

# Pathological Changes in Diabetes Mellitus

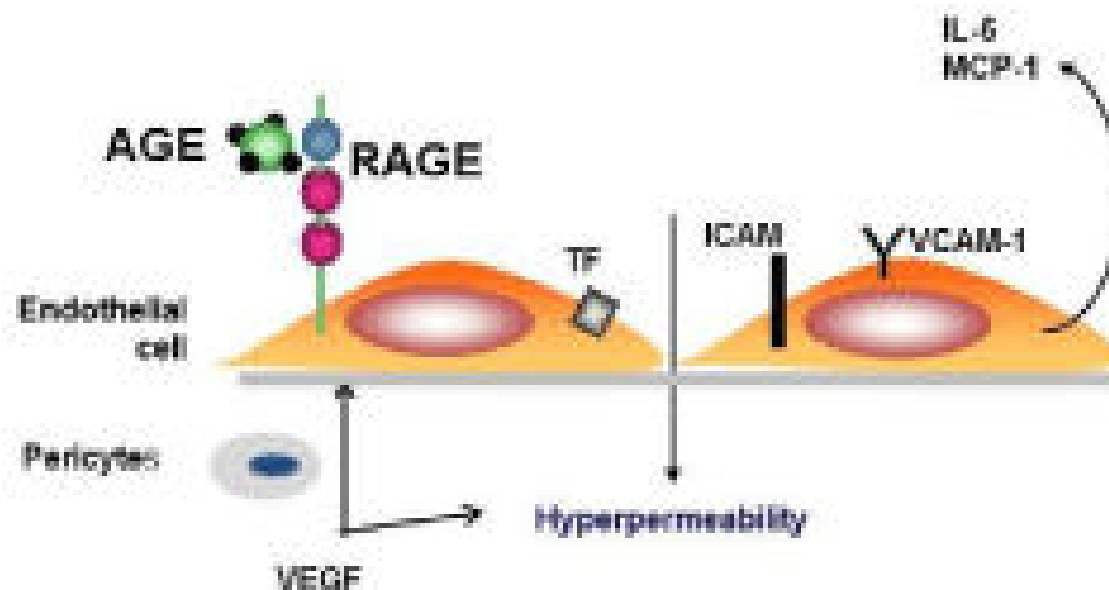
- Pancreas
- Diabetic Nephropathy
- Diabetic Cardiomyopathy
- Diabetic Retinopathy
- Diabetic Neuropathy

# Four distinct mechanisms

***1-Formation of Advanced Glycation End Products.*** *Advanced glycation end products (AGEs) are formed as intracellular*

glucose derived dicarbonyl precursors+ amino groups  
→ advanced glycation end product(AGEs)  
(glyoxal, methylglyoxal, and 3-deoxyglucosone)

- AGEs bind to a specific receptor (**RAGE**) that is expressed on inflammatory cells (macrophages and T cells), endothelium, and vascular smooth muscle.



## AGE-RAGE signalling axis

- **TGF $\beta$ -excess basement membrane material**
- *vascular endothelial growth factor* (VEGF)- neovascularization
- reactive oxygen species (ROS) in endothelial cells
- procoagulant activity
- Enhanced proliferation of vascular smooth muscle cells and synthesis of extracellular matrix

## ***2-Activation of Protein Kinase C.***

second messenger diacyl glycerol (DAG) is an important signal transduction pathway.

Intracellular hyperglycemia---→ *de novo* synthesis of DAG--→excessive PKC activation-→ vascular permeability and angiogenesis

## ***3-Oxidative Stress and Disturbances in Polyol Pathways***

- Sustained hyperglycemia---- aldol reductase-- progressive depletion of intracellular NADPH --→ decreased regeneration of reduced glutathione(GSH) -→ increasing cellular susceptibility to oxidative stress

### ***4-Hexosamine Pathways and Generation of Fructose-6- Phosphate***

Hyperglycemia ---→ increases intracellular levels of *fructose-6-phosphate* via *HM*- → *excess proteoglycans* -→ abnormal expression of TGFβ or PAI-1---→ exacerbate the end-organ damage

## **Pancreas**

### **Pancreatic Islets-**

#### **1-Insulitis:**

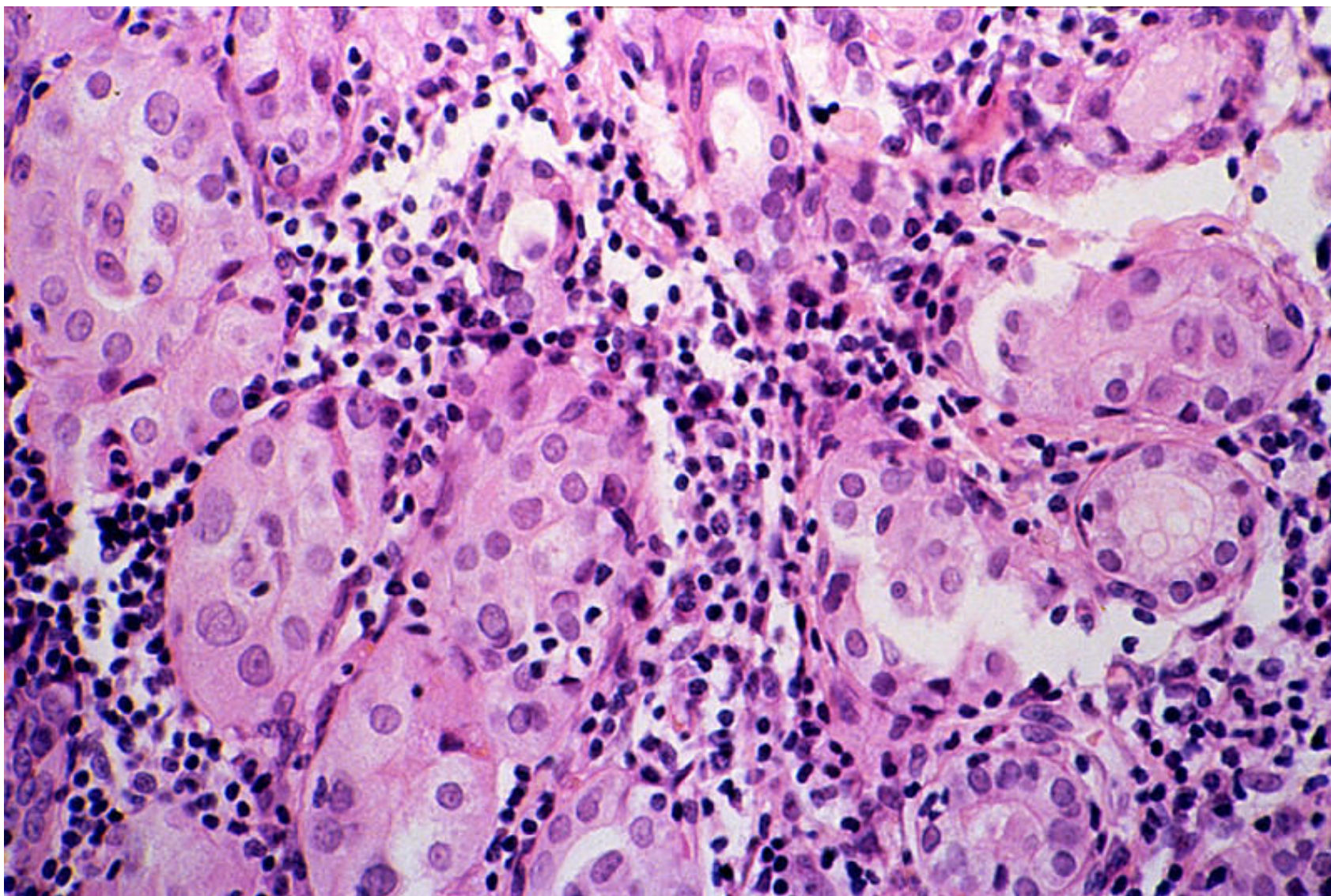
- In type 1 DM-
  - lymphocytic infiltrate, macrophage and few polymorphs
- In type 2 DM-
  - variable degree of fibrous tissue in the islets

## 2-Islet cell mass:

- Type-1- loss of pancreatic  $\beta$ -cells and its hyalinisation
- In type 2 DM-hyperplasia and hypertrophy of islets

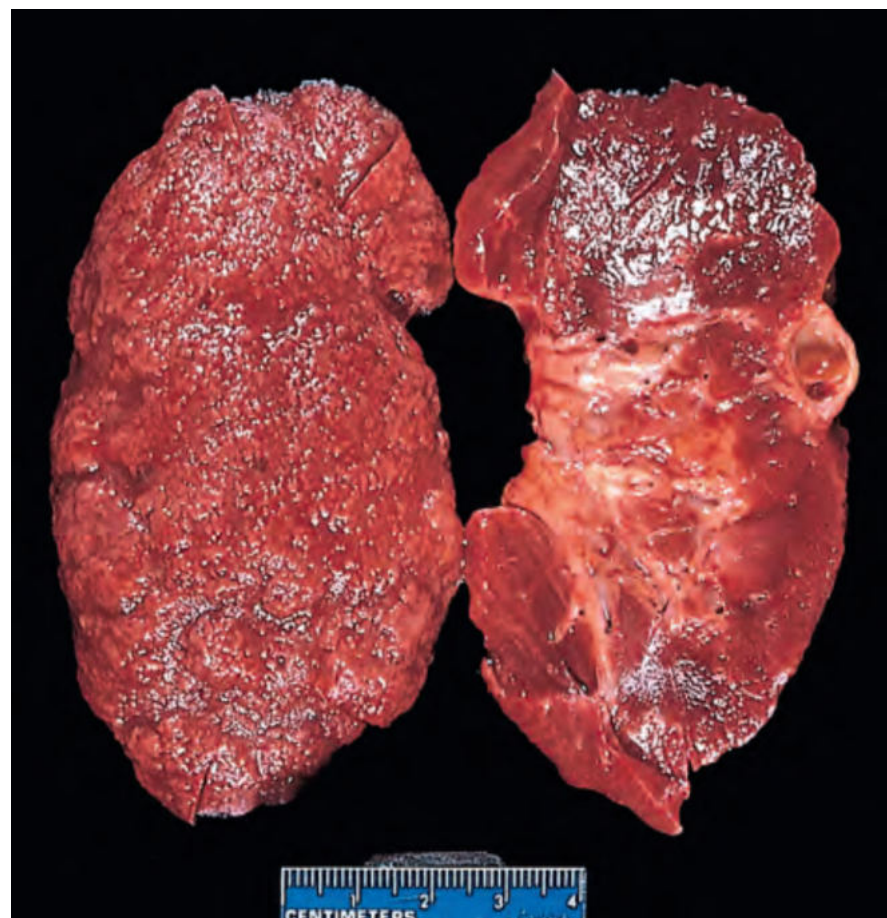
## 3-Amyloidosis:

- type 1 DM- absent
- Type-2DM-around the capillaries of the islets causing compression and atrophy of islet tissue

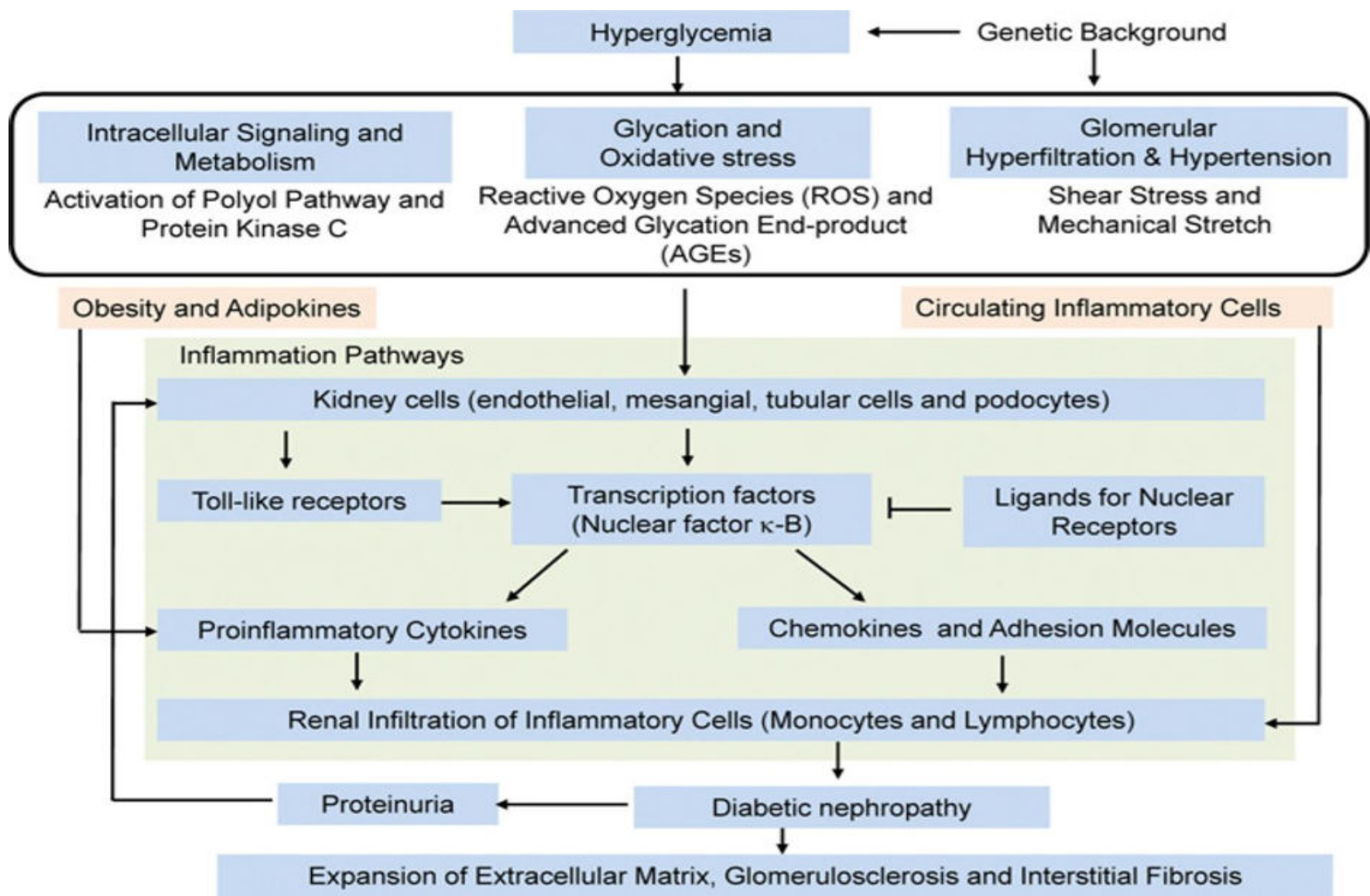


# Diabetic Nephropathy

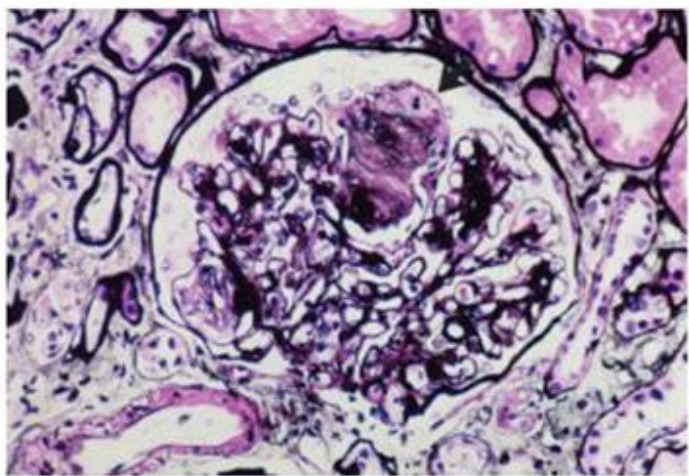
## Nephrosclerosis



# Pathogenesis in Diabetic nephropathy



## Sequence of Glomerular Changes



Morphologic changes similar in Type I and Type II

No glomerular alterations



Thickening of glomerular basement membranes



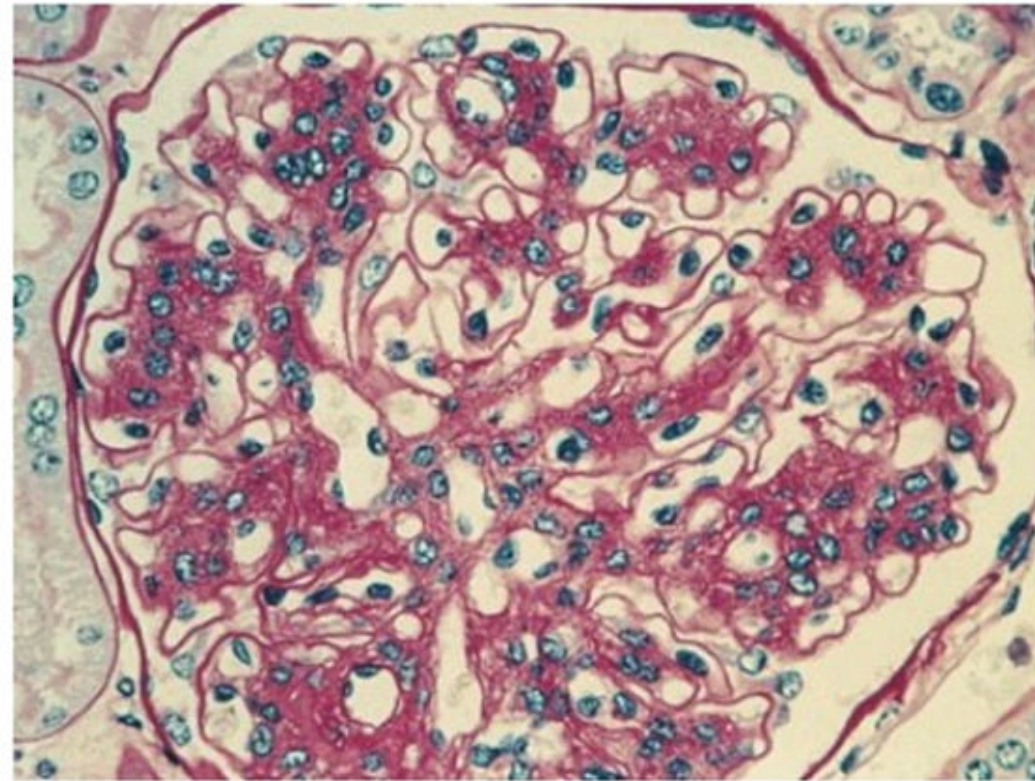
Global mesangial widening  
“diffuse mesangial sclerosis”;



“Kimmelstiel-Wilson” nodules  
(Nodular glomerulosclerosis)

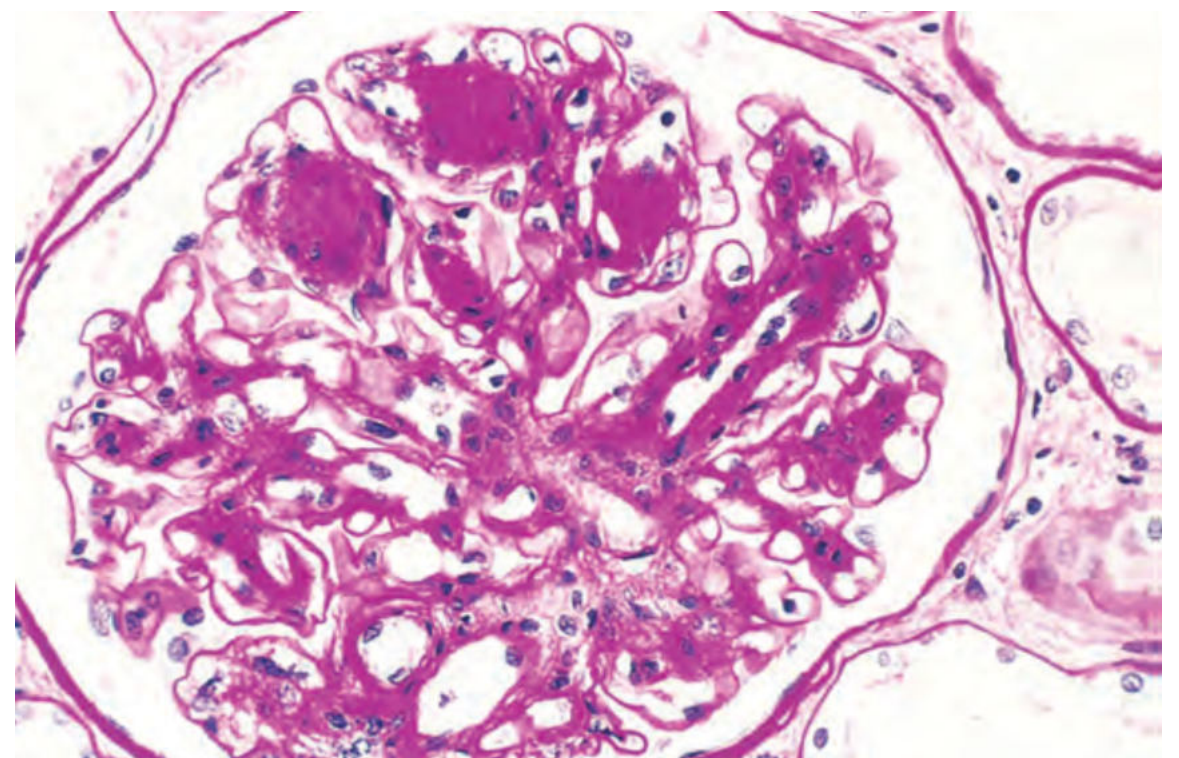
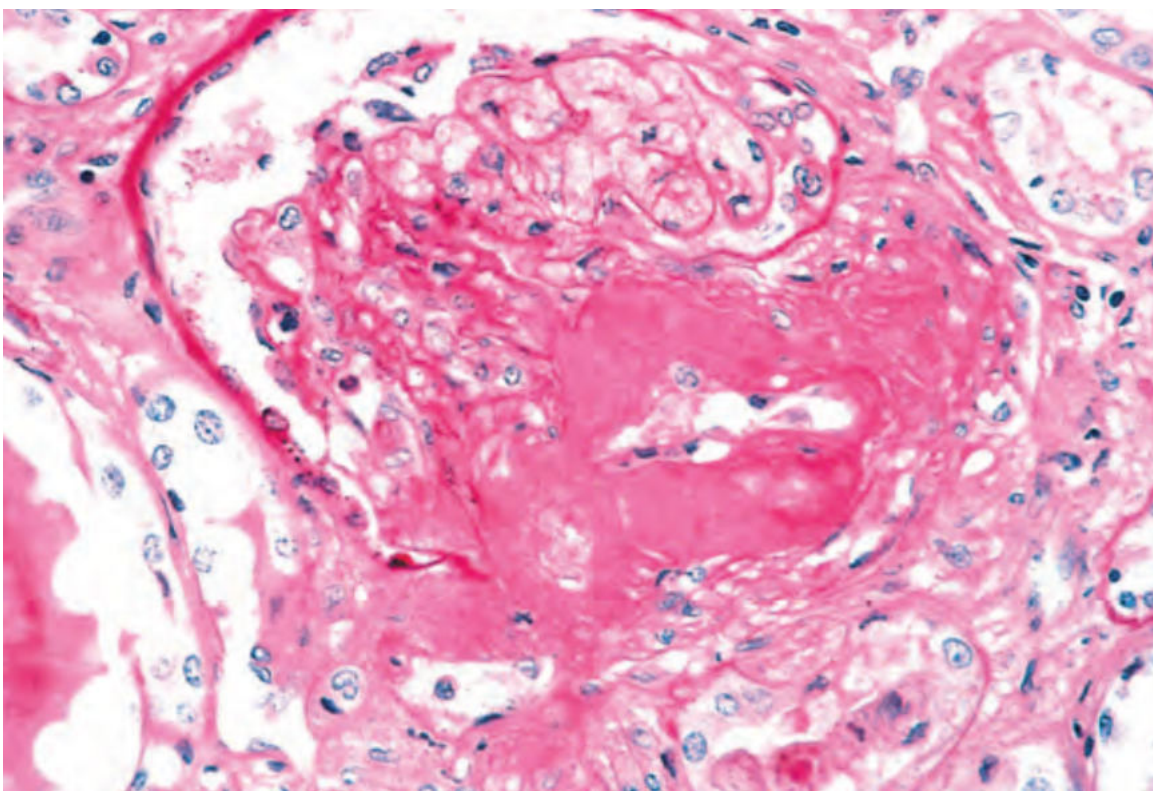
## PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

The basement membranes of the glomerular capillaries thicken and can obliterate the blood vessels.

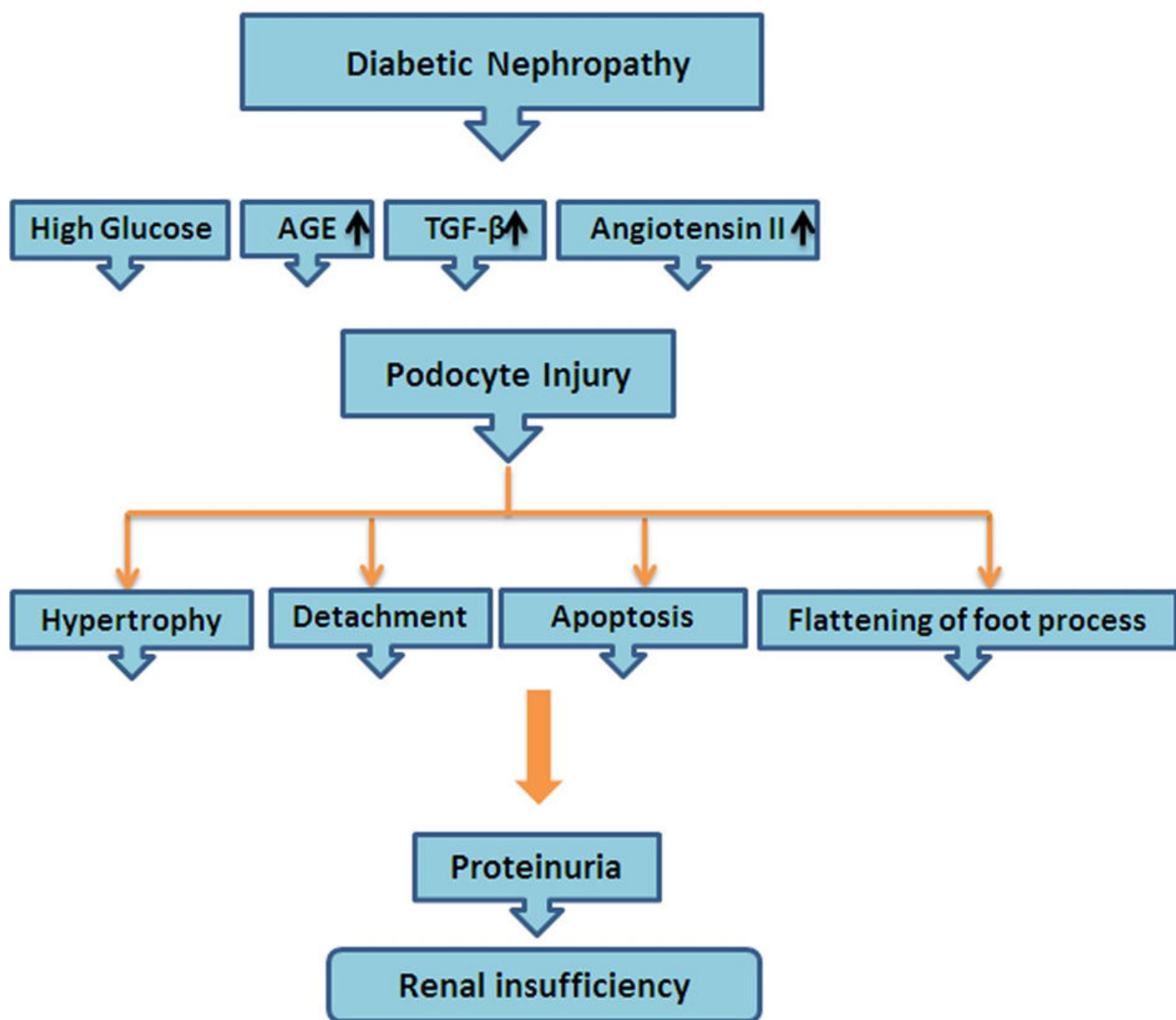


Histological changes in diabetic nefropatía: basal membrane thickening.

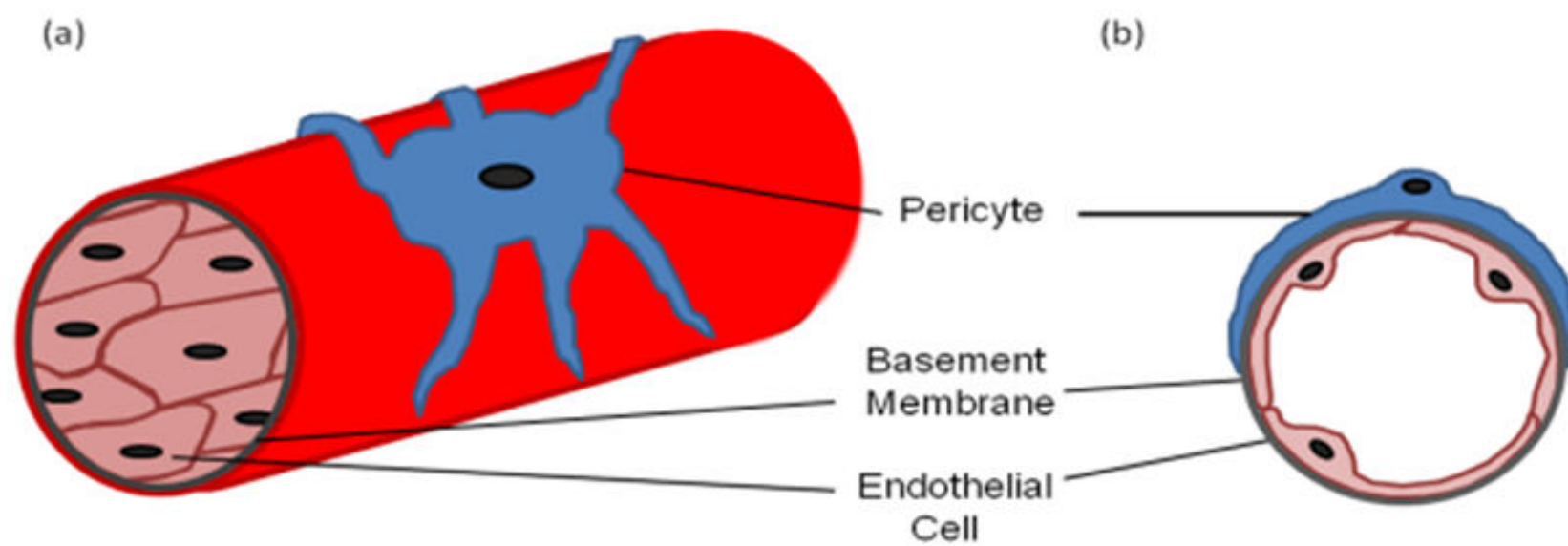
Dr. Carlos Azañero Inope



## Podocyte Injury in Diabetic Nephropathy



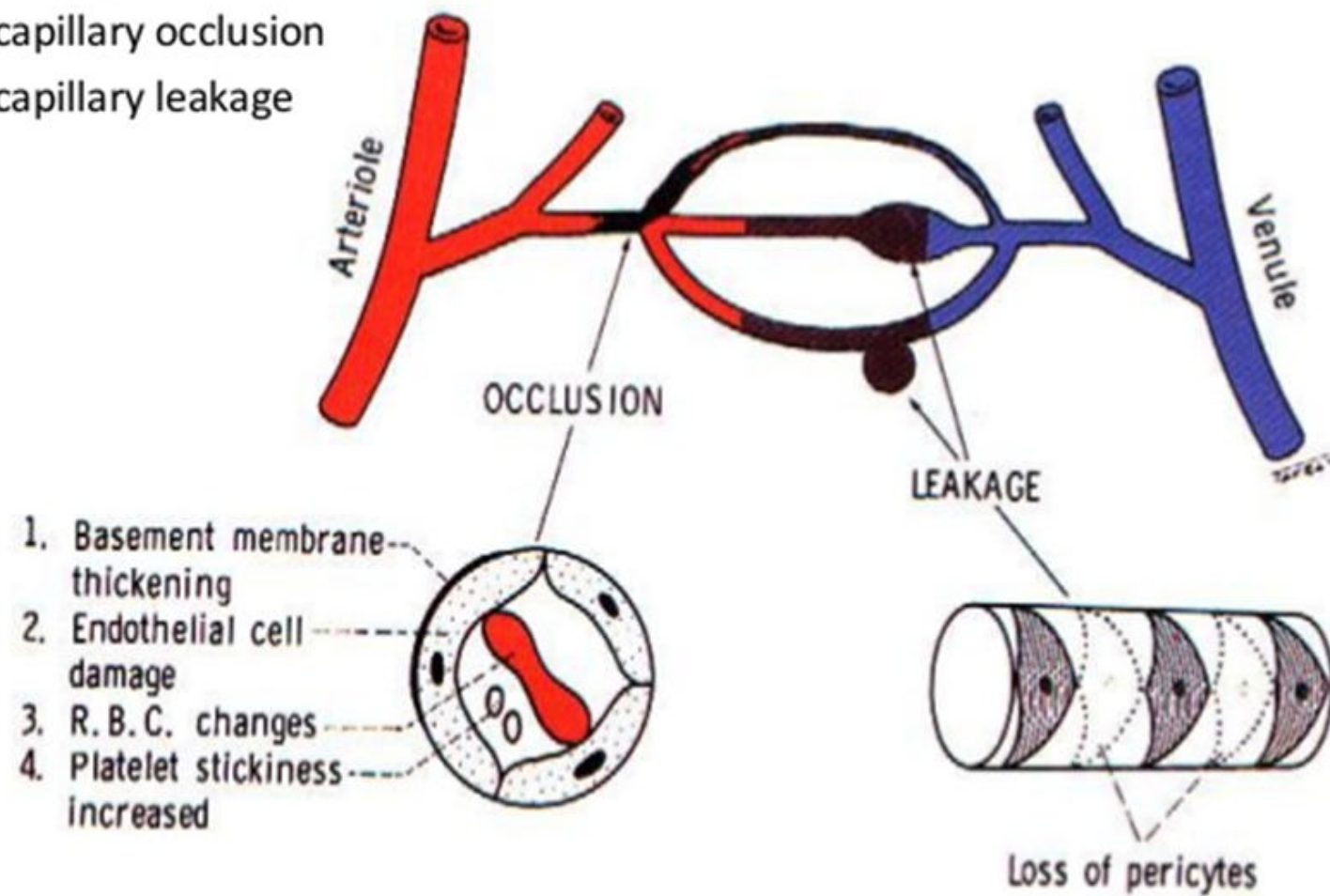
# Diabetic Retinopathy



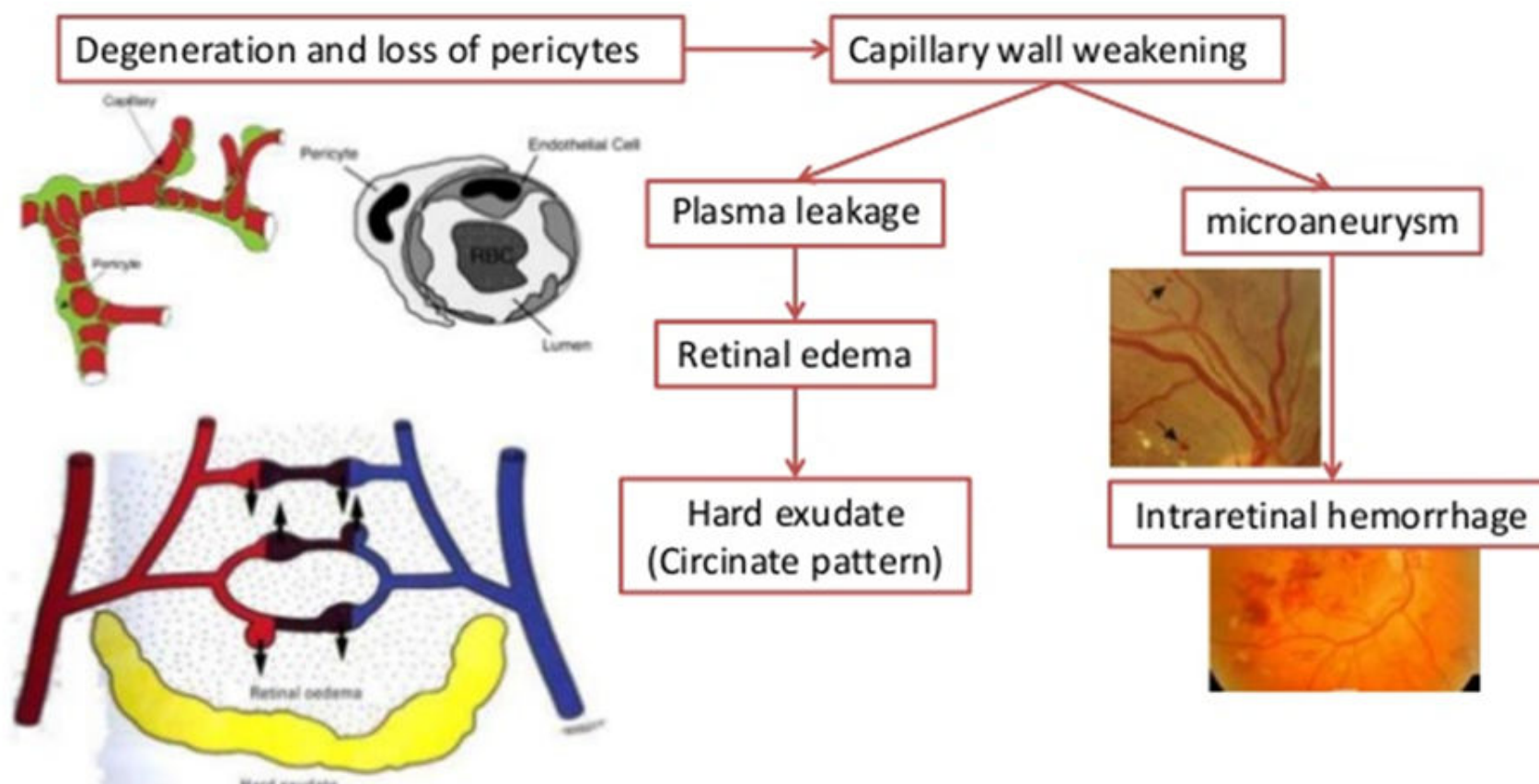
# PATHOGENESIS

It is a microangiopathy caused by effect of hyperglycemia on small blood vessels leading to -

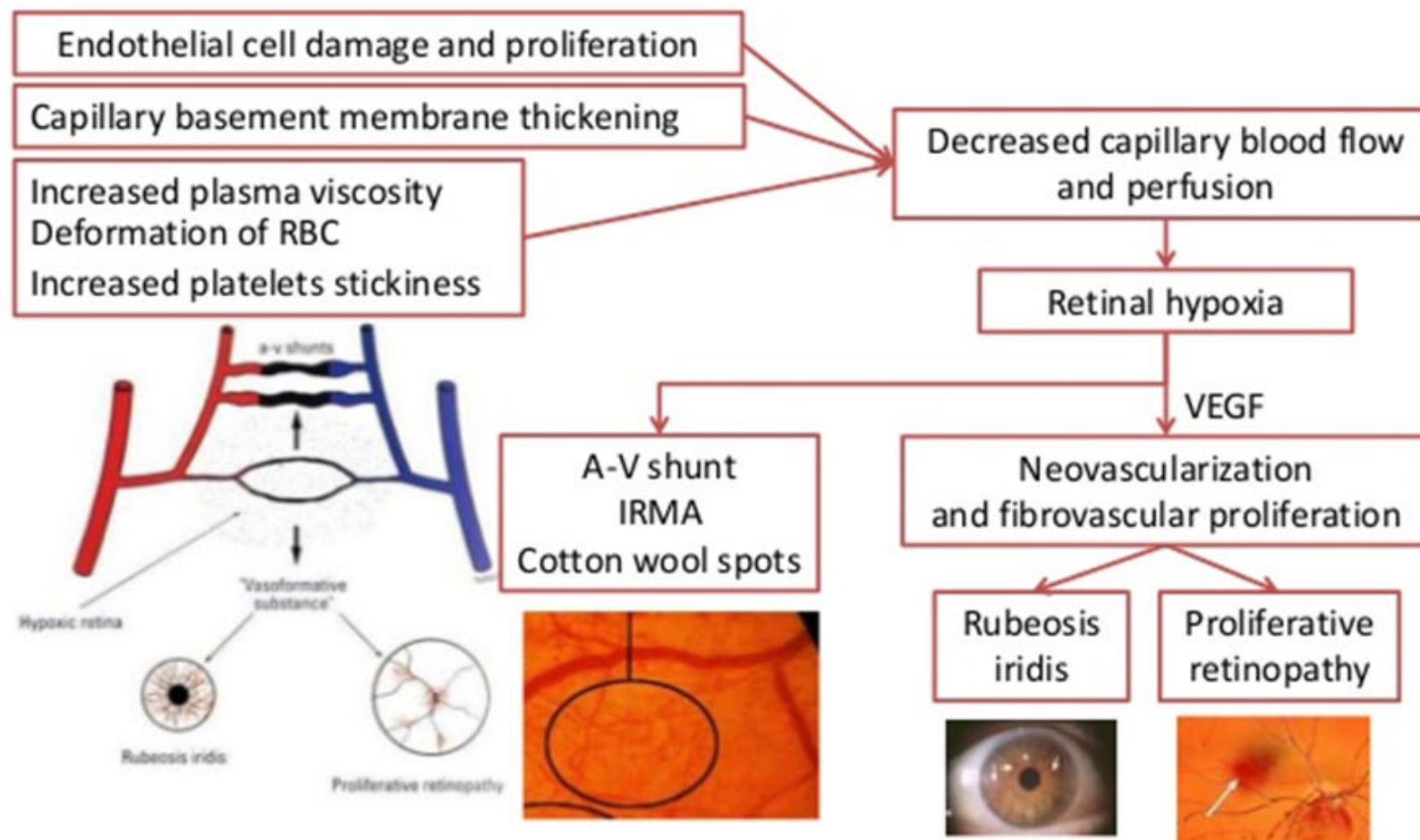
- Retinal capillary occlusion
- Retinal capillary leakage



## Microvascular leakage



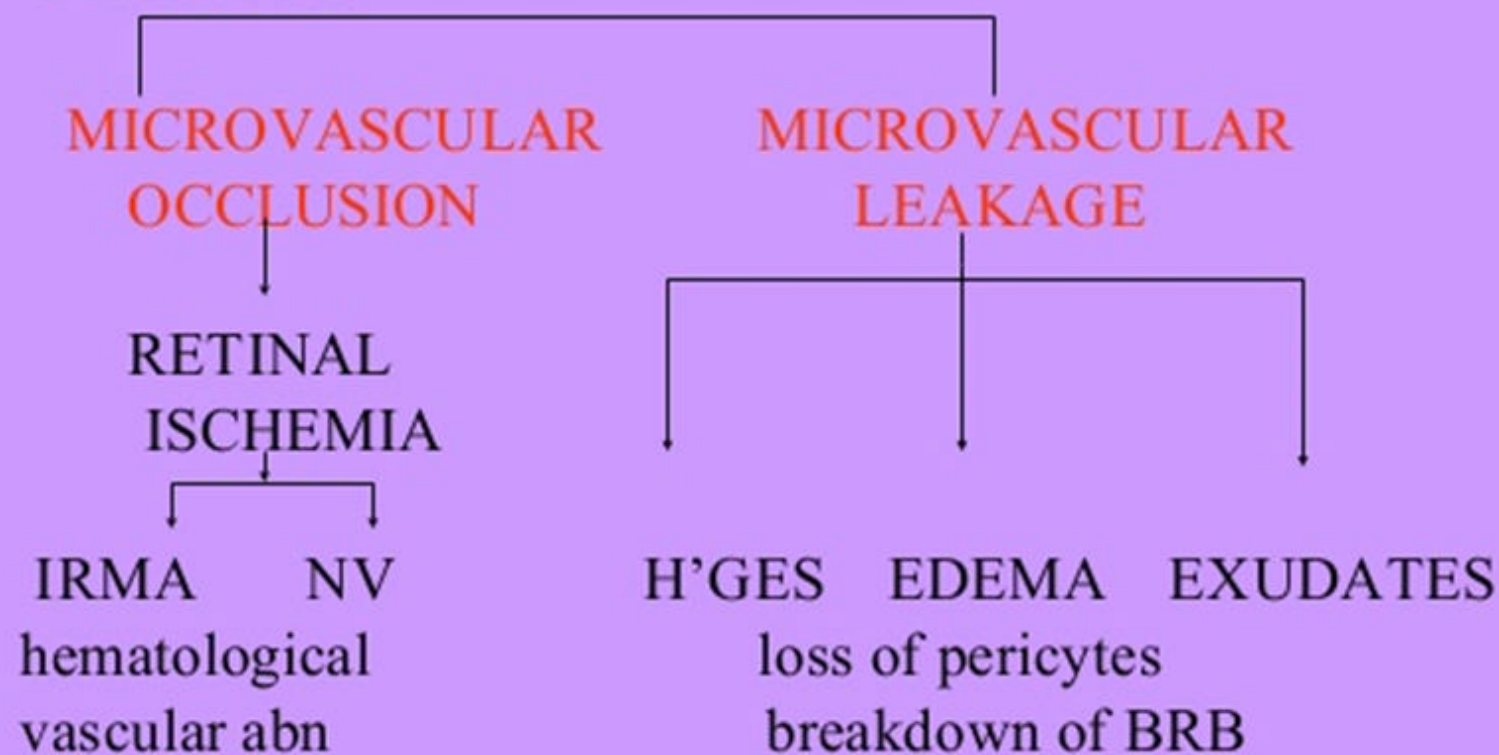
# Microvascular occlusion

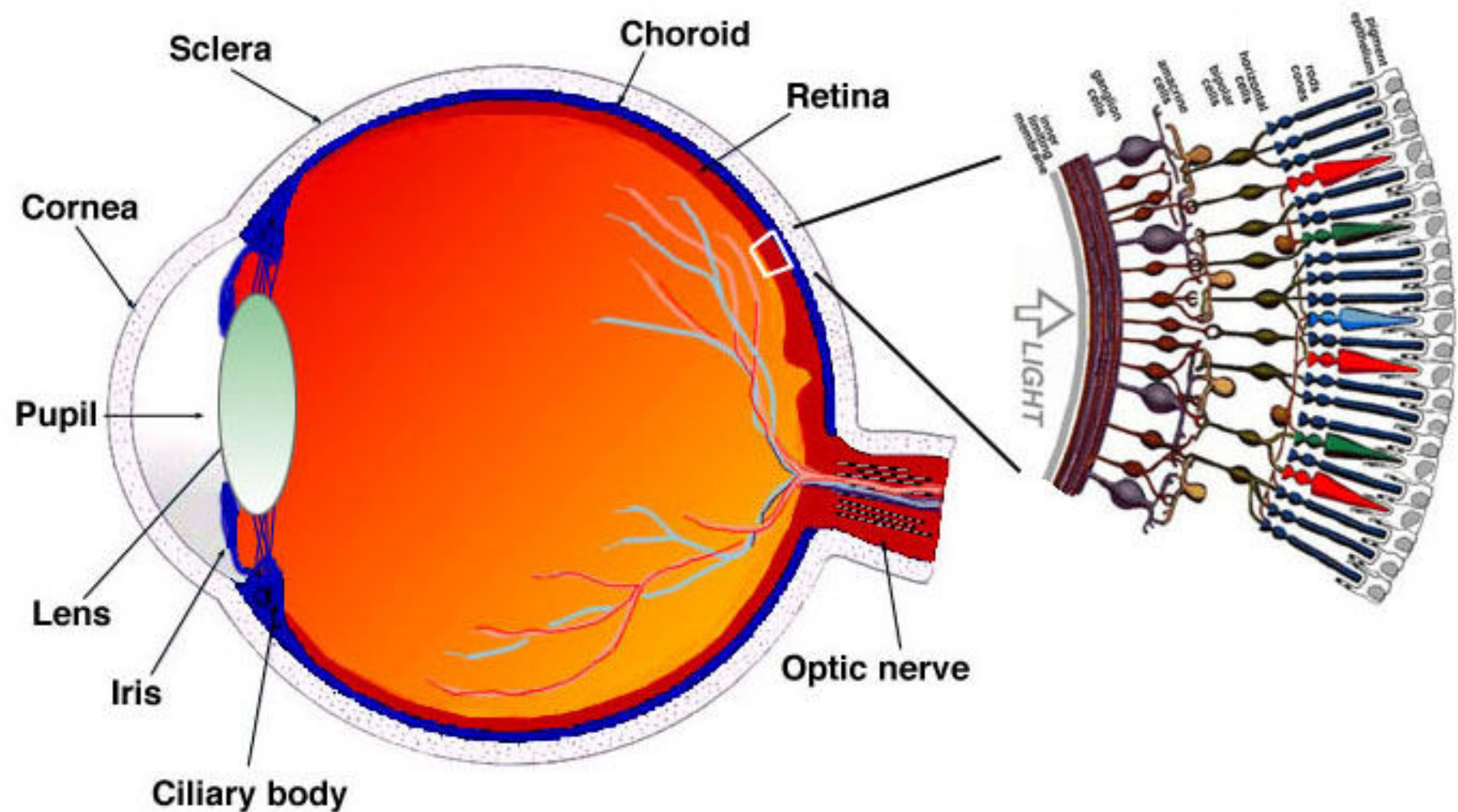


## PATHOGENESIS

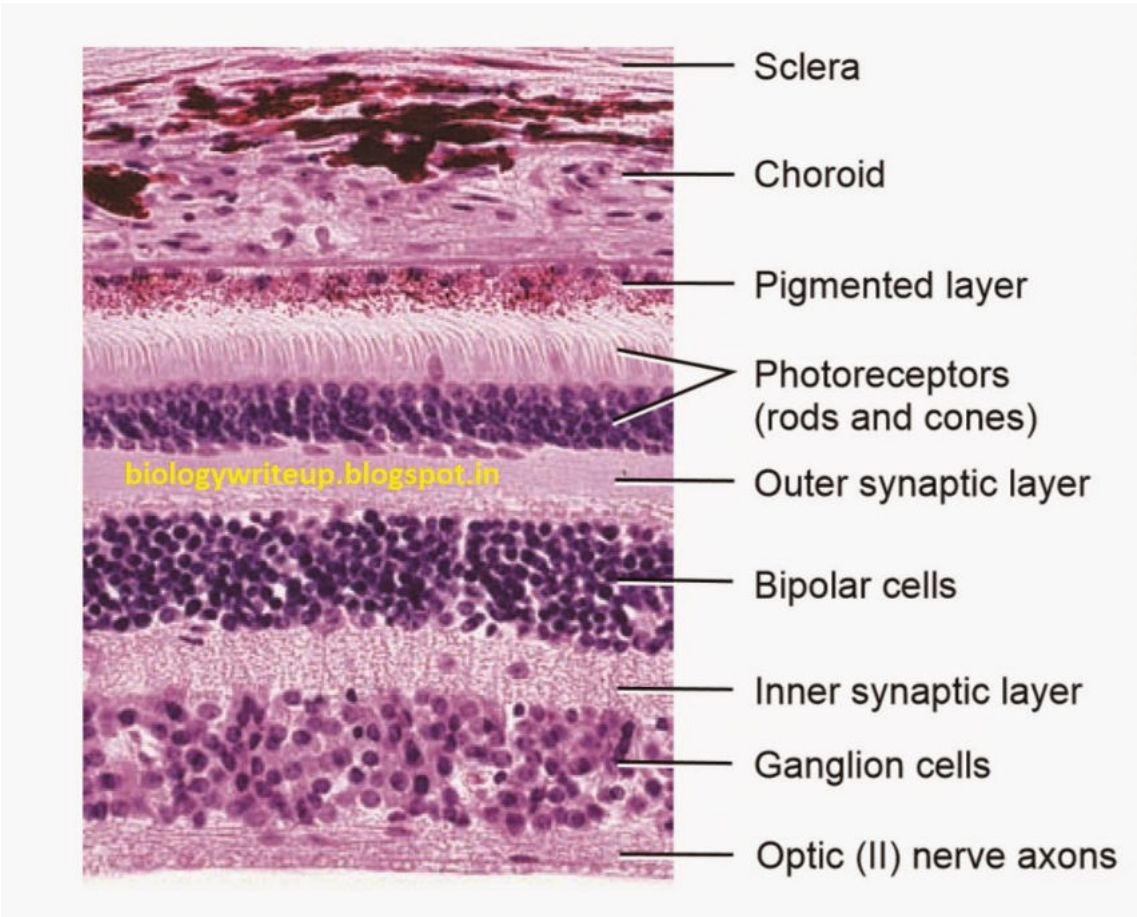
- MICROANGIOPATHY AFFECTING PRE CAPILLARIES ARTERIOLES, CAPILLARIES & VENULES.

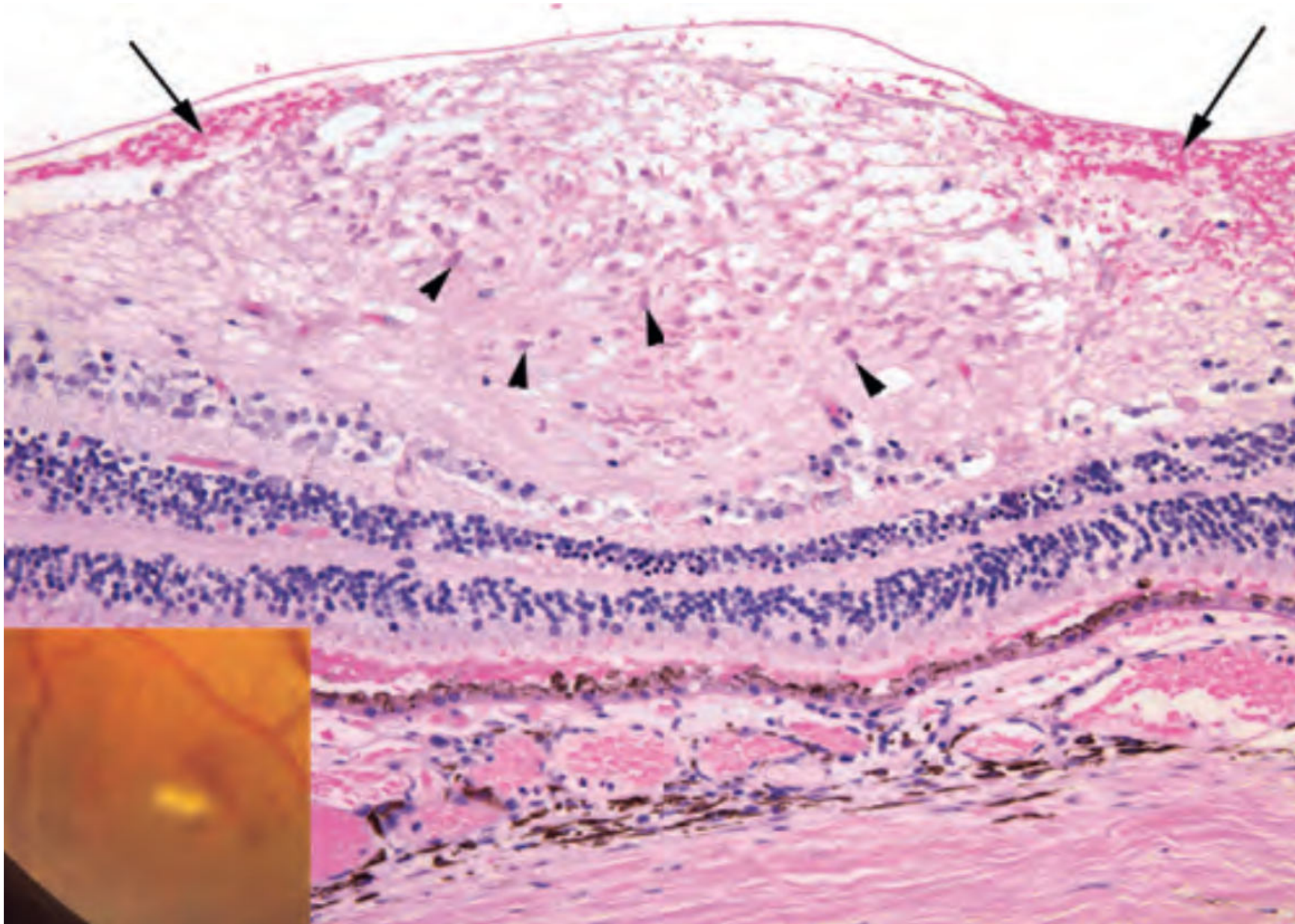
- FEATURES



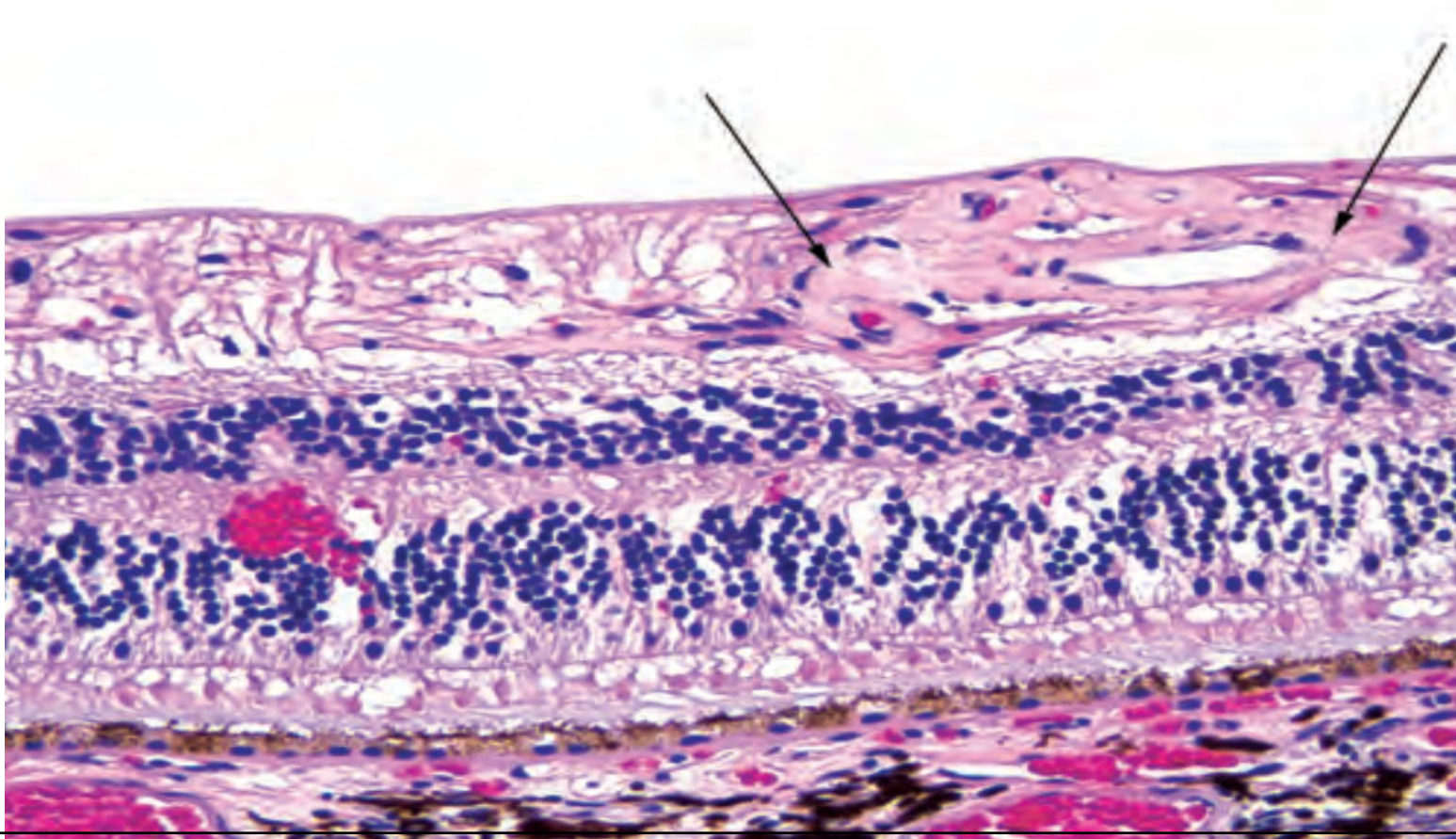


**Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.**

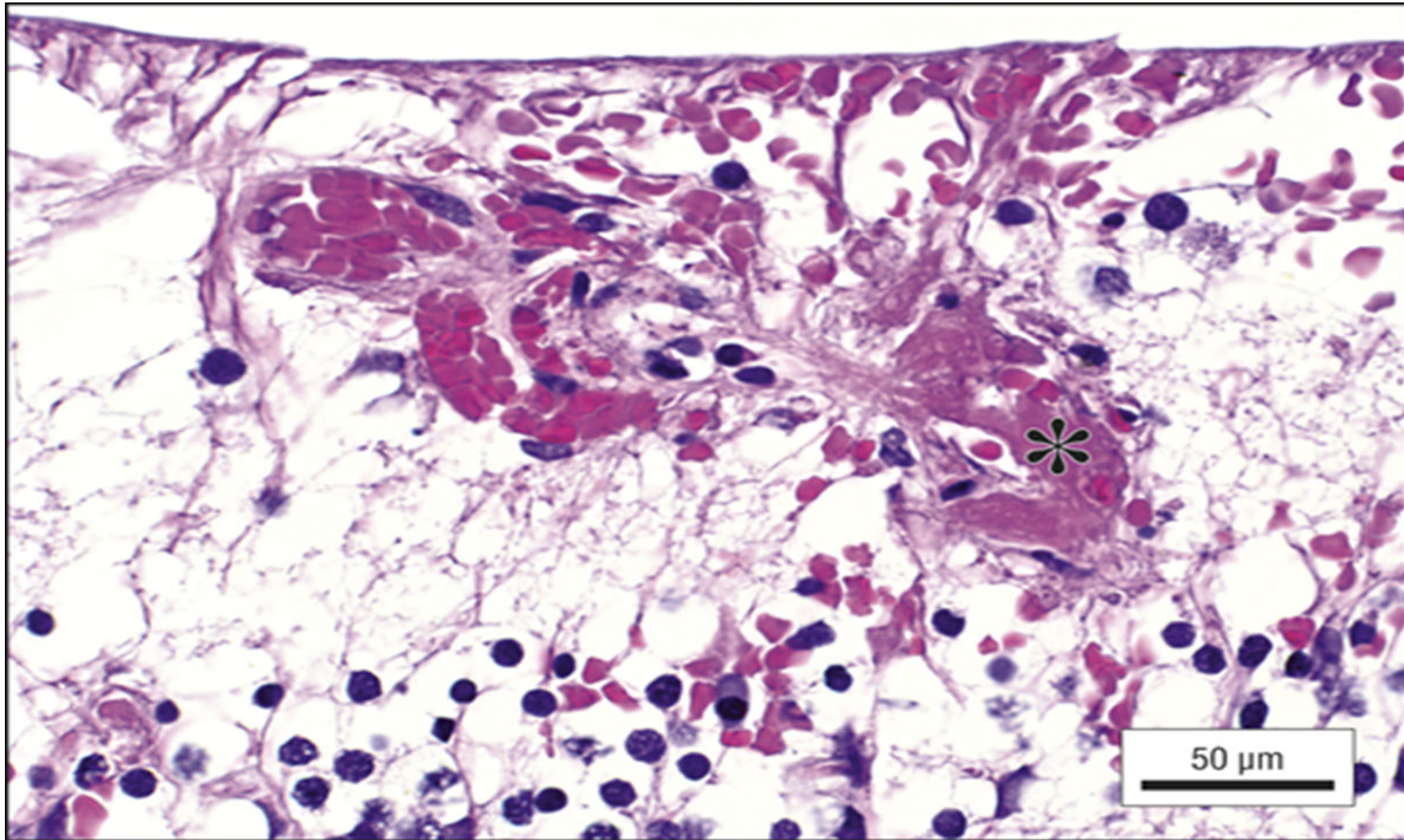




Intra retinal microangiopathy (IRMA)(NPDR)



# Neovascularization



## Diabetic Cardiomyopathy

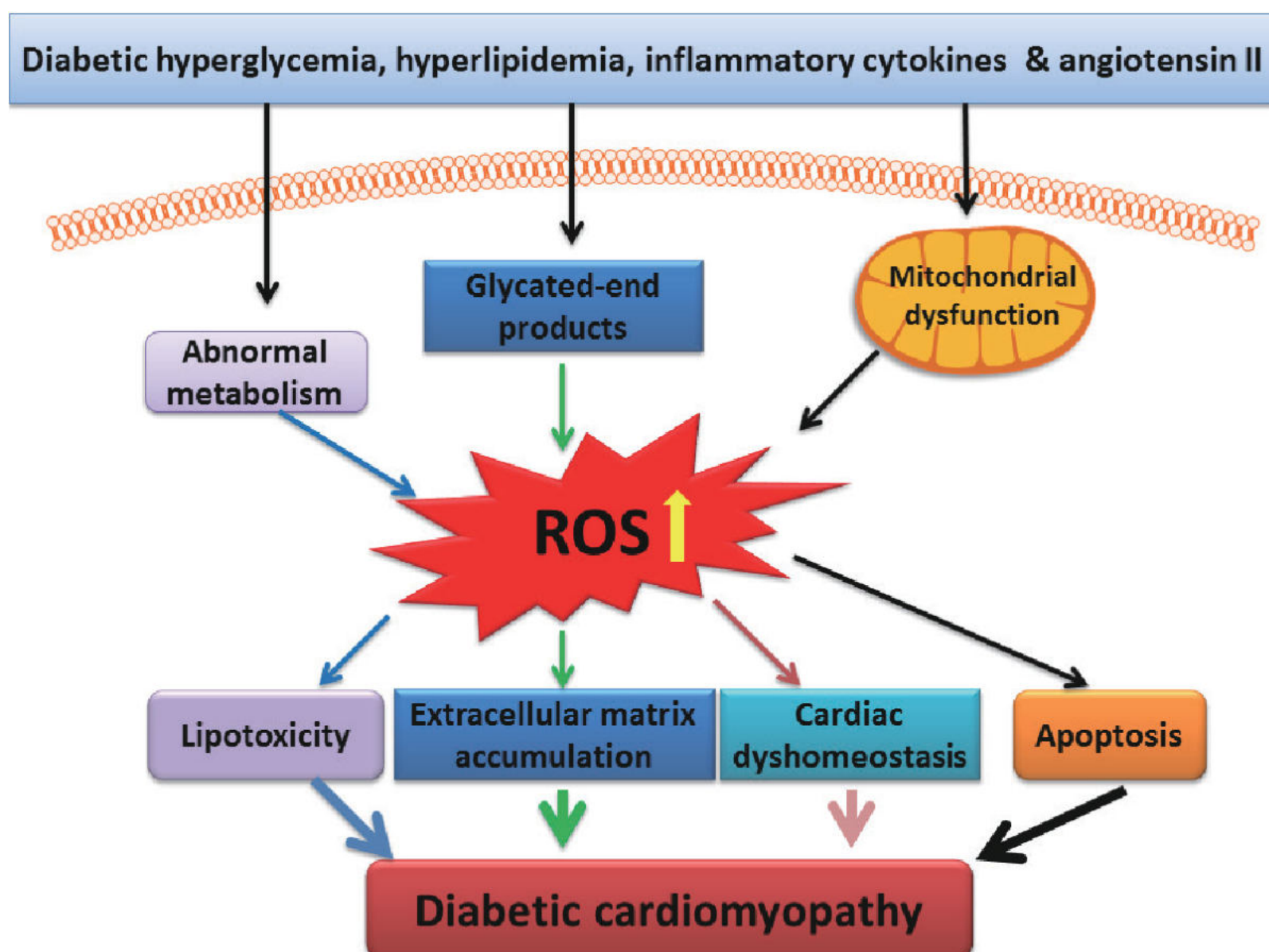
## Definition of Diabetic cardiomyopathy

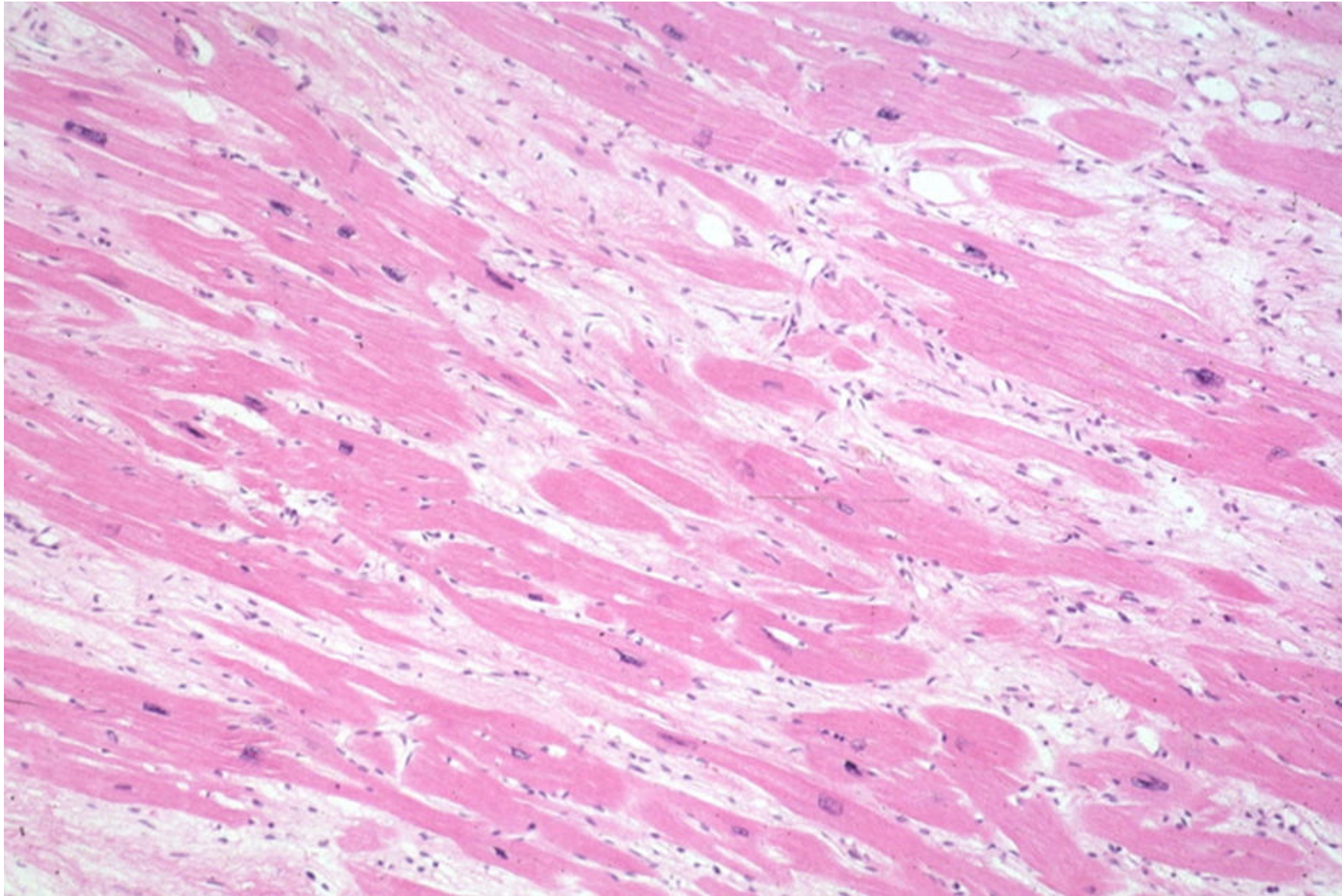
- ✓ Characterized by myocardial dilatation & hypertrophy
- ✓ Decrease in systolic & diastolic function
- ✓ Independent of the coexistence of ischemic heart disease or hypertension
- ✓ Subclinical for long time
- ✓ Hyperglycemia pathogenetic factor



3

Voulgari C, Papadogiannis D, Tentolouris N. Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies. Vascular health and risk management. 2010 Oct 21;6(1):883-903.





## Diabetic Neuropathy

