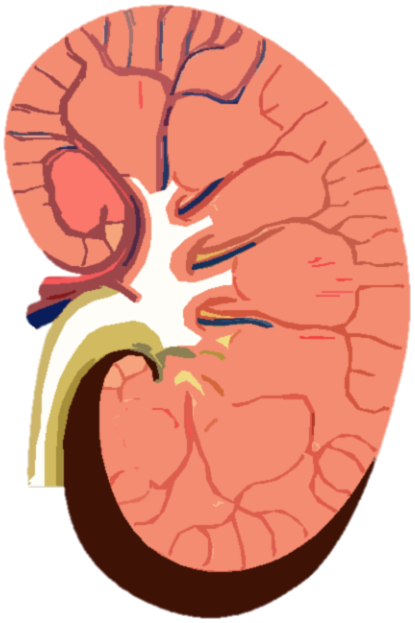
Immune Complex Nephritis

Renal block

First lecture



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Objectives:

- Understand the importance of immune complexes in the pathogenesis of renal injury.
- Learn that immune complexes form in the circulation and may deposit in different tissues.
- Understand the dynamics of deposition of complexes which depend on the size and rate .
- Identify the different types of renal disease based on the site of deposition of the immune complexes.

Black : Slides

Purple: Extra notes for further understanding

Orange: Notes said by the doctor

Red : important

- Introduction:

We'll be discussing number of diseases causing disruption in renal function because of the inflammatory process in relation to Immune complexes.

Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved, size and time taken for the reaction to occur. Sometimes a particular (disease) may involve more than one type of a reaction.

What's important to understand here is both type 2 and type 3 hypersensitivity reactions:

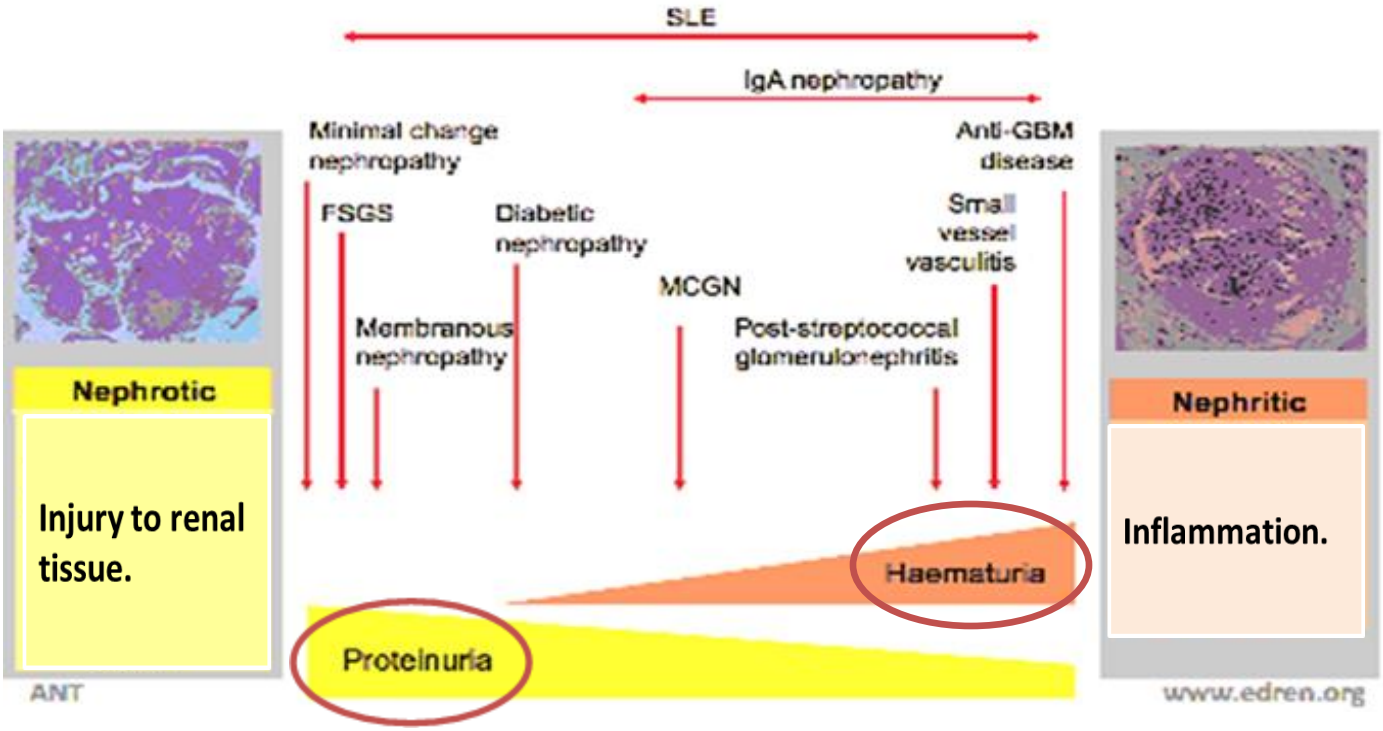
Type2: the antigens are part of the cell membrane of any tissue. Then antibodies of these antigens bind to it directly forming (Immune complexes) which activate the complements that initiate the inflammatory process.

Complements: are glycoproteins found in the serum.

Type3: the antigens are circulating in the blood (floating antigens) the antibodies bind to them and form (immune complexes).

So basically we have immune complexes in both type 2 and type 3 hypersensitivity, but in type 2 the immune complex is on the tissue while in type 3 it will be found in the circulation. If immune complexes of type 3 hypersensitivity got deposited on the tissue it will become type 2 hypersensitivity. So both types of hypersensitivity overlap each other.

The spectrum of glomerular diseases



Complexes of antibody with various microbial (non-self antigens) OR self antigens induce type II or III hypersensitivity reactions in the kidney :

Many immunological disorders cause renal dysfunction to the extent

Nephrotic syndrome:

Characterized by heavy proteinuria.

Nephritic syndrome:

Characterized by hematuria mainly microscopic that can be visible or not.

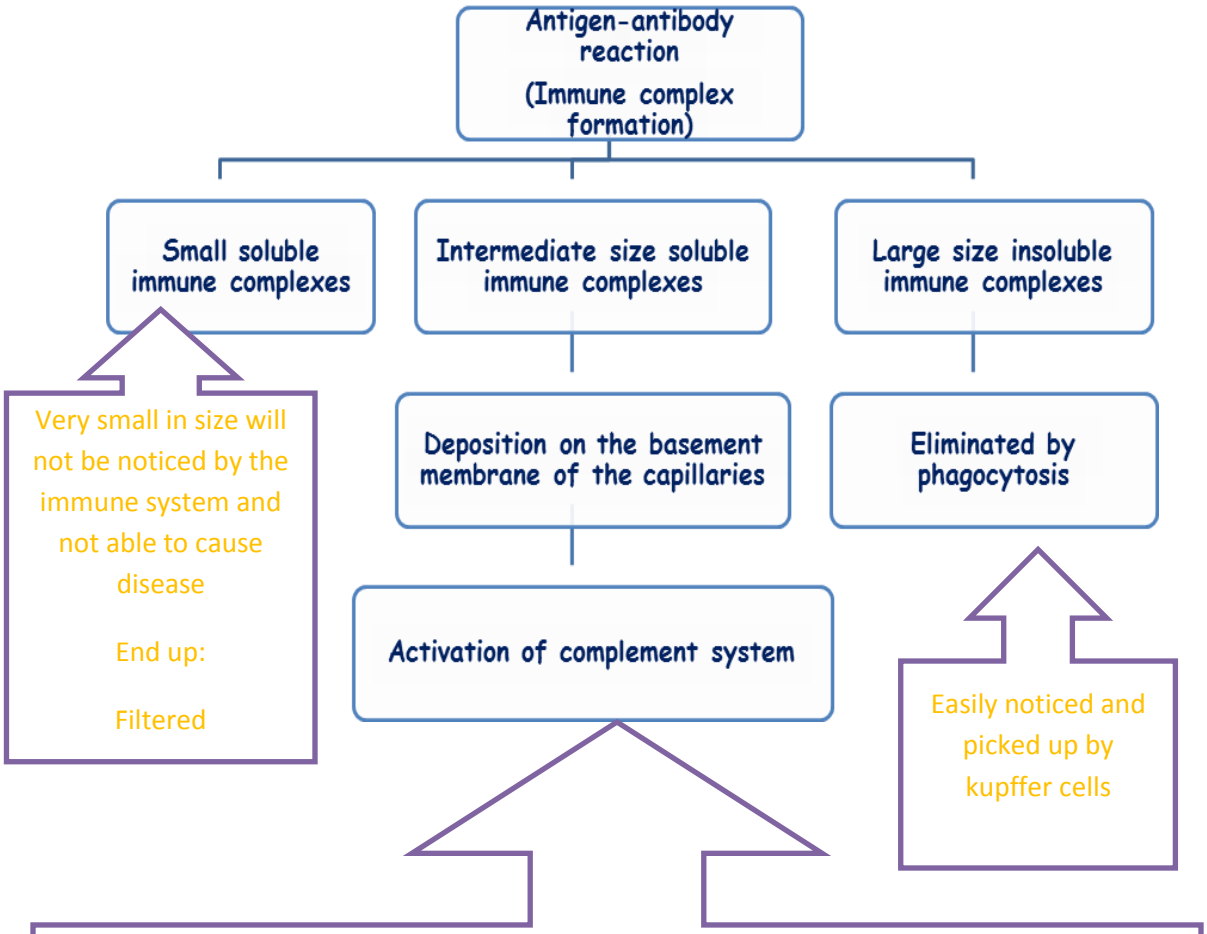
(doctor mentioned that these are the most important points to remember from the graph)

SLE: characterized by Hematuria and proteinuria

As well as other immunoligcal disorders that we will be mentionging during the lecture.

We normally produce Immune complexes in our body daily but they're cleared by (reticular endothelial system) in the liver. Macrophages of the liver (kupffer cells) engulf them and remove them to keep us healthy.

Immune complexes are categorized according to their size and rate of production:



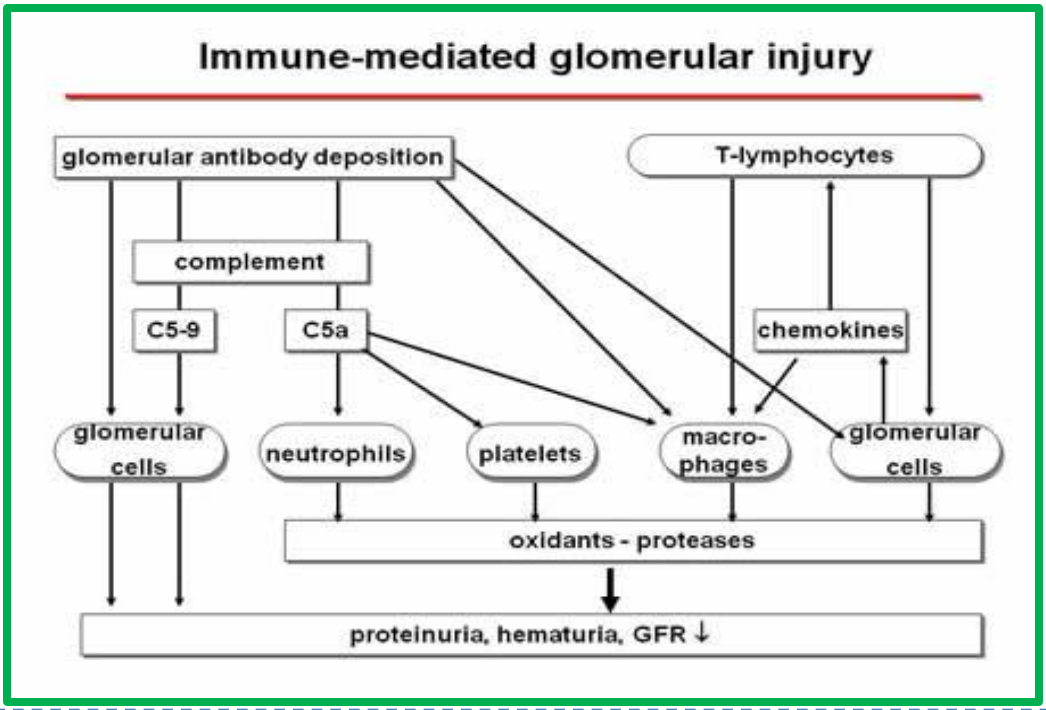
-Not effectively picked up by the kupffer cells

-Able to deposit in the tissues

-Rate of production: like in SLE (autoimmune disease)

(The antigens are self-proteins which mean that the immune complexes are continuously released in high amounts over a prolonged period of time).

These high amounts can't be effectively picked up by reticular endothelial system. And excessive amounts keep on circulating and eventually it will deposit in different tissues (like kidneys for example arterioles of the glomerulus are highly convoluted and the pressure inside is high so the chance of immune complexes to deposit is high) and start inflammation (the most dangerous immune complexes are the medium sized ones)



*Glomerulonephritis it's an injury initiated by the immune complexes deposited in tissues → activate complements (C5-9\ c5a) → infiltration of different cells (neutrophils\platelets\macrophages\glomerular cells) and activation of T cells lead to the release of chemokines and more inflammatory cells aggregation → destruction of the tissue (glomeruli) → ⇩ GFR , proteinuria and hematuria. **(Main Features of Glomerulonephritis last 3 points)**

* Mcarophages are the cells causing a connection between innate immunity (first line of defense mainly here phagocytosis) and adaptive immunity (2nd line of defense which is divided into humoral immunity (Abs) and cellular immuity (T-cells)).

Remember: the constant release of inflammatory cells and enzymes to defeat the infected area will increase the risk to move to the next stage (Acute glomerulonephritis) ⟶ (Chronic glomerulonephritis)

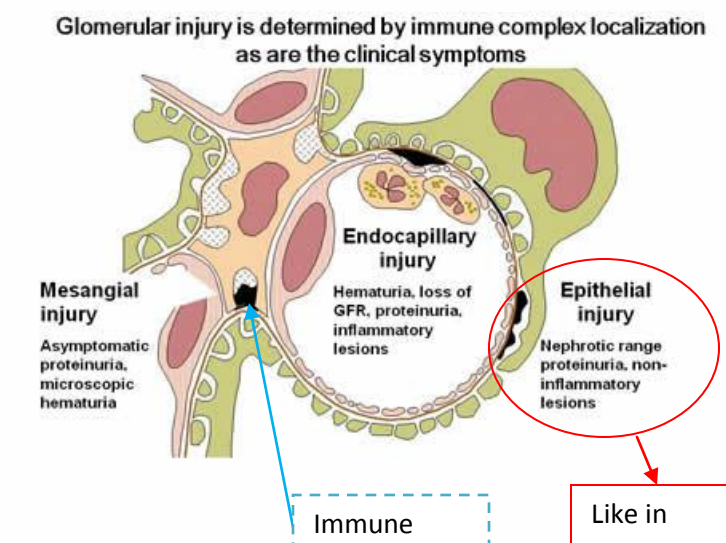
Site of deposition: (Mostly likely get deposited at)

Complexes accumulate in tissues where filtration of plasma occurs. This explains the high incidence of:

1-Glomerulonephritis (deposition in the kidney) because the glomerulus contains tufted capillaries, besides the very packed tubules will make immune complexes deposition easier.

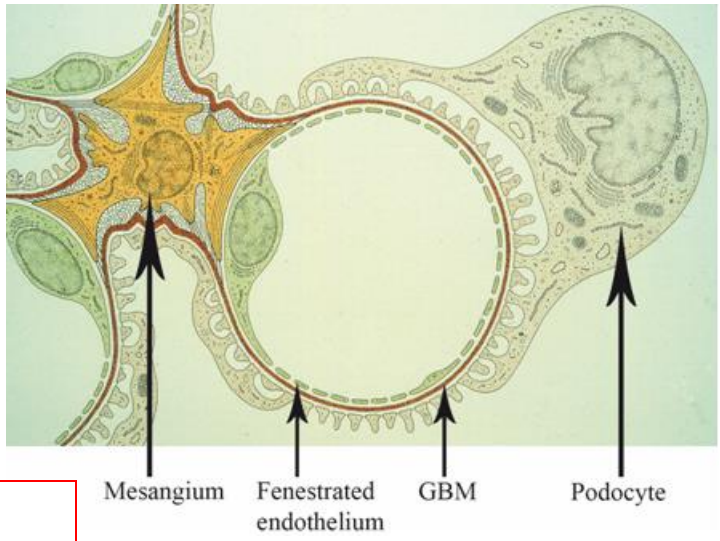
2-Vasculitis (deposition in the arteries) because many antigens circulate in the blood forming complexes with antibodies which will deposit eventually in the blood vessels walls. It can happen at any blood vessels (CNS, skin, ..etc.).

3-Arthritis (deposition in the synovial joints) joints have high chance of complexes deposition and example of immune mediated arthritis is (rheumatoid arthritis).



Immune complexes

Like in nephrotic syndrome



- Types of immune mediated renal injury (Antibody-mediated Injury):

Membranoproliferative glomerulonephritis

IgA nephropathy

Membranous glomerulonephritis

Post infectious glomerulonephritis (like streptococcal post infections leading to autoimmune damage same idea of RF)

Antiglomerular basement membrane (GBM) disease

*Remember that when we talk about deposition it will be either an antibody that will get deposited on an antigen found in the tissue OR an already formed immune complex deposition.

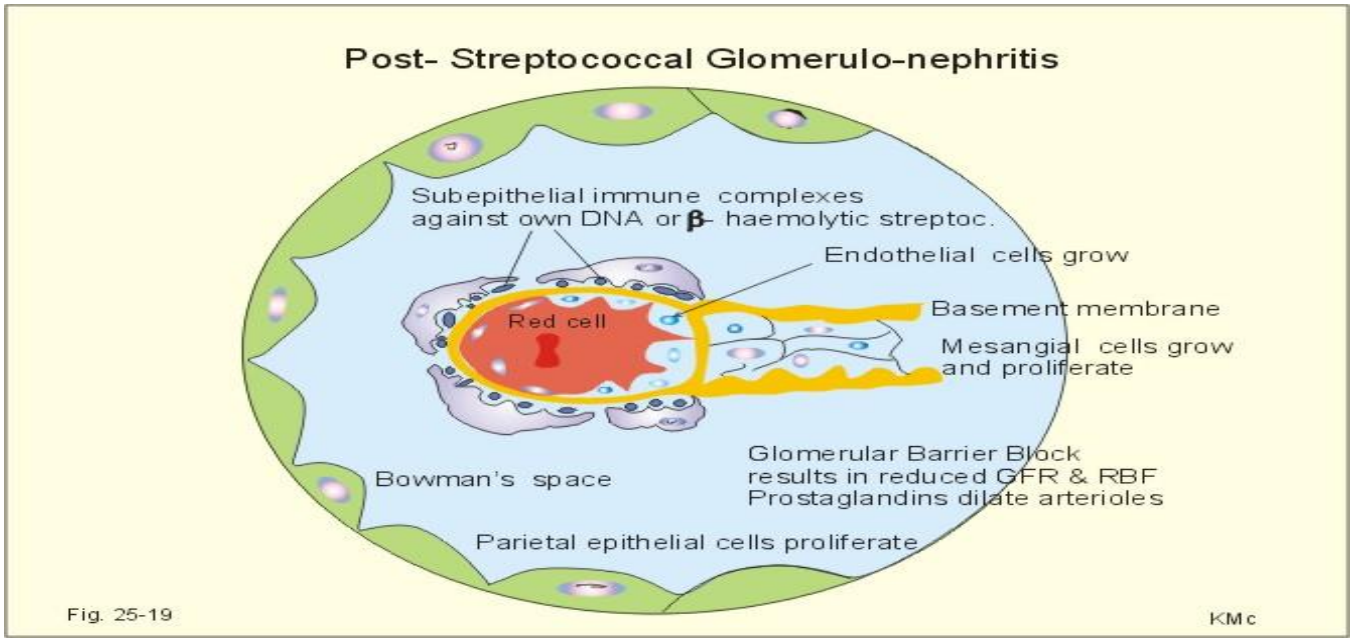
1-Post Infectious Glomerulonephritis (GN) (Post-streptococcal)

- Caused by known streptococcal types called: nephritic strains
- Presentation:
  - 7-14 days *after* pharyngitis. (until the microorganism and the symptoms of its infection disappear)
  - 14-21 days *after* (skin infection) (in skin infections it takes longer time)
  - Abrupt onset (Acute nephritic syndrome) (after a period of time when there is no more symptoms of the post infection , a sudden onset of the antibody mediated disease post infectious glomerulonephritis)
- Strep antigens trigger antibodies that cross-react to glomeruli (Same concept of Rheumatic fever that we took in cardiovascular block where the sequence of the glomeruli tissue is the same as streptococci bacteria so we can say that the antibody will get kind of confused so it will decide to affect both!! causing an autoimmune disease the infectious agent (streptococci) will be gone but the glomeruli is part of our body it won't go away so continuous damage will be found)
- Circulating immune complexes during filtration in the glomerulus deposit in the kidney.
- Immune complexes activate complement initiating the inflammation and causing destruction of the tissue.
- Remember: glomerulonephritis is typically type 2 hypersensitivity reaction but also some antigens can be found in the circulation so it's type 2 and type 3 overlapping.
- Diffuse proliferation of glomerular cells and frequent infiltration of leukocytes (especially neutrophils) in acute glomerulonephritis.
- Typical features of immune complex disease :
  - Hypocomplementemia (less complements in the circulation cause they got deposited on glomerular basement membrane (GBM))
  - Granular deposits of IgG & complement on GBM

- In most children bacterial culture will be negative
- Anti –streptolysin-O antibody(ASO) will be the only evidence.

- The anti-DNAse B titre is a better indicator of streptococcal skin sepsis than the ASO titre.
- Cholesterol and lipids in skin suppress the ASO antibody response but not the anti-DNAse B antibody titre.

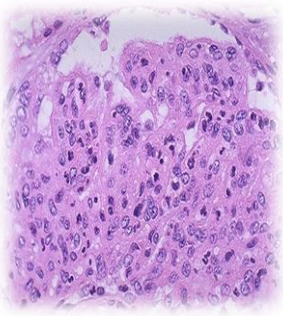
Lipids (especially in skin infections) can interfere with the ASO test by binding the complexes together and preventing them from getting recognized by the test. That's why anti-DNAse B antibody titre test is better to be used in skin infection to prevent masking the test.



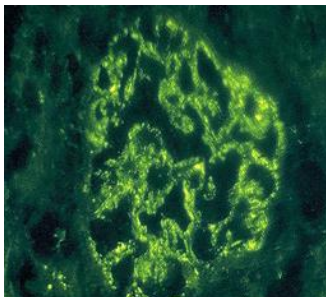
Pathogenesis: the immune complexes cross the basement membrane and deposit under the pdocytes sub-epithelial coming from the circulation.

Post streptococcal GN. Diffuse Proliferative GN
(Generalized damage to glomeruli)

The immune deposits are distributed in the capillary loops in a granular, bumpy lumpy pattern because of the focal nature of the deposition process.

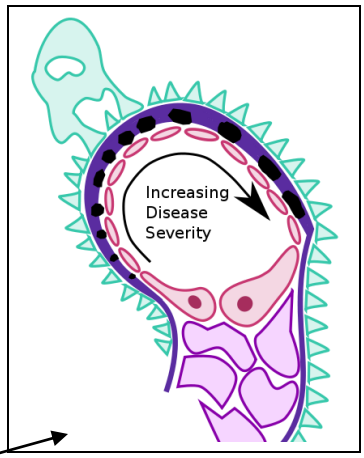


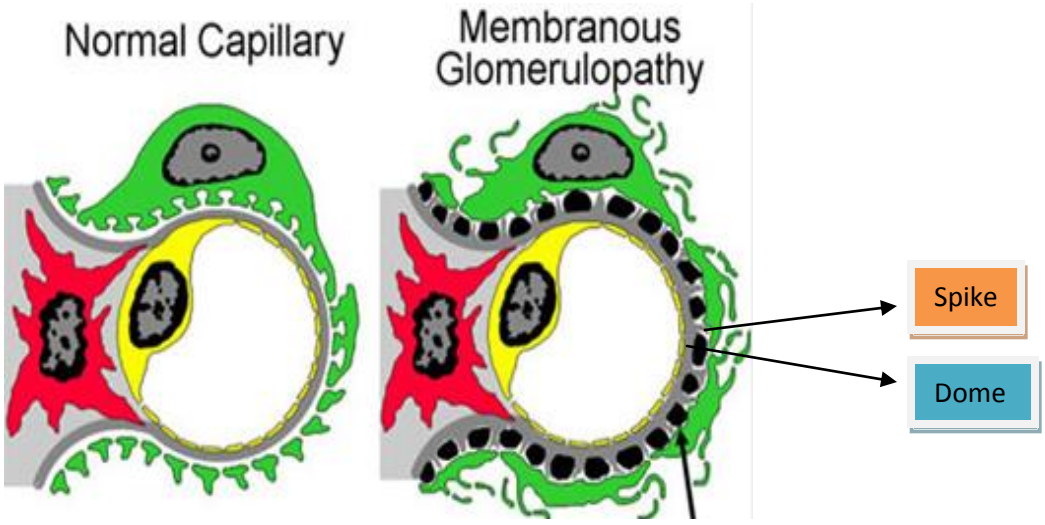
Deposition of immune complexes and Iggs is detected by immunofluorescence. We use a special microscope with polarized light to see a sample coming from a renal biopsy. First we will add Iggs or C3 produced in animals like rats for example to the slide mixed with fluorescent stain, if there was any interaction it will appear by shining. The pattern of shining will differ according to the disease.



○ 2-Membranous Glomerulonephritis-(Membranous nephropathy)

- **A slow progressive disease**
- **A form of chronic immune-complex nephritis**
- **Activation of C5 - C9 complements that usually Lead to tissue destruction.**
- **Most common between 30 - 50 years**
- **Immune complexes (black) are deposited in a thickened basement membrane creating a "spike and dome" appearance on electron microscopy only**





Membranous Glomerulonephritis

Is classified into

Primary/idiopathic

85% of MGN cases are classified as *primary membranous glomerulonephritis*

Idiopathic = unknown reason

Secondary

The remainder is secondary due to:

- Autoimmune conditions (e.g., Systemic lupus erythematosus)
- Infections e.g., (syphilis, malaria, hepatitis B)
- Drugs e.g., Captopril, NASIDs etc.)
- Inorganic salts e.g., gold mercury
- Malignancies e.g., tumors, hematological

*Gold and mercury are used as treatment in subcontinents, with time they get deposited in the kidney causing permanent renal damage without any possible treatment.

*Malignancies can cause MGN in an either direct or indirect manner.

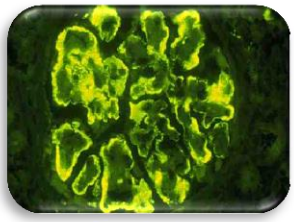
○ 3-Membranoproliferative Glomerulonephritis (MPGN) OR Mesangiocapillary GN :

- It is a chronic progressive glomerulonephritis that occurs in older children and adults

Membranoproliferative Glomerulonephritis has two types

Type I MPGN (80% of cases)

- Circulating immune complexes have been identified
- May occur in association with :
  - hepatitis B&C antigenemia
  - extra-renal infections
  - SLE
- Characterized by **subendothelial and mesangial** deposits
- Activation of complement by **classical pathway**



Type II MPGN

- Also known as: **dense deposit disease**

-Similar to Type I but complement activation is by **alternative pathway**

-Some patients have autoantibody against C3 convertase called: **C3 nephritic factor** causing intense activation of C3

With the factor influence C3 convertase is further activated, so even more consumption and less amount concentration of C3 in the blood.

-Half of the cases progress to end stage renal disease within 10 years

○ Important notes:

***In type 1, how do you know it's the classic pathway?**

By detecting C2 or C4 and C3 we will find that their levels in the plasma are decreased.

***In type 2 however, C2 and C4 will be normal as opposed to C3 which will be highly decreased in alternative pathway (C3 is the first to be activated in this pathway so it's consumed but anything before it i.e. C2, 4 will remain within the normal range and anything after C3 will be consumed).**

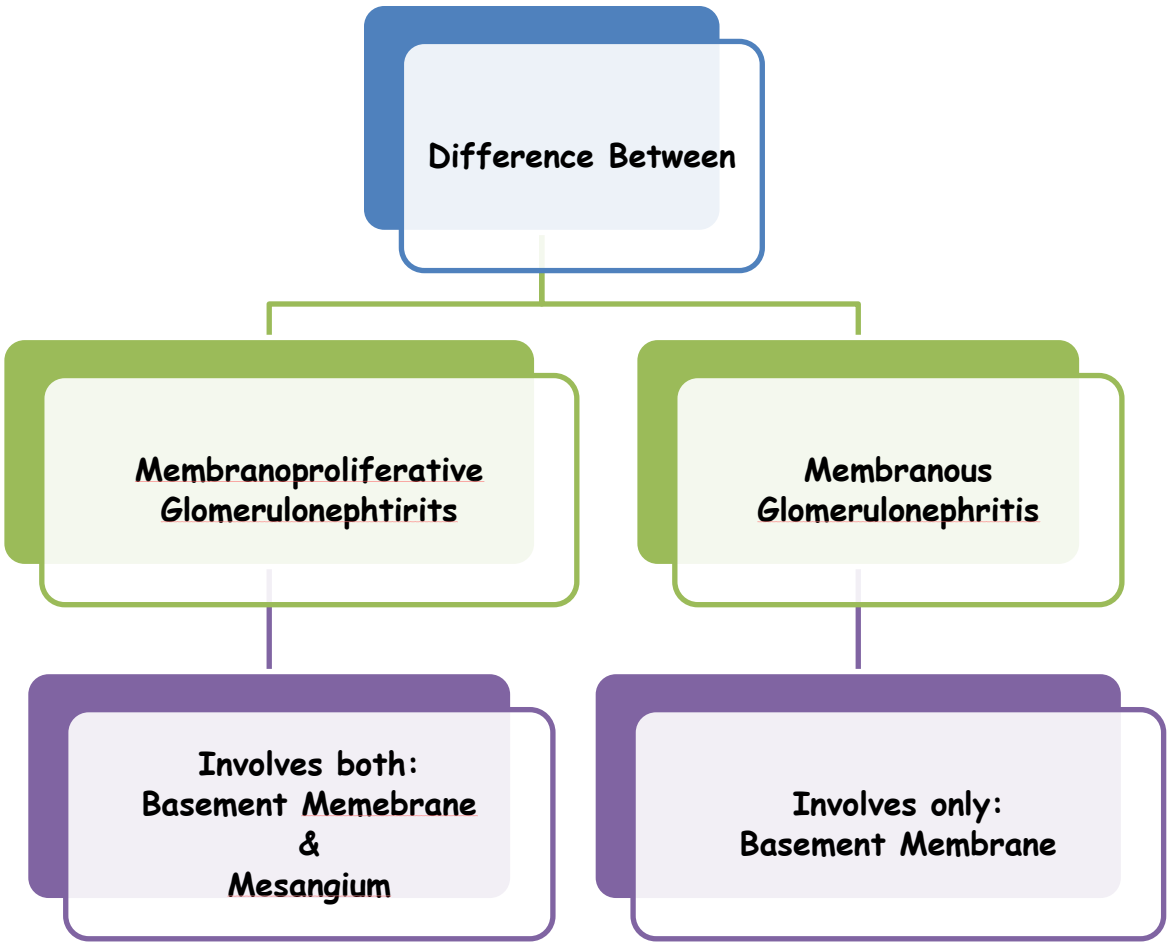
***C3 convertase is responsible for activating C3.**

***Type 2 is a very serious condition, because unlike other diseases mentioned it doesn't get repaired.**

Reminder :

the complement system has 3 Pathways of activation :

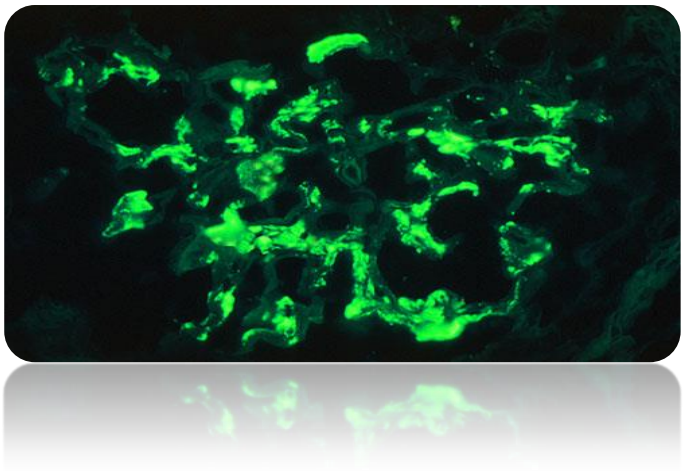
- Classical. (Requires antigen-antibody binding)(**C1,C4,C2,C3,C5,C6,C7,C8,C9)**
- Lectin. (Activated by mannan binding protien binding manose groups of bacterial carbohydrates)(-**C4,C2,C3,C5,C6,C7,C8,C9)**
- Alternative.(Activated by bacterial products)(- **C3,C5,C6,C7,C8,C9)**



- 4-IgA Nephropathy (Berger disease):

- The most common form of primary glomerulonephritis in the world
- Affects children and young adults
- Begins as an episode of gross hematuria that occurs within 1-2 days of a non-specific upper respiratory tract infection (viral)
- The pathogenic hallmark is :
- Deposition of IgA & complement C3 in the mesangium
- There is evidence of :
  Activation of complement by the alternative pathway (serum complement C2 and C4 will be normal).

The actual cause is unknown but the assumption goes between two etiologies:
1-The kidney itself is damaged which leads to deposition of IGA.
2-The IGA itself is abnormal and is deposited causing the damage
***When it occurs in combination with vacuities and multi-organ involvement then is referred to as Henoch-Schonlein purpura (Small vessel vacuities)**
***(On the biopsy IGA appears patchy.**



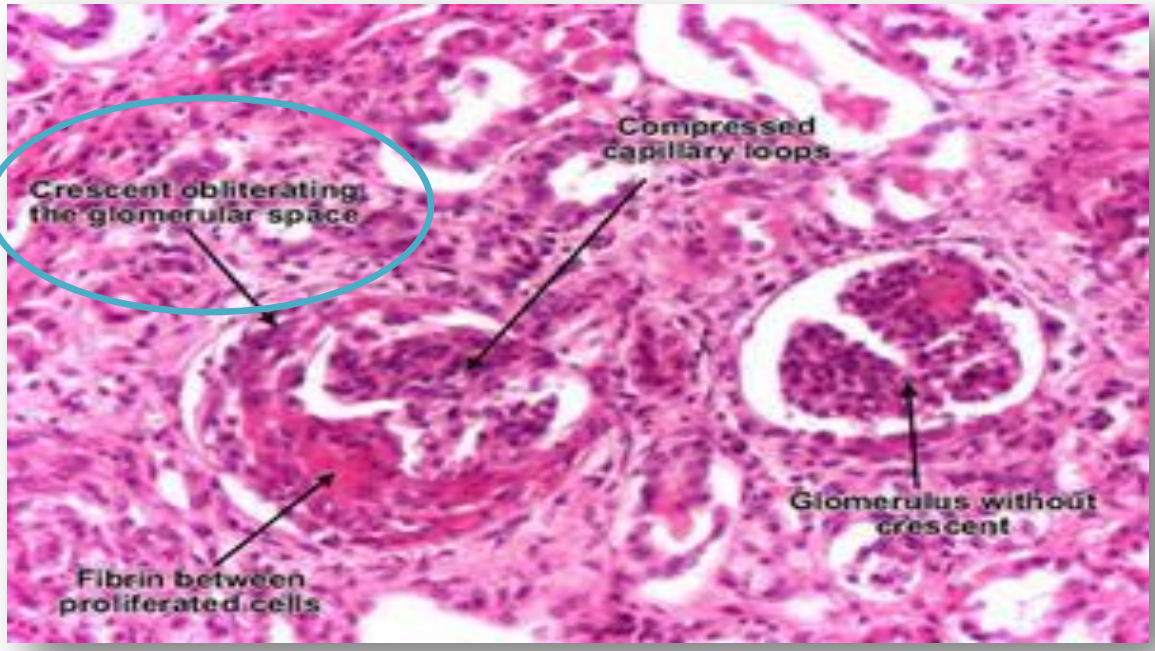
This immunofluorescence pattern demonstrates positivity with antibody to IgA. The pattern is that of mesangial deposition in the glomerulus. This is IgA nephropathy.

○ 5- Rapidly Progressive (Cresentic) Glomerulonephritis (RPGN)

- RPGN is a clinical syndrome and not a specific form of GN
- 50% decline in the glomerular filtration rate (GFR) within

  3 months if left untreated death may occur in months due to acute renal failure
- In most cases the glomerular injury is immunologically mediated
- A practical classification divides CrGN into three groups

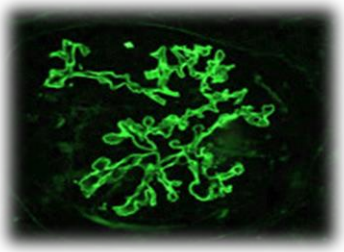
  on the basis of immunological findings (listed below)



Type I (Anti-GBM antibody)(Cresentic GN)

Characterized **by linear deposition** of IgG and C3 on the GBM.

-Goodpasture syndrome Antibodies bind also in the pulmonary alveolar capillary basement membranes.

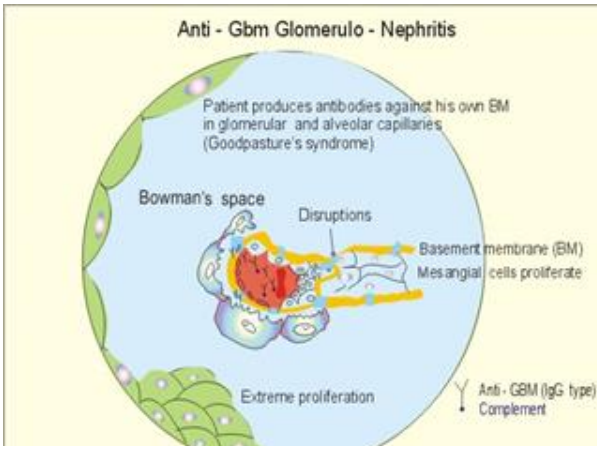


*usually when we have antibodies we will have also complements.

*Here the antigen is part of the basal membrane so the antibody attacks it creating immune complexes around the basal membrane then C3 is activated the cascade of events is the same as the one mentioned earlier in the lecture.

*If a patient comes to you with hemoptysis and renal failure you immediately should think of Good pastures syndrome.

*This is a type 2 hyper sensitivity example



This picture shows the destruction of the membrane →leakage of blood components (fibrin) →this will cause rapid multiplication of cells at Bowman 's capsule and infiltration of the macrophages and the lymphocytes into the space →causing the cresentic appearance.

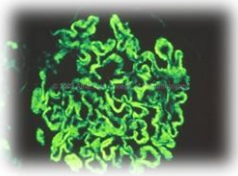
Type II (Immune complex - mediated Cresentic GN)

May occur as a complication of any of the immune complex nephritides

- Post infectious.
- SLE
- IgA nephropathy

Characteristic granular (lumpy-bumpy) pattern of staining of the GBM for immunoglobulin & complement

*it is not a primary disease of its own, it's a result of other diseases.



Type III (Pauci-immune) Cresentic GN

Defined by the lack of anti-GBM antibodies.

- Most cases are associated with:Anti-neutrophil cytoplasmic antibodies (ANCA) in serum and systemic vasculitis

Pauci = lack of

*How ANCAs are activated is an unknown mechanism But two assumptions are made one in which they bind to PMNs → activate them so they can attack and destroy the basement membrane. Or its presence of already activated neutrophils activates these ANCAs and they cause the damage.

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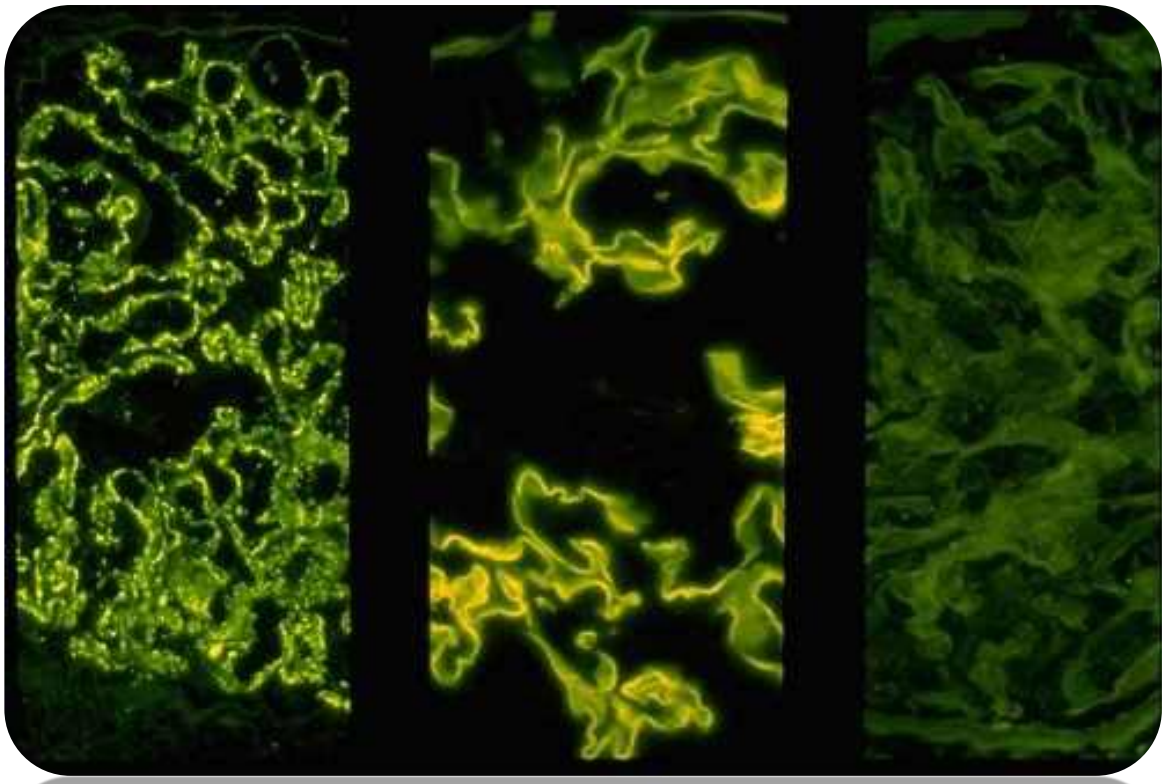
Type four is there but very rare and won't be further discussed



1-Granular staining (Immune complex)	2-Linear staining (Anti-GBM)	3-No antibody staining(Pauci associated with vasculitis)

This is just to demonstrate different patterns of IF and different Immune mediated diseases.

- Take home message :
  - Immune complexes underly the pathogenesis of many of the glomerulo-nephritides.
  - Activation of the complement system is an integral part of the process, and measurement of the complement proteins help in diagnosis and follow-up of patients.
  - Immunofluoresence of renal biopsy demonstrate the presence of immune complexes and confirm the diagnosis.

- MCQs :

1- Which glomerular disease would you suspect most in a patient with linear pattern of immune complex deposition:

a) Membranous glomerulonephritis

b) Berger's disease

c) Lupus nephritis

d) Goodpasture syndrome

2- Which ONE of the following complement pathways is activated in type 1 Membranoproliferative Glomerulonephritis disease:

a) Classical pathway

b) Alternative pathway

c) Lectin pathway

3- The site of immune complexes deposition in Membranous glomerulonephritis is:

a) Mesangium

b) Basement membrane

c) Basement membrane & mesangium

d) Parietal layer of bowman's capsule

4- Which ONE of the following patterns of staining of the GBM is usually found in Pauci-Immune Glomerulonephritis disease:

a) Lumpy-bumpy staining

b) No antibody staining

c) Linear staining

d) Patchy staining

5- Which glomerular disease would you suspect most in a patient with the following findings, deposition of IgA & complement C3 in the mesangium with normal serum complement C2:

a) Crescentic glomerulonephritis
b) Post-streptococcal glomerulonephritis
c) IgA nephropathy
d) Antiglomerular basement membrane disease

Key answers:

1- d
2- a
3- b
4- b
5- c