

C3G – An Update

What is C3 Glomerulopathy Anyway?

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C3 Glomerulopathy – Overview

- Discuss C3 Glomerulopathy (C3G)
 - How did we get to the current classification
 - What are the subsets of C3G
 - Demonstrate the pathologic features
 - What are the Pitfalls!
 - Algorithmic Approach

C3 Glomerulopathy – An Update

- But first, what we are leaving out

Complement in Glomerular Disease

- Post-Streptococcal GN
- Membranous Glomerulopathy
- Lupus Nephritis
- ANCA-Associated GN
- Humoral Transplant Rejection
- And on

These will NOT be discussed

C3 Glomerulopathy (C3G)

- This has become a very 'hot' diagnosis
- Source of some contention and a lot of confusion
 - C3G appears first in J Med Genet in 2007?
 - But lets move forward...

Servais A, Fremeaux-Bacchi V, Lequintrec M, Solomon R, Blouin J, Knebelmann B, Grunfeld J-P, Lesavre P, Noel L-H, Fakhouri F. Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. J Med Genet 44: 193-199, 2007

C3 Glomerulopathy

- The Problem is:
 - A Collision between Glomerular Pathology (MPGN) and the Rapid Advancement in our Understanding of Complement-Related Renal Disease



MPGN Today

- MPGN has become a ***clinico-pathologic*** waste basket
- The use of the term ***MPGN*** does NOT lead to a clear clinical understanding!
- MPGN is a **PATTERN**, ***NOT*** a **DISEASE!**
- One more time...

MPGN Today

- MPGN is a **PATTERN**,
NOT a **DISEASE!**

MPGN is a *Pattern*, NOT a *Disease*

This is how it stood in 2010 when MPGN was STILL a ***DISEASE***

- Primary: MPGN I, II, III
- Secondary
 - Associated with:
 - Autoimmune diseases
 - Dysproteinemias
 - Neoplasms
 - Renal allograft
- Secondary
 - Associated with:
 - Infections
 - Rheumatologic Diseases
 - Malignancy
 - Inherited Diseases
 - ***Other***

MPGN is a *Pattern*, NOT a *Disease*

- MPGN Pathogenetic Mechanisms
 - Autoimmunity and Immune Complex Deposition
 - Chronic Infection
 - Complement Dysregulation
 - Monoclonal Ig Deposition Disease
 - Chronic Thrombotic Microangiopathy
 - Idiopathic

Classification of MPGN 2010

- “...vigorous attempts to identify the underlying mechanisms must be undertaken whenever the MPGN pattern of injury is found on renal biopsy!”
- In other words, when the Dx is MPGN, you still don't know what the patient has!

Classification of MPGN

- We have progressed from post-mortem analysis of glomerular changes (Volhard & Fahr 1900's)
- Through detailed histopathologic descriptions
 - MPGN and all its subtypes
- To various pathogenetic mechanisms all associated with a membranoproliferative pattern
- But we have NOT arrived at the final destination
 - It is premature to think we have it figured out

Classification of MPGN

- Diagnostic Confusion
 - We still rely on the biopsy but must add more analysis

Complement and MPGN

- A Sea-Change Begins in 2007
 - Servais et al (2007) Glomerulonephritis C3
 - And a host of other publications
 - And that is what we will now discuss

Then and Now Pathology

- What was MPGN
 - Membranoproliferative Glomerulonephritis
 - Primary v Secondary
 - MPGN I, DDD or MPGN II, III

Then and Now Pathology

- Membranoproliferative Glomerulonephritis is

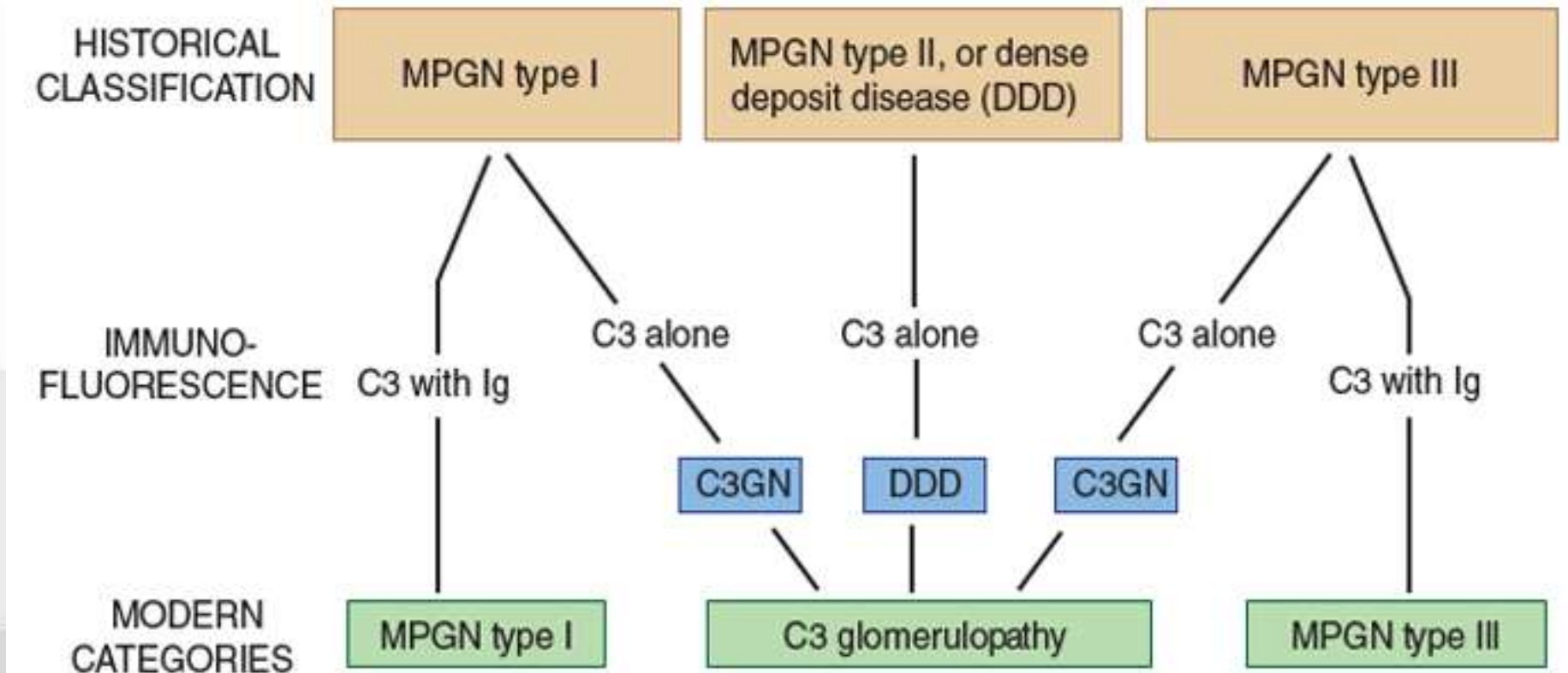
Now – *Membranoproliferative Pattern*

- This pattern is associated with a variety of clinical syndromes and pathogenetic mechanisms

Pathology and Complement

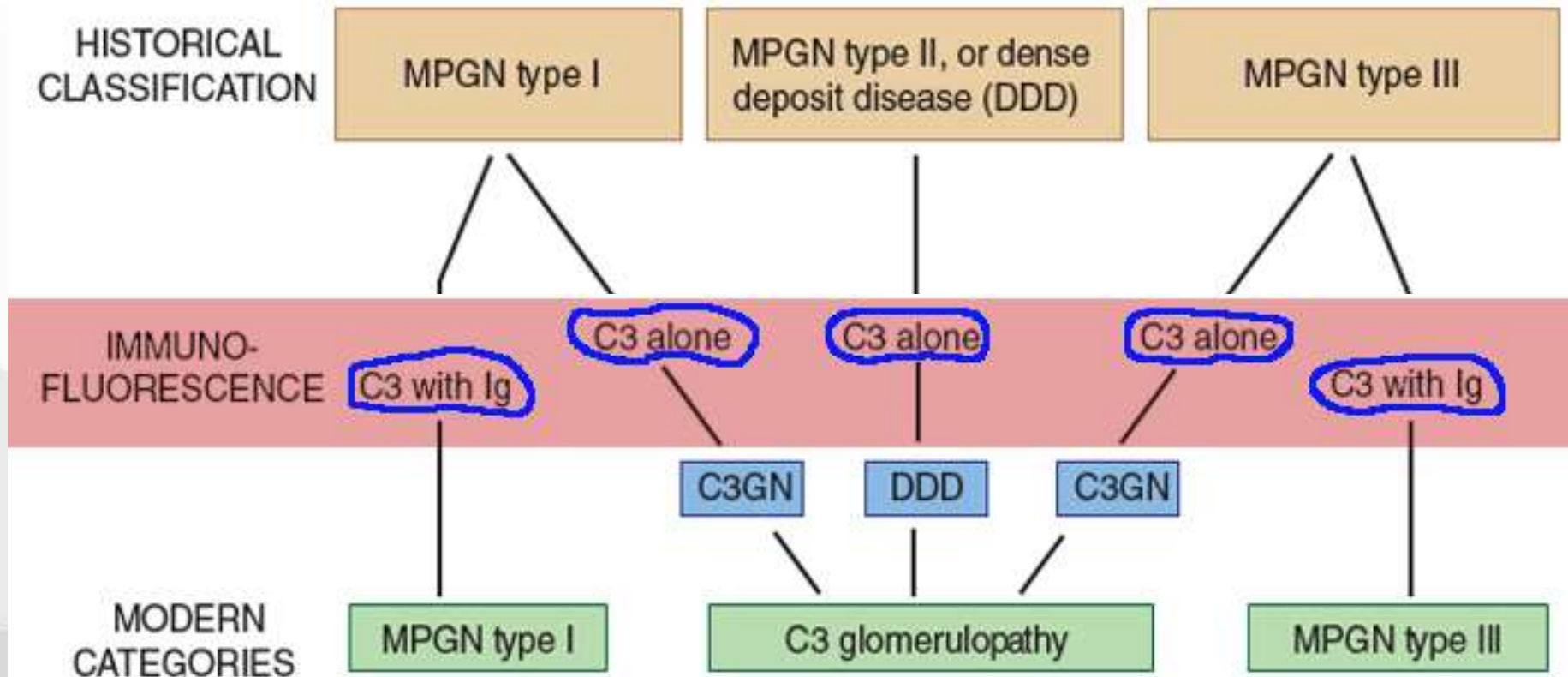
- ***Membranoproliferative Pattern*** may be associated with complement abnormalities
- Abnormalities of the ***Complement System*** are associated with a variety of histopathologic patterns

Changes in Primary MPGN - 2012



D'Agati, V.D., and Bomback, A.S. **2012**. C3 glomerulopathy: what's in a name? *Kidney Int* 82:379-381.

Changes in Primary MPGN - 2012

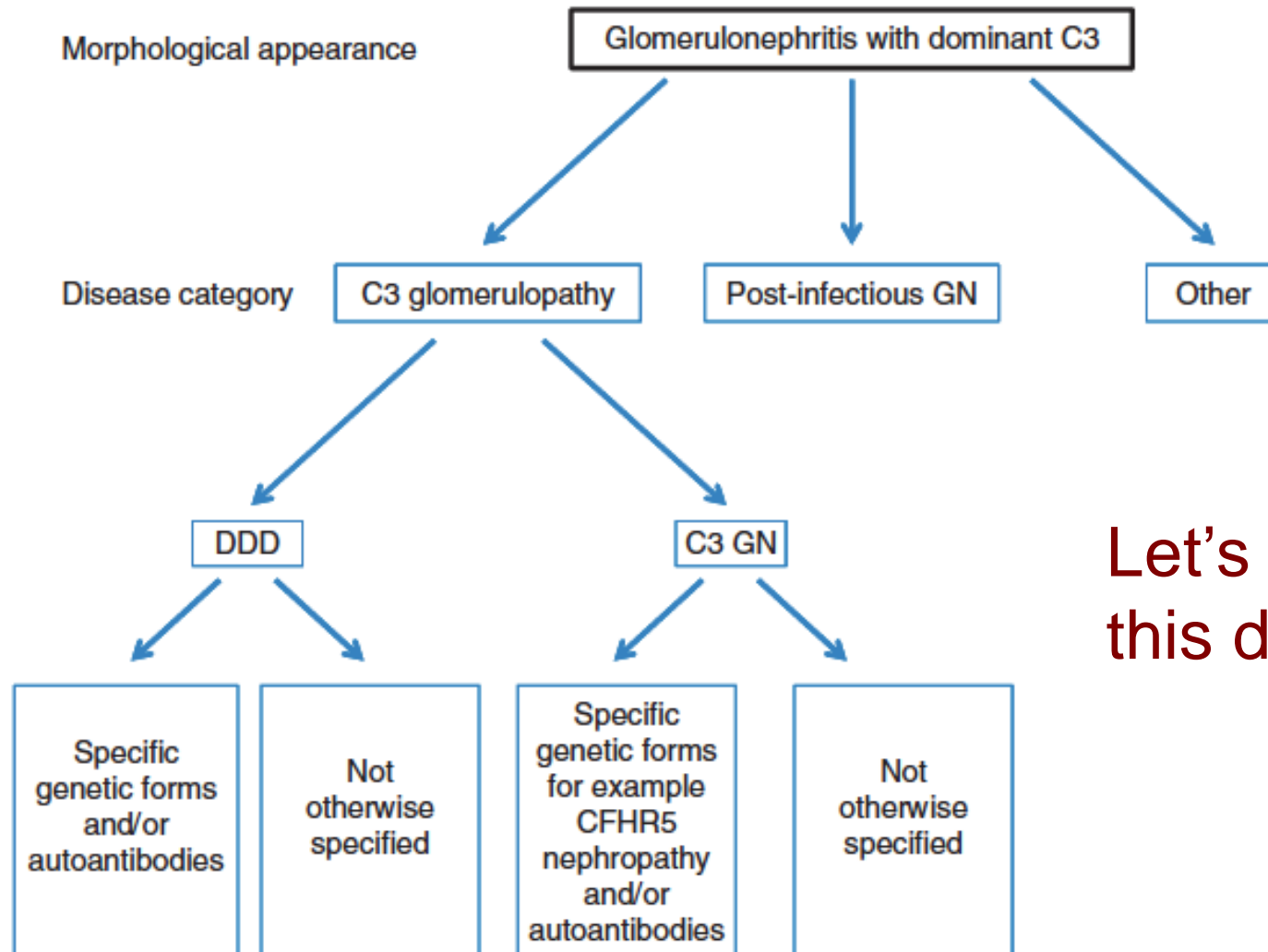


- Still Not Right! C3GN often has Ig deposits

C3 Glomerulopathy Consensus Conference 2013

- This is outstanding work! A Significant Advance
- Defined:
 - C3 Glomerulopathy
 - Outlined appropriate Complement work up
 - Explored treatment options

Consensus Conference Diagnostic Algorithm



Let's break this down

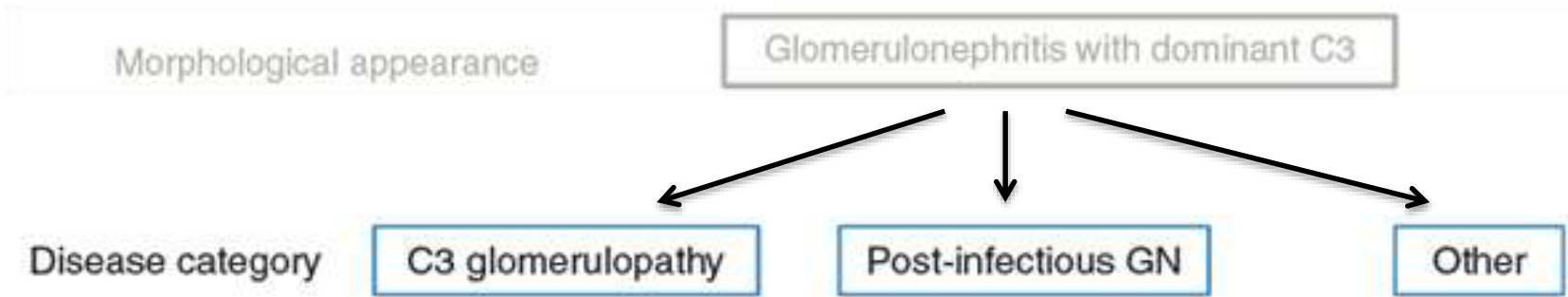
Consensus Conference Diagnostic Algorithm

Morphological appearance

Glomerulonephritis with dominant C3

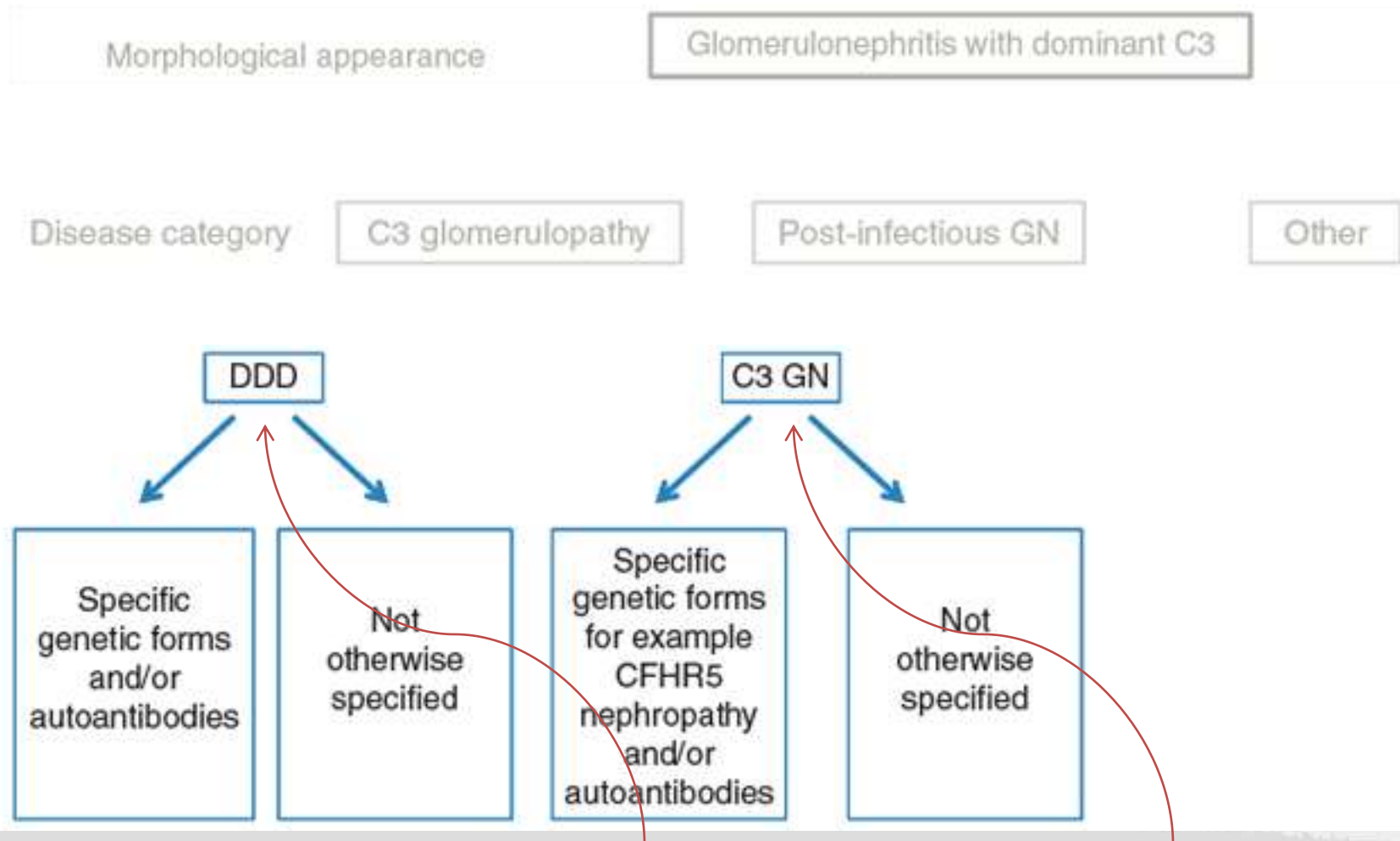
- Glomerulonephritis, not just MPGN
- C3 Dominant rather than C3 ONLY

Consensus Conference Diagnostic Algorithm



- C3 Dominant is not a diagnosis, but leads down a path

Consensus Conference Diagnostic Algorithm

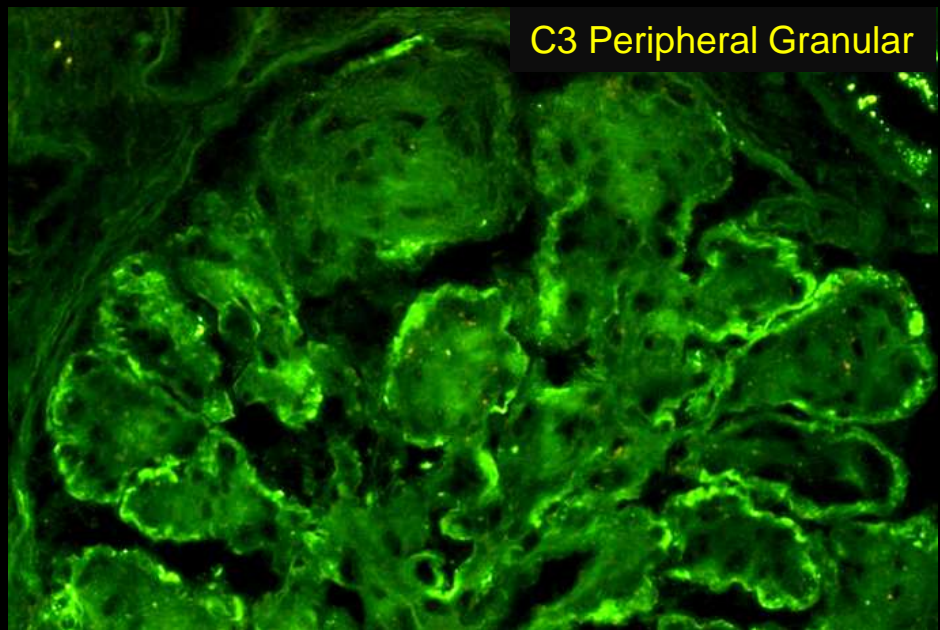
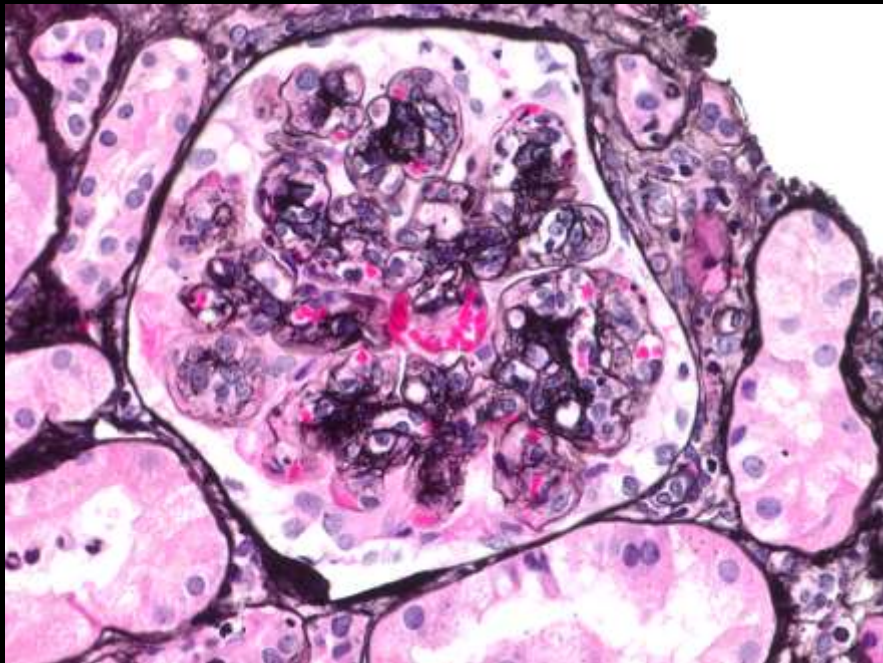
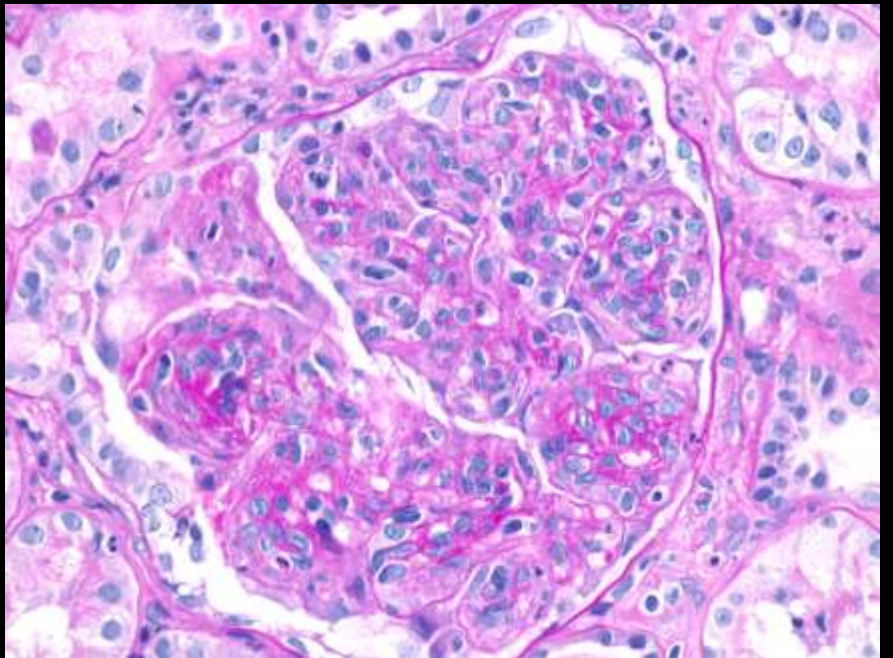
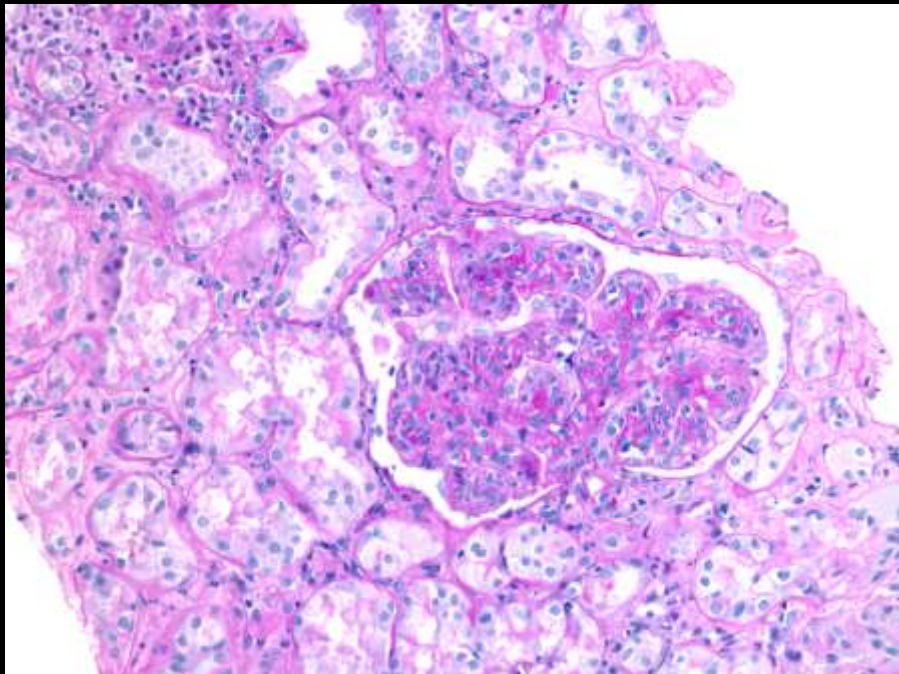


- C3G breaks out into two main patterns

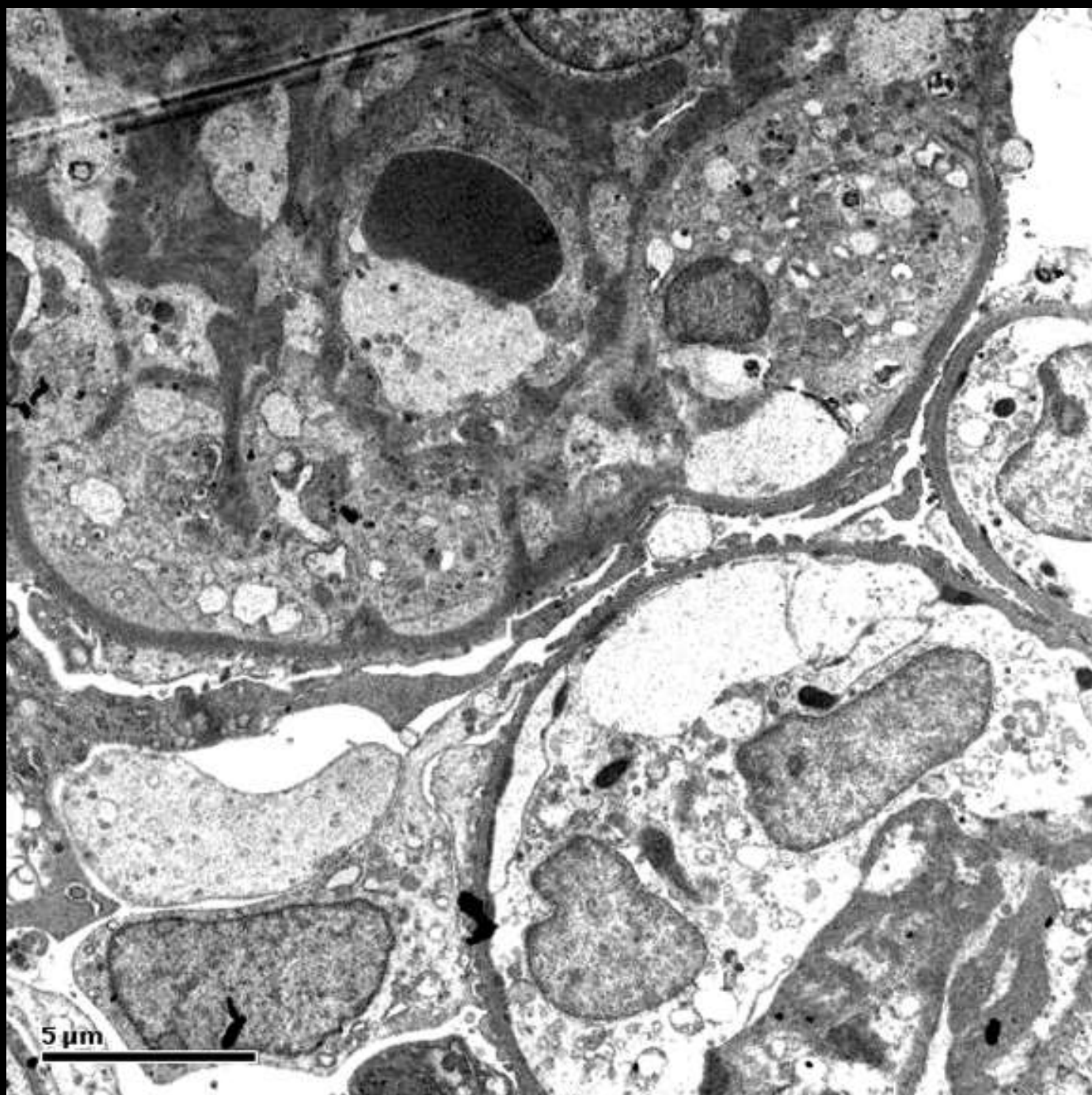
C3 Glomerulopathy

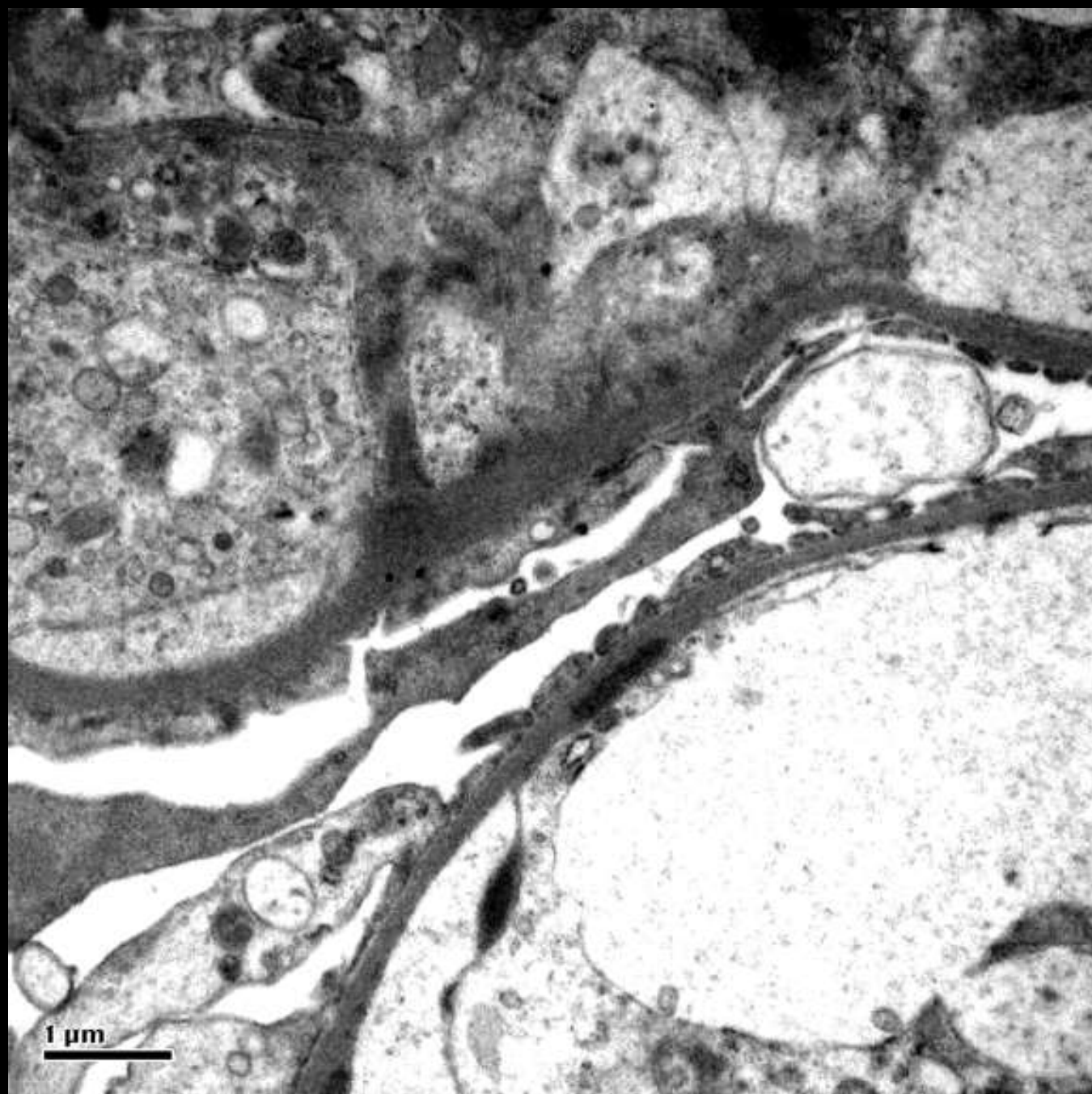
(C3G is the new abbreviation)

- Light Microscopy
 - Membranoproliferative Pattern – 65%-70%
 - Mild Glomerular abnormalities – 30%-35%
- Immunofluorescence Microscopy
 - C3 Dominant, not Only
- Electron Microscopy
 - Mesangial, Subendothelial and, Less Commonly Membranous Deposits



C3 Peripheral Granular

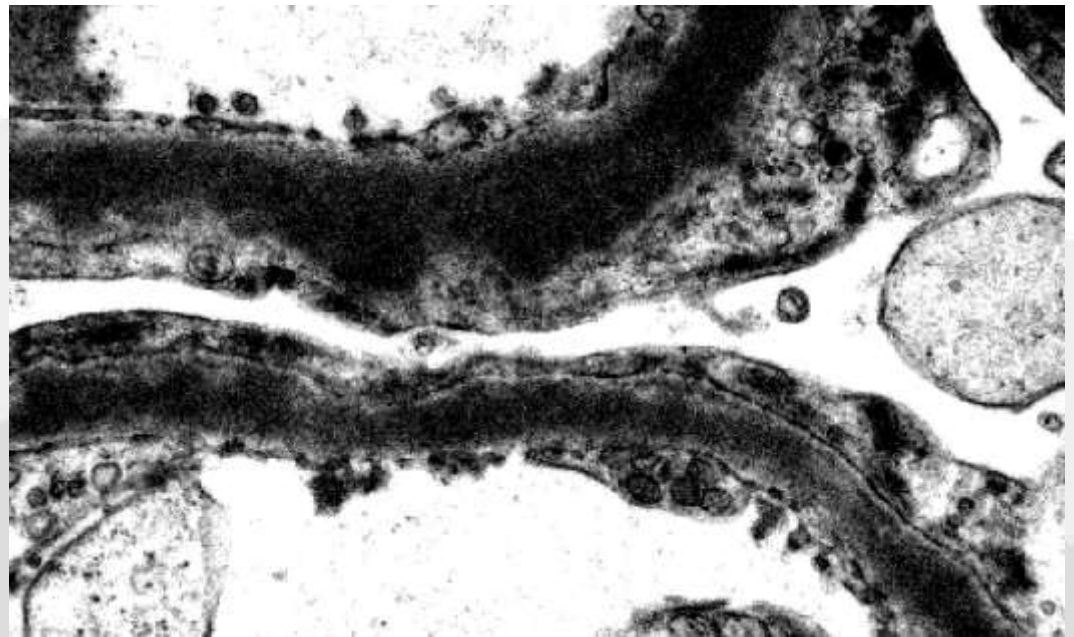




Dense Deposit Disease

- DDD has a distinctive pathologic appearance using the Electron Microscope

Unique Electron Dense Transformation of Glomerular Basement Membranes



Dense Deposit Disease

- The light microscopic appearance is variable
 - Membranoproliferative DDD (20-25%)
 - Mesangial Proliferative DDD (40-45%)
 - Crescentic DDD (15-20%)
 - Acute Proliferative and Exudative DDD (10-15%)

Walker PD et al Modern Pathol 20: 605-616, 2007

Nasr SH et al Clin J Am Soc Nephrol 4: 22-32, 2009

Moving to today

- C3G Focus Group was held in Upsalla, Sweden, June, 2015
 - Updated everything to current
 - Pathology to mechanisms to treatment
 - My job in the pathology section was to pose the ‘Most Pressing Question’

C3G Focus Group – 2015

- The Pressing Question?
 - How to Get the Diagnosis Right...
 - Without the right diagnosis
 - We are comparing apples to pears
 - We are better off than we were, but we still need to improve

The Pressing Question?

- How to Get the Diagnosis Right...
 - Too much overcalling and, the other way
 - C3G cases are being missed

The Pressing Question?

- Get the diagnosis right...
 - Review some of the known pitfalls
 - And add a new one

C3G is ***Not*** always C3 only

- DDD is the prototypic C3G

	IgG	IgM	IgA	C3	C1q
pdw	20%	34%	13%	100%	19%
nasr	27%	37%	13%	100%	10%
n=94	22%	35%	13%	100%	16%

– Ig's are present in a significant percentage of cases of DDD

Misdiagnosis the other way

- Are we missing cases of C3G **BECAUSE** they have Ig's? Servais et al looked at it *the other way*
- Started with patients with ***An abnormality of the Alternative Pathway of Complement***
- ***8 of 26 had a membranoproliferative pattern and all had C3 and one or more Ig's***

C3 '*only*' is not really C3G

- These are the Major Entities miscalled C3G
 - Autoimmune Diseases (e.g. SLE)
 - Infection-Related GN (e.g. Infective Endocarditis)
 - Paraprotein-related disease

C3 'only' is not really C3G

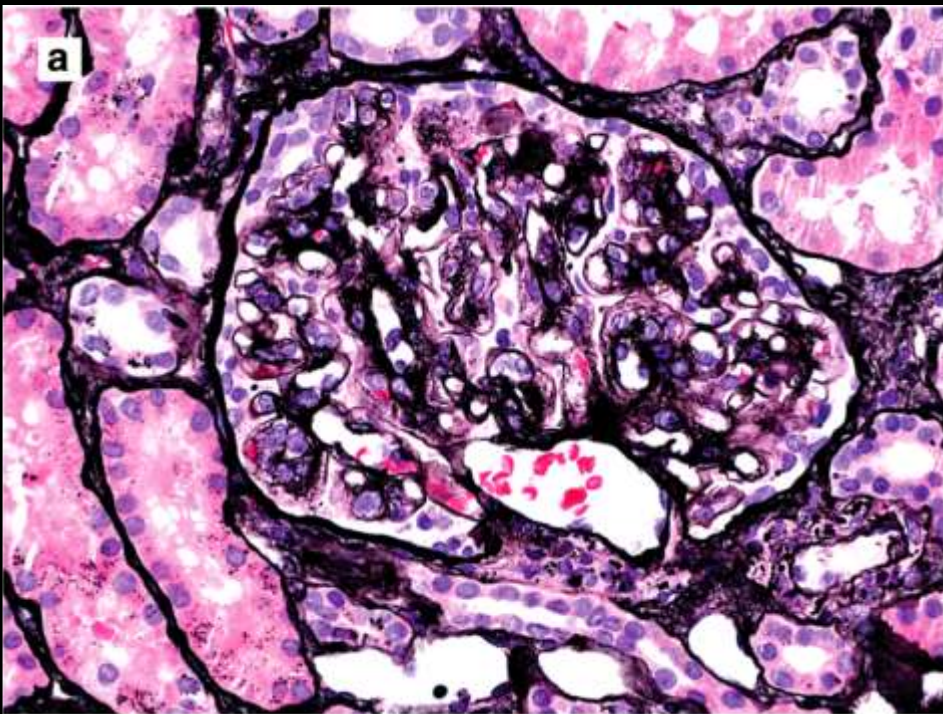
- These are the Major Entities miscalled C3G
 - Autoimmune Diseases (e.g. SLE)
 - Infection-Related GN (e.g. Infective Endocarditis)
 - Paraprotein-related disease
- Why? Because they are NOT C3 ONLY
- If it is Called C3G and it is NOT C3G –
***Wrong* Work Up and *Wrong* Treatment**

C3 'only' is not really C3G

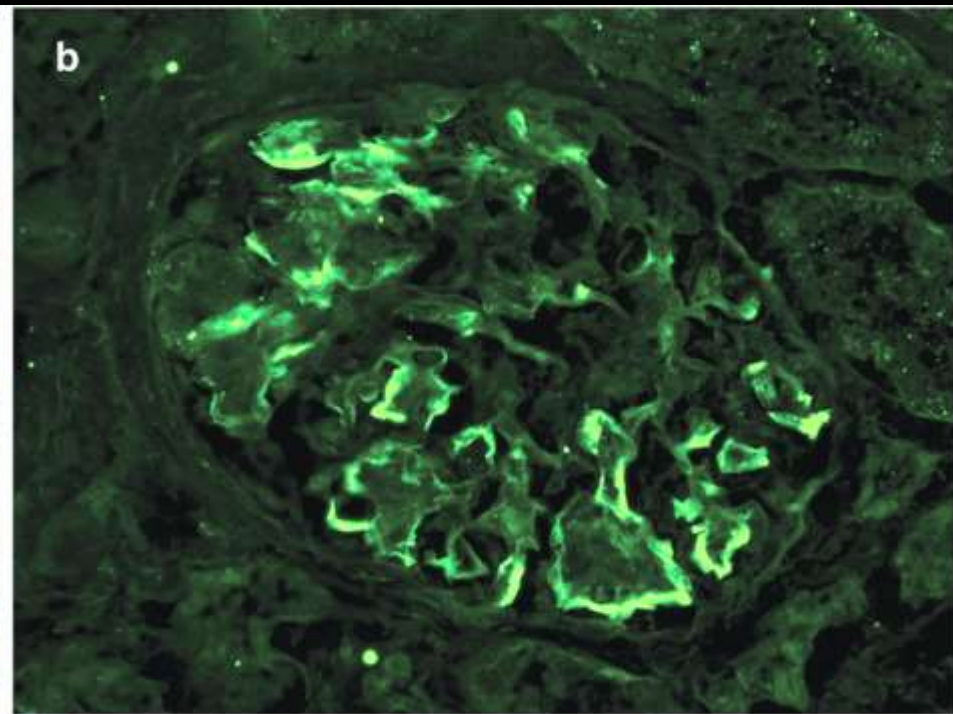
- Paraffin IF can unmask these pretenders
 - Messias NC, Walker PD, Larsen CP. Paraffin immunofluorescence in the renal pathology laboratory: more than a salvage technique. *Mod Pathol* 2015 28: 854-60.
 - Larsen CP, Messias NC, Walker PD, Fidler ME, Cornell LD, Hernandez LH, Alexander MP, Sethi S, Nasr SH. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. *Kidney Int* 2015 Accepted for Publication

C3 'only' is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine



Membranoproliferative Pattern



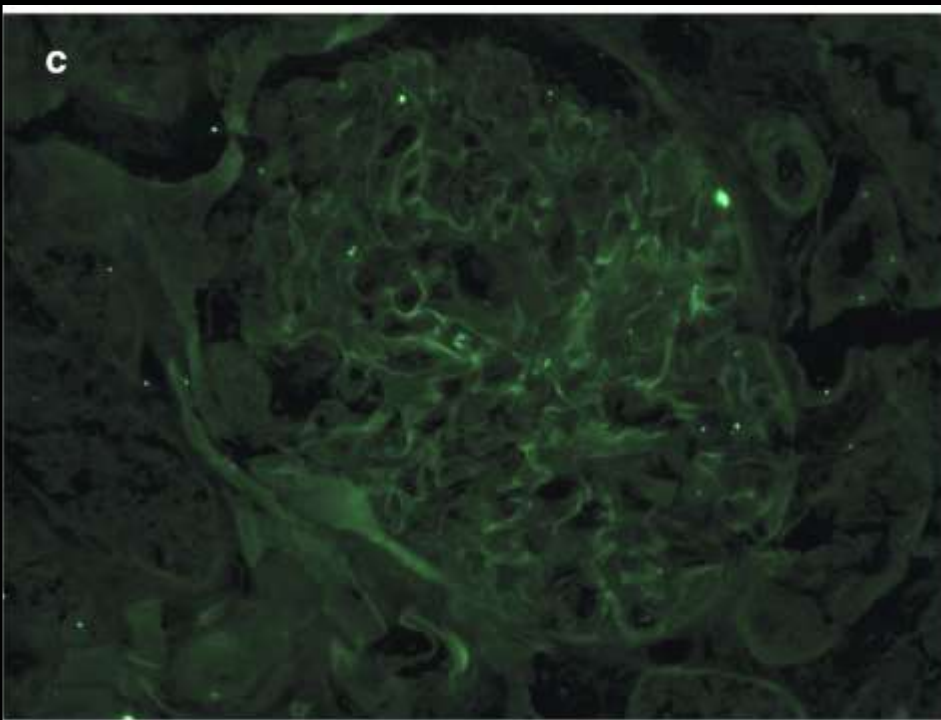
C3 Only, all others Negative

C3 'only' is not really C3G

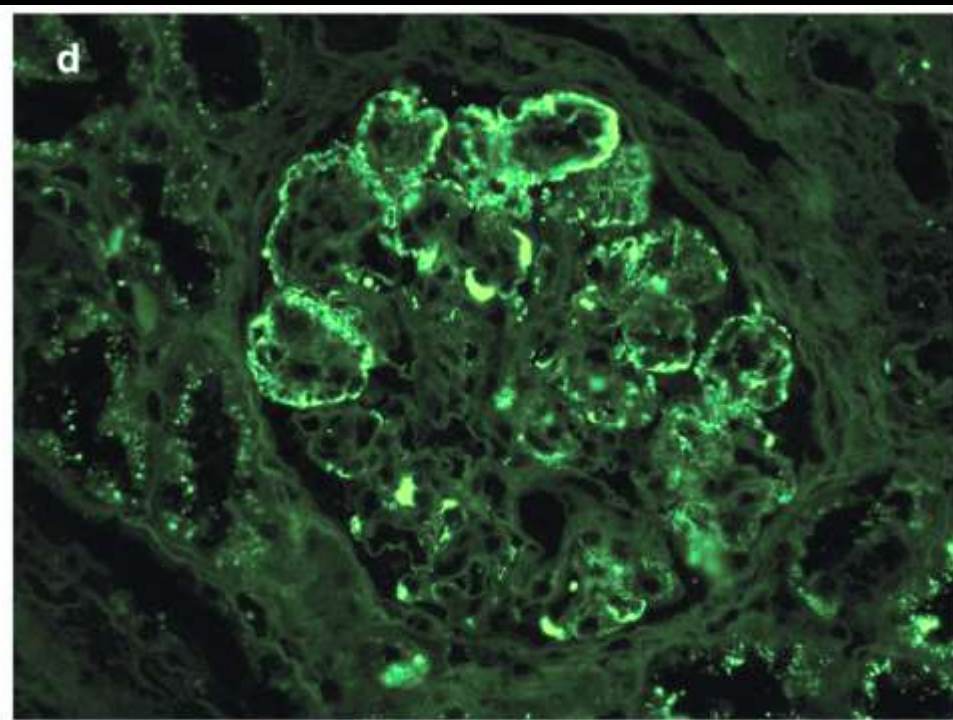
- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine
- Preliminary Diagnosis: Membranoproliferative Pattern with IF features consistent with C3 Glomerulopathy

C3 'only' is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine



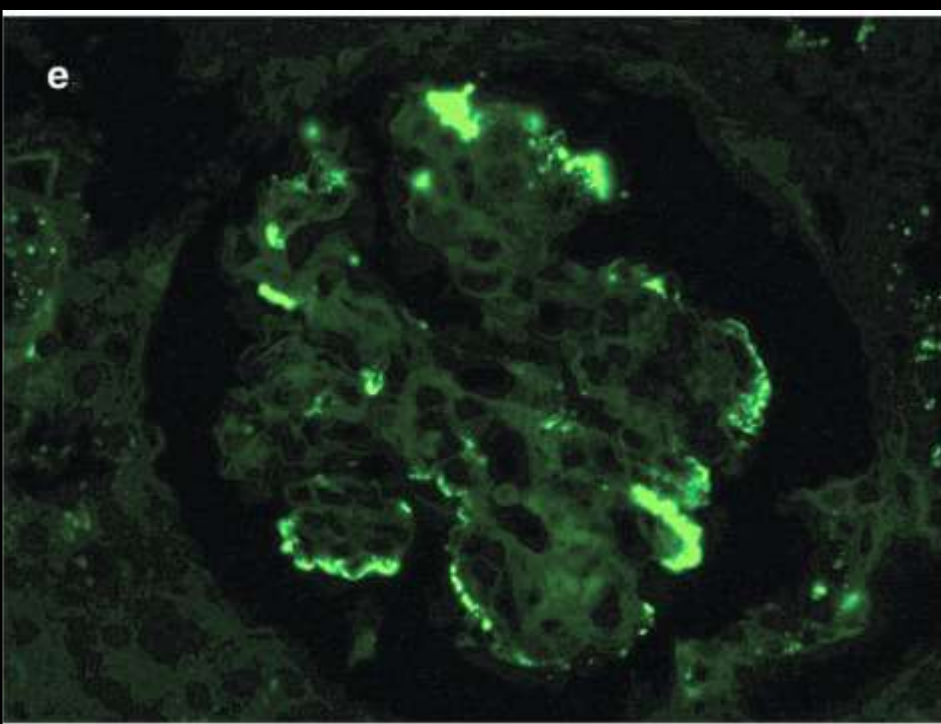
Routine IgG



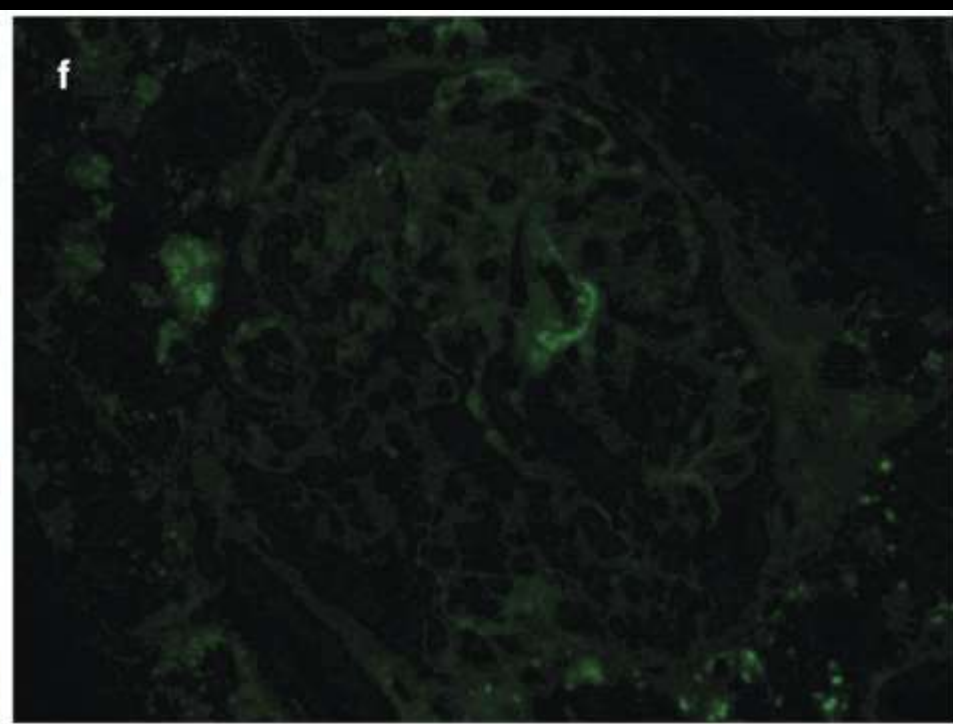
IgG on Paraffin IF after Protease

C3 'only' is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine



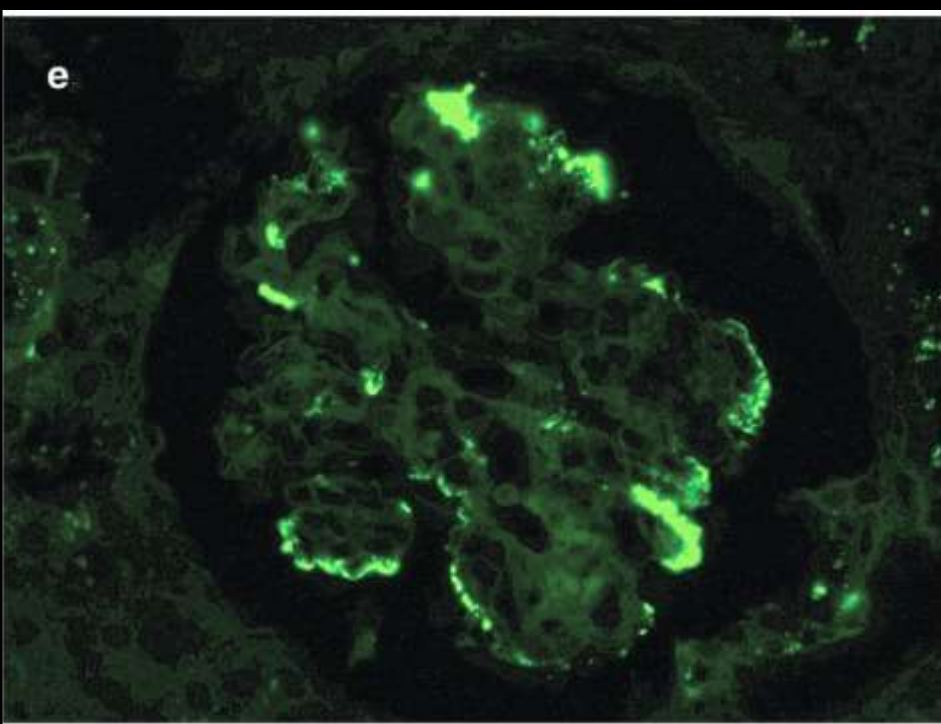
Kappa on Paraffin IF after Protease



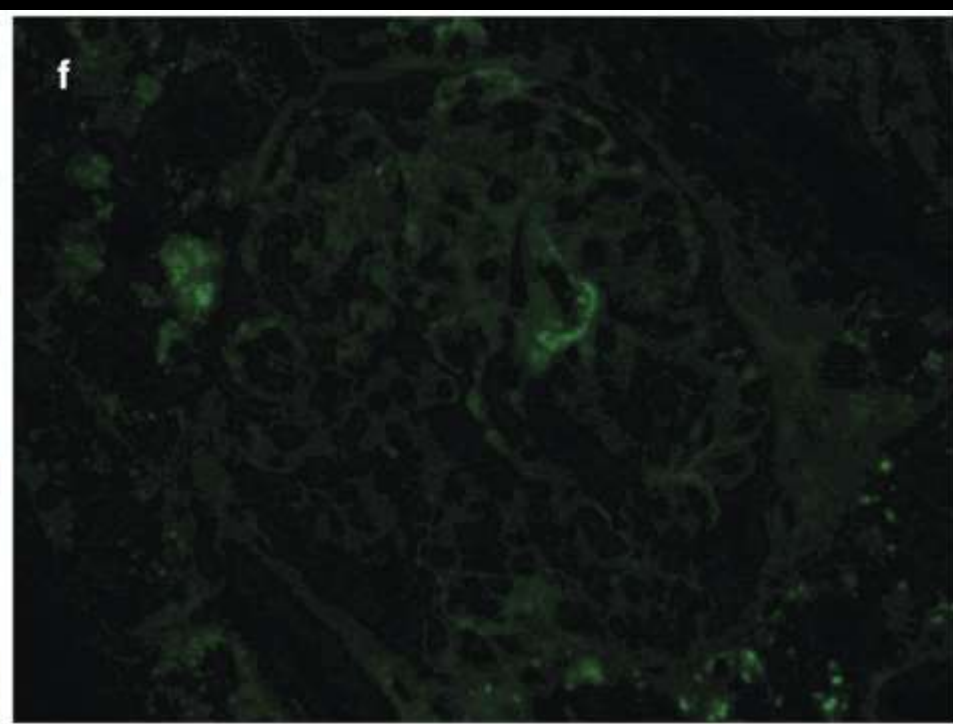
Lambda on Paraffin IF after Protease

C3 'only' is not really C3 ONLY

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine



Kappa on Paraffin IF after Protease



Lambda on Paraffin IF after Protease

C3 'only' is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine
- Final Diagnosis: Membranoproliferative Pattern with IgG/Kappa deposits
 - Comment: rule out paraprotein-related disease
- Patient found to have a B-cell lymphoma

C3 'only' is not really C3G

- Patient found to have a B-cell lymphoma
- C3G is WRONG
 - Would have led to delayed diagnosis at best
 - Incorrect and Expensive Work Up
 - Possibly the Wrong Treatment

GN and only C3 are *NOT* all C3G

- Worldwide, the most common cause of a glomerulonephritis with C3 deposits in the absence of immunoglobulins is?

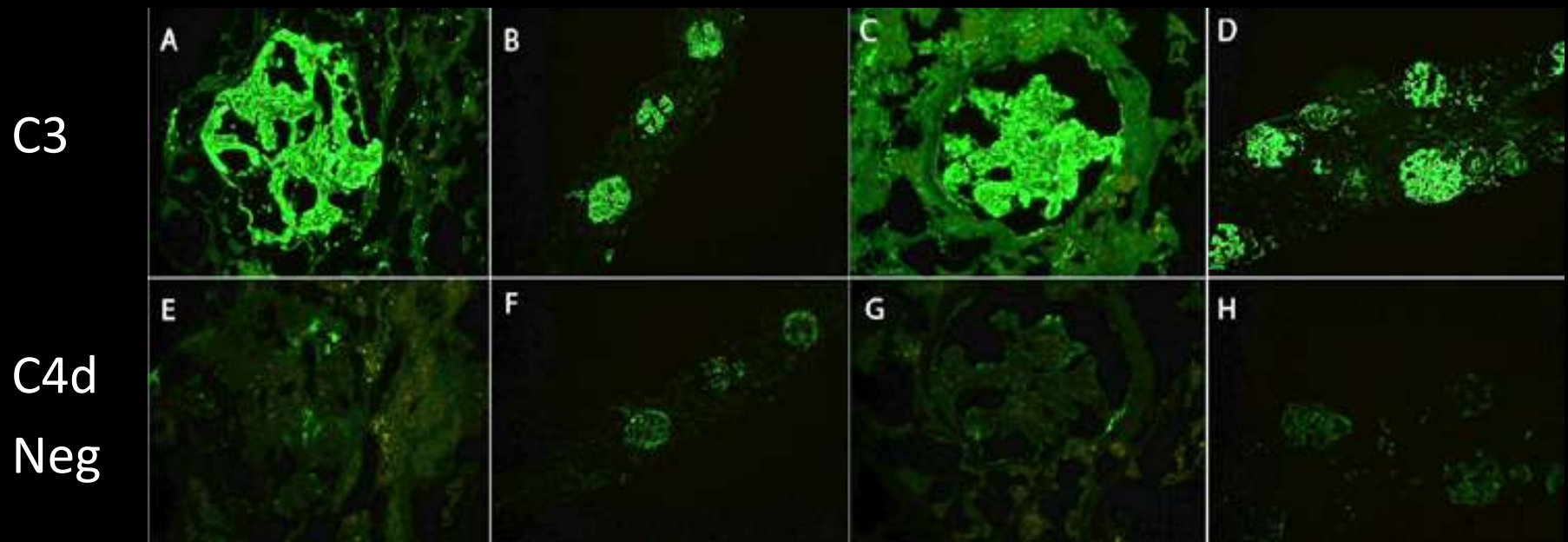
GN and only C3 are *NOT* all C3G

- Worldwide, the most common cause of a glomerulonephritis with C3 deposits in the absence of immunoglobulins is?
- **INFECTION-ASSOCIATED GLOMERULOPATHY**
 - Co-infectious or Post-infectious

C4d as a Diagnostic Tool in Proliferative GN

Sanjeev Sethi,* Samih H Nasr,* An S. De Vriese,[†] and Fernando C. Fervenza[‡]

J Am Soc Nephrol 26: ●●●–●●●, 2015. doi: 10.1681/ASN.2014040406



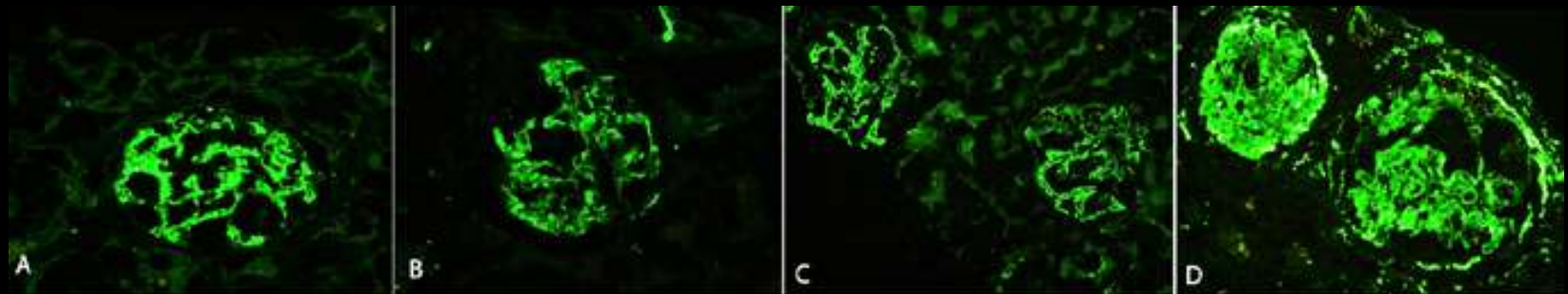
Patients with true C3G are negative for C4d

C4d as a Diagnostic Tool in Proliferative GN

Sanjeev Sethi,* Samih H Nasr,* An S. De Vriese,[†] and Fernando C. Fervenza[‡]

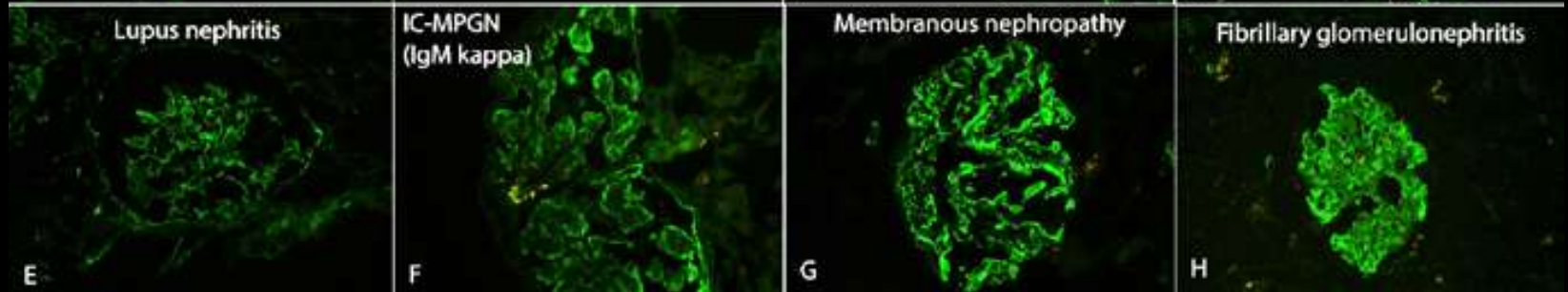
J Am Soc Nephrol 26: ●●●–●●●, 2015. doi: 10.1681/ASN.2014040406

C3



C4d

Pos



C4d Positive in different forms of ICGN

So, in Summary

- C3G is **Not** always C3 only
 - DDD is the prototypic C3G and frequently has Ig's
- On the other hand...
 - MPGN with Ig's may be due to an abnormality of the alternative pathway of complement, in effect a C3G
- Consensus conference addresses this – but must be used

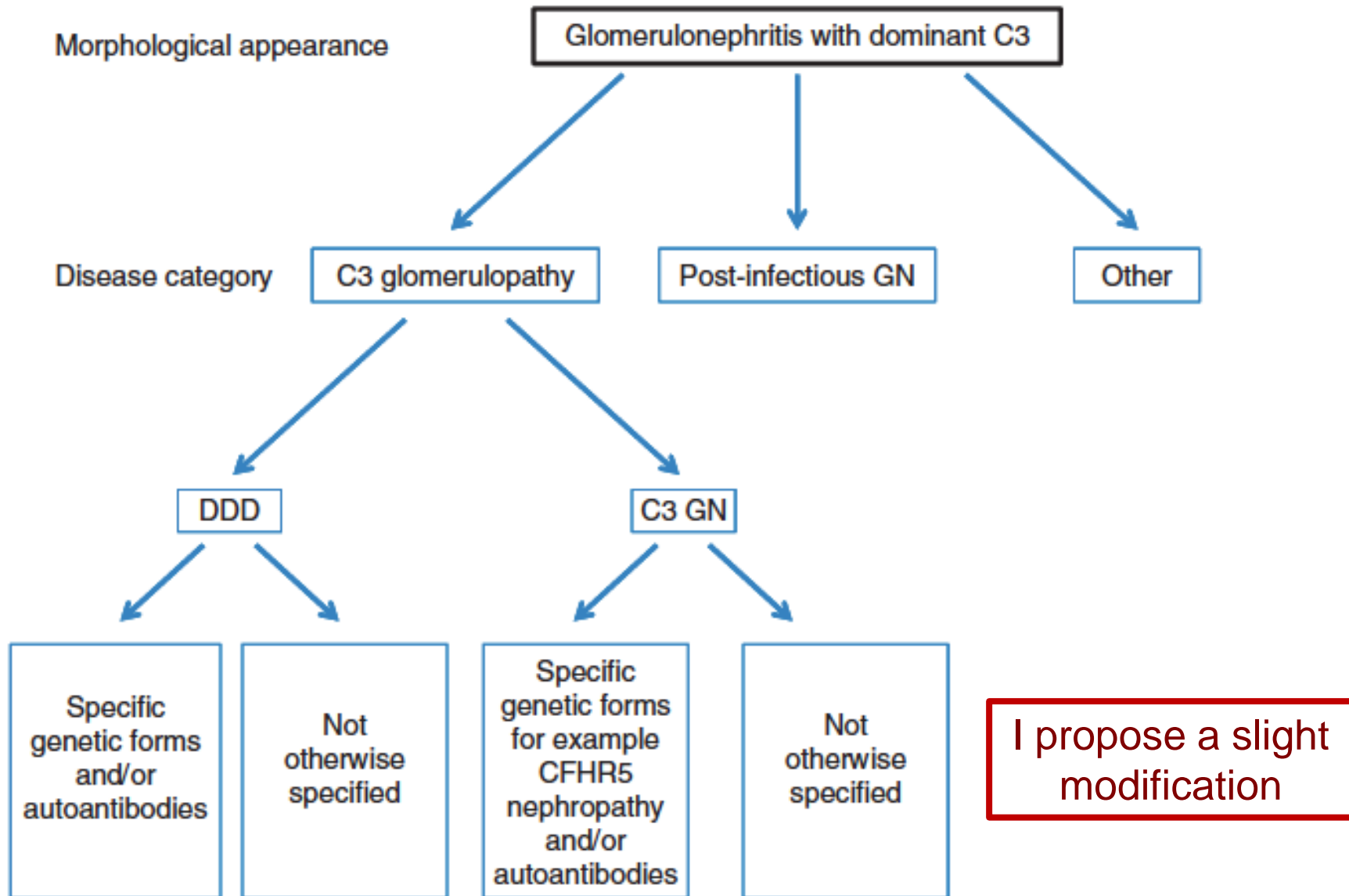
Summary

- MPGN with C3 only may Not be C3G
 - Paraffin IF with protease digestion
 - C4d
- GN and only C3 are **NOT** all C3G
 - The most common cause is Infection-Associated Glomerulonephritis

Proposal

- The goal is to identify patients with abnormalities of the Alternative Pathway of Complement

The Algorithm from the Consensus Conference is Excellent



C3 Dominant (not 'Only') Proliferative GN with or without Membranoproliferative Features

R/O Infection-Related GN
R/O Autoimmune Related GN

Negative

Paraffin IF & C4d

Both Negative

Paraffin IF Positive

C4d Positive

W/U Abnormalities
of the Alternative
Pathway of Complement

Positive

Negative

Other

C3 Glomerulopathy

Other

So far only paraprotein-related diseases have been unmasked. Still, Clinico-pathologic correlation is required. May still be a C3GP or due to an 'Other'

Thank you

- Organizers
- Sponsors
- To You
- And to all the patients we serve, but who actually are our best teachers