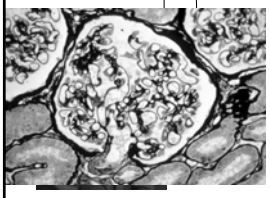
CPC: Glomerulonephritis

Gerald B Appel, MD

Vivette D'Agati, MD



Classification of Renal Glomerular Diseases

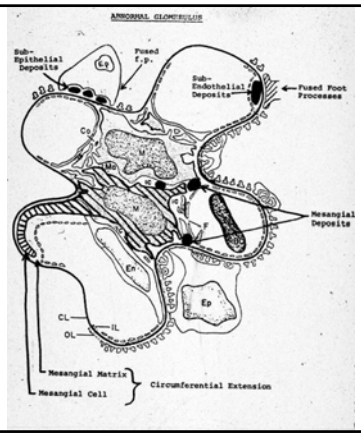
- Morphological
- Immunological
- Etiological
- Clinical

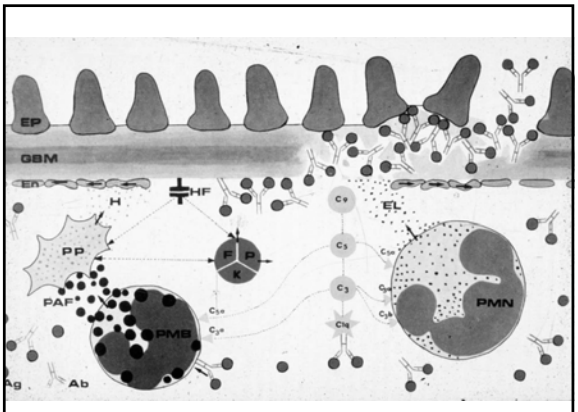
Vulnerability of Glomerulus to IC Injury

1. 20-25% Cardiac Output
2. High glomerular capillary pressure
3. Fenestrated endothelium
4. Concentration (sieving effect)

Mechanisms of Immunologic Injury to the Glomerulus

1. Glomerular deposition of circulating Ag-Ab complexes
2. Binding of Circulating Ab to structural glomerular Ag (i.e. anti-GBM Ab)
3. In situ immune complex formation





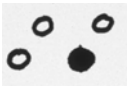
Glomerular Proliferation

1. Endocapillary

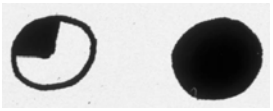
2. Extracapillary (crescentic)

Patterns of Glomerular Disease

1. Focal Vs Diffuse



2. Segmental Vs Global

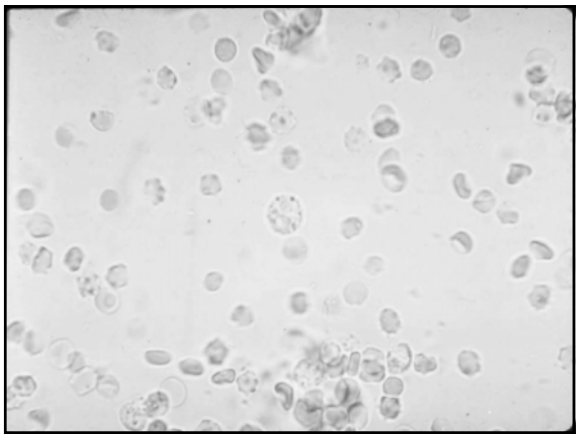


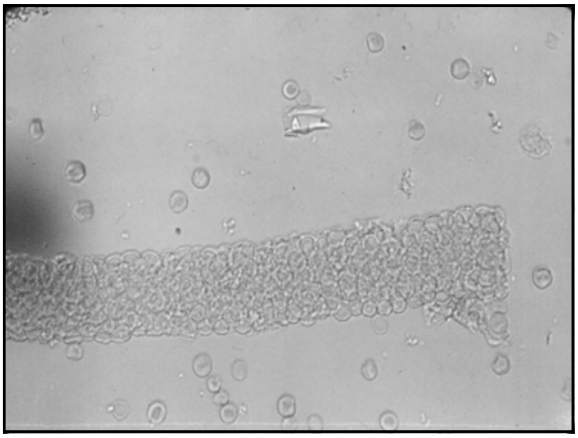
Signs of Glomerular Disease

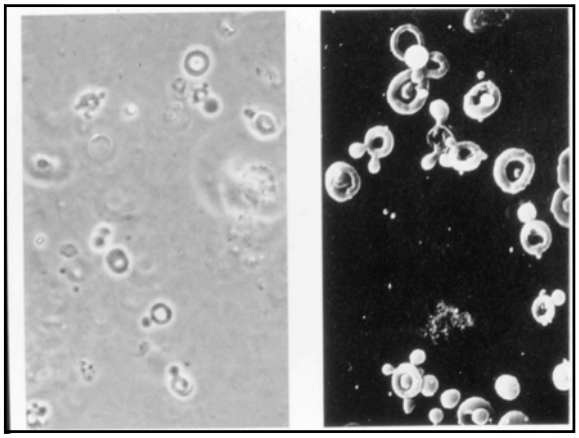
Erythrocyte Casts

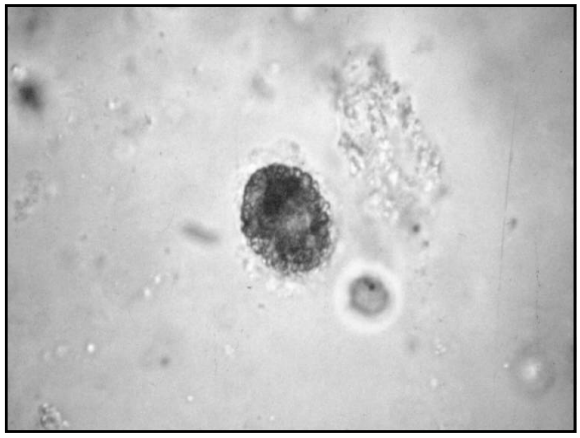
Deformed-Crenated Urinary RBC's

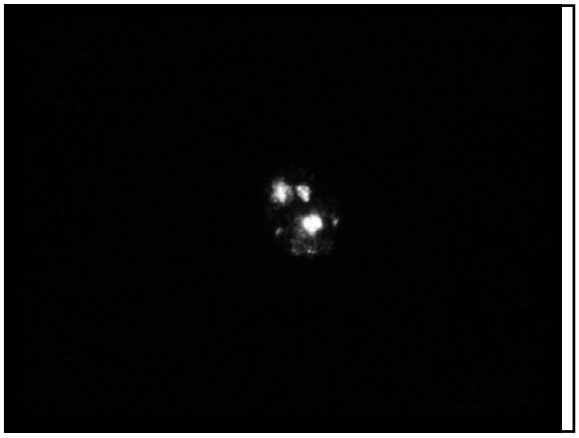
Large amounts Albuminuria (>3g/D)

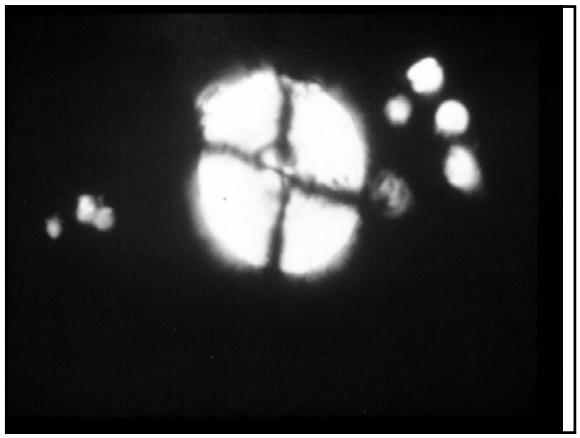






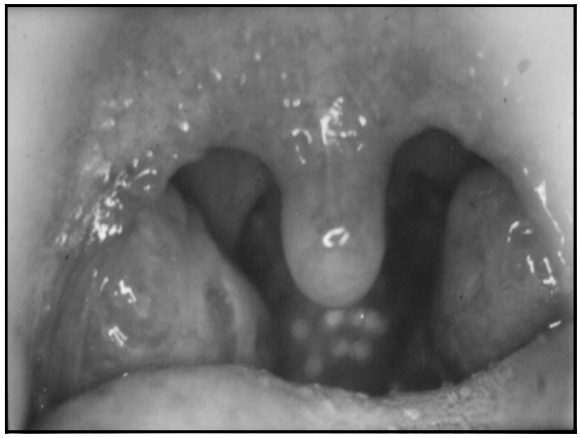


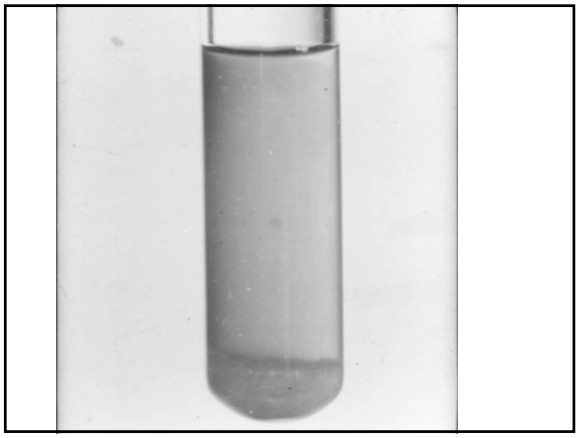


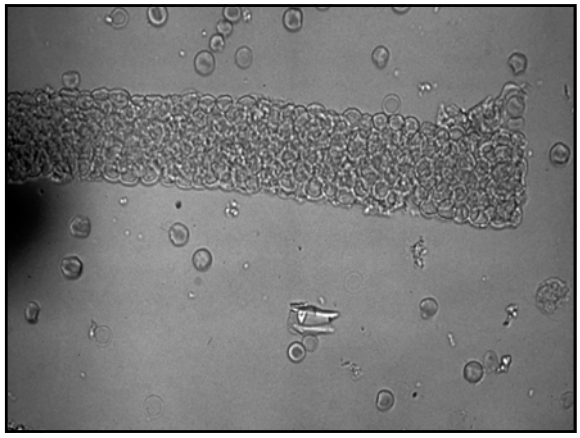


- 7 y o W M c/o x several days bad sore throat + low grade temperature; he is given acetaminophen, and recovers uneventfully. 2 wks later develops dark, coca-cola colored urine and notes urinating less. On Px pedal edema and an elevated blood pressure.

- Labs:
  - **U/A rbc's, rbc casts, 2+ prot.**
  - **Creatinine 2.4 mg/dl**
  - **Complement 22 (normal 50-150)**
  - **C3 level low**
  - **ASLO 1250 (normal < 250)**

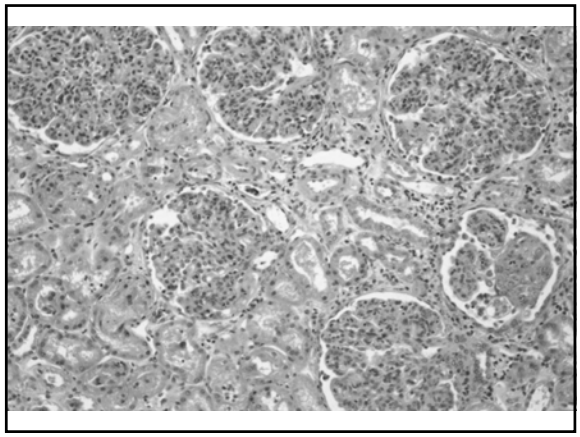


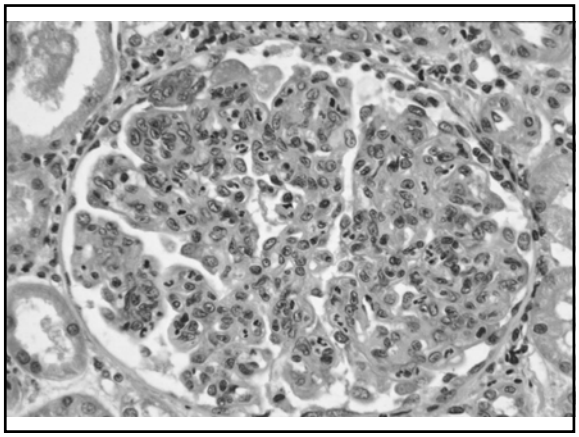


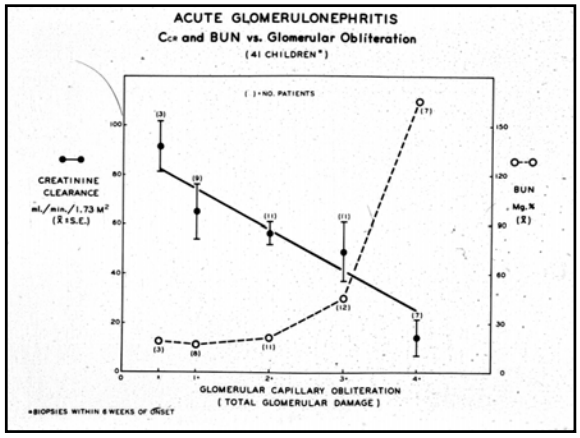


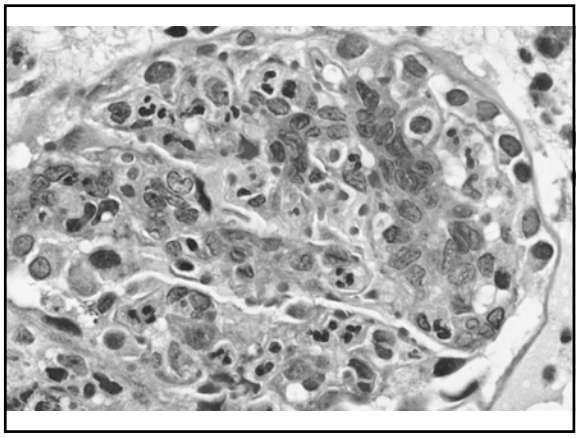
Nephritic Syndrome

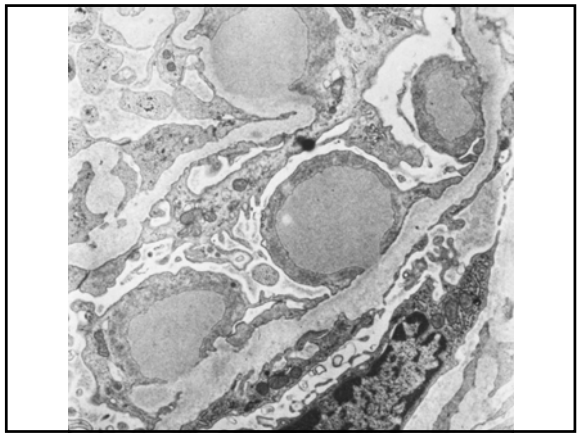
- **Decreased GFR**
- **Oliguria**
- **Edema**
- **Hypertension**
- **Active urinary sediment**

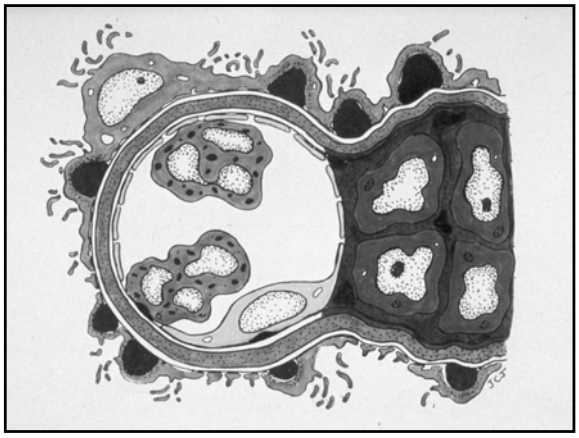


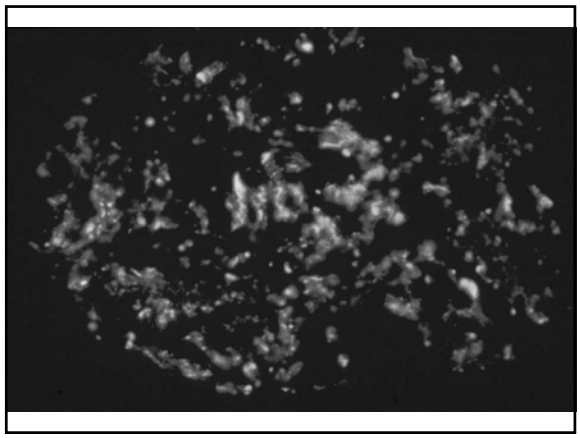


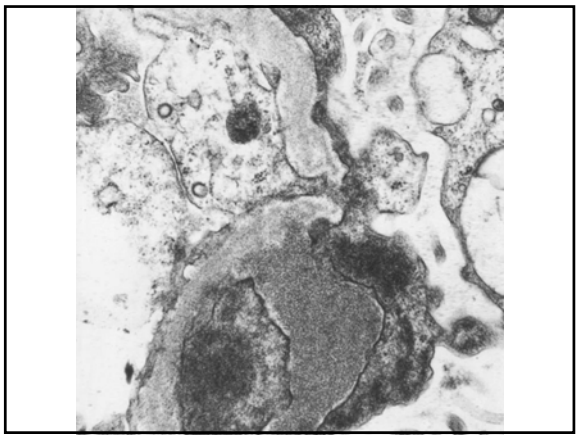


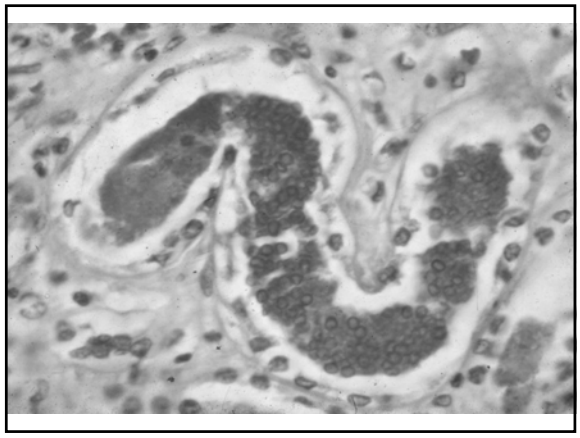


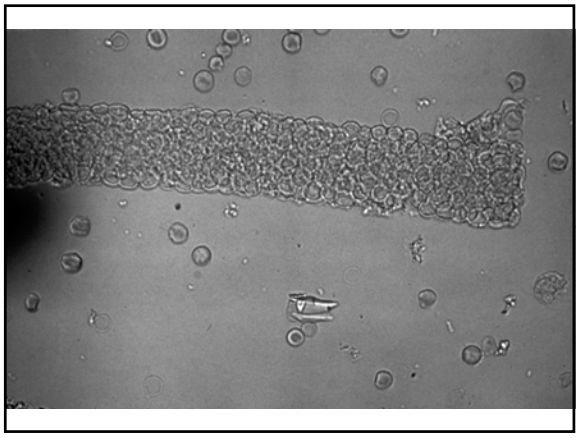


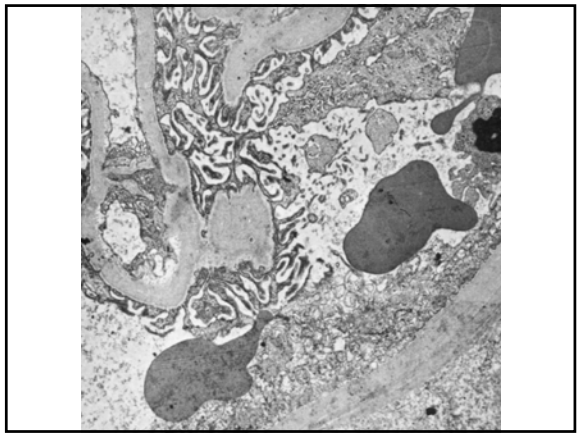


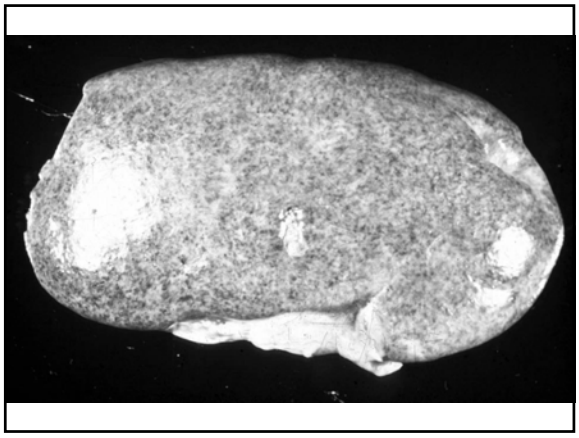


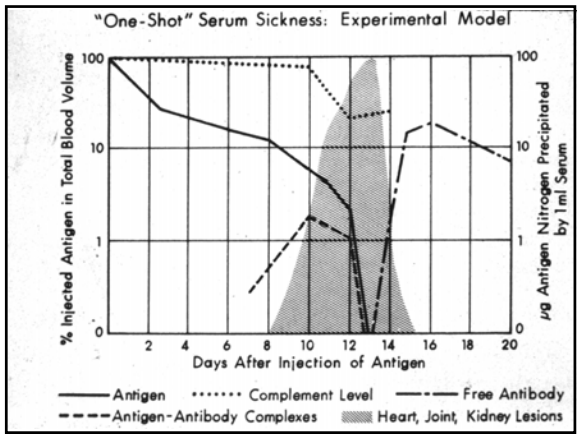


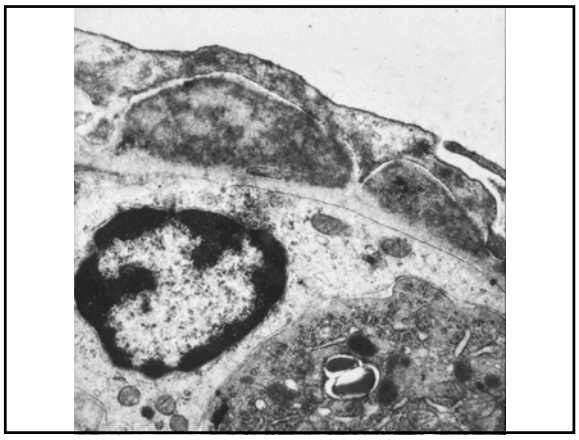


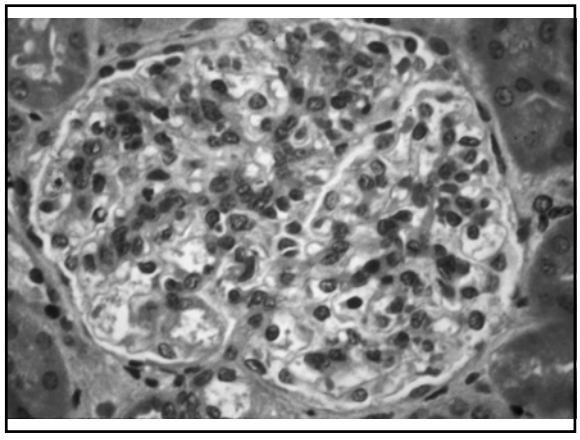


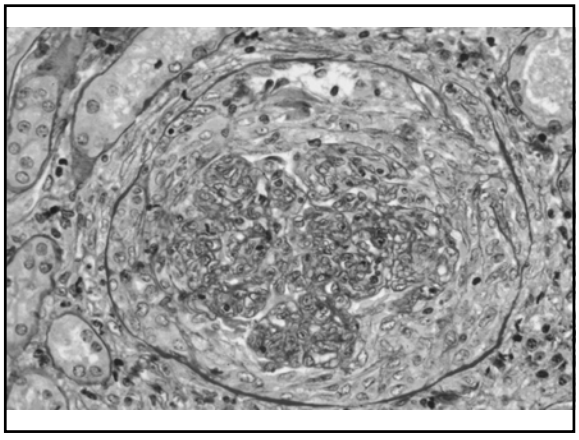


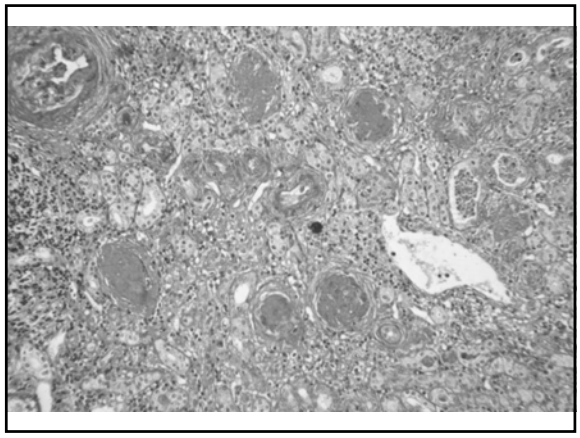


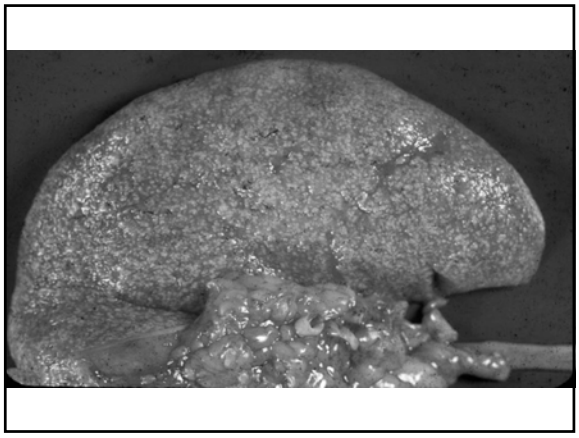

"One-Shot" Serum Sickness: Experimental Model
% Injected Antigen in Total Blood Volume
μg Antigen Nitrogen Precipitated by 1 ml Serum
100
10
1
0
2 4 6 8 10 12 14 16 18 20
Days After Injection of Antigen
Antigen
Complement Level
Free Antibody
Antigen-Antibody Complexes
Heart, Joint, Kidney Lesions

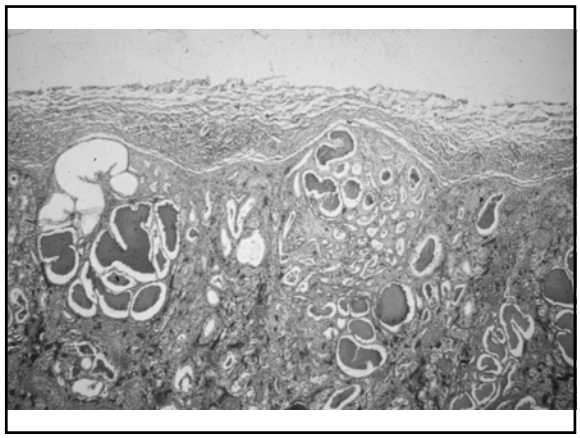


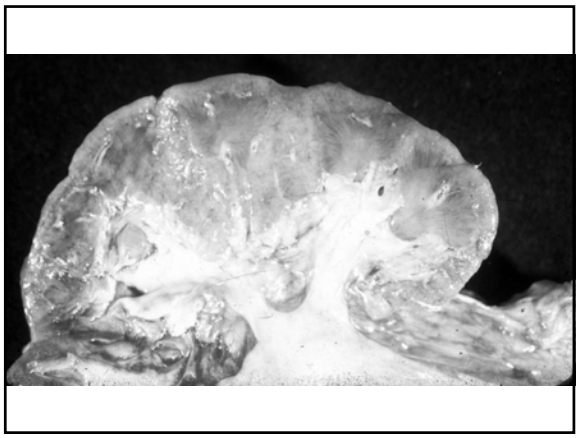


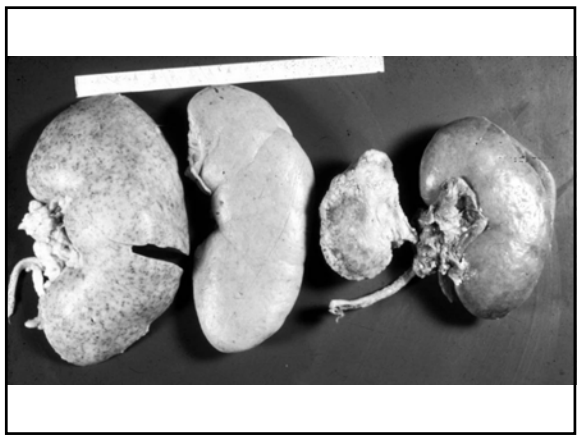


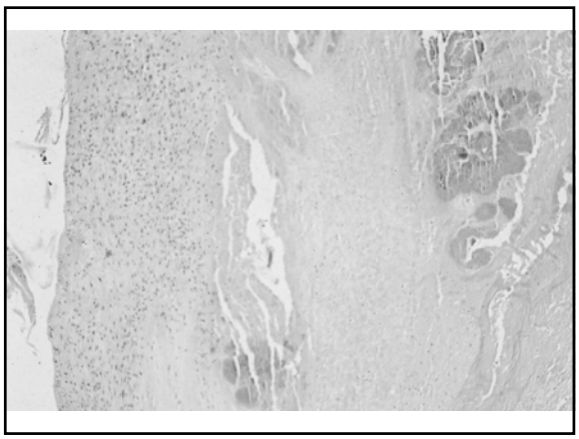


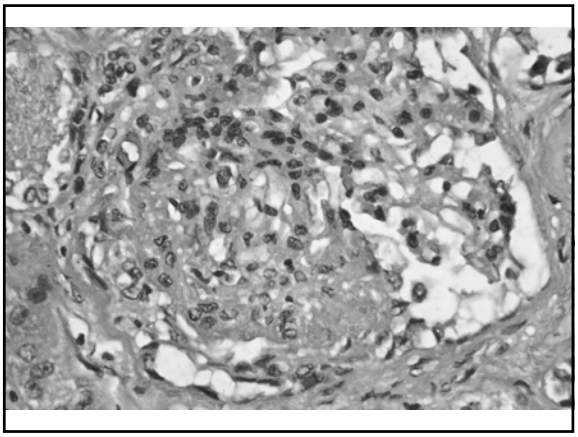












Post-Streptococcal GN

- **Follows certain serotype streptococcal infections – sore throats, impetigo, etc.**
- **Children more common than adults**
- **Time lag between infection & kidney disease**
- **Nephritic picture common**
- **Serologic tests for strept infections +**
- **Low complement and C3 levels**
- **Excellent prognosis children, +/- in adults**

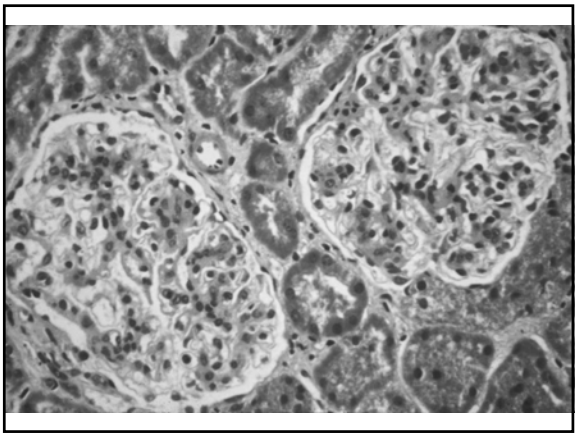
Serum Complement in GN

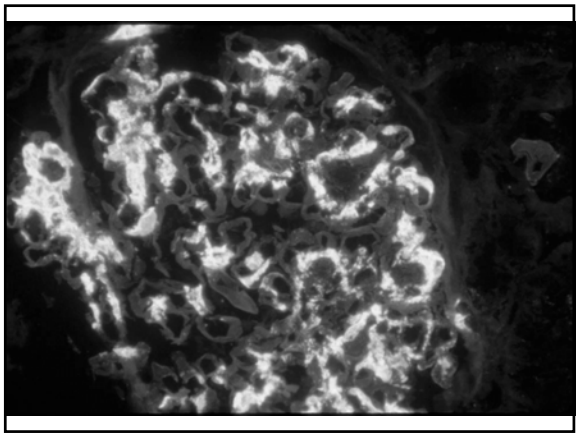
- **Low Levels**
  Post-infectious GN
  SLE
  Cryoglobulinemia
  Idiopathic MPGN

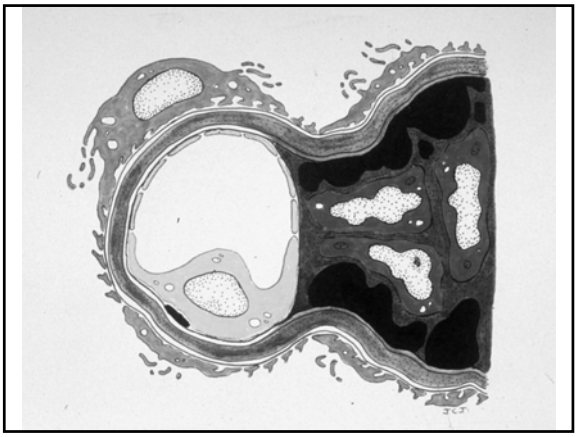
- **Normal Levels**
  MCD, FSGS, Memb Neph, Amyloidosis, IgA, DM, ANCA + RPGN, Goodpastre's, HSP, etc.

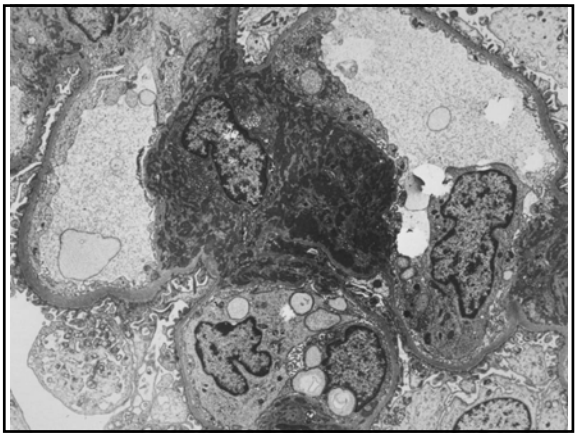
- **A 16 y o high school junior notices dark brown urine after playing basketball. Urinary sediment has rbc's and rbc casts**.

- Labs:
  - **Creatinine 1.1 mg/dl**
  - **Creatinine clearance 128 cc/min**
  - **660 mg proteinuria/day**
  - **Serologic tests are normal or negative**









Demographics of IgA Nephropathy

Ages	4 – 80 (mean 25) years
	(65% of patients in 2nd/3rd decade)
M/F = 2/1	
Rare in blacks	

Incidence	**(% primary glomerulopathies)**
5-10%	N. America
	U.K.
	Scandinavia
20-30%	Europe
	Australia
25-45%	Asia

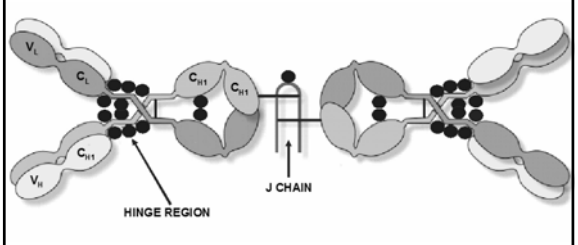
Classification

- Primary
  - IgA Nephropathy
  - Henoch-Schonlein Purpura
- Secondary
  - Liver Cirrhosis
  - Inflammatory Bowel Disease

Pathogenesis

1. Defective hepatic clearance
   - Liver cirrhosis
2. Increased IgA production
   - Association with elevated serum IgA
   - Onset may follow URI or Gastroenteritis
3. Defect of antigen exclusion at the mucosal surface
   - URI
   - Gastroenteritis
   - Celiac disease

Structure of Human Secretory IgA (sigA)



IgA Nephropathy

- **Most common idiopathic GN in world**
- **Defined by IgA deposition in mesangium**
- **Presents- Young – gross hematuria**
  Adults – Proteinuria + hematuria
- **Not benign hematuria (Berger's Dis)**
- **20-30 % progress ESRD over 20 years**
- **Rx – ACE inhib. + Stds, F.O., MMF**

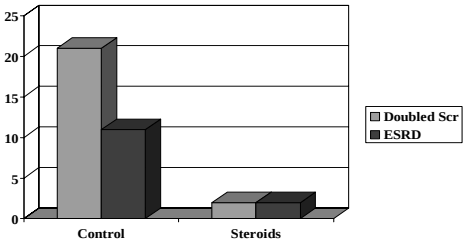
Corticosteroids in IgAN: a controlled trial

86 Pts Uprot 1-3.5g/D Pcreat < 1.5 mg/dl
Rx cyclic Pulse SM + QOD stds vs PBO x 6 mo.
Endpoint 50% rise in Pcreat. Follow 6 yrs

Endpoint 9/43 Rx vs. 14/43 PBO (p<.05)
High risk Pts : vascular sclerosis, males, no Steroid Rx
No major side effects

Pozzi et al. Lancet 353:883, 1999

IgA Nephropathy: A Controlled Trial of Steroids (Pozzi, et al)

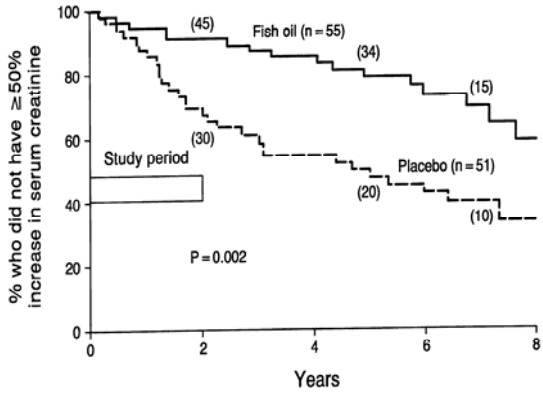


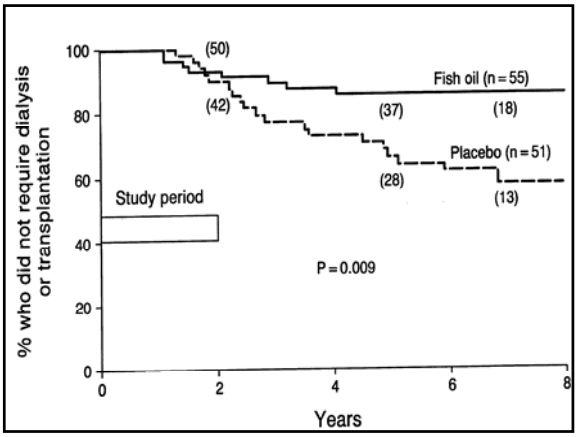
Controlled Trial of Fish Oils in IgAN

106 Pts 78M/28F age 36yo
Uprot > 1 g/D HBP 60%
Rx Max EPA 12g/D (58) vs Olive oil (51)
Rx 2yr follow 5 yr
Endpoint 50% increase Pcreat.

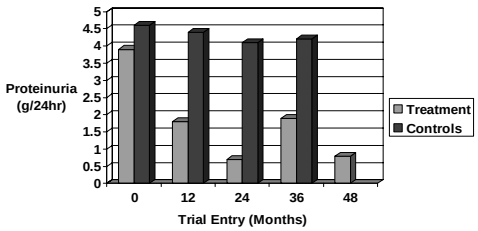
Endpoint	**6% Rx EPA**	**vs**	**33% PBO**
Change Pcreat	**.03 mg/dl**	**vs**	**.14 mg/dl**
DDT	**10%**	**vs**	**40%**

Donadio et al N Eng J Med 1994

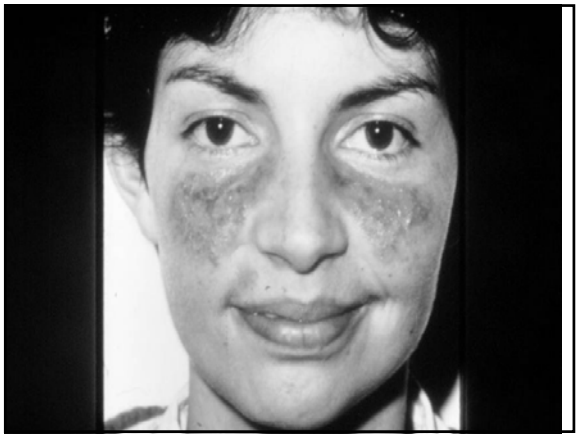




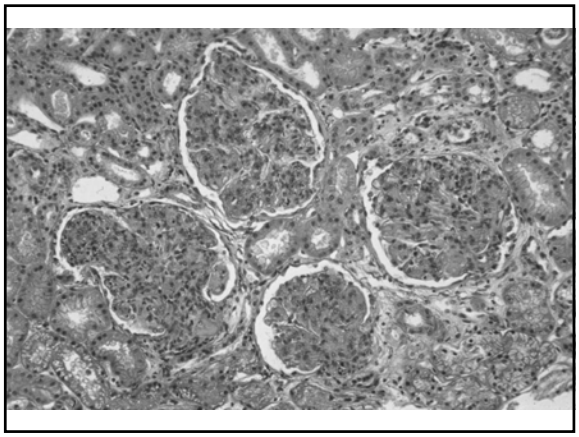
Immunosuppressive Rx for IgAN
Change in Proteinuria

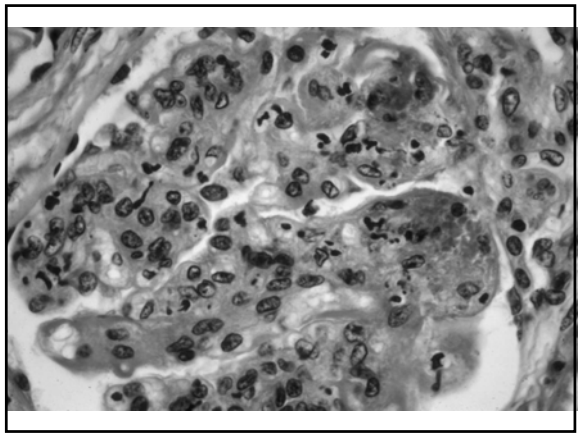


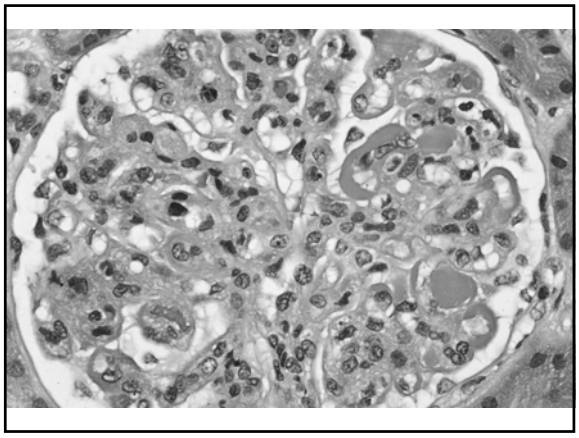
Ballardie, FW, Roberts, ID. J Am Soc Neph, 13:142-148, 2002.

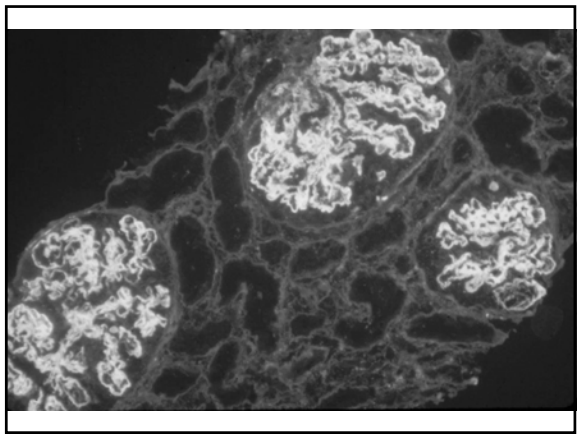


- **A 29 y o saleswoman develops arthritis of multiple joints, fever, lymphadenopathy, and a malar rash.**
- **Labs:**
  - **Urinalysis 3+ protein, crenated rbc's**
  - **Creatinine 1.2 mg/dl**
  - **24 hr. protein 1.8 g/dl**
  - **Complement 18% (normal 50-150%)**
  - **ANA positive, Anti-DNA antibody positive**

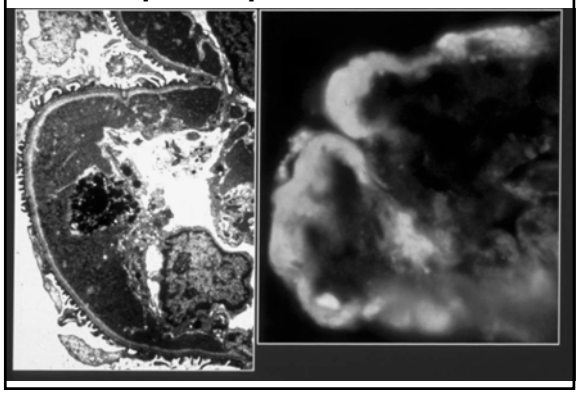


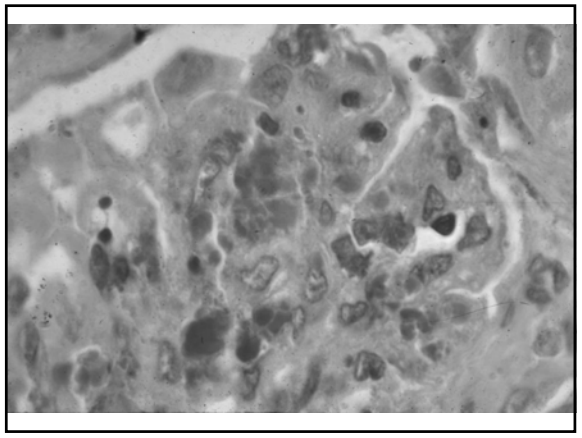


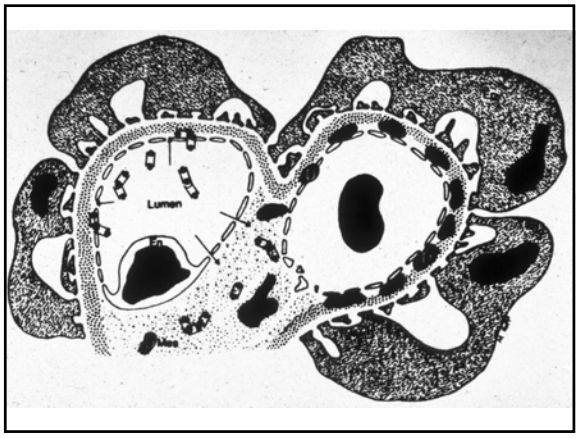




Lupus Nephritis Class IV





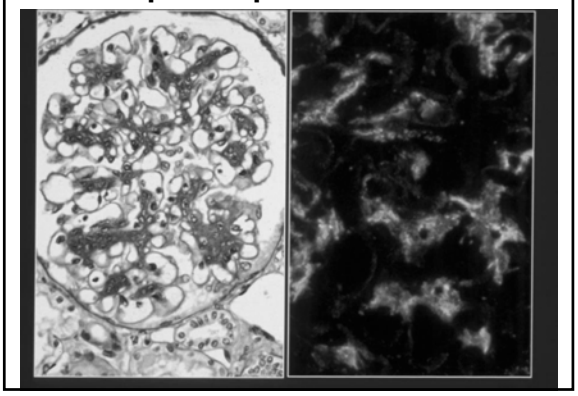


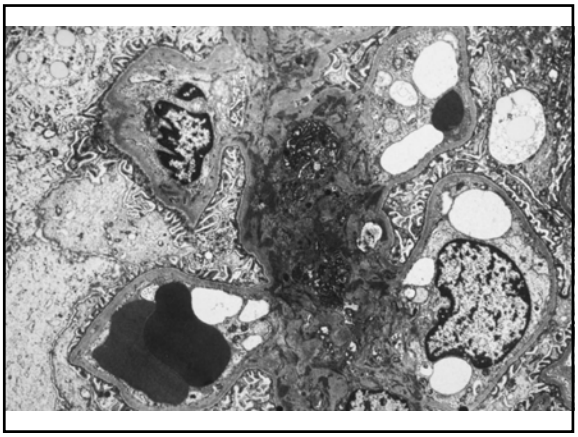
Lupus Nephritis <u>WHO Classification</u>

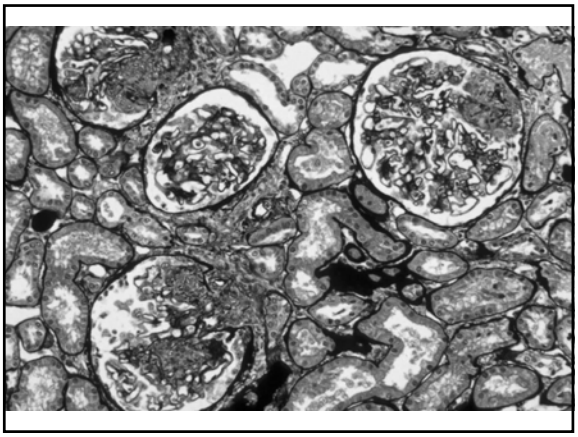
CLASSES

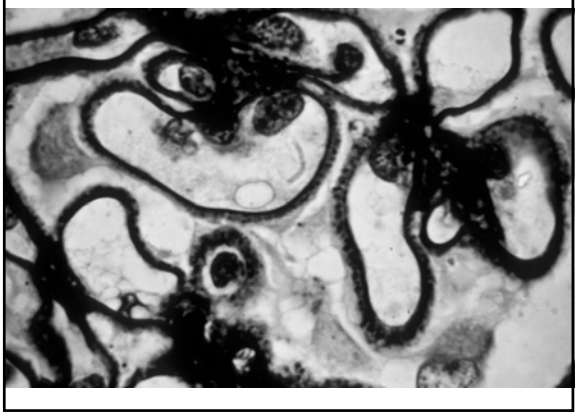
I Minimal mesangial
II Mesangial Proliferative
III Focal Segmental Proliferative
IV Diffuse Proliferative
V Membranous

Lupus Nephritis Class II









Treatment of Lupus Nephritis by Class

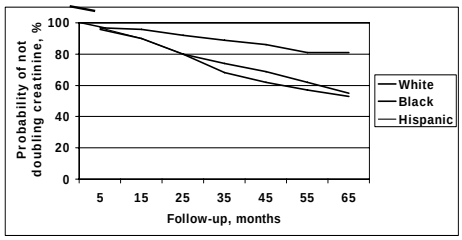
- Class I and II – Treat extra-renal findings
- Class III -FPLN – Vigorous Rx if necrotizing features, crescents, extensive proliferation.
- Class IV – DPLN – Vigorous Rx immunosuppressives
- Class V – Memb LN – Treat to induce remit proteinuria – Nephrotic syndrome

Predictors of Progression of Lupus Nephritis in Three Ethnic Groups

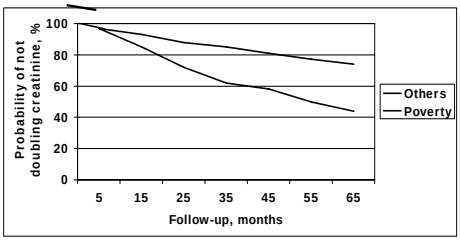
New York City Cohort:

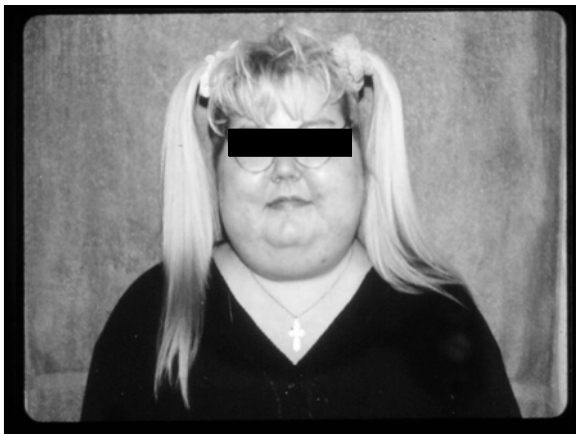
- 129 pts -51 H, 22 AA, 55 C Class III -IV LN
- Predictors (age-adjusted hazard ratio)
  - Hispanic ethnicity (3.7)
  - African – American race (3.1)
  - Living in neighborhood with high poverty (2.9)
  - Government insurance – Medicare (3.2)
  - Elevated creatinine (4.3)
  - Proteinuria (3.8)
  - Hypertension (3.2)
  - WHO Class IV (3.3) *Barr…Appel et al, 2003*

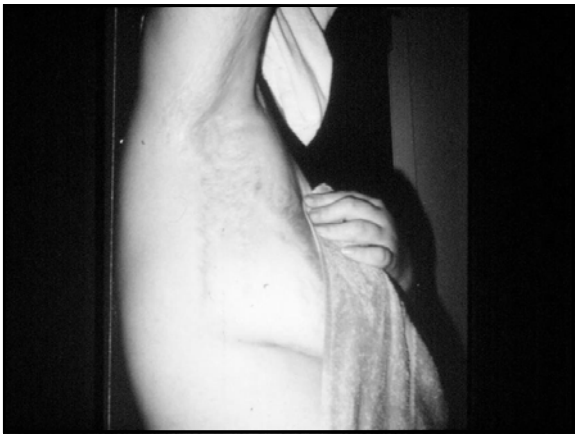
Impact of Race on Renal Prognosis – NYC n= 129



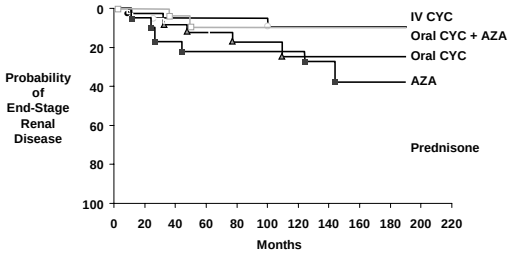
Impact of Poverty on Renal Prognosis- NYC



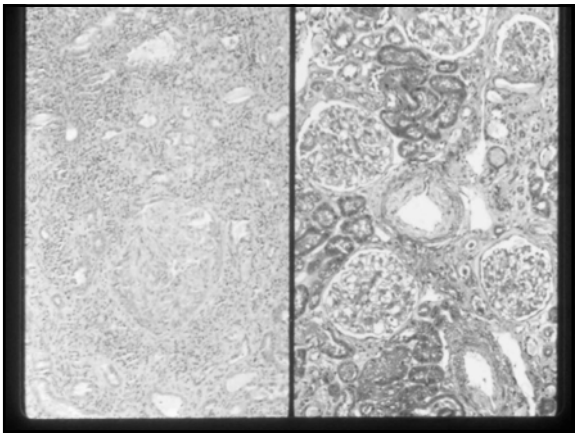


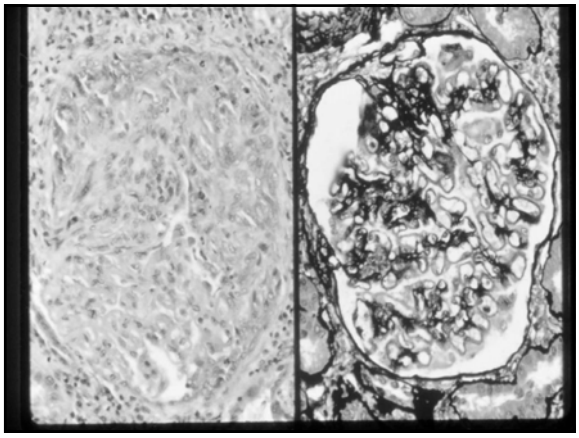


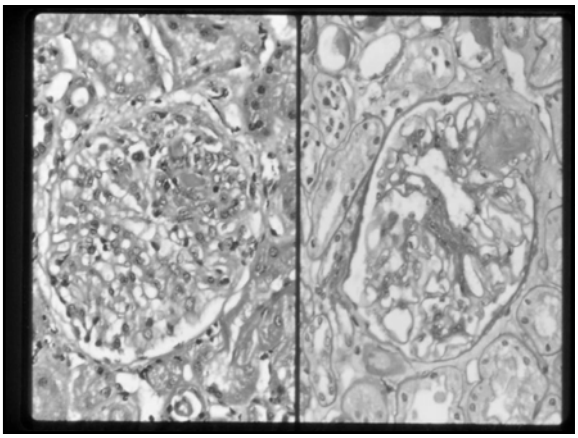
Probability of Developing End-Stage Renal Disease: Comparison Among Lupus Nephritis Treatment Regimens

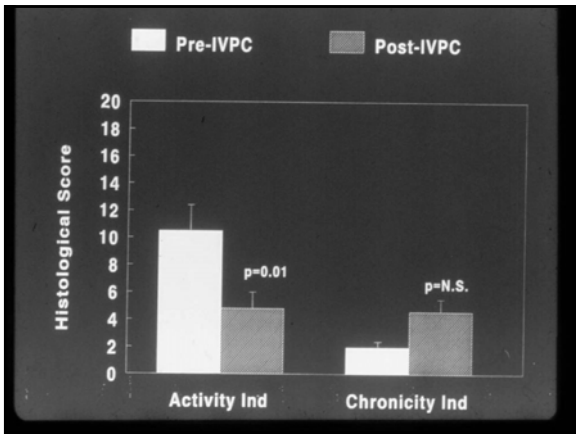


CYC = cyclophosphamide; AZA = azathioprine.
Steinberg AD, Steinberg SC. *Arthritis Rheum.* 1991;34:945-950.









Multicenter Trial of MMF vs IVCyc for Induction Therapy of Severe LN

- **Multicenter, randomized, nonblinded trial of induction RX for severe active LN**
- **Designed as equivalence trial**
  - **Calculated sample size: 64/ Rx arm**
- **Hypothesis: MMF has equivalent efficacy with superior toxicity/tolerability profile vs. IVC**

ACR Ginzler et al 2003, ASN Appel et al 2003

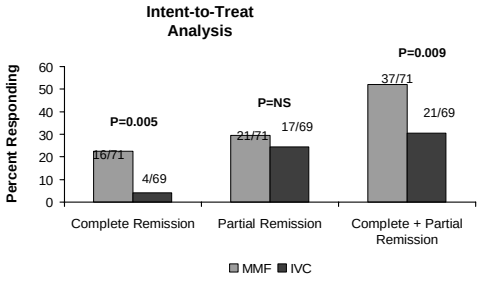
Baseline Patient Characteristics

	MMF (n=71)	IVC (n=69)
Age (yrs)	32.5 ± 10.0	31.0 ± 9.0
Female	61 (86%)	65 (94%)
Black	43 (61%)	36 (52%)
Duration of SLE, mo.	43.72 ± 66.88	58.70 ± 80.64
Screatinine, mg/dL	1.06 ± 0.52	1.08 ± 0.49
Urine protein, g/24 hr	4.06 ± 3.14	4.41 ± 3.51
Urine sediment		
RBC/hpf	24.1 ± 50.3	33.2 ± 115.5
WBC/hpf	12.6 ± 23.5	10.3 ± 17.3
Salbumin, g/L	2.81 ± 0.95	2.69 ± 0.56

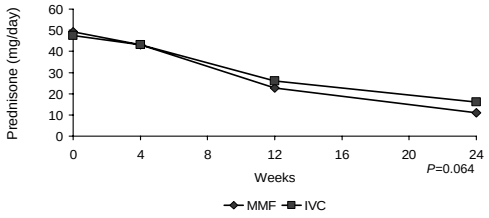
WHO Renal Biopsy Classification of Study Population

	MMF (n=71)	IVC (n=69)
Proliferative		
Class IV	**39**	**37**
Class III	**11**	**11**
Membranous (V)	**14**	**13**
Mixed	**7**	**8**

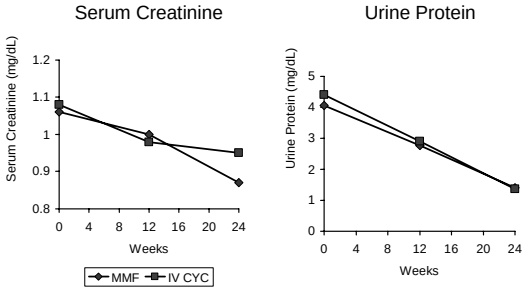
Remission Rates: MMF vs. IVC



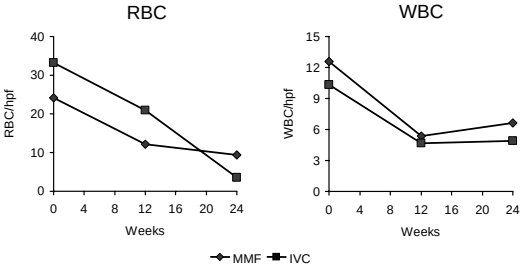
Change in Prednisone Dose



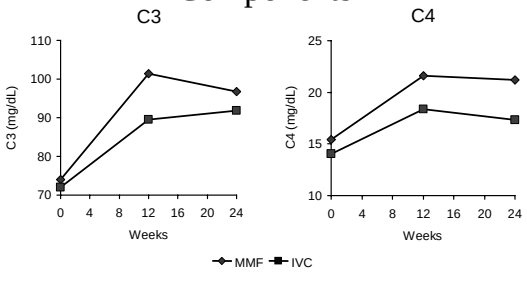
Change in Serum Creatinine and Urine Protein Excretion



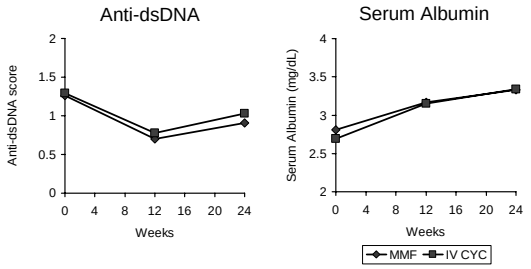
Change in Urine Sediment



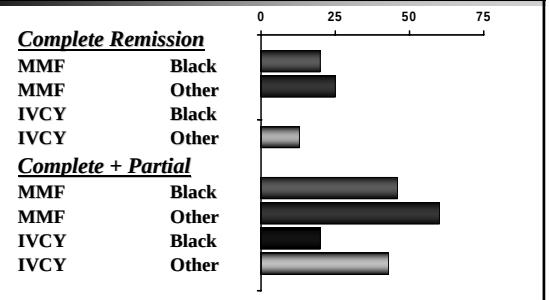
Change in Complement Components



Change in Anti-dsDNA and Serum Albumin

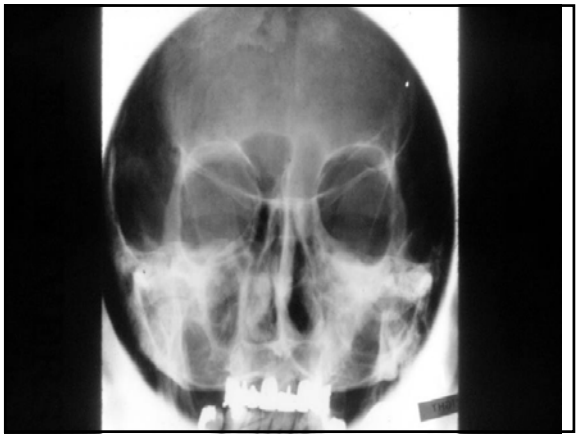


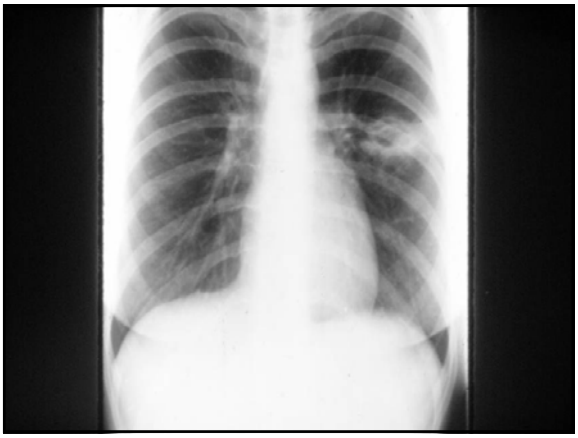
MMF *vs* IVCY Induction - *24 Wk Remission Rates: AA vs Others*

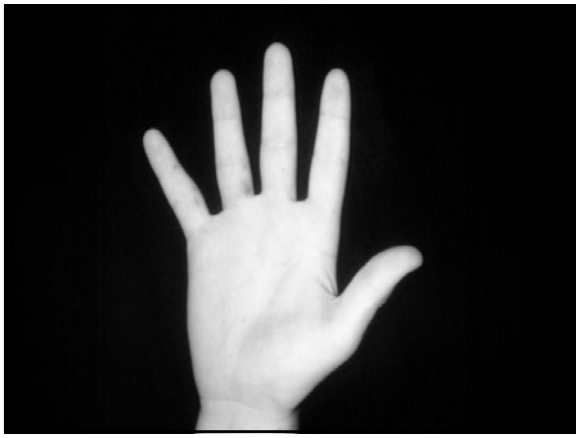


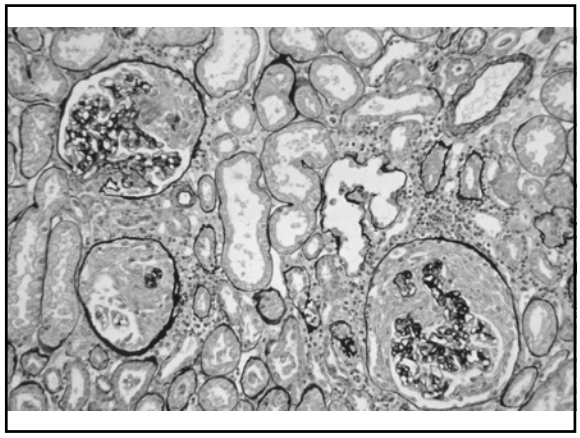
Appel et al, ASN 2003

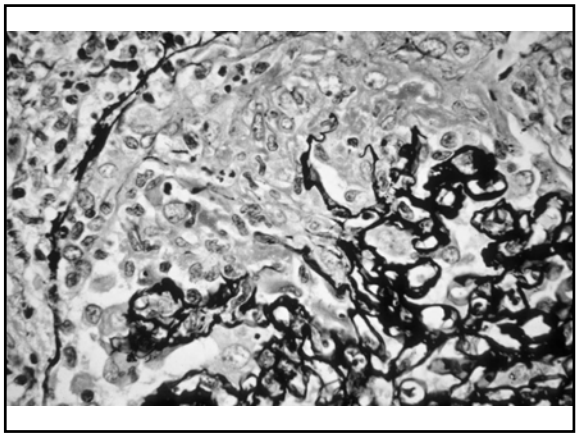
- A 58 y o insurance salesman develops sinusitis, weight loss, malaise and a dry cough over three weeks. His sinus films show opacification of the left maxillary sinus, and he is found to have a cavitary lesion on his chest X-ray.
- Labs:
  - **Urinalysis: rbc's, wbc's, and rbc casts**
  - **Creatinine 2.7 mg/dl**
  - **Serum complement is normal**
  - **Anti-GBM antibodies are absent**
  - **ANCA is positive**

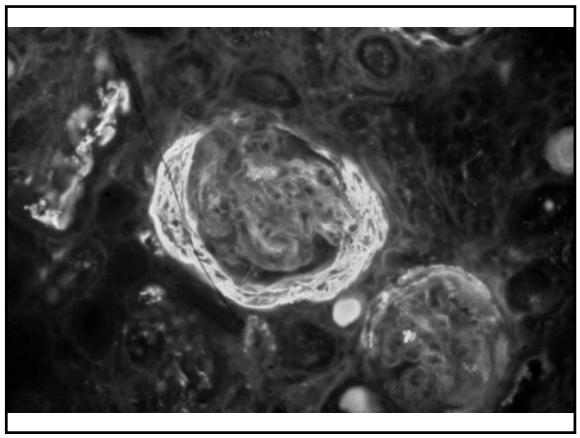


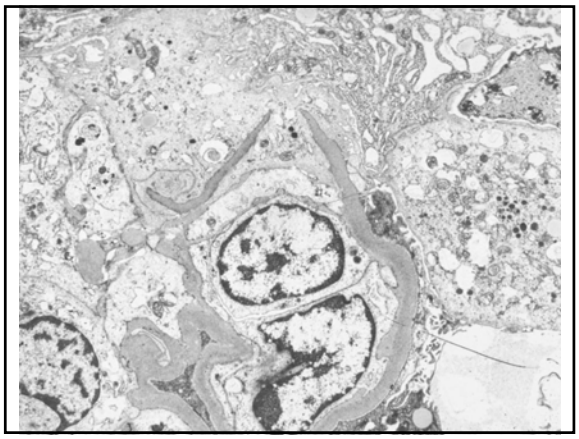


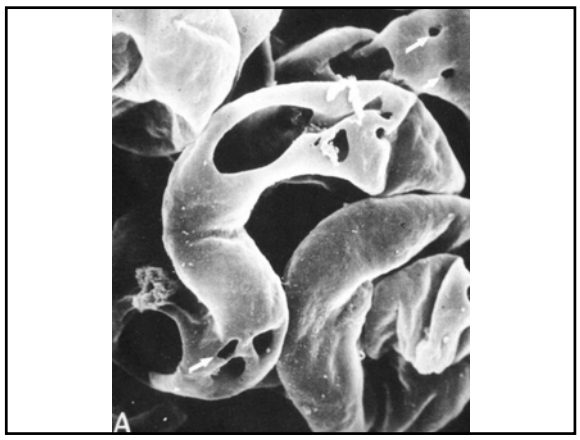


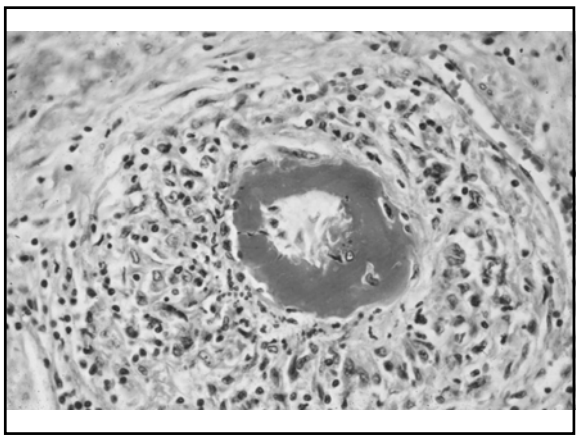


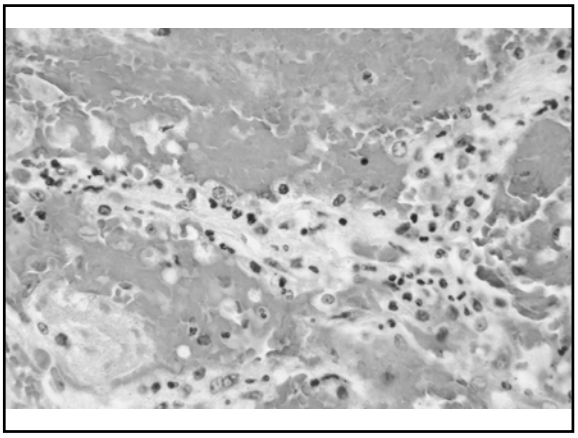


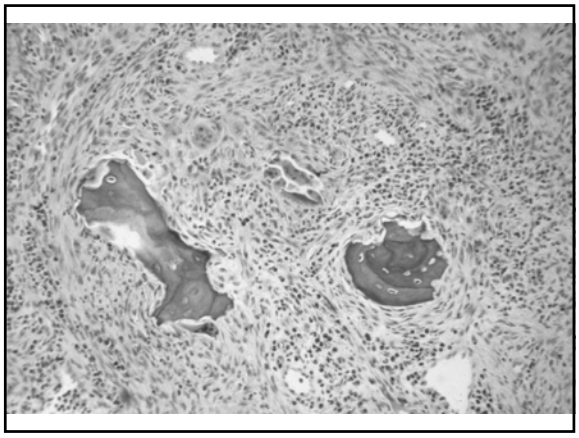


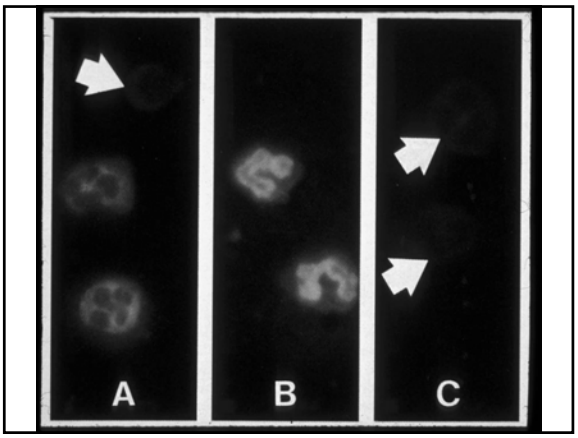


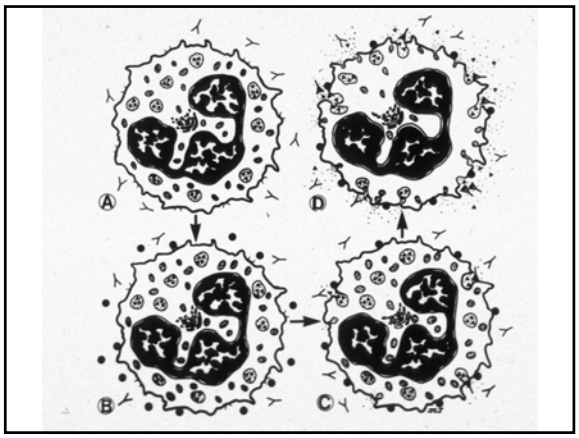

A







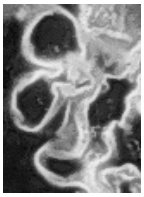
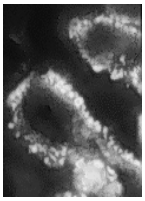
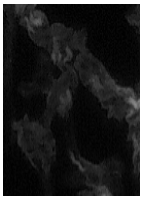




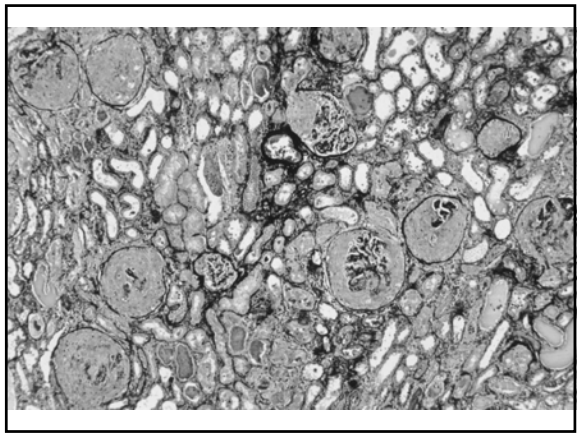
Pulmonary-Renal Vasculitic Syndrome

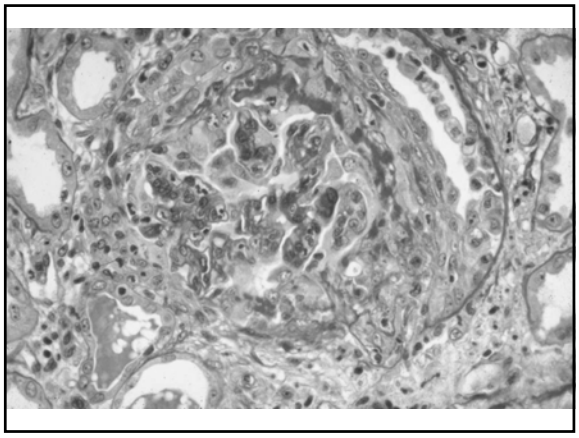
- Pauci-immune (usually ANCA-associated)
  - Wegener's granulomatosis
  - Microscopic Polyangiitis
- Immune Complex Deposits (granular)
  - SLE
  - Cryoglobulinemic vasculitis
- Anti-Glomerular Basement Membrane Antibody Deposits (linear)
  - Goodpasture's Syndrome

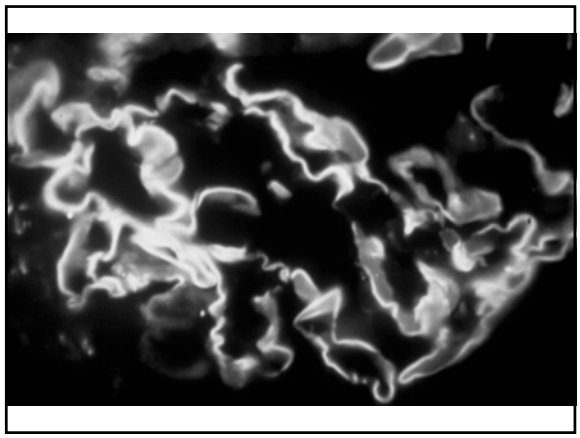
ANTIBODY MEDIATED GLOMERULONEPHRITIS

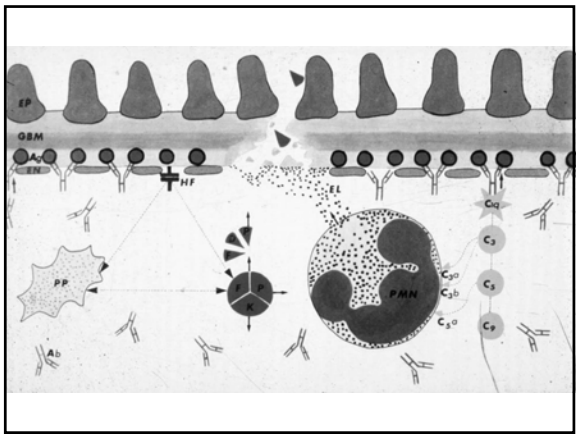
Circulating anti-GBM antibodies with linear glomerular IF staining	Glomerular immune complex localization with granular IF staining	Circulating ANCA with paucity of glomerular IF immunoglobulin staining
		

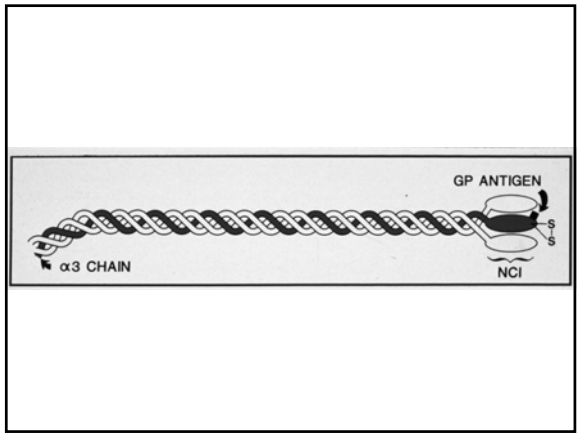
>80% ANCA+

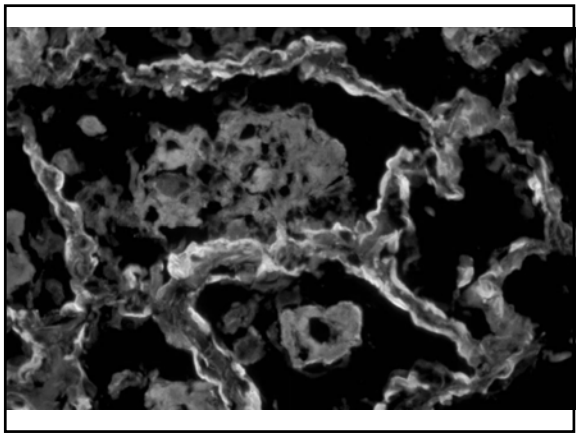


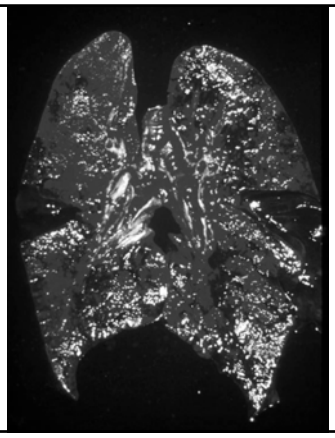


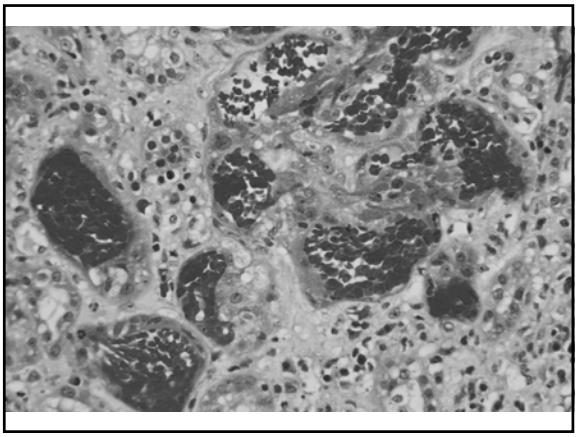



EP
GBM
EN
HF
EL
PP
PMN
Ab


GP ANTIGEN
S
S
α3 CHAIN
NCI







Rapidly Progressive Glomerulonephritis

A severe form of GN leading to RF in days to months

RPGN = Crescentic GN

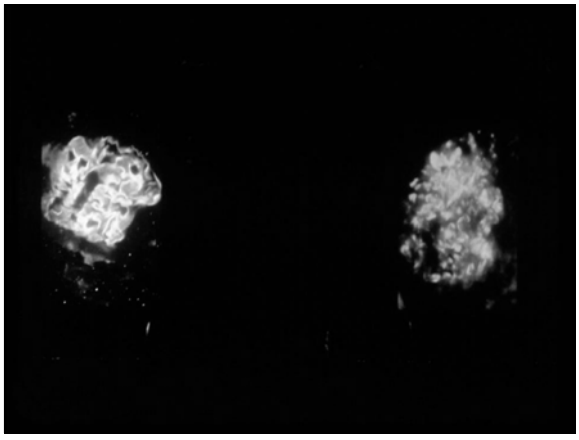
Secondary RPGN (SLE, HSP, Post-infectious, etc.)

Primary RPGN
- **anti-GBM disease**
- **immune complex GN**
- **pauci-immune GN**

Rx and Course depend on etiology and stage

Treatment of RPGN

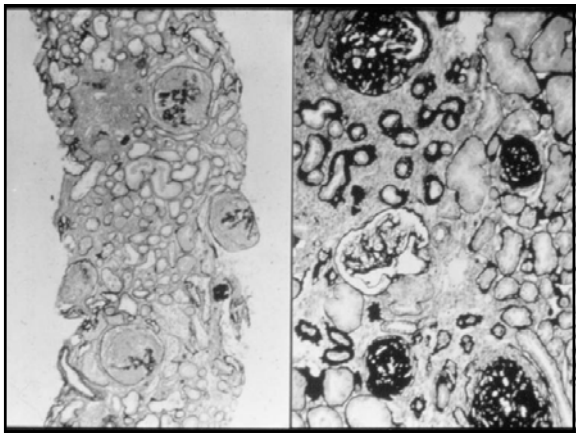
- **Anti-GBM disease – Steroids , cytotoxics, and plasmapheresis**
- **Immune Complex GN – Treat underlying disease**
- **Pauci-immune RPGN (ANCA +) – Cytotoxics (Iv or P.O.)**



Anti-Neutrophil Cytoplasmic Antibodies

- **C-ANCA cytoplasmic against serine proteinase 3 (PR3)**
- **P-ANCA perinuclear against myeloperoxidase (MPO)**
- **P-ANCA is an artifact of alcohol fixation**

ANCA is to RPGN as Anti-DNA is to SLE



Renal Pulmonary Syndromes

• **Goodpasture's Synd.**	**Anti GBM Abs**
• **SLE lung dis. + LN**	**aDNA + CH50**
• **RPGN, Weg.G., PAN**	**ANCA**
•	
• **Pulmonary emboli**	**RVT (memb NS)**
• **Pneumonia**	**Immune complex GN**
• **Uremic Lung**	**CHF + Renal failure**