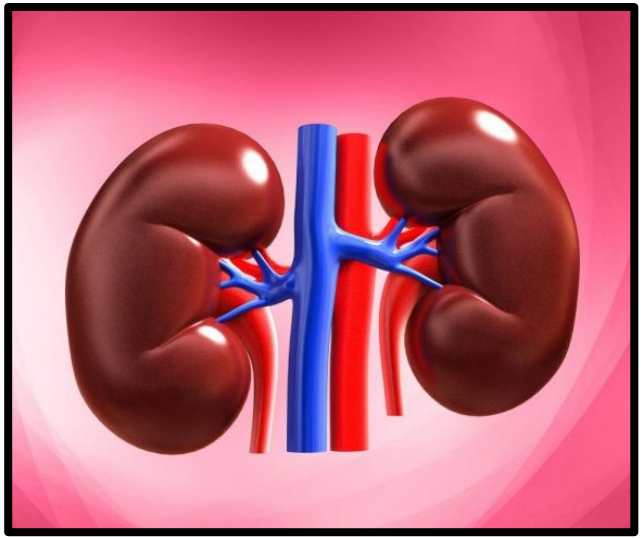
The Kidney



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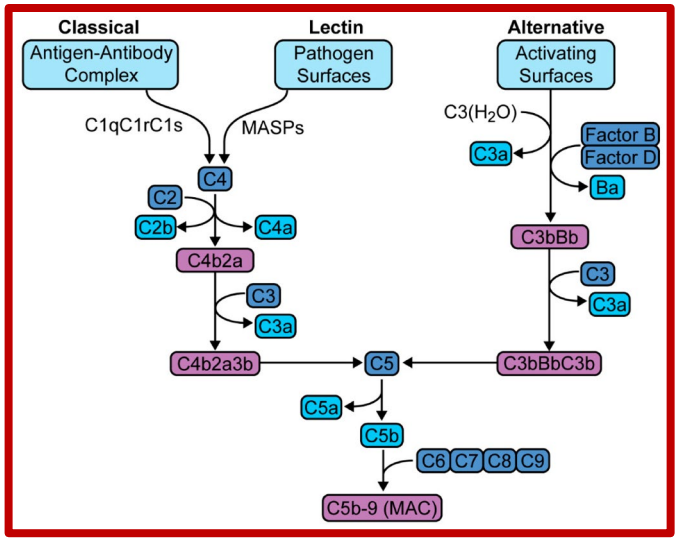

Complement

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Goals –

1. To understand renal anatomy and how C3G is diagnosed

2. To understand how the complement cascade normally functions

3. To understand the four pillars of a complement evaluation

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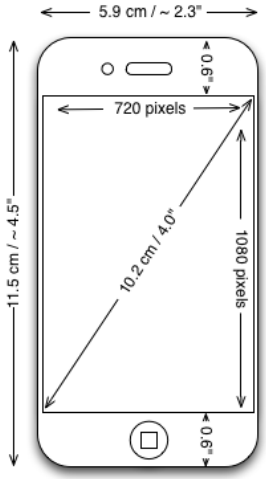
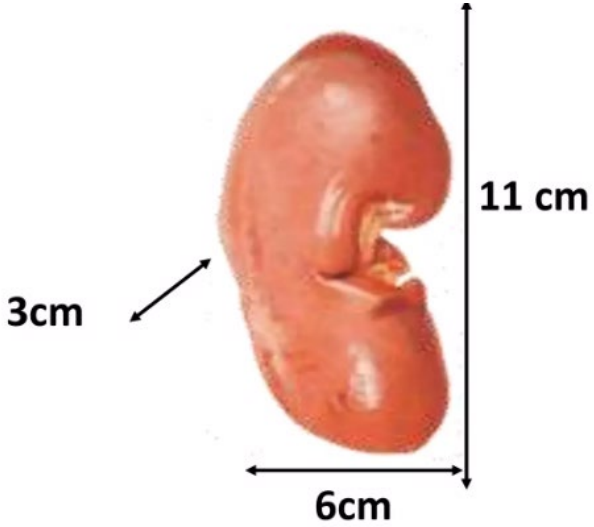
2. Each kidney weighs ~0.2 to 0.5 pounds. A can of Coke weighs 0.75 pounds.





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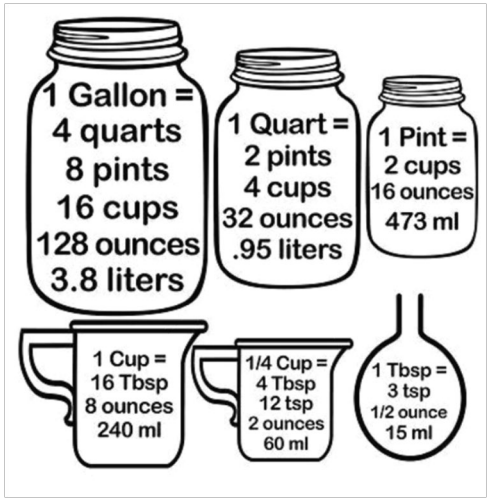

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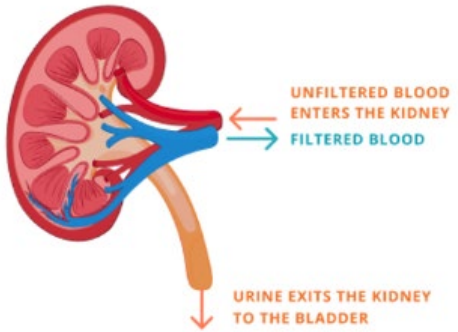

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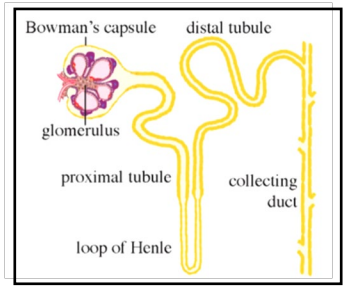
5. Each filtering unit is called a nephron.

The Nephron



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5. Each filtering unit is called a nephron.
6. Each kidney has about 1,000,000 nephrons (range 200,000-1,800,000). So with two kidneys, you have about 2,000,000 nephrons working 24-7.

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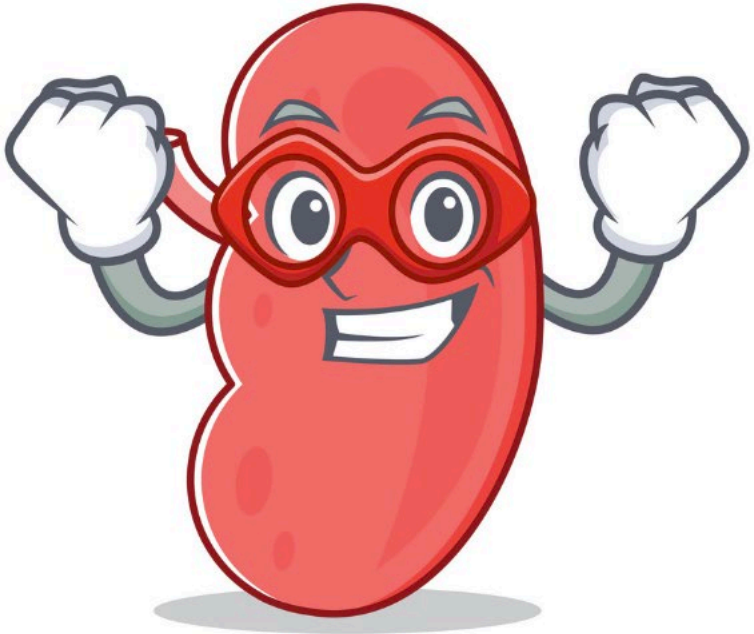
Your Kidneys

7. Your kidneys control your blood pressure.

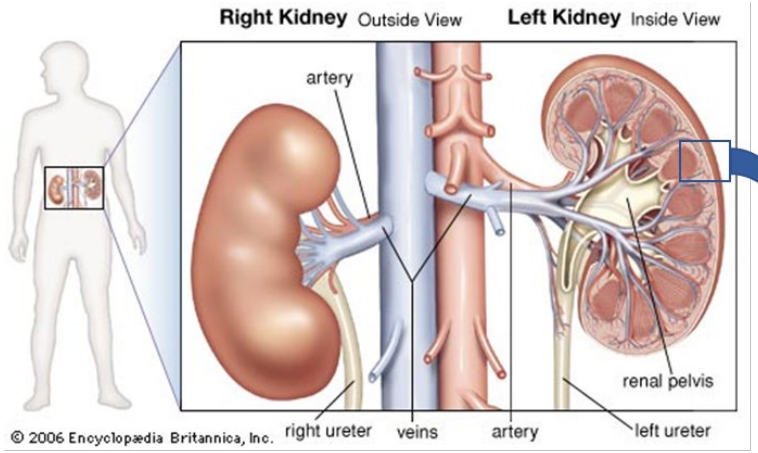
8. Your kidneys make erythropoietin (EPO), which is produced by the peritubular cells of the kidney. EPO is needed to make red blood cells.

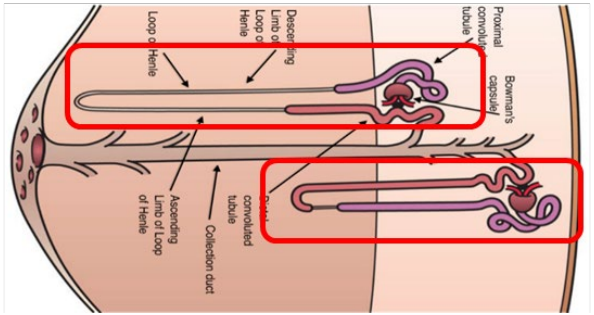
9. Your kidneys convert vitamin D to its active form.

10. Your kidneys control the pH of your blood.



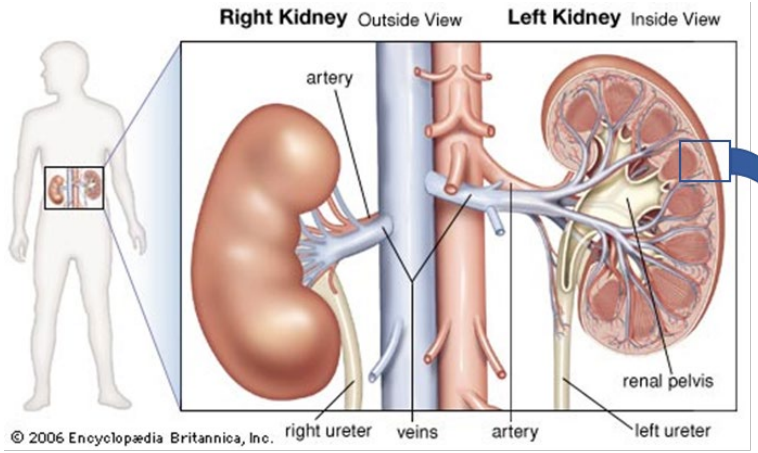
Getting a Kidney Biopsy

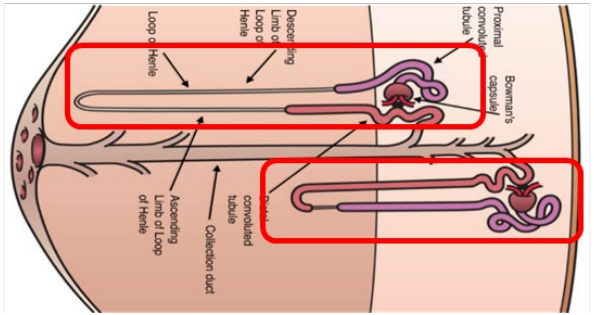


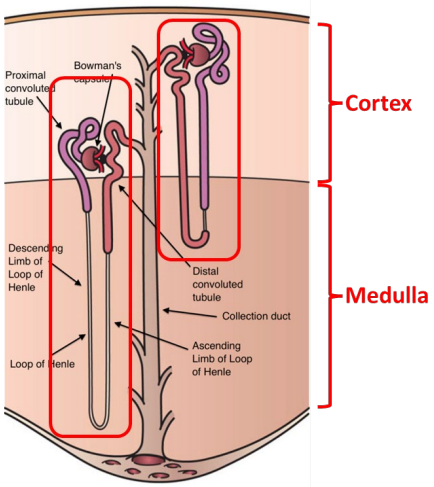


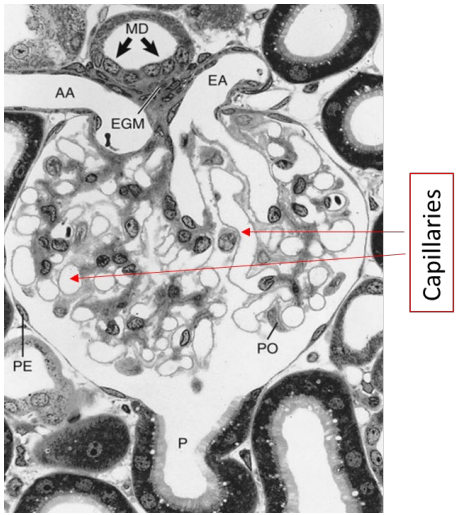
Nephrons – the working units of the kidney

Getting a Kidney Biopsy









For C3G we are interested in the glomerulus

Nephrons – the working units of the kidney

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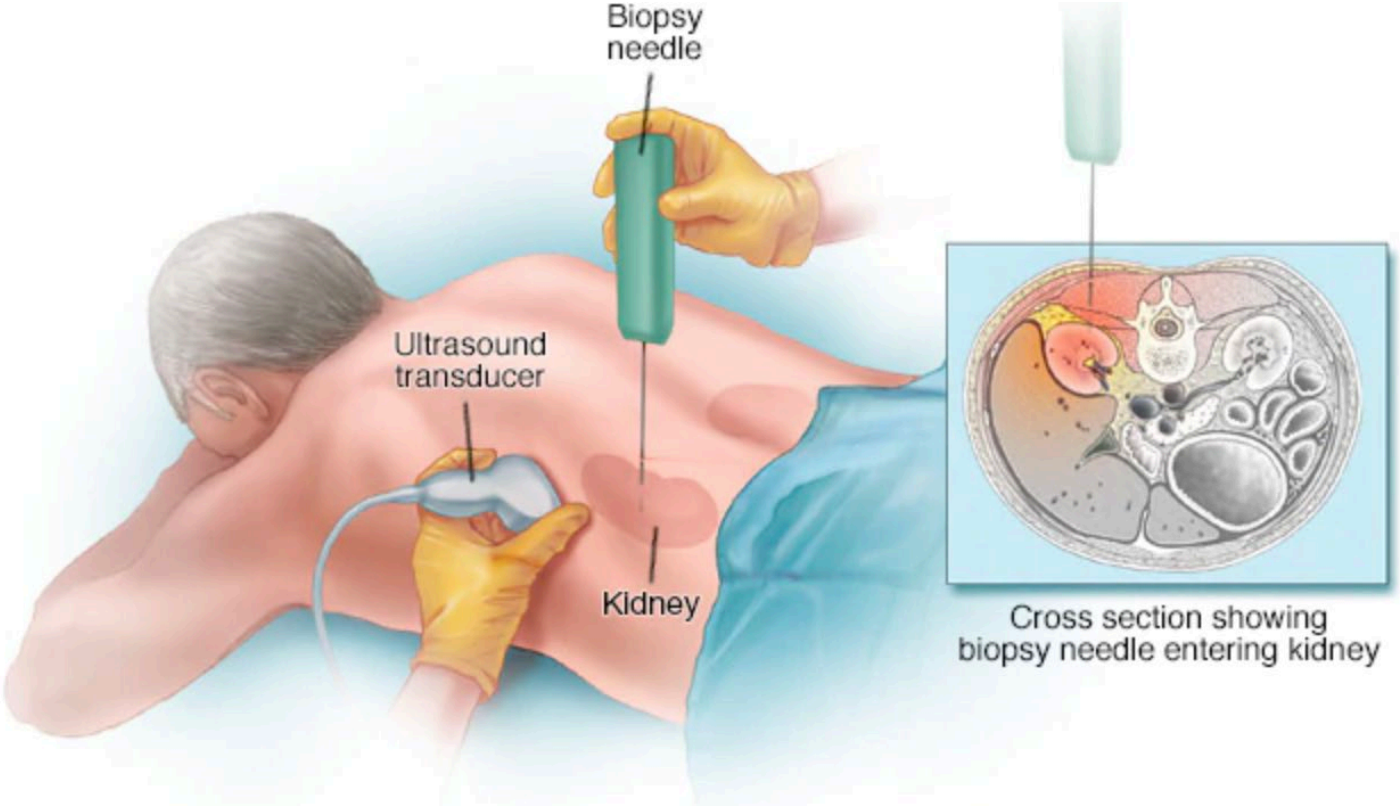
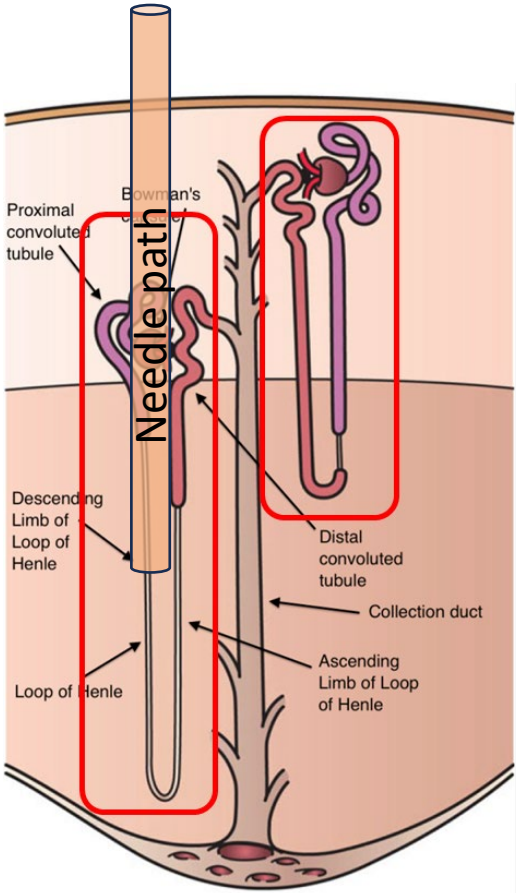
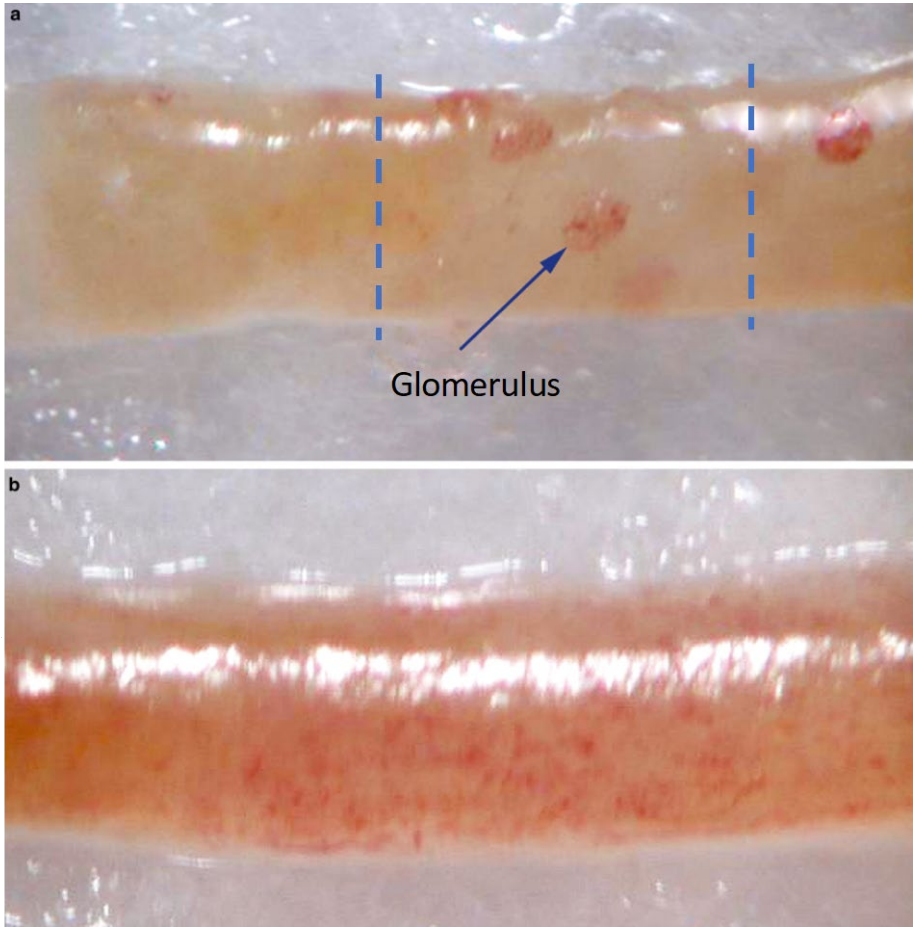
Getting a Kidney Biopsy





About 1 mm x 20 mm



Nephrons – the working units of the kidney

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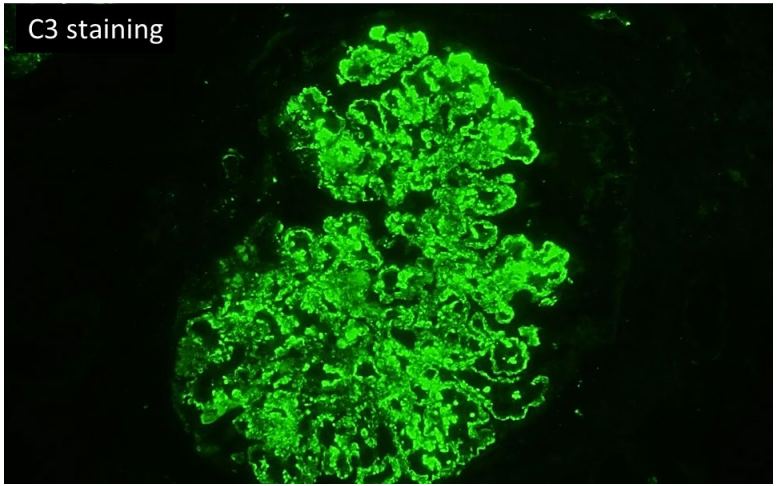
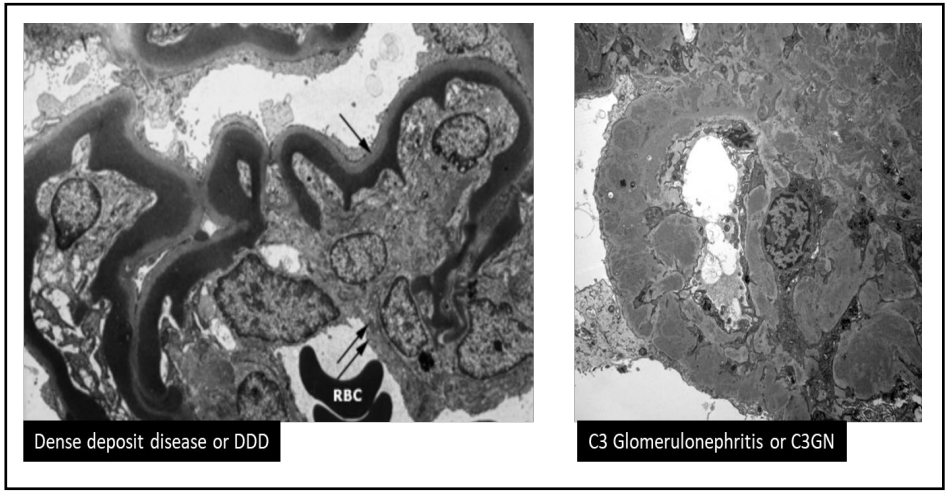
Interpreting the Kidney Biopsy

1. Light microscopy
2. Immunofluorescence microscopy (or IF)
3. Electron microscopy (or EM)



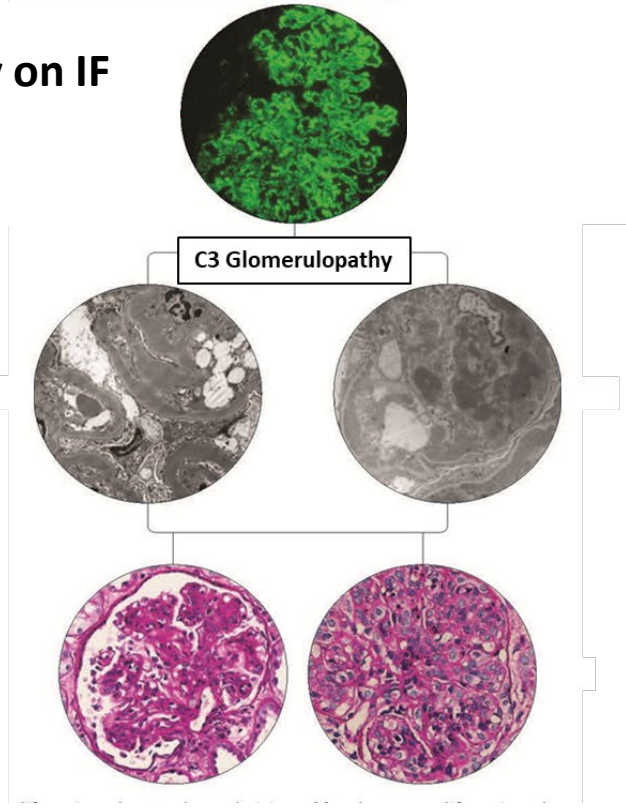


Interpreting the Kidney Biopsy

C3 DOMINANT GLOMERULOPATHY

You MUST have C3 positivity on IF

You MUST have EM to tell DDD from C3GN



Pickering et al *KI* 2013

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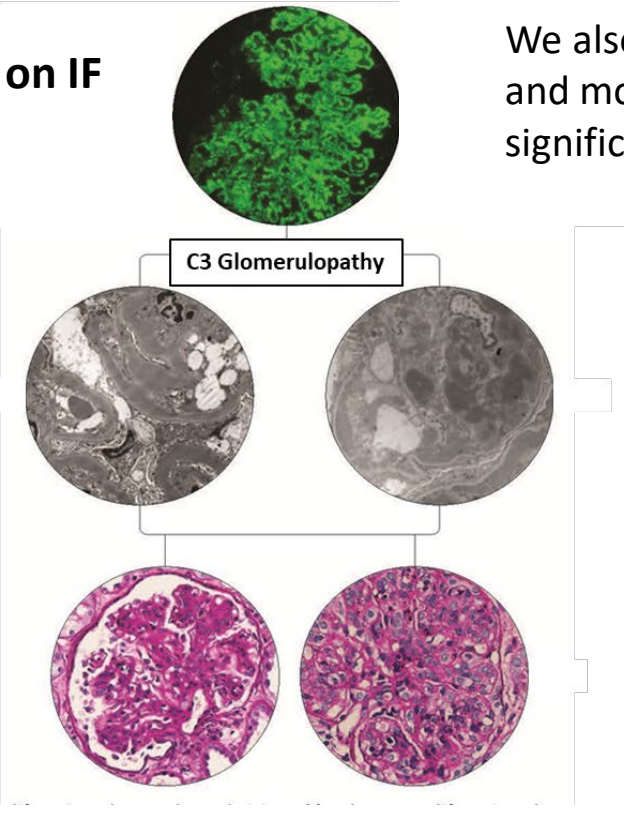

We also think of post-infectious GN and monoclonal gammopathy of renal significance and must **EXCLUDE** them

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Pickering et al *KI* 2013

Interpreting the Kidney Biopsy

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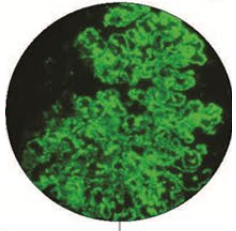

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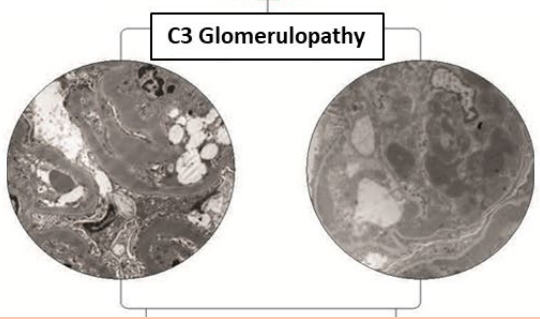

This classification is **ONLY descriptive**. It does **NOT** tell you what is causing the problem, but it suggests the tests to do to determine what is going on.

Pickering et al *KI* 2013

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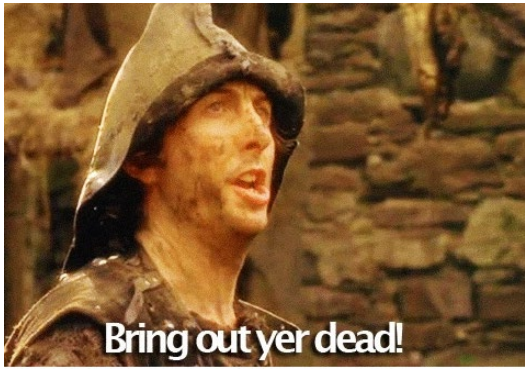
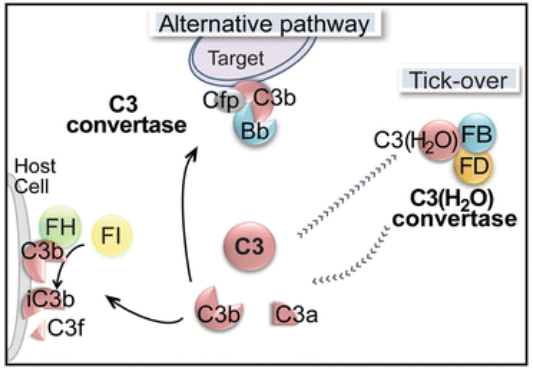
The Complement Cascade

1. It provides the first line of defense against infection
2. It marks dead and foreign cells as garbage so they can be removed
3. It talks to other systems in your body so your response is coordinated
4. It is “on” all the time. We call that **“tick over”**





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The Complement Cascade

Activation

Too much activation

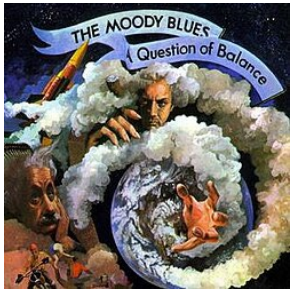
Inflammation

The Setting

Regulation

Too much control

Infection



Dysregulation = Disease

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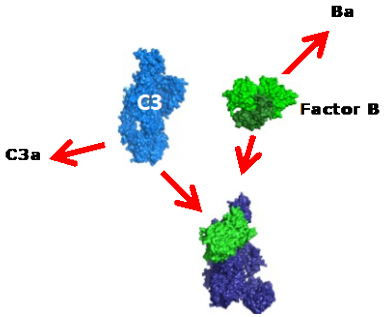
The Three Phases

1. Initiation phase: get the complement system going
2. Amplification phase: ramp it up
3. Terminal phase: do the work - inflammation, cell destruction, and marking cells for removal (garbage pickup)

Phase 1 Initiation

Alternative Pathway

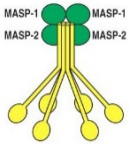
Activating surfaces



C3bBb
C3 Convertase

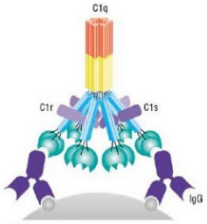
Mannose Binding Lectin

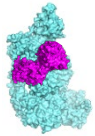
Microbial carbohydrates



Classical Pathway

Immune complexes





C4b2a
C3 Convertase

Phase 1
Initiation

Alternative Pathway

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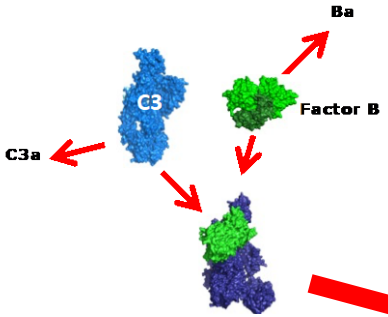

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C3 Convertase

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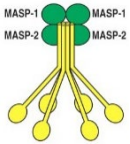

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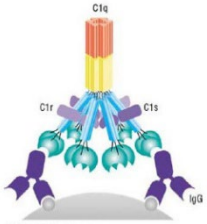
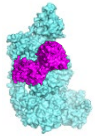
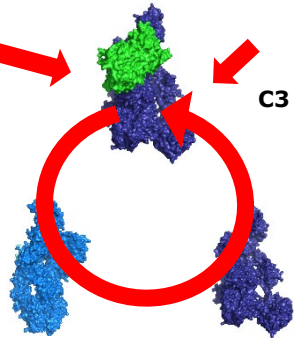




C4b2a
C3 Convertase



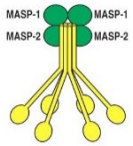
Phase 2
Amplification

Amplification is powerful that about ten billion C3b molecules are formed in about 15 minutes.

Phase 1
Initiation

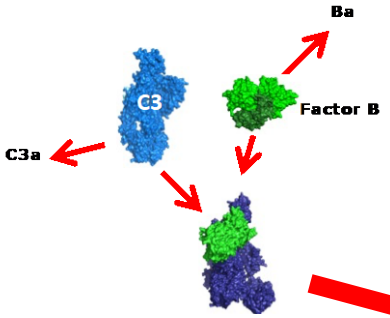
Mannose Binding Lectin

Microbial carbohydrates



Alternative Pathway

Activating surfaces



C3bBb
C3 Convertase

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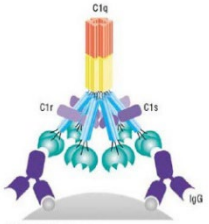

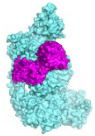

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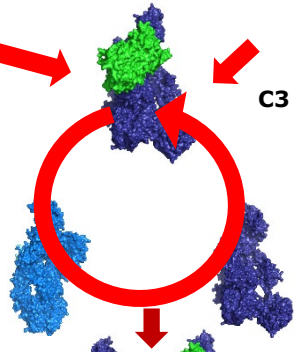
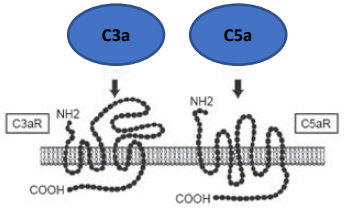
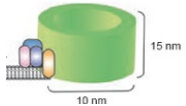


Phase 2
Amplification Loop

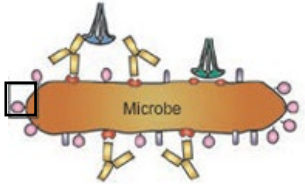
Phase 3
Terminal



Inflammation



Cell destruction



Garbage pickup

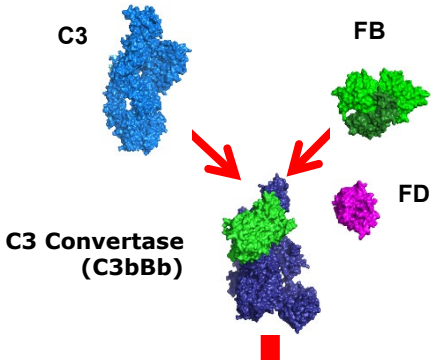
Generation of C5a, MAC, and soluble C5b-9

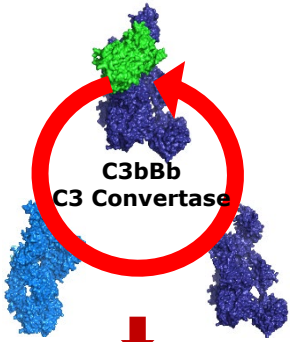
Alternative Pathway

Phase 1
Initiation

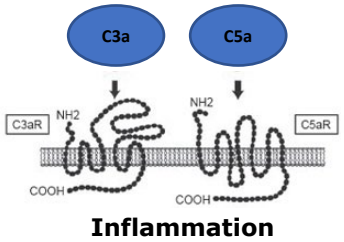
Phase 2
Amplification loop

Phase 3
Terminal
pathway

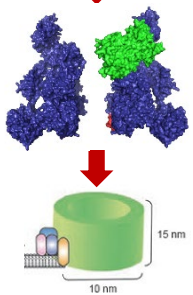




Most relevant to C3G



Inflammation



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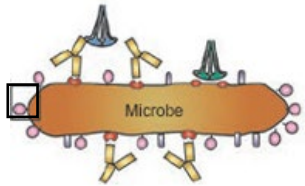

Garbage pickup

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The Four Pillars

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The MORL Renal Group provides unrivaled expertise in complement diagnostics for patients with C3G and the TMAs.