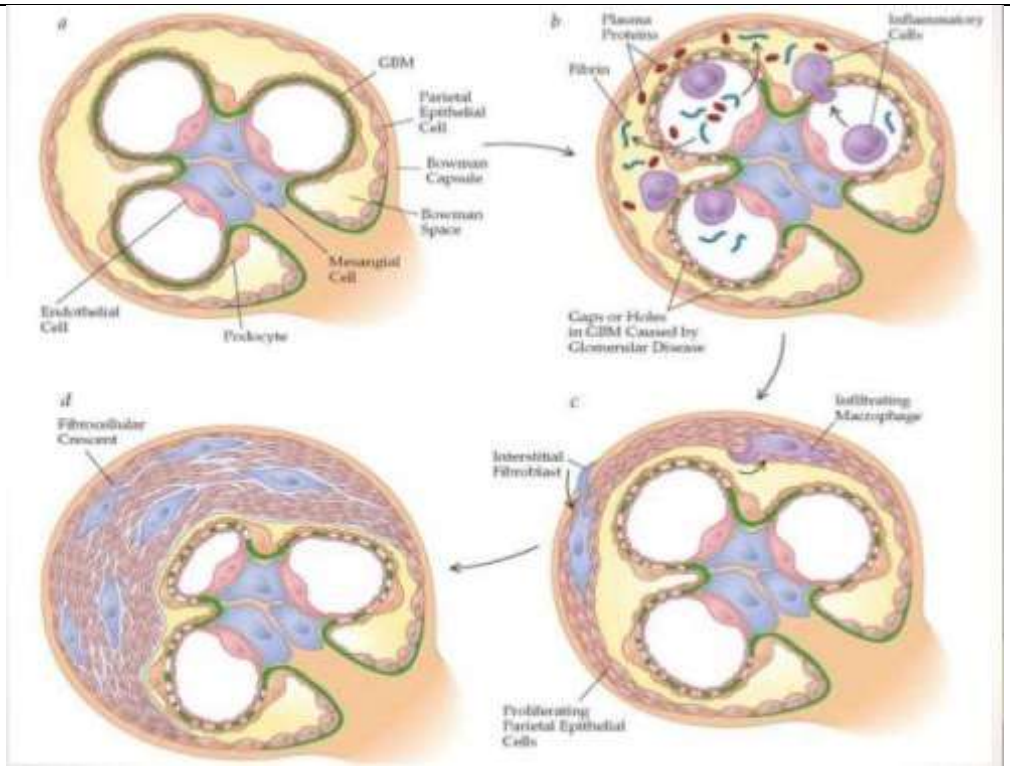
Pathologic Responses of the Glomerulus to Injury

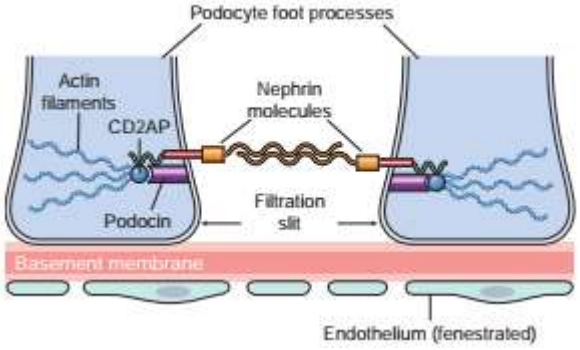
Various types of glomerulopathies are characterized by one or more of four basic tissue reactions.

I- Hypercellularity:

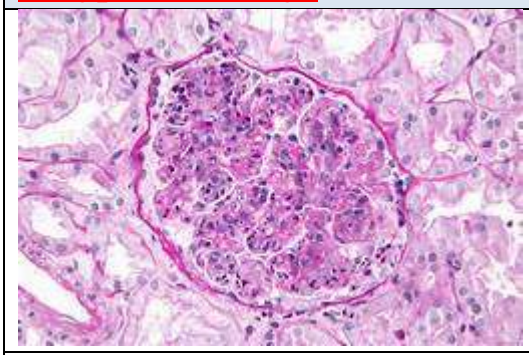
II- Basement Membrane Thickening:

III- Hyalinosis and Sclerosis:





I- Hypercellularity:



- Some *inflammatory diseases* of the glomerulus are characterized by **an increase the number of cells in the glomerular tufts.**

This hypercellularity results from one or more of the following:

1. ***Proliferation* of mesangial or endothelial cells.**
2. ***Infiltration of leukocytes,***
3. ***Formation of crescents.***

1. *Proliferation* of mesangial or endothelial cells.

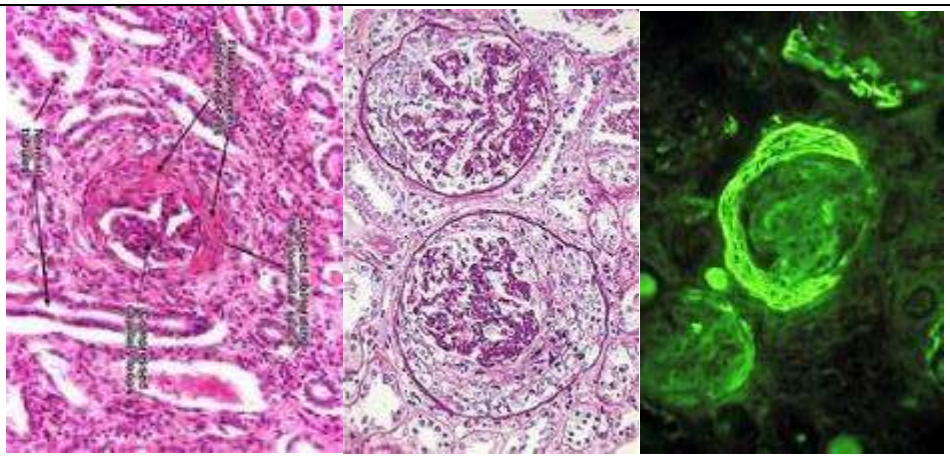
2. *Infiltration of leukocytes,*

Including:

- Neutrophils,
- Monocytes, and,
- In some diseases, lymphocytes.

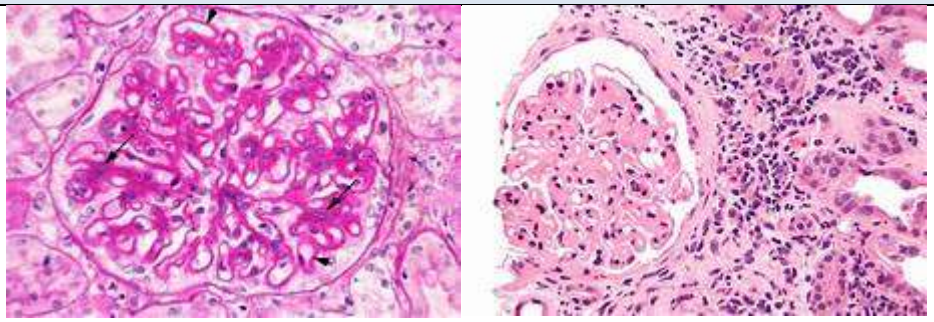
The combination of infiltration of leukocytes and swelling and proliferation of mesangial and/or endothelial cells is often referred to as ***endocapillary proliferatio***

3. *Formation of crescents.*



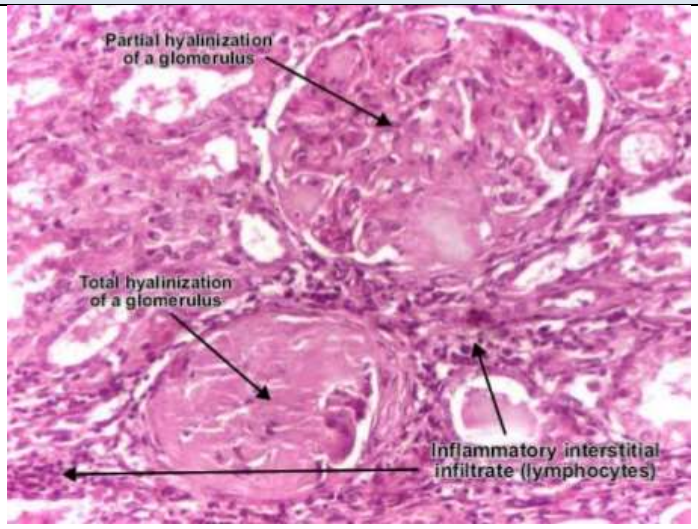
- These are accumulations of cells composed of proliferating glomerular epithelial cells (predominately parietal but including some visceral cells) and infiltrating leukocytes.
- The epithelial cell proliferation that characterizes crescent formation occurs following an immune/inflammatory injury involving the capillary walls.
- Plasma proteins leak into the urinary space, where it is believed that exposure to pro-coagulants such as tissue factor leads to fibrin deposition.
- Activation of coagulation factors such as thrombin is suspected of being a trigger for crescent formation, but the actual mechanisms are still unknown.
- Molecules that have been implicated in recruitment of leukocytes into crescents include multiple proinflammatory cytokines.

II- Basement Membrane Thickening:



- **By light microscopy**, this change appears as thickening of the capillary walls, best seen in sections stained with periodic acid-Schiff (PAS).
- **By electron microscopy** such thickening takes one of three forms:
  1. Deposition of **amorphous electron-dense material, most often immune complexes**, on the
     - Endothelial side of the basement membrane or
     - Epithelial side of the basement membrane or
     - Within the basement membrane (GBM) itself.
  2. **Fibrin, amyloid, cryoglobulins, and abnormal fibrillary proteins** may also deposit in the GBM.
  3. **Increased synthesis of the protein components** of the basement membrane, as occurs in diabetic glomerulosclerosis.
  4. **Formation of additional layers of basement membrane matrices**, which most often occupy subendothelial locations and may range from poorly organized matrix to fully duplicated lamina densa, as occurs in **Membranoproliferative glomerulonephritis.**

III- Hyalinosis and Sclerosis:

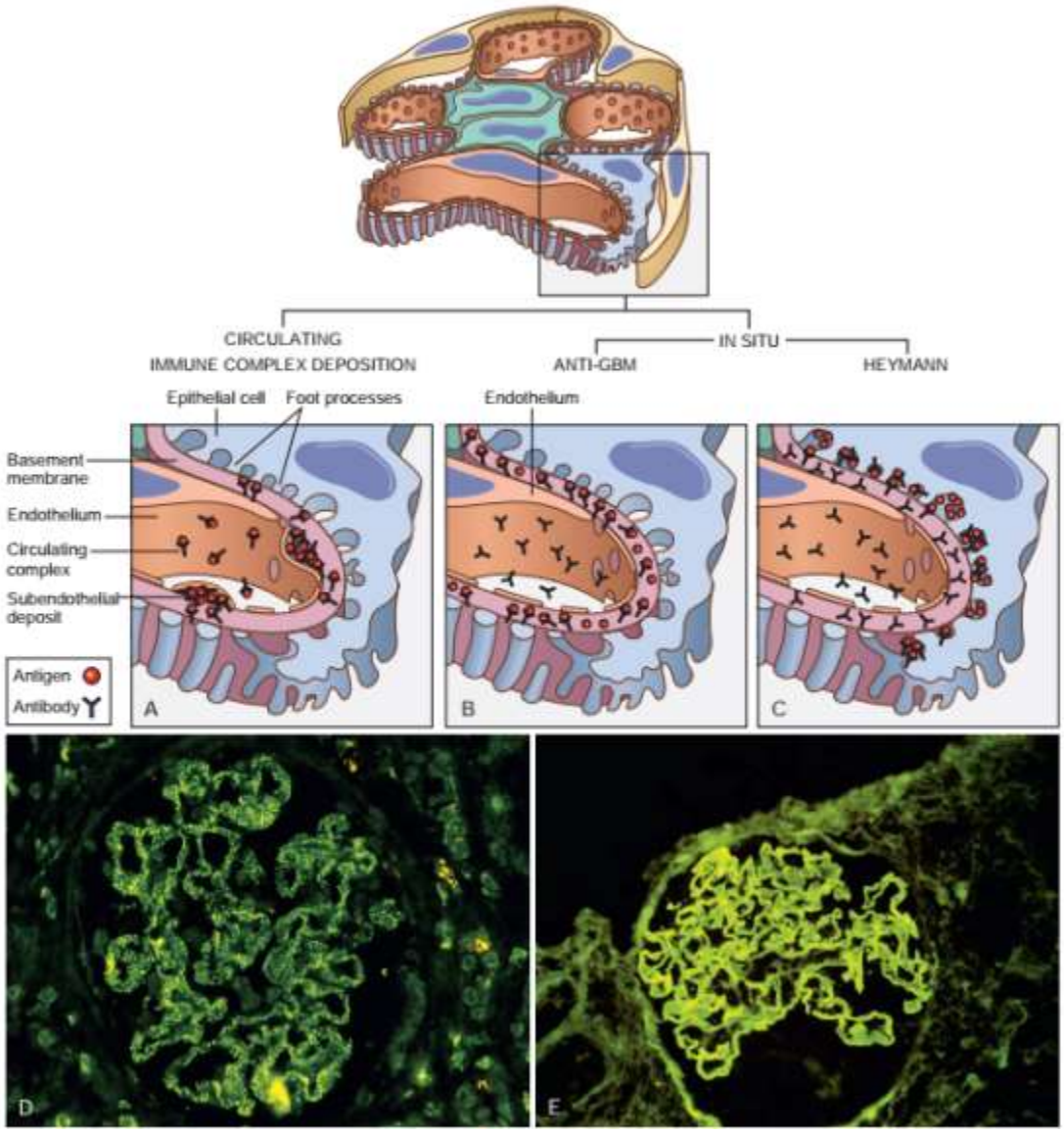


- **Hyalinosis, as applied to the glomerulus**, denotes the accumulation of material that is homogeneous and eosinophilic by light microscopy.
- **Hyaline is an extracellular**, amorphous material composed of plasma proteins that have insudated from the circulation into glomerular structures.
- When extensive, these deposits may obliterate the capillary lumens of the glomerular tuft.
- Hyalinosis is usually a consequence of endothelial or capillary wall injury and typically the end result of various forms of glomerular damage.

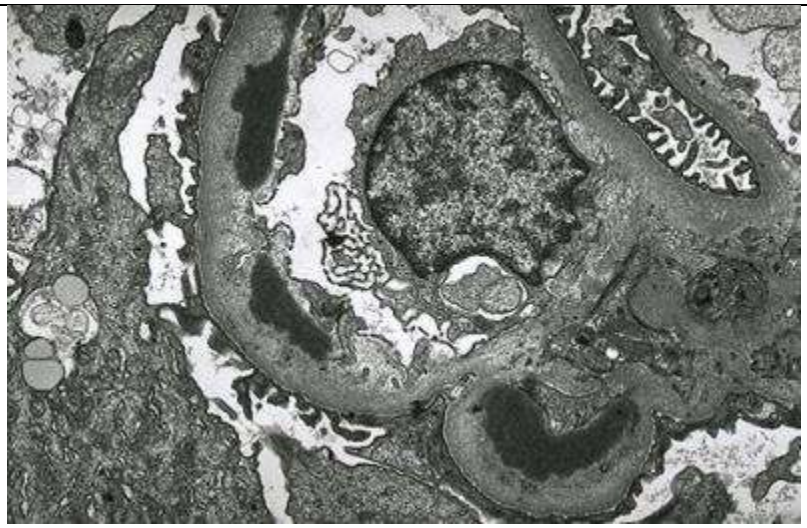
Pathogenesis:

Diseases Caused by In Situ Formation of Immune Complexes

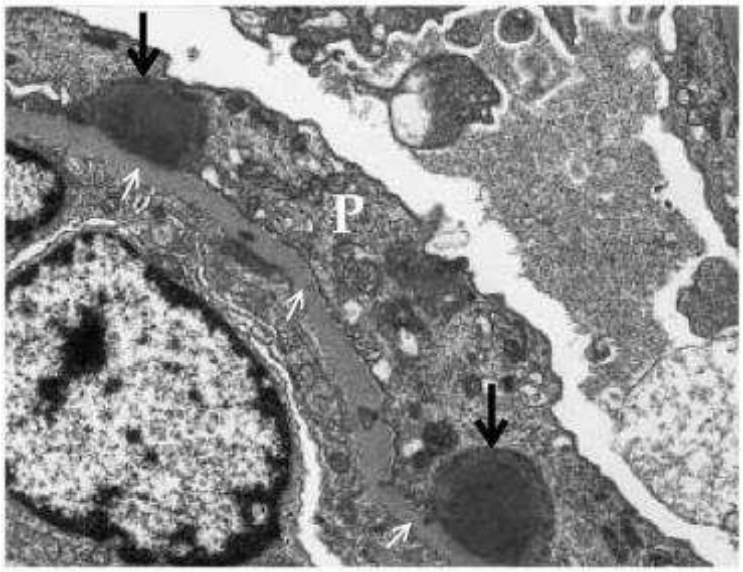
- **In this form of injury, immune complexes are formed locally by antibodies that react with intrinsic tissue antigen or with extrinsic antigens "planted" in the glomerulus from the circulation.**
- Membranous nephropathy is the classic example of glomerular injury resulting from **local formation of immune complexes**.
- It has a well-studied experimental counterpart in the Heymann nephritis rat model, from which much of the underlying pathophysiology of glomerular immune complex–mediated diseases has been deduced.
- The Heymann model of glomerulonephritis is induced by immunizing rats with an antigen, now known to be *megalin*, which is present in epithelial cell foot processes (Fig. 20-4*C*).
- The rats develop antibodies to this antigen, and disease develops from the reaction of antibody with the megalin-containing protein complex located on the basal surface of visceral epithelial cells, leading to localized immune complex formation.



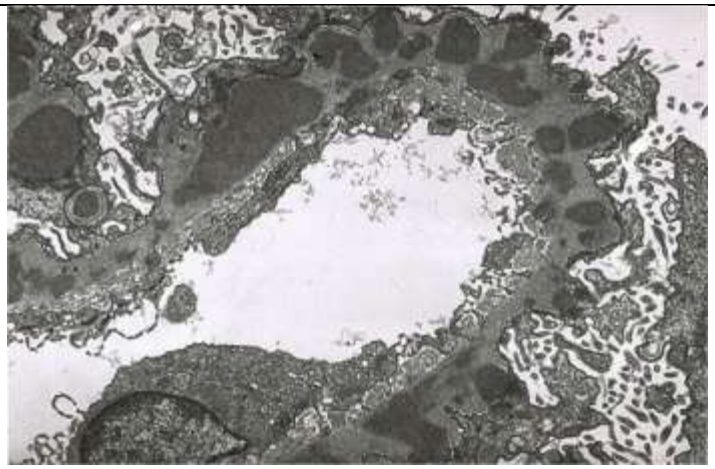
(A) Antibody-mediated glomerular injury can result either from the **deposition of circulating immune complexes or**,
(B) more commonly, **from in situ formation of complexes** exemplified by anti-GBM disease or
(C). D and E, **Heymann nephritis.**
Two patterns of deposition of immune complexes as seen by immunofluorescence microscopy:
(D) **Granular**, characteristic of circulating and in situ immune complex nephritis, and
(E).**Linear**, characteristic of classic anti-GBM disease



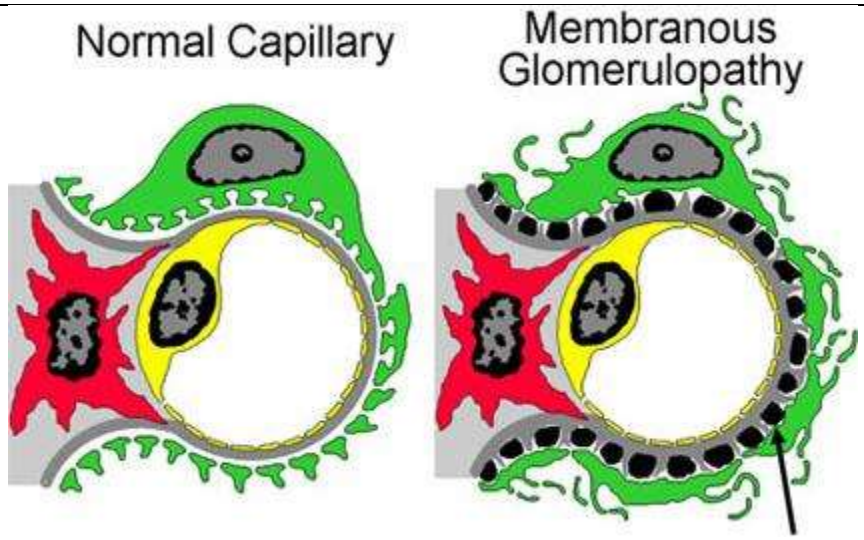
Sub endothelial deposit of Immune complex



Sub epithelial (podocytes) deposition of immune complex



Trans membrane deposit of immune complex with spikes formation



- A major advance in our understanding of glomerulonephritis came from the identification of the M-type phospholipase A2 receptor (PLA2R) as the antigen that underlies most cases of primary human membranous nephropathy.
- Antibody binding to PLA2R present in the glomerular epithelial cell membrane is followed by complement activation and then shedding of the immune aggregates from the cell surface to form characteristic deposits of immune complexes along the **subepithelial aspect *of the basement membrane***

Location of immune deposits in glomerulus

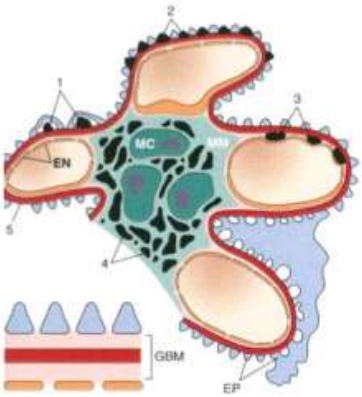
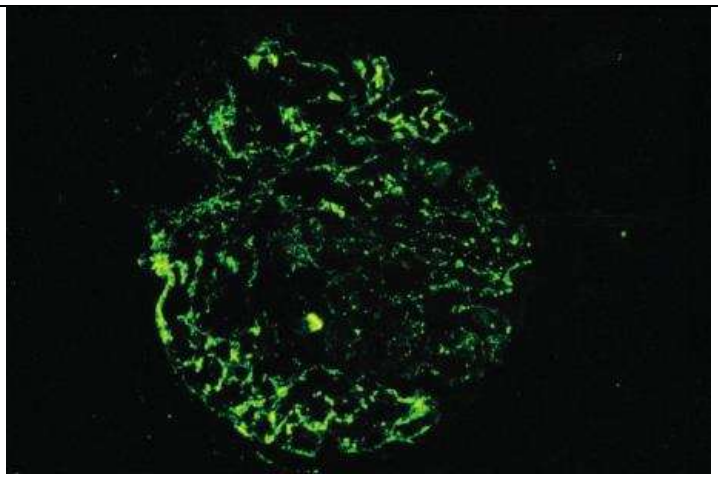


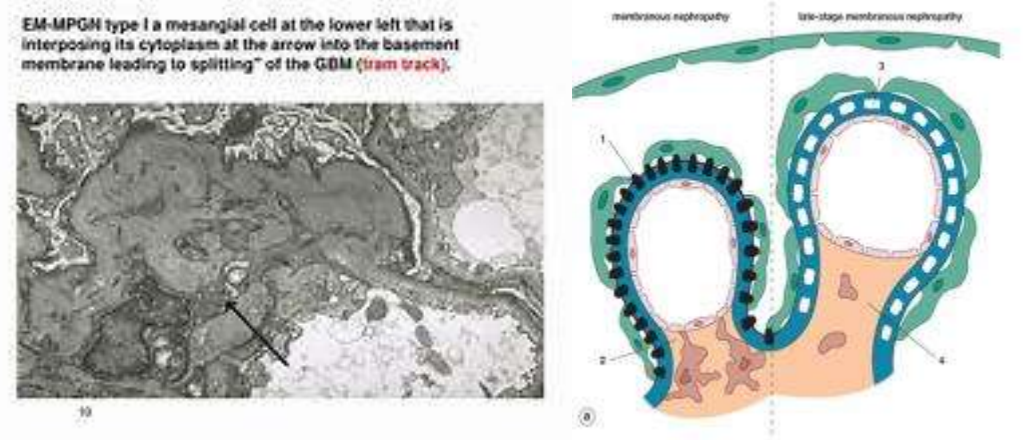
FIGURE LEGEND

1 – Subepithelial large deposits ("humps")
2 – Subepithelial deposits
3 – Subendothelial deposits
4 – Mesangial deposits
5 – Basement membrane

1. On electron microscopy the glomerulopathy is characterized by the presence of numerous **discrete subepithelial electron dense deposits (made up largely of immune reactants).**
2. **The pattern of immune deposition by immunofluorescence microscopy is granular rather than linear, reflective of the much localized antigen-antibody interaction.**

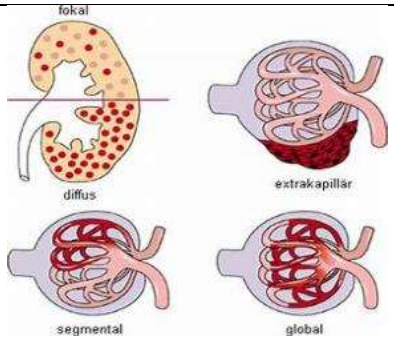


- These subepithelial complexes, with resultant host responses, can result in a **thickened basement membrane** appearance by light microscopy; hence the term ***membranous nephropathy*** has been applied to both the experimental model and human disease.



- In humans, primary membranous nephropathy is an autoimmune disease; caused by antibodies ***to endogenous*** **Sclerosis is *characterized by deposition of extracellular collagenous matrix.***
- It may be confined to mesangial areas, as is often the case in diabetic glomerulosclerosis, involve the capillary loops, or both.
- The sclerosing process may also result in obliteration of some or all of the capillary lumens in affected glomeruli.

- **Many primary glomerulopathies are classified by their histology**, as seen in Table 20-2.
- The histologic changes can be further subdivided by their distribution into the following categories:
- ***Diffuse,*** involving all of the glomeruli in the kidney;
- ***Global,*** involving the entirety of individual glomeruli;
- ***Focal,*** involving only a fraction of the glomeruli in the kidney;
- ***Segmental,*** affecting a part of each glomerulus; and
- ***Capillary loop* or *mesangial***, affecting predominantly capillary or mesangial regions.



- Pathogenesis of Glomerular Injury Although much remains unknown about etiologic agents and triggering events, it is clear that **immune mechanisms underlie most forms of primary glomerulopathy and many of the secondary glomerular disorders**
- Glomerulonephritis can be readily induced experimentally by antigen-antibody reactions.
- Furthermore, glomerular deposits of immunoglobulins, often with components of complement, are found in the majority of individuals with glomerulonephritis.
- Cell-mediated immune reactions also may play a role, usually in concert with antibody-mediated events.
- We begin this discussion with a review of antibody instigated injury.

- Two forms of antibody-associated injury have been established:
- **(1) Injury by *antibodies reacting in situ within the glomerulus,*** either binding to insoluble fixed (intrinsic) glomerular antigens or extrinsic molecules planted within the glomerulus, and
- **(2) Injury resulting from *deposition of circulating antigen-antibody complexes in the glomerulus.***
    - It is clear that the major cause of glomerulonephritis resulting from formation of antigen-antibody complexes is the consequence of in situ immune complex formation, and not deposition of circulating complexes as was once thought.