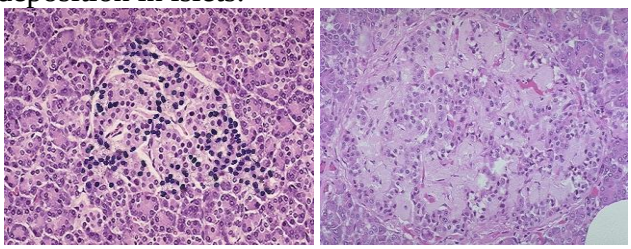
Unit IV – Problem 2 – Pathology: Complications of Diabetes Mellitus

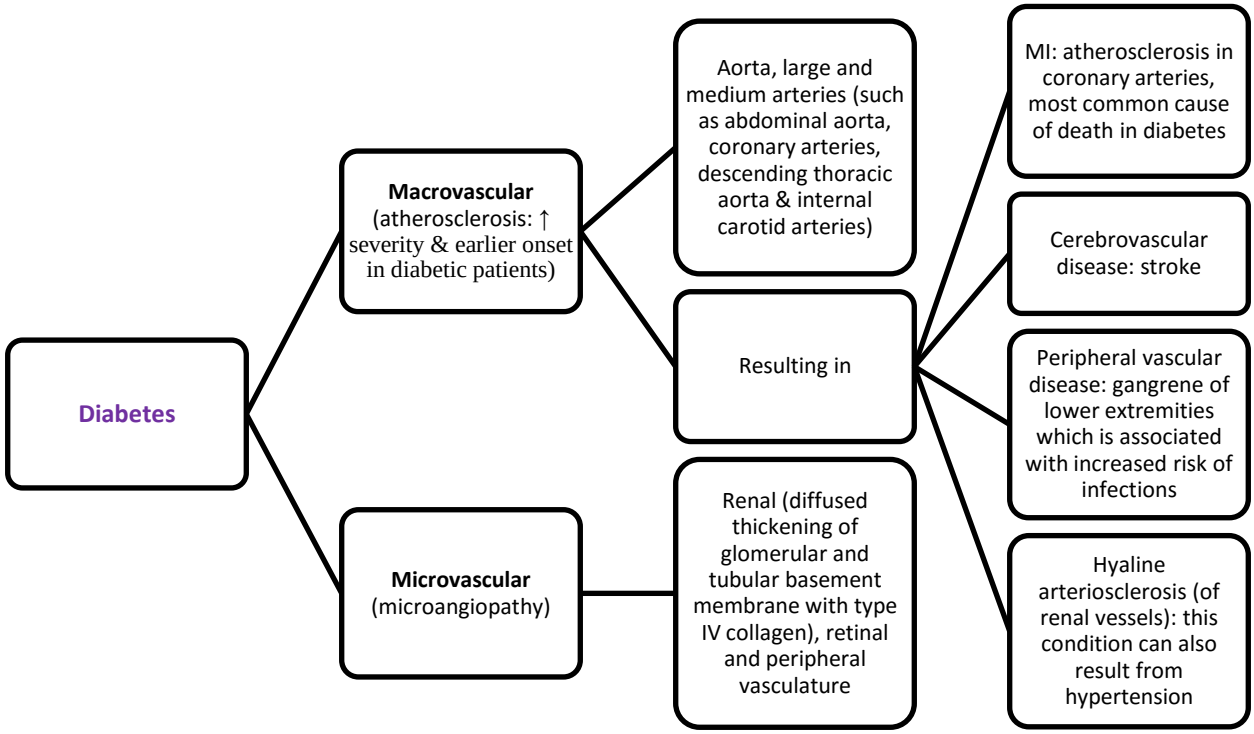
- **There are two main cell types in the pancreas:**
  - **α-cells**: secreting glucagon.
  - **β-cells**: secreting insulin.
- **Pathological changes of diabetes in pancreas:**
  - **Type-I**: insulitis (infiltration with T-lymphocytes) + destruction of β-cells of islets of Langerhans.
  - **Type-II**: amyloid deposition in islets.



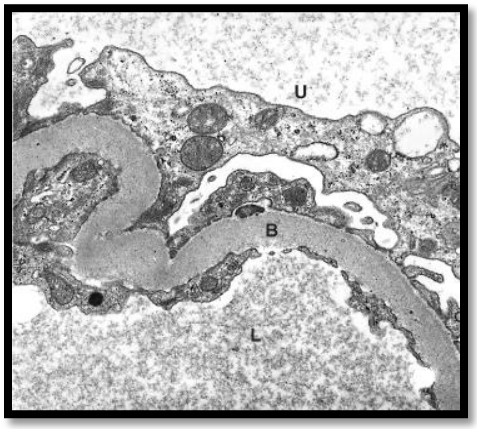
- **There are three mechanisms for complications of diabetes:**
  - **Nonenzymatic glycosylation with the formation of irreversible advanced glycosylation end products (AGEs):**
    - ✓ AGEs bind to a specific receptor (RAGE) which is expressed on:
      - ❖ Inflammatory cells (macrophages and T-cells).
      - ❖ Endothelium.
      - ❖ Vascular smooth muscle.
    - ✓ Then, a signaling axis will be generated which includes:
      - ❖ Monocyte emigration.
      - ❖ Generation of reactive oxygen species in endothelial cells.
      - ❖ Increased procoagulant activity in endothelial cells.
      - ❖ Enhanced proliferation of vascular smooth muscle cells and synthesis of extracellular matrix.
    - ✓ AGEs can directly cross-link extracellular matrix proteins:
      - ❖ With collagen type-I molecules in large vessels: predisposing vessels to endothelial injury.
      - ❖ With collagen type-IV in basement membrane: increased endothelial permeability.
      - ❖ With proteins: decreased protein removal with enhancement of protein deposition.
      - ❖ AGE-modified matrix components: trapping non-glycated plasma or interstitial proteins.
      - ❖ In large vessels: trapping of LDL (bad cholesterol) in tunica intima of vessels thus accelerating atherogenesis.
  - **Activation of protein kinase C (PKC):**
    - ✓ Intracellular hyperglycemia leads to de novo synthesis of Diacyl Glycerol (DAG).
    - ✓ Glycolytic intermediates will lead to activation of protein kinase C (which is related to long-term complications of diabetic microangiopathy.
    - ✓ Effects of activated protein kinase C:
      - ❖ Production of Vascular Endothelial Growth Factor (VEGF) which leads to neovascularization characterizing diabetic retinopathy.
      - ❖ Increased vasoconstriction by (endothelin-1) and decreased vasodilation by (NO).
      - ❖ Production of TGF-β which leads to deposition of extracellular matrix and basement membrane material.
      - ❖ Production of plasminogen activator inhibitor resulting in vascular occlusive episodes.

- **Intracellular hyperglycemia and disturbances in polyol pathway:**
  - ✓ This occurs in tissues not requiring insulin for entry of glucose such as: lens, kidney, Schwann cells of peripheral nerves and blood vessels.
  - ✓ A disturbance in polyol pathway will lead to accumulation of sorbitol which causes increased intracellular osmolarity (in tissue mentioned above) and resulting in osmotic cell injury (such as cataract when sorbitol is accumulating in the lens).
  - ✓ In addition, increased glucose level inside these cells will result in depletion of NADPH by aldol reductase (which is converting this excess glucose to sorbitol). Therefore, reduced glutathione cannot be generated leaving cells susceptible to oxidative stress.

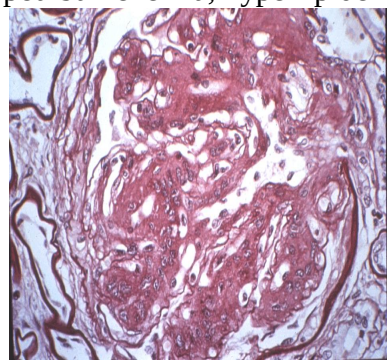
- **Diabetes affect vessels of all sizes:**



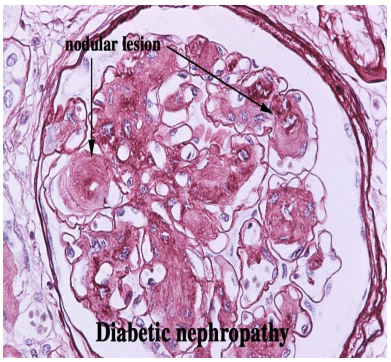
- **Diabetic nephropathy:**
  - Renal failure is the 2nd cause of death in diabetic patient (after MI).
  - **Three lesions are encountered:**
    - ✓ Glomerular lesions:
      - ❖ *Capillary basement membrane thickening*: entire length thickening which takes years to develop and might be asymptomatic.



- *Diffuse glomerusclerosis (mesangial):* diffuse increase in mesangial cells and matrix which is always associated with basement membrane thickening and takes about 10 years to develop. This will be manifested as nephritic syndrome (which is characterized by: proteinuria > 3.5, hypoalbumenemia, hyperlipidemia and edema).

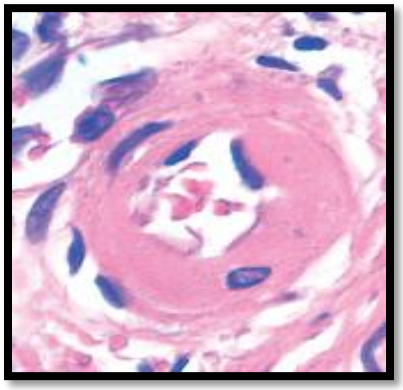


- *Nodular glomerulosclerosis:* characterized by ball-like deposits in the periphery of the glomerulus. This condition induces ischemia which causes overall fine scarring of the kidneys with finely granular cortical surface.



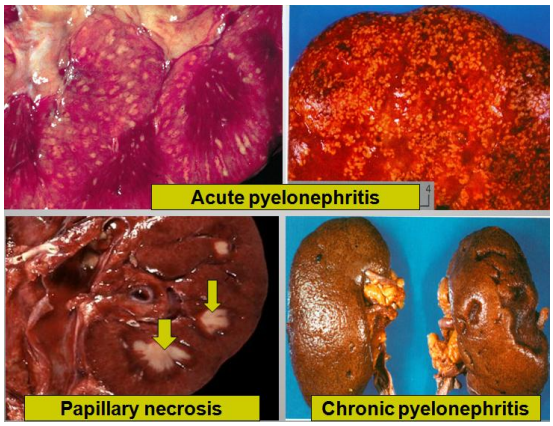
✓ Hyaline arteriosclerosis:

- Constituting part of the macrovascular disease in diabetics.
- affecting both afferent and efferent arterioles.
- *Morphology*: thickened arterioles with deposition of amorphous pink material in the thickened vascular wall (hyaline).

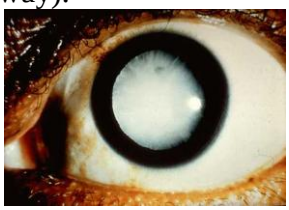


✓ Pyelonephritis:

- Acute or chronic inflammation of the kidneys beginning in the interstitial tissue and then spreading to affect the tubules.
- Diabetic patient also have increased risk to develop papillary necrosis.



- **Diabetic ocular complications:**
  - 4^{th} leading cause of blindness.
  - **Include the following:**
    - ✓ Retinopathy: which can be
      - ❖ *Non-proliferative*: micro-aneurysms, hemorrhage, exudates (soft or hard), venous dilation and edema.
      - ❖ *Proliferative*: fibrosis, neovascularization and retinal detachment.
    - ✓ Cataract formation: due to increase in intracellular osmolarity (osmotic injury due to disturbed polyol pathway).



    - ✓ Glucoma.
- **Diabetic neuropathy (due to disturbed polyol pathway and non-enzymatic glycation of proteins):**
  - **Central neuropathy**: represented by
    - ✓ Hemorrhages and stroke.
    - ✓ Degenerative brain and spinal cord changes.
  - **Peripheral neuropathy**: which can be
    - ✓ Distal symmetric sensory or sensory-motor neuropathy: loss of pain sensation will lead to ulcers which heal poorly because of the diffuse vascular injury in diabetes.
    - ✓ Autonomic neuropathy: results in postural hypotension, sexual dysfunction, GI disturbances and incomplete emptying of urinary bladder.
    - ✓ Focal or multifocal asymmetric neuropathy.