scl-70,SSB	Scleroderma Sjogren's syndrome, Mixed connective tissue disease,SLE
Nucleolar	4-6S sRNA	Scleroderma,SLE,RA Sjogren's syndrome, Progressive systemic sclerosis.

# Importance Of ANA

- Serologic hallmarks of patients with systemic autoimmune disease (ANA diseases).
- Can provide further diagnostic and prognostic data concerning patients who have minimal symptoms or who have clinical features of more than one autoimmune disease.



# Limitations of ANA

- Their presence does not mandate the presence of illness, since they can also be found in otherwise normal individuals.
- Accurate interpretation of different nuclear patterns is confounded several difficulties as:
- One nuclear pattern may obscure and prevent the recognition of another pattern if several antibodies are present simultaneously.

# Treatment

- Some autoimmune diseases are treated with medications that alleviate specific symptoms.
- Haemolytic anaemia: Treated with Vit B<sub>12</sub>
- Throtoxicosis: Treated with antithyroid drugs.
- Myasthenia Gravis: Treated with Choline esterase inhibitors
- Rheumatoid Arthritis: Anti-inflammatory drugs
- Lupes Erythematosus: Treated with immunosuppressive or antimetabolic drugs such as Corticosteroid, Cyclophosphamide and azathioprine.

# Summary

- Autoimmune diseases and conditions exist when the body produces abnormal cells, which attack the body, itself
- Most autoimmune diseases strike women more often than men
- The causes of autoimmune diseases are not known but some autoimmune diseases seem to run in families
- Strike any part of the body, symptoms vary widely and diagnosis and treatment are often difficult
- Medical science is striving to design therapies that prevent autoimmune diseases