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Rapidly progressive glomerulonephritis

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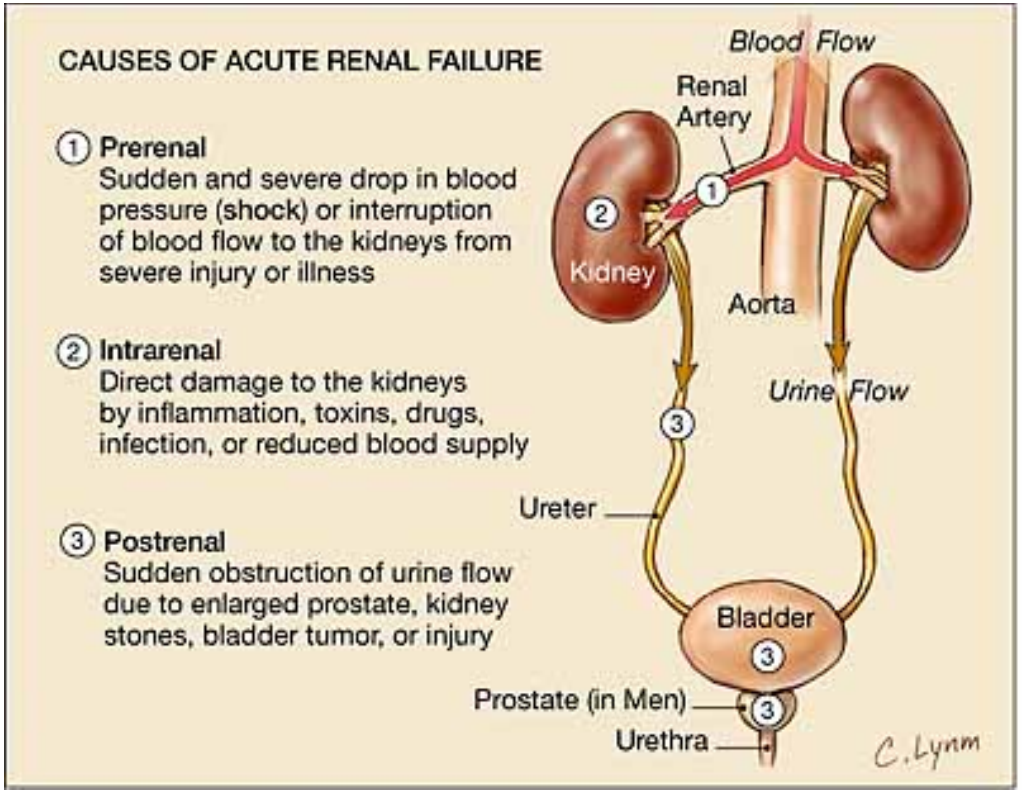
Remember this….

- AKI ≠ Acute tubular injury
- Not all AKI is caused by sepsis or volume depletion
- AKI is caused by an underlying process that must be diagnosed

All kidney disease can be classified according to this scheme



50% Pre-renal

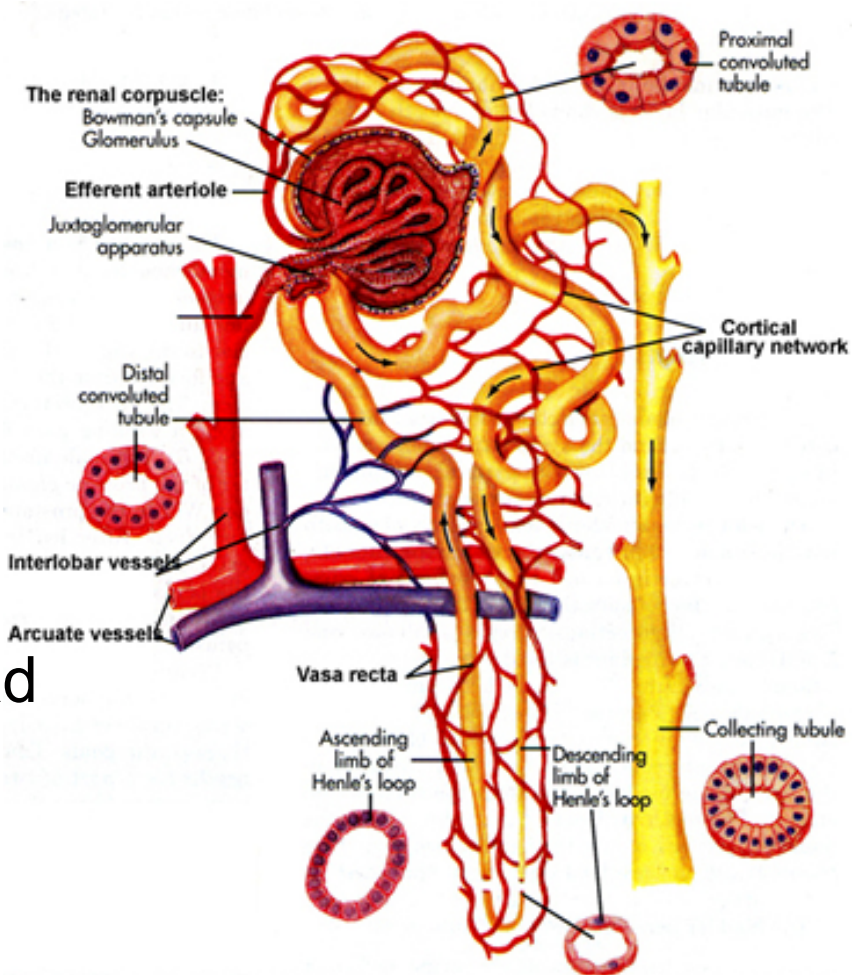
35% Intrinsic

15% Post-renal

Acute kidney injury means a sudden drop in GFR

Parenchymal or intrinsic causes

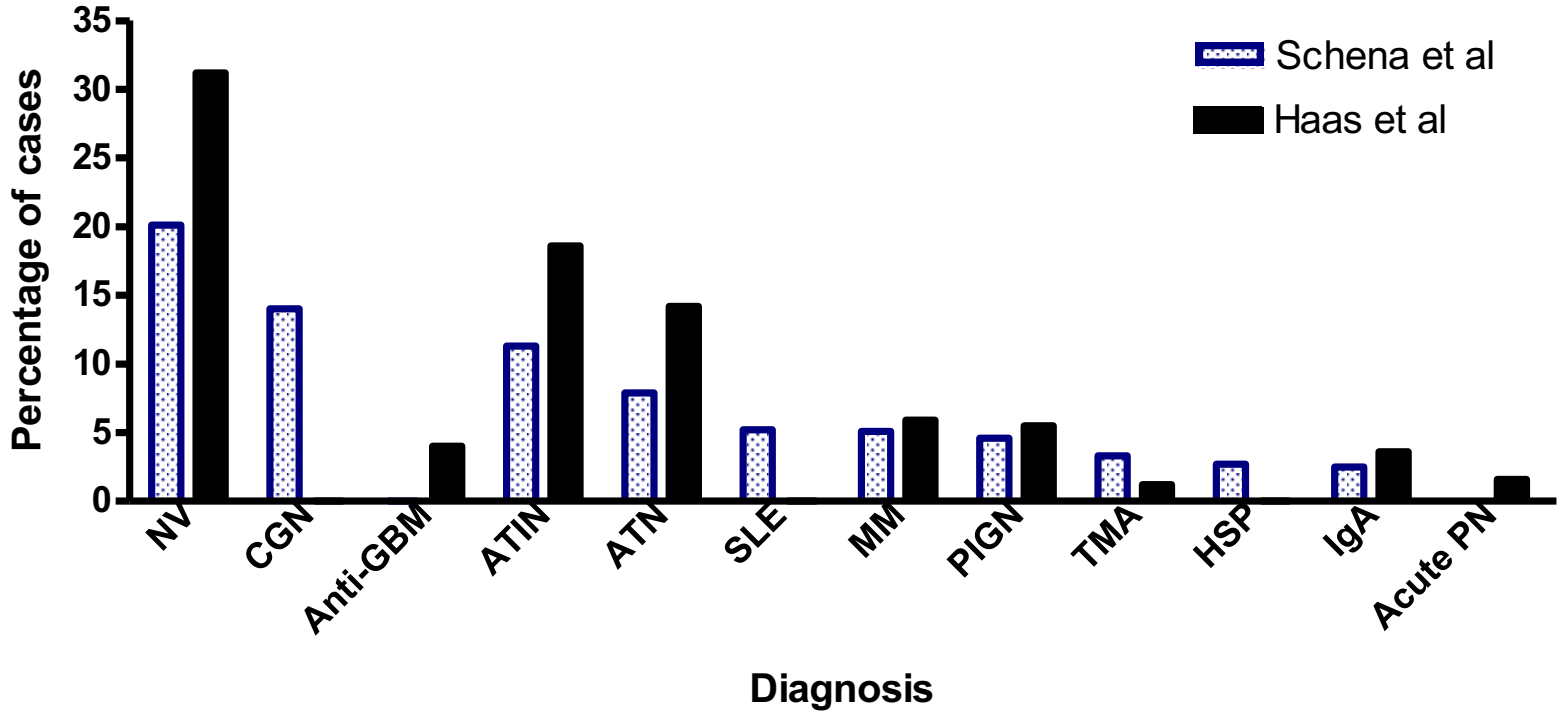
3 Major kidney compartments :
Glomeruli
Tubules
Blood vessels



Damage to any of these can lead to a rapid decline in kidney function and AKI
They can co-exist
Eg MCD and ATI

Biopsy diagnoses in AKI

Patients without obvious clinical cause of ATN
Haas n=259; pts >60 years
Schena n=1273; all adult pts



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Case

- 79 year old woman
- IHD and dilated cardiomyopathy
- Poor LV function (EF 20%)
- ICD for ventricular tachyarrhythmia

- Admitted under medical team with breathlessness and hypotension
- Treated for pulmonary oedema
- Negative cardiac investigations including normal troponin and no evidence of arrhythmias
- Creatinine 97 Hb 14.8 CRP 32

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Case

Macroscopic haematuria

MSU: E.coli (fully sensitive)

Treated with trimethoprim

Cr 131 CRP 42 Hb 13.6

Discharged home

Readmitted 5 days later

Unwell, breathless ?sepsis

Cr 425 Hb 11.5 CRP 92

Antibiotics- ertapenim, diuretics

- What do you as medical registrar/consultant do next?
- What is likely diagnosis?

- What do you as medical registrar/consultant do next?
- What is likely diagnosis?
- Would you biopsy her?

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Case

- Referred to renal team
- Cr 519 Ur 36 Alb 31 Ca 1.8 PO4 2.0 CRP 131
- Hb 10.1 WCC 13.8
- anuric
- Started intermittent dialysis
- Acute screen sent
- ? Sepsis/ATN

Case

HCV, HbSAg, HIV all negative

ANCA negative, C3/C4 normal

Proceeded to biopsy:

7 glomeruli, all with crescents, mild interstitial infiltrate

Linear IgG deposition

No chronic damage

Case

HCV, HbSAg, HIV all negative

ANCA negative, C3/C4 normal

Proceeded to biopsy:

7 glomeruli, all with crescents, mild interstitial infiltrate

Linear IgG deposition

No chronic damage

Anti-GBM Ab >900 IU/ml

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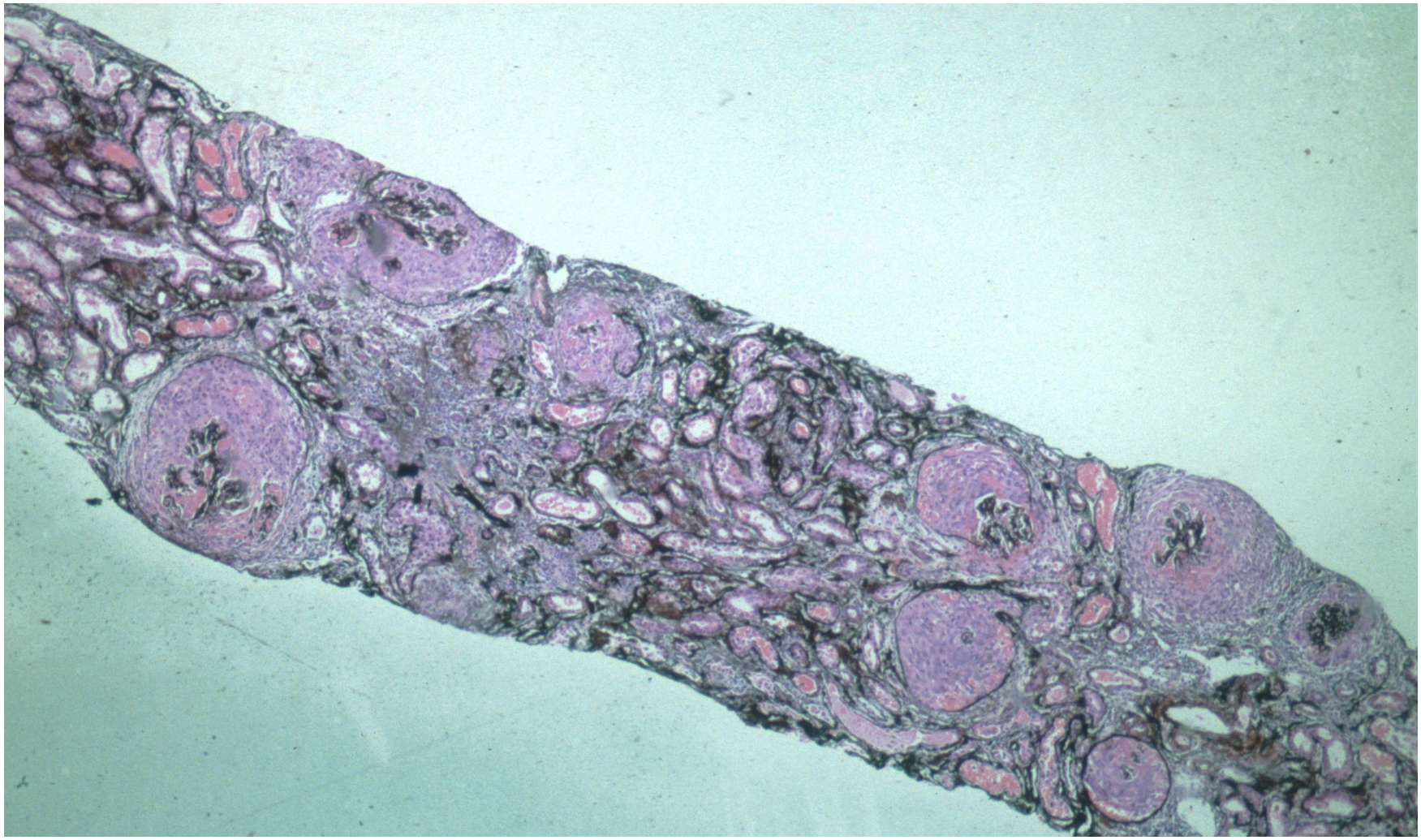
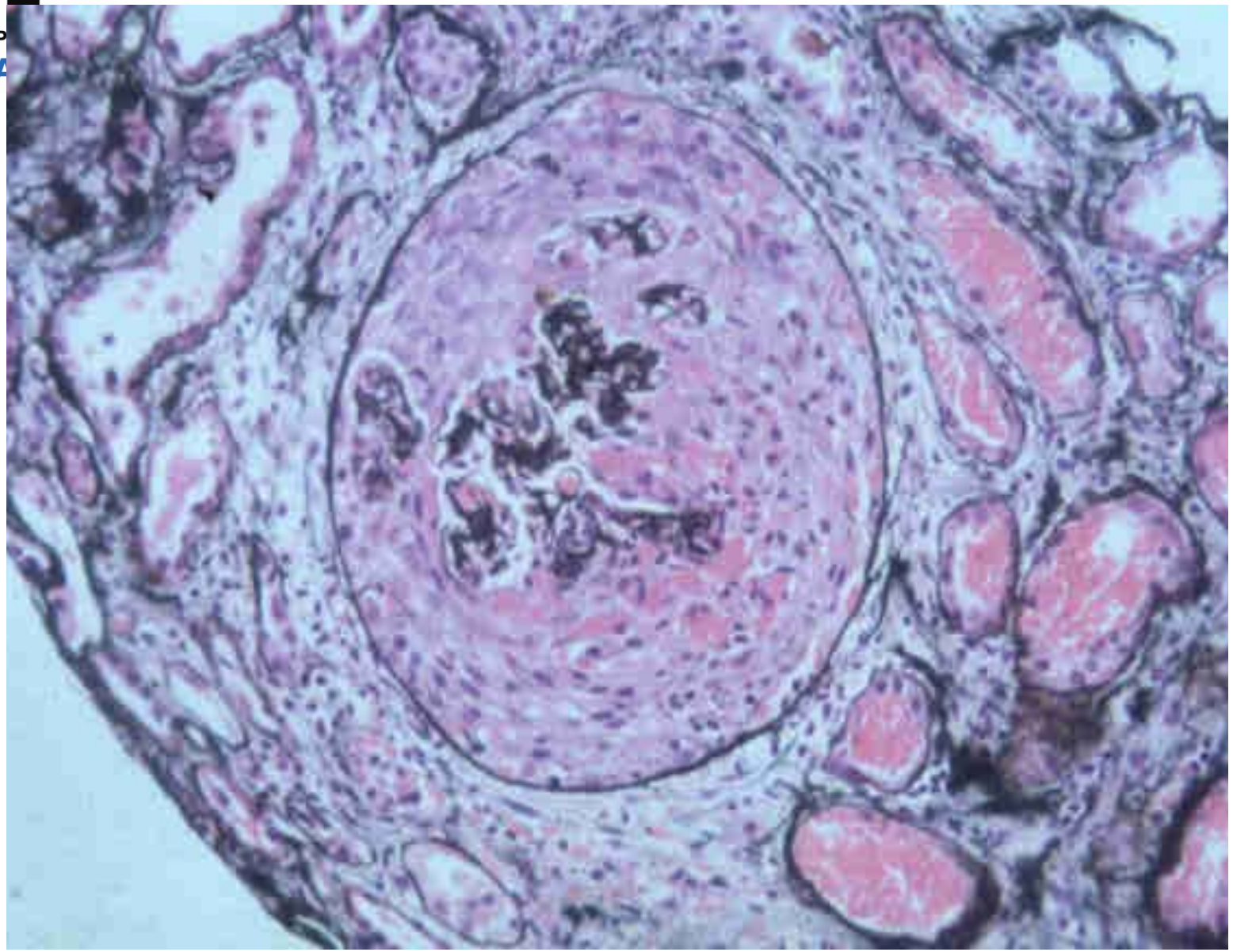
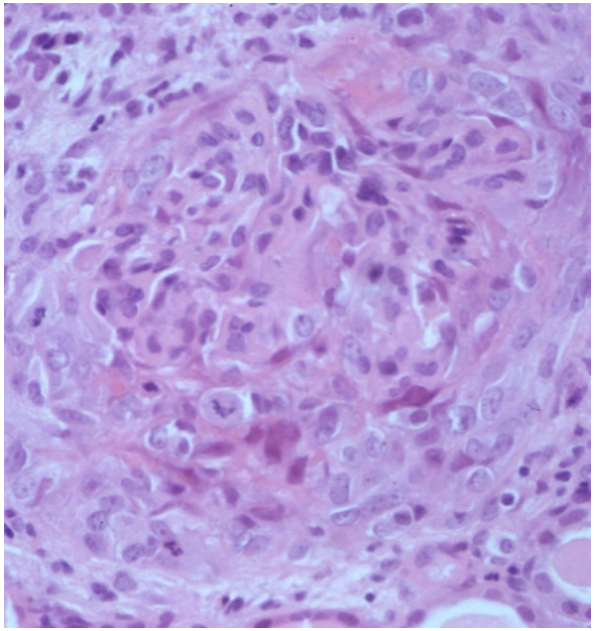
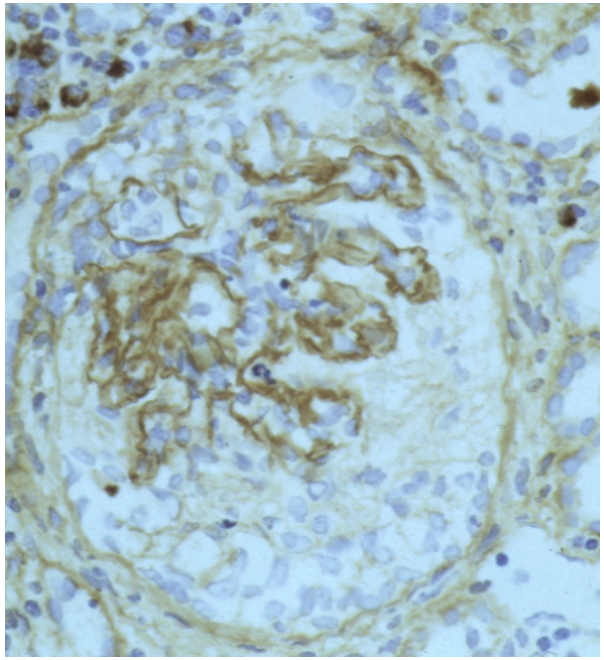




H and E



IgG



Diagnosis: Crescentic glomerulonephritis due to Anti-GBM disease

Following discussion with patient and family-
Plasmapheresis and Pred/CYC

Stopped after 4 weeks when no renal recovery found

Rapidly Progressive Glomerulonephritis

- Clinical definition of rapid deterioration in renal function (doubling of SCr or halving of GFR within 3 months), due to crescentic glomerulonephritis
- Crescentic glomerulonephritis – may be used for glomerulonephritis with any crescents but WHO suggests >50%

- Critical to make this diagnosis as time = nephrons!
- Think of it if renal function deteriorating and no obvious reason for ATN

Crescentic glomerulonephritis

- Crescents are an indication of severity of glomerulonephritis rather than its cause
- Complete pathological diagnosis requires analysis of immunofluorescence, electron microscopy and serology

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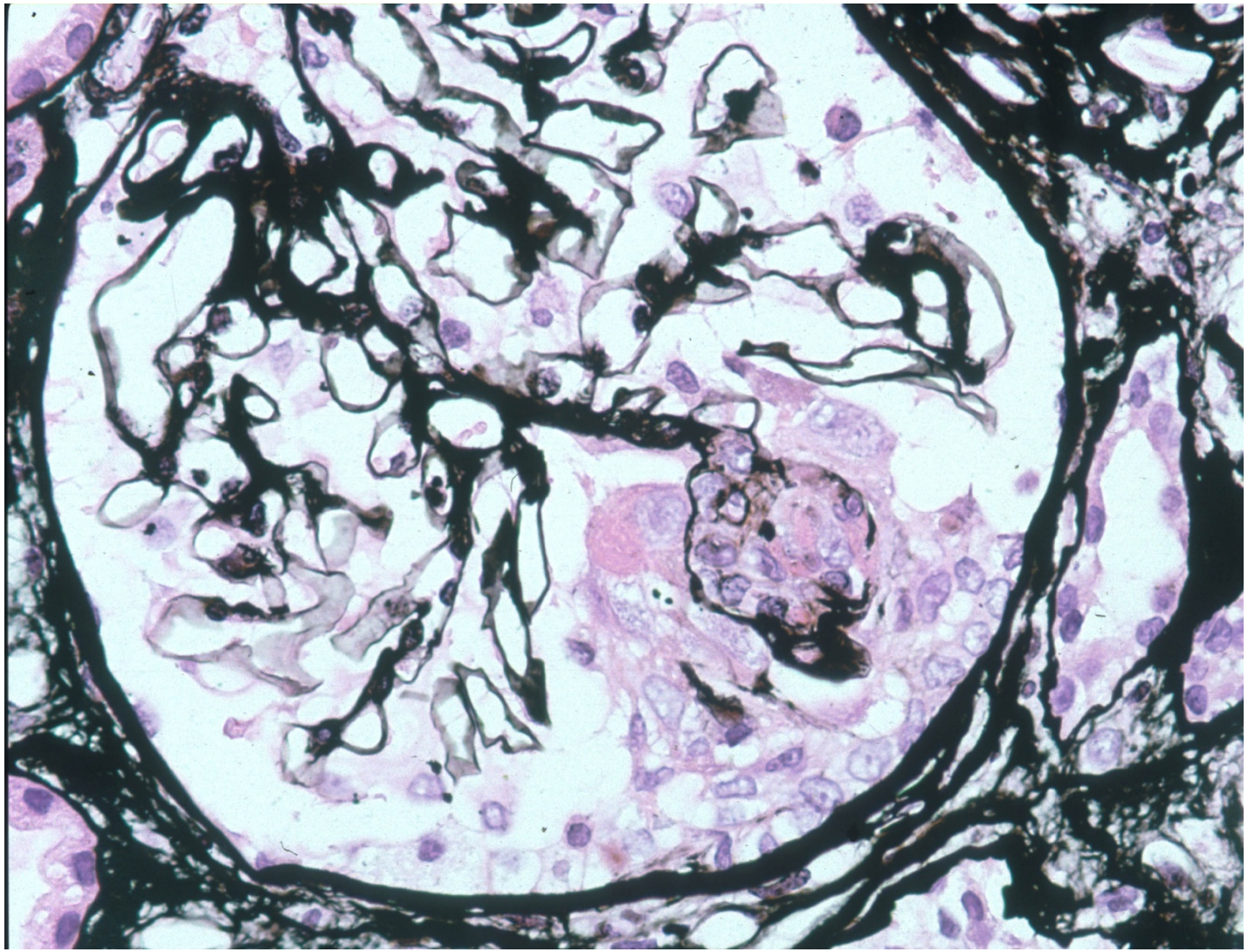
Early crescent



"Holes" in basement membrane

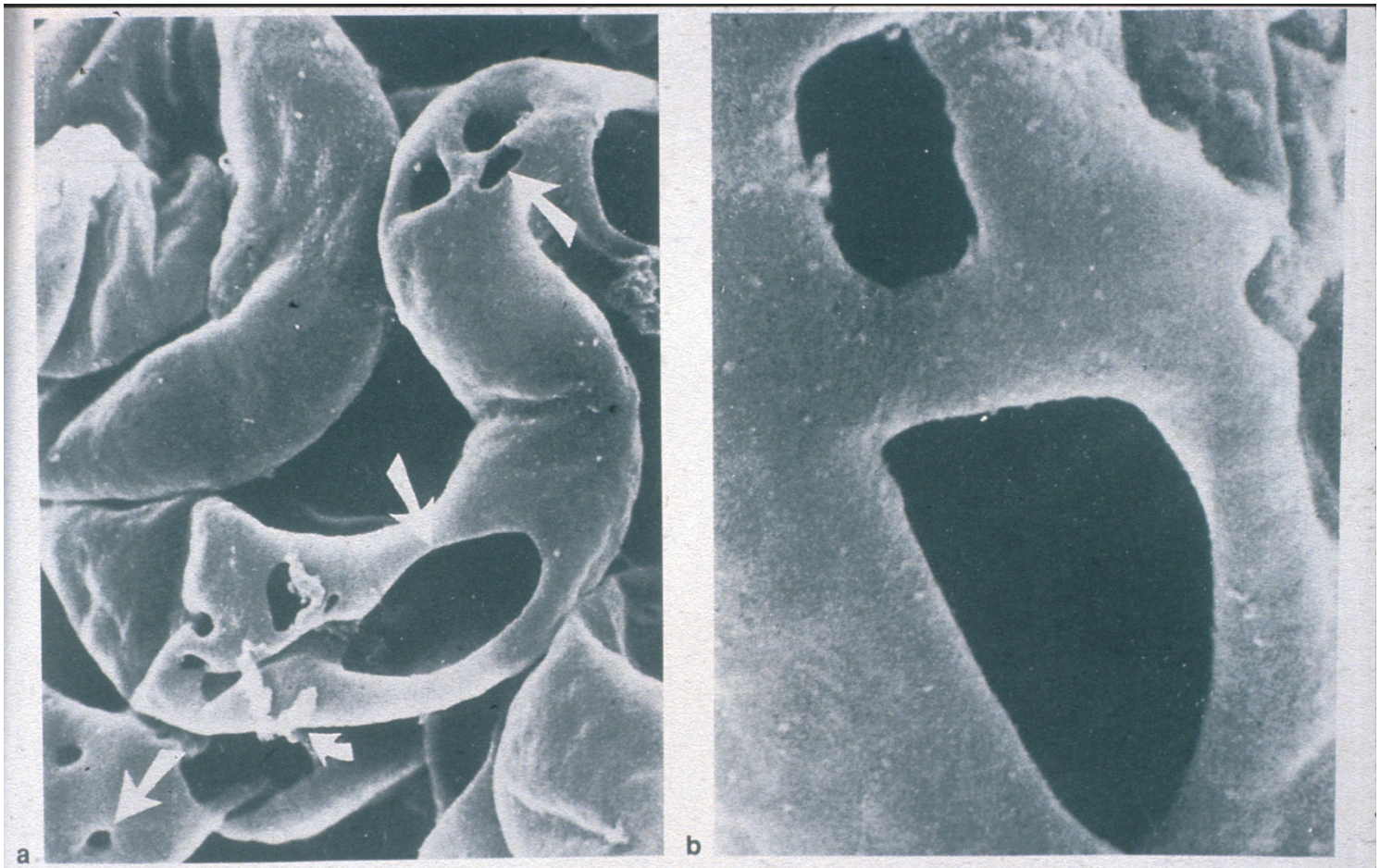


Fig. 7.10 Diffuse crescentic glomerulonephritis. (**a**) Scanning electron micrograph of a glomerular capillary loop after digestion of the cells leaving only the basement membrane. There are multiple perforations (arrows) of variable sizes in the membrane. The curved arrow indicates residual tissue debris. (**b**) Two perforations in a glomerular capillary. The sharply demarcated edges curl slightly into the capillary lumen.
(**a**) × 2000; (**b**) × 6000
Reproduced by permission from: Bonsib SM. Am J Pathol 1985; 119: 357 (Figs 2B, C)

Classification of RPGN based on IF findings on renal biopsy

Linear deposits	anti-GBM disease
Granular deposits	1^{o} or 2^{o} immune complex GN
No (or few) deposits	ANCA-associated GN

Frequency of types of crescentic GN

	Age (years)			
	10-19	20-39	40-64	>65
Anti-GBM	15%	24%	2%	11%
Immune complex	50%	48%	30%	8%
Pauci-immune	35%	28%	69%	82%

Jennette, Heptinstall's Pathology of the Kidney 1998

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Crescent formation in different glomerular diseases

Frequency	**Patients with any crescents**	**Patients with >50% crescents**
Anti-GBM disease	95	81
Pauci-immune (ANCA-associated)	90	48
Lupus GN (class III and IV)	40	11
Henoch-Schonlein purpura	53	5
IgA nephropathy	27	5
Postinfectious GN	25	3
Fibrillary GN	20	7
Type I membranoproliferative GN	20	3

Jennette, Heptinstall's Pathology of the Kidney 1998

Goodpasture's disease

- Pulmonary-renal syndrome
- 2 peaks of incidence age 20-30, 60-70
- Slight male predominance
- Incidence 0.5-1 case/million/year
- Paucity of prodromal symptoms (unlike AAV)
- 20% cases present with anuria

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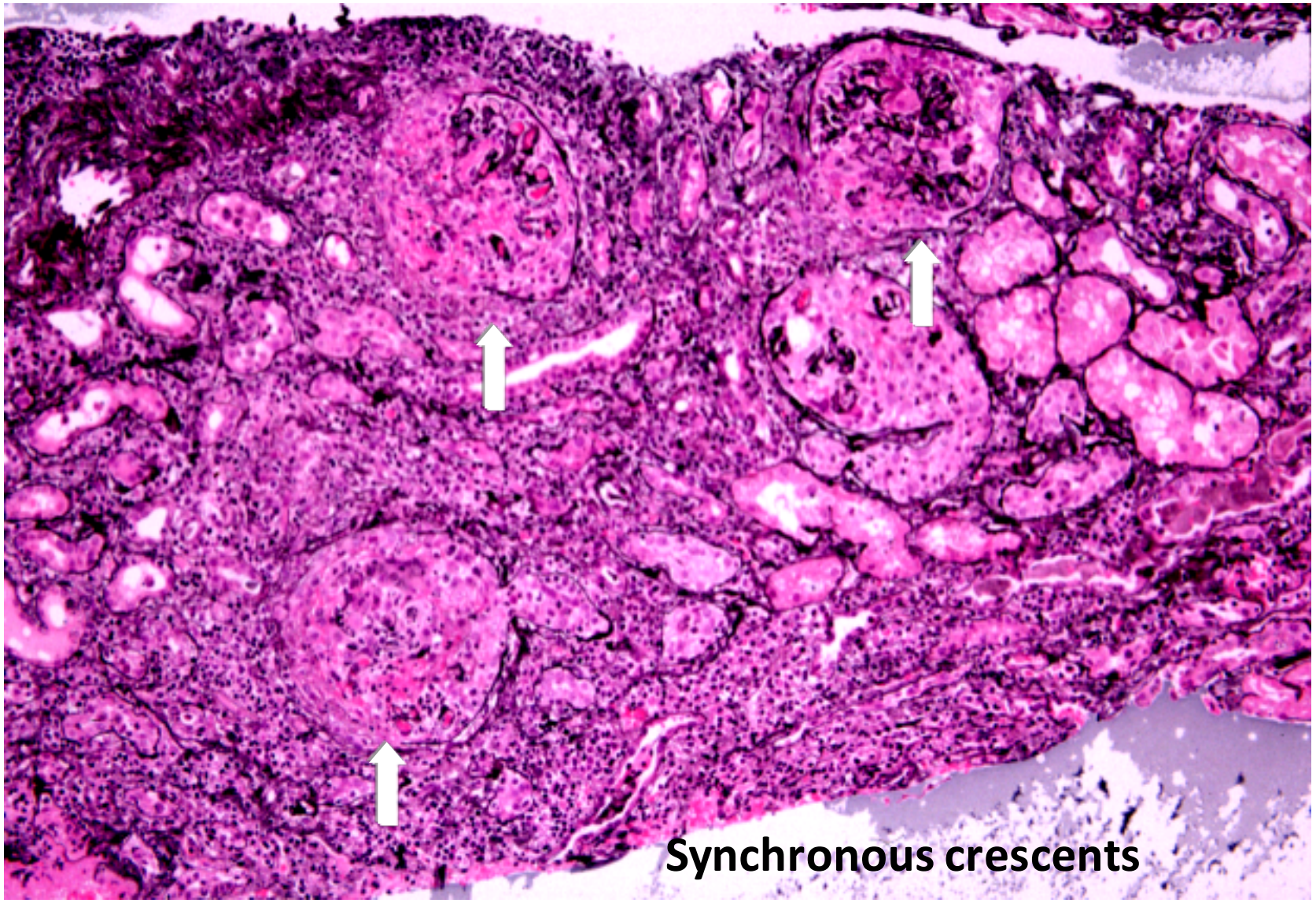
Goodpasture's disease



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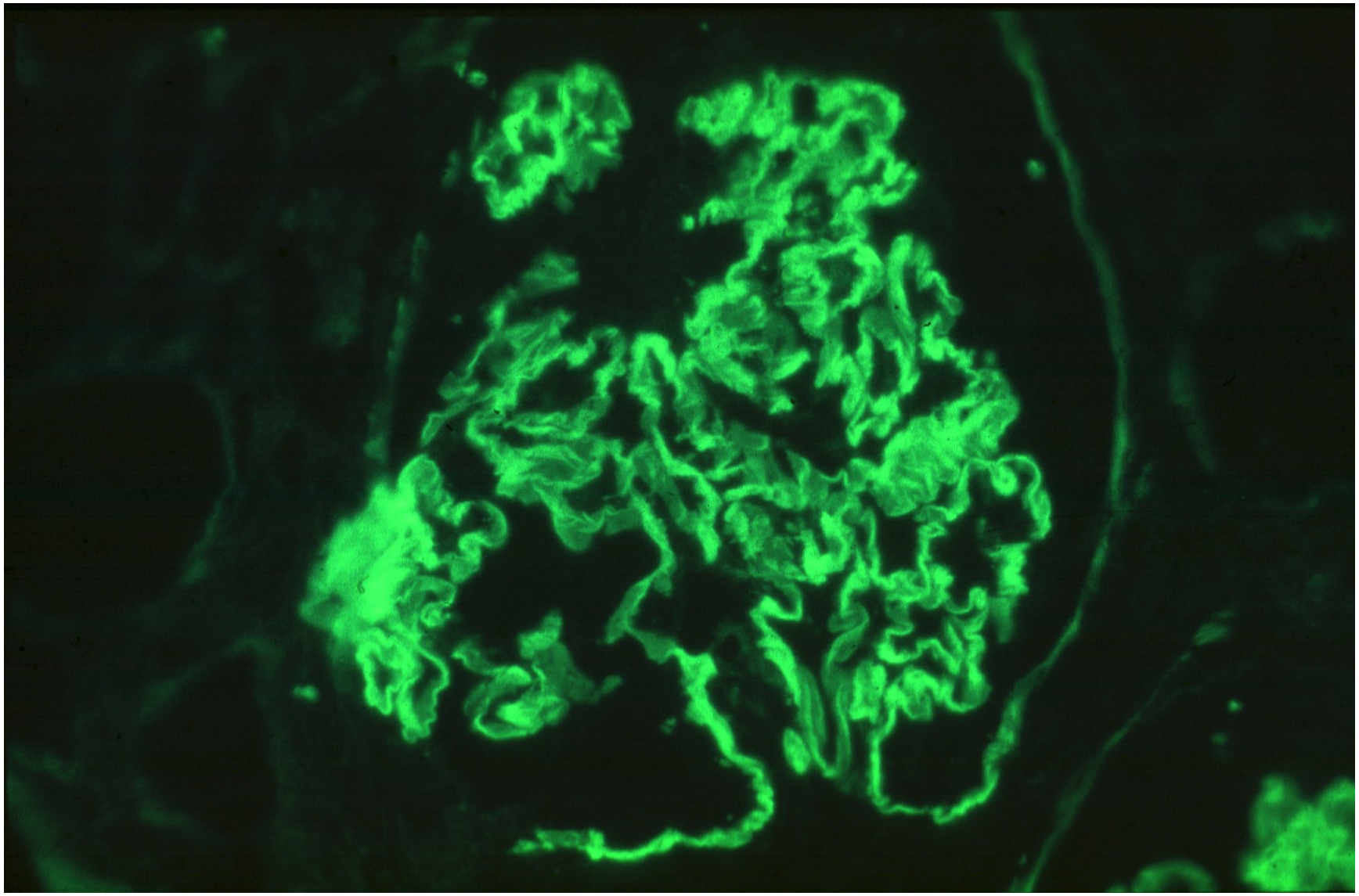
Linear Ig deposition on GBM



Outcome of treated anti-GBM disease

- 71 patients, median age 40 (17-76), 40 male
- Diagnosis made by assay for anti-GBM antibodies and direct IF on renal biopsy
- 55% on dialysis, 18% creat >500
- Lung haemorrhage in 62%
- All treated with pred/cyclo/PE

Levy, Ann Intern Med 2001

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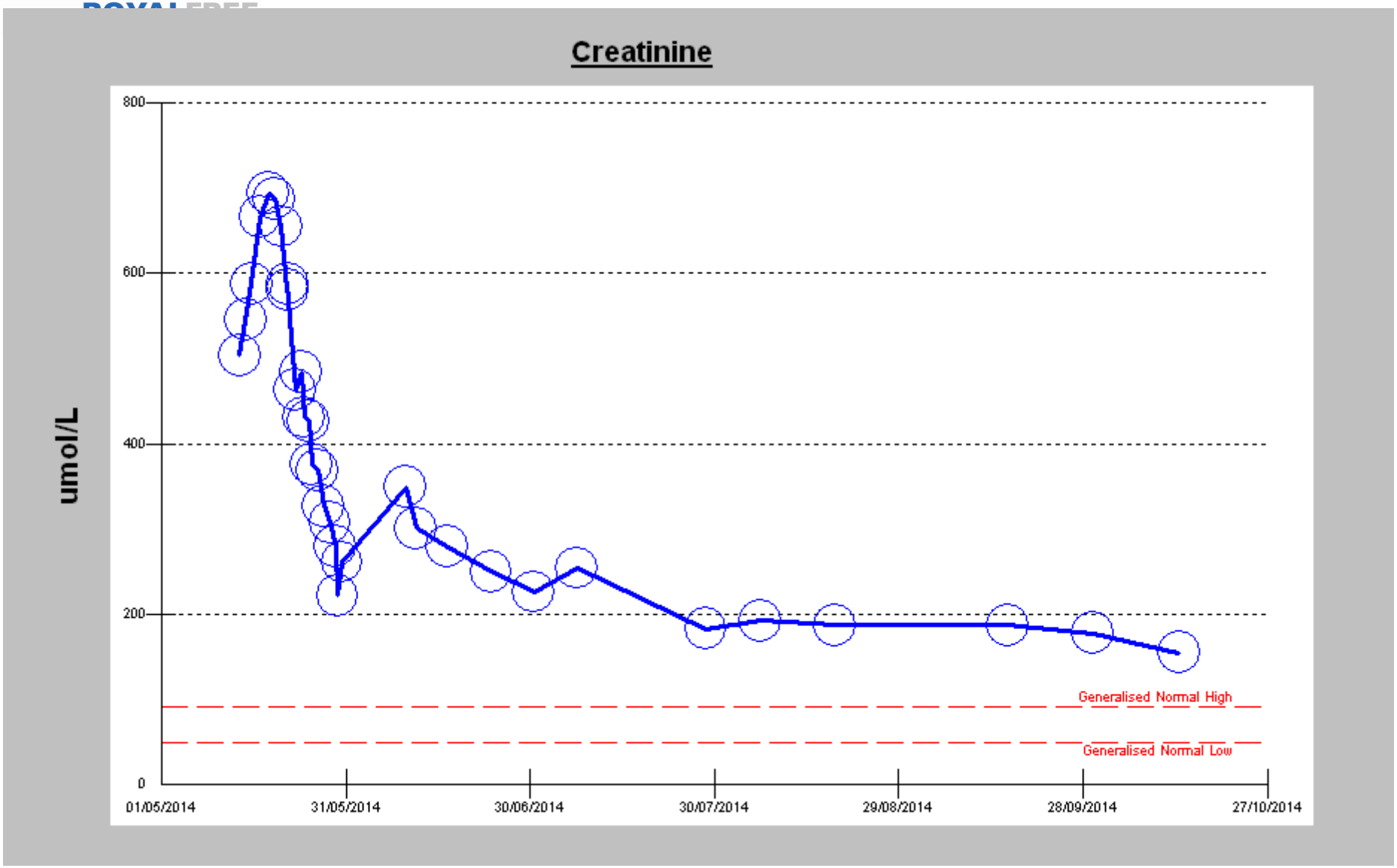
One year outcome in treated anti-GBM disease

	n	Patient survival (%)	Renal survival (%)
Creat <500	19	100	95
Creat >500	13	83	82
Dialysis	39	65	8
Total	71	77	53

Oliguria is an important determinant of whether dialysis is immediately required

Levy, Ann Intern Med 2001


Creatinine
umol/L
800
600
400
200
0
Generalised Normal High
Generalised Normal Low
01/05/2014
31/05/2014
30/06/2014
30/07/2014
29/08/2014
28/09/2014
27/10/2014

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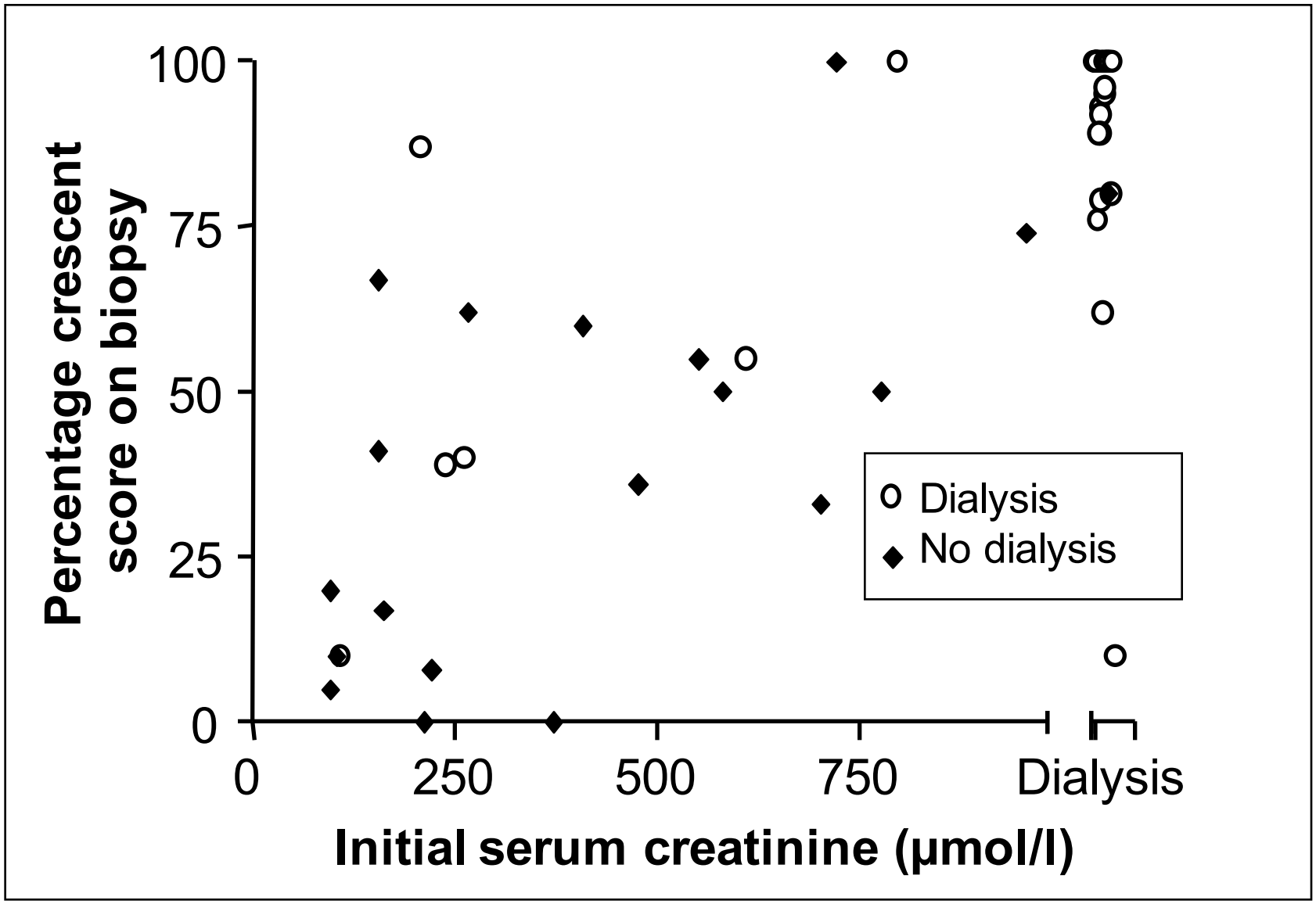
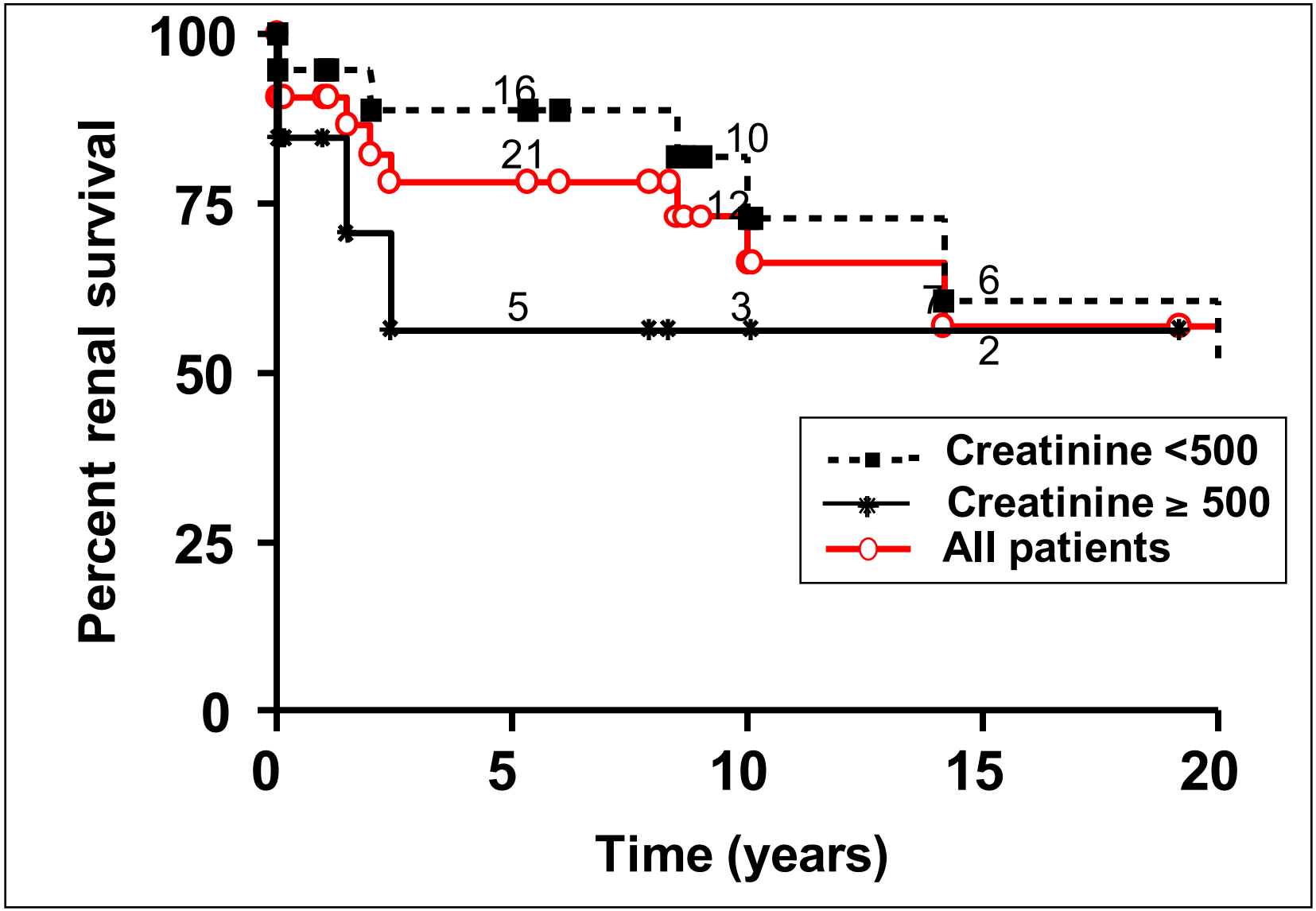
Percentage crescents and initial creatinine vs outcome in GD



Renal survival in anti-GBM disease



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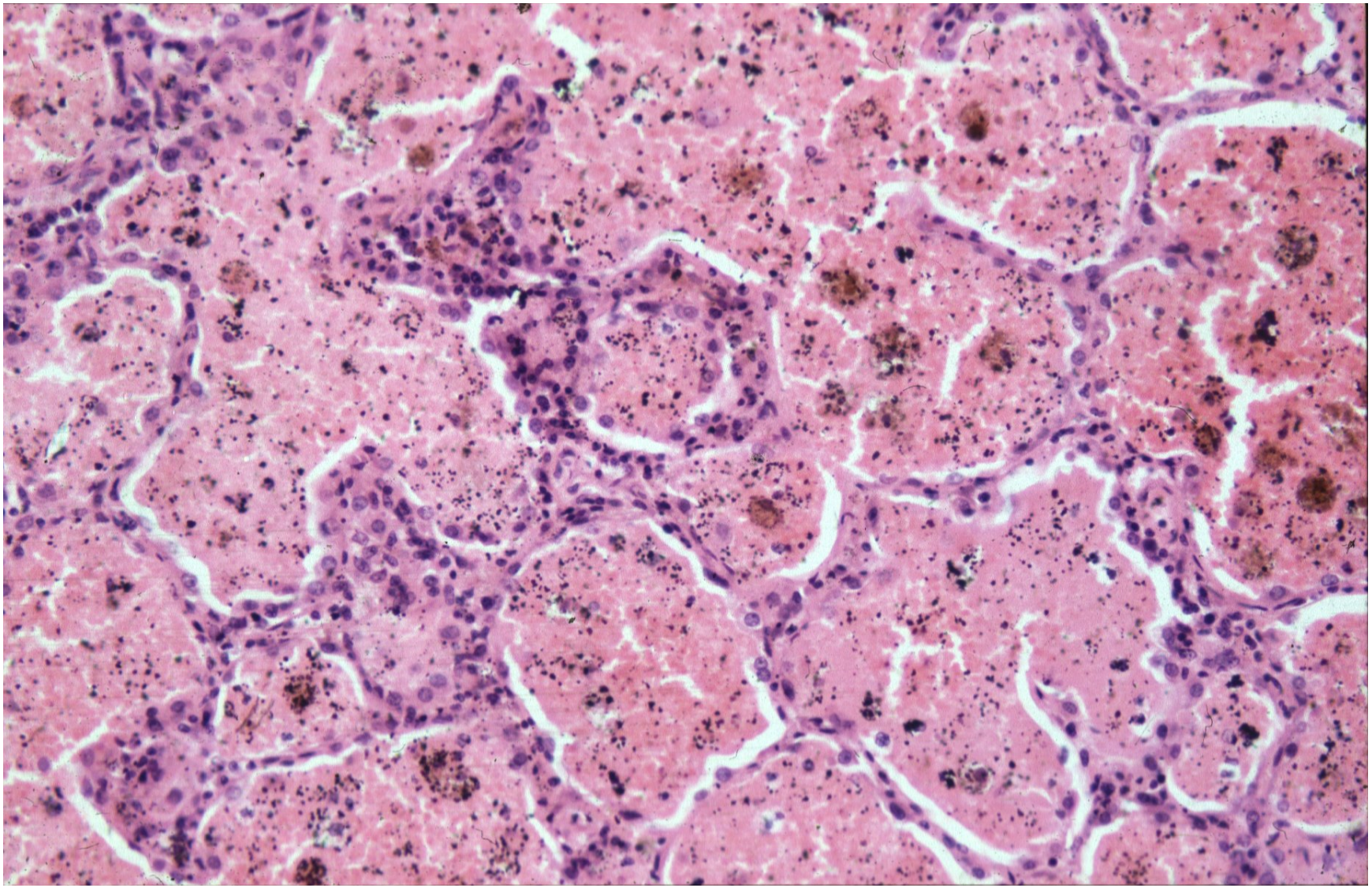
Goodpasture's disease



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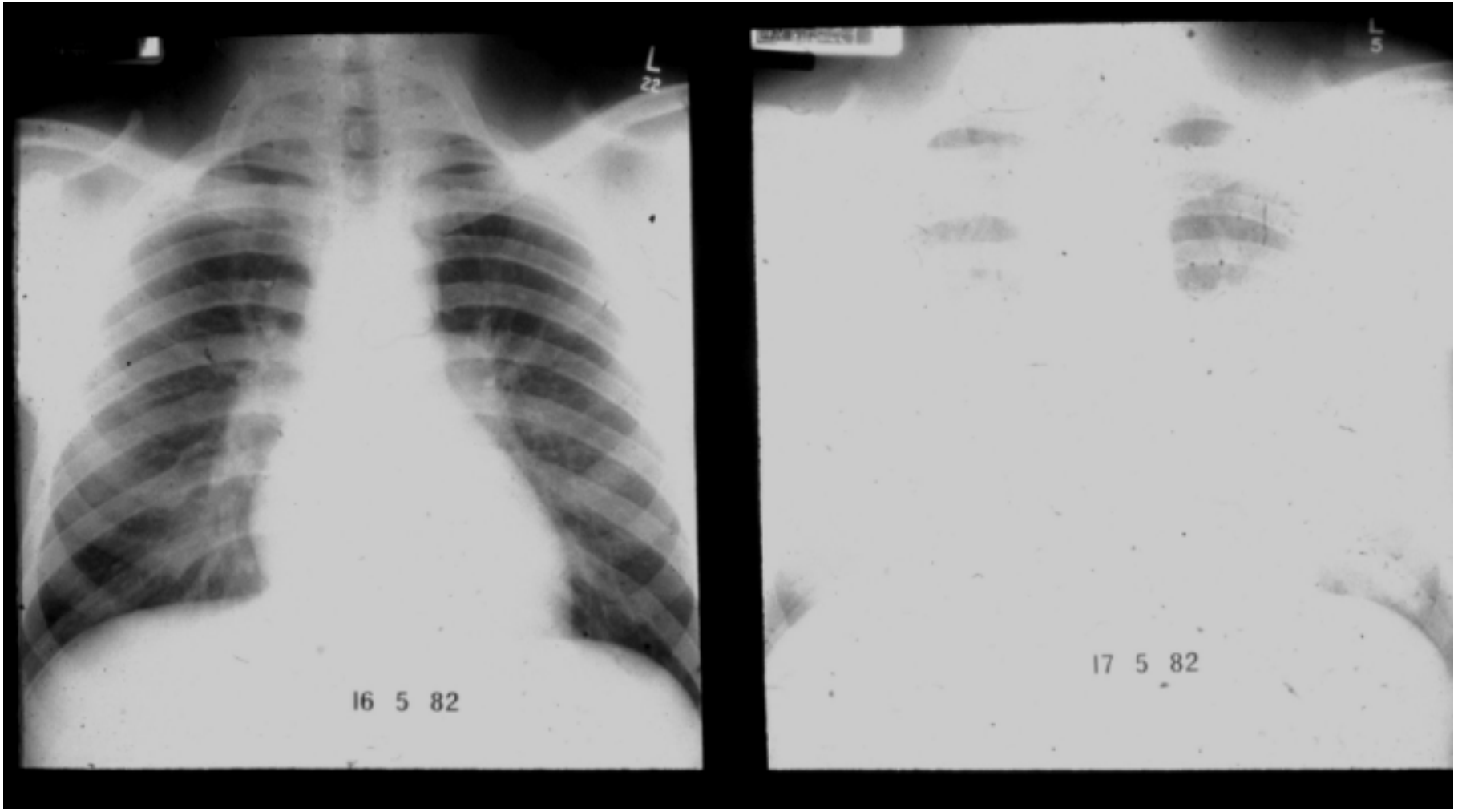
Goodpasture's disease



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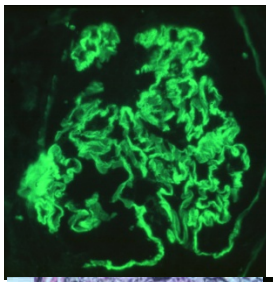
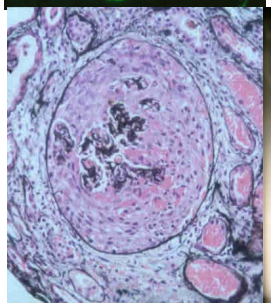
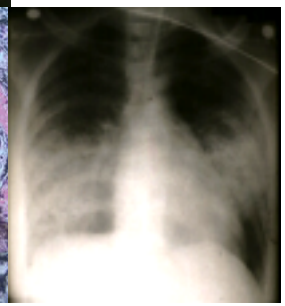
Anti-GBM antibodies in Goodpasture's disease

- Recognise α3 chain of type IV collagen
- Specific and sensitive marker for clinical disease
- Levels correlate with disease severity
- Reduction in levels (by PE) accompanied by clinical response
- Disease recurs in transplanted kidney if antibody still detectable
- Passive transfer of disease to monkeys by antibodies from patients







Circulating anti-GBM antibodies

Negative ELISA

- Number of patients with crescentic GN and linear IgG staining but no detectable circulating Ab
- Biopsy becomes critical
- May be worth performing Western blotting

False positive ELISA

- Polyclonal B cell stimulation e.g. HCV, HIV
- May be worth performing Western blotting

Double positivity for anti-GBM ab and ANCA

- 5% of 954 ANCA+ samples anti-GBM+
- 32% of 121 anti-GBM+ samples ANCA+
- Clinical details obtained on 27 patients, **81%** with anti-MPO ab
- Mean creatinine 636, 68% on dialysis,
  41% lung haemorrhage
- **Outcome similar to anti-GBM ab alone, but treatment variable**
- **Patients with creat <500 did well, but no dialysis dependent cases recovered RF**

Levy, Kidney Int (2000)

Treatment of Goodpasture's disease

Prednisolone

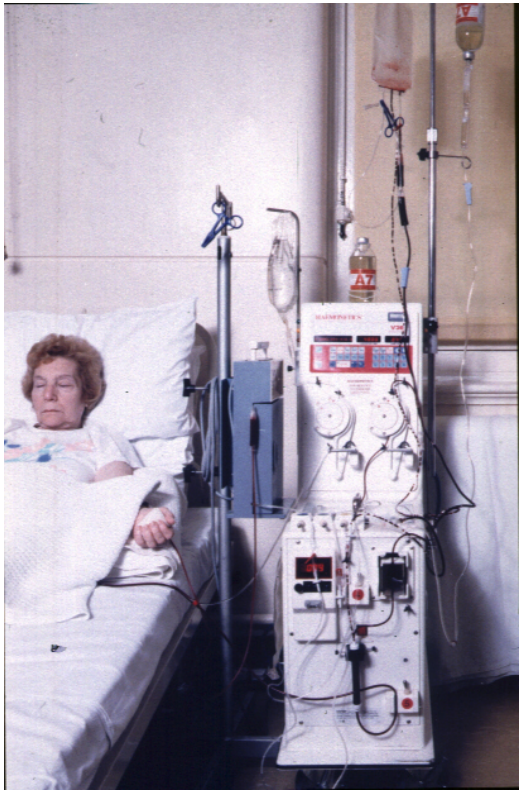
1mg/kg daily (max 60mg), tapering weekly
Discontinue by 6 months

Cyclophosphamide

2mg/kg daily (adjusted for age and renal function)
Discontinue by 3 months

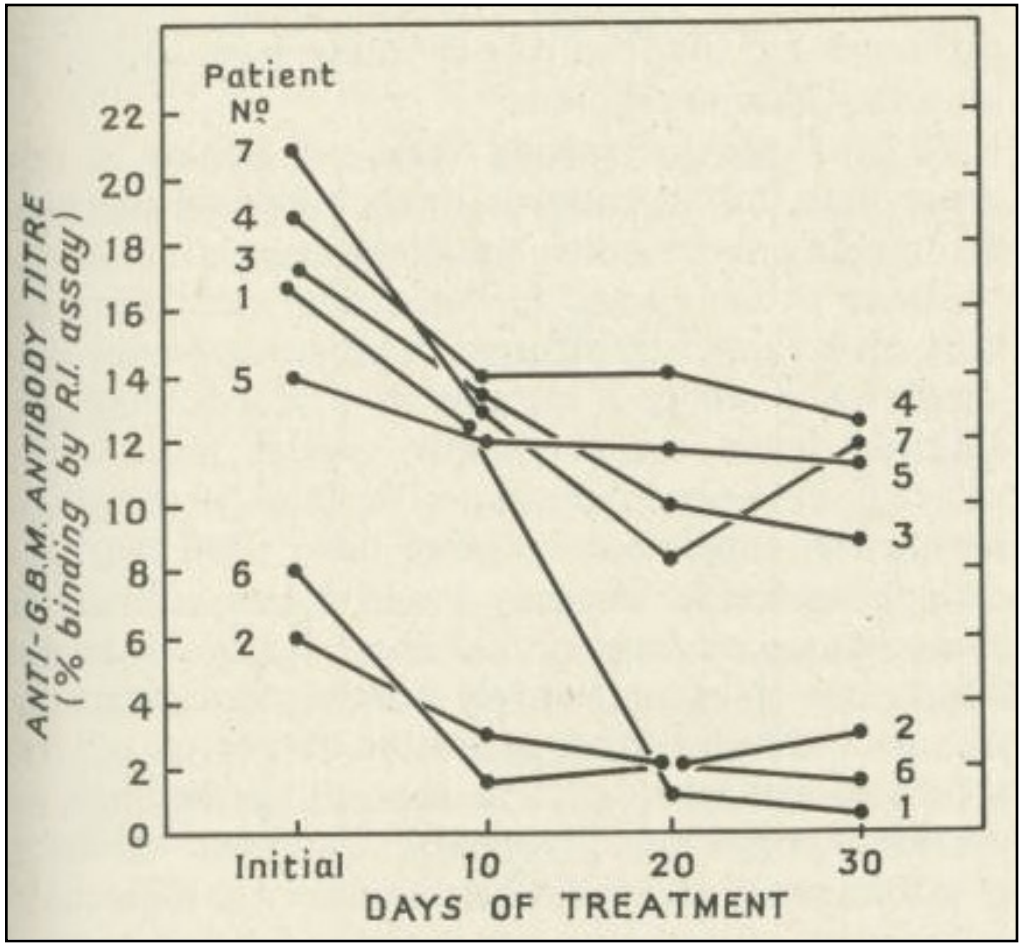
Plasma exchange

60ml/kg (max 4L) for 14 days or until anti-GBM neg
Use HSA with addition of FFP if risk of bleeding



IMMUNOSUPPRESSION AND PLASMA-EXCHANGE IN THE TREATMENT OF GOODPASTURE'S SYNDROME

C. M. LOCKWOOD
A. J. REES
T. A. PEARSON
D. J. EVANS
D. K. PETERS



Lockwood, Lancet 1976

Trial of PE in anti-GBM disease

- Comparison of PE + immunosuppressive drugs vs drugs alone
- More rapid fall in anti-GBM antibody levels
- Fewer patients on dialysis (2/8 vs 6/9)
- But - less severe disease in PE group

Johnson, Medicine 1985

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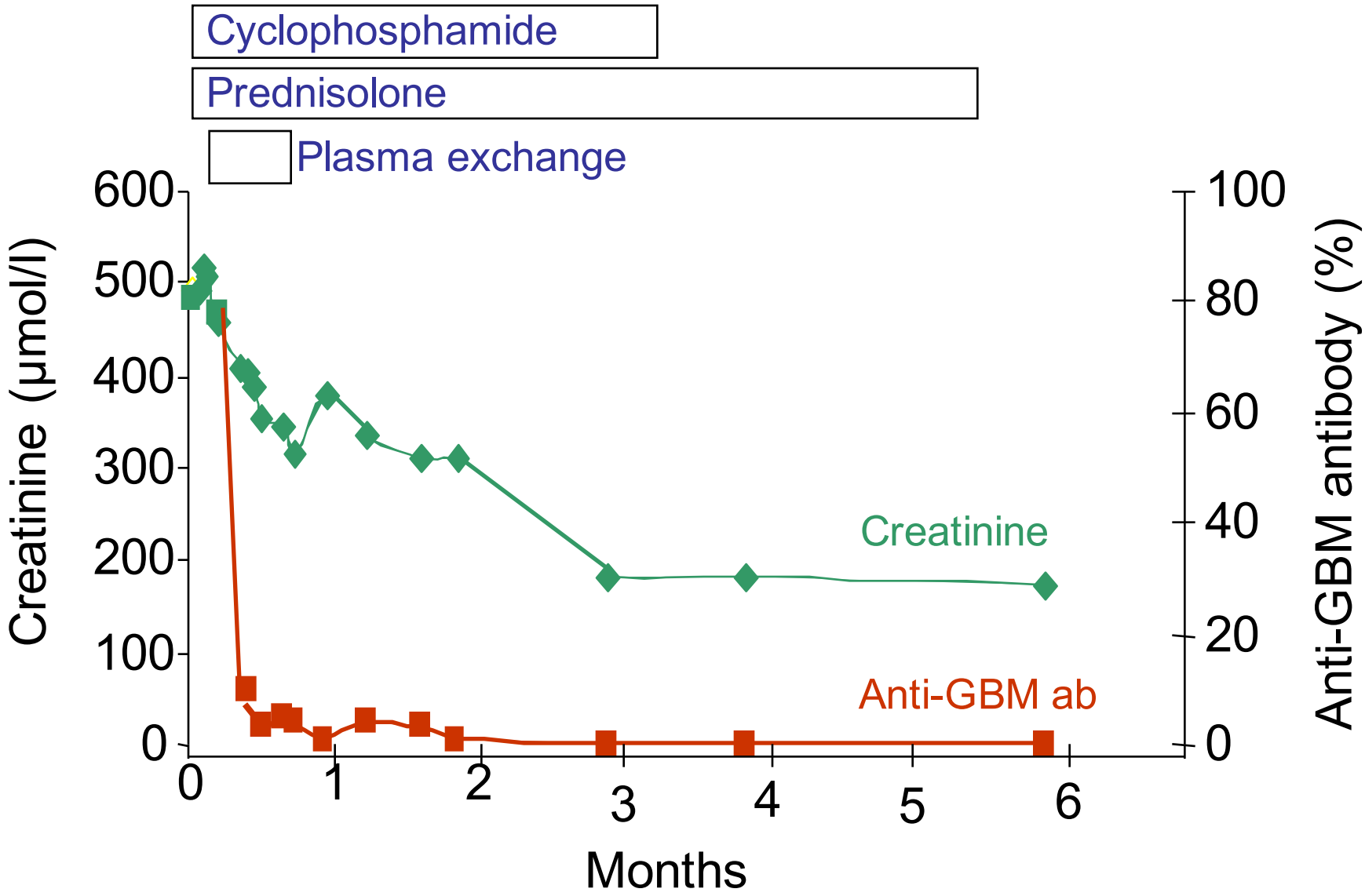
Effect of treatment



Future treatment

- Case reports of use of RTX, MMF, CsA in patients who are intolerant of cyclophosphamide
- Speed of onset of these agents?
- SYK antagonists

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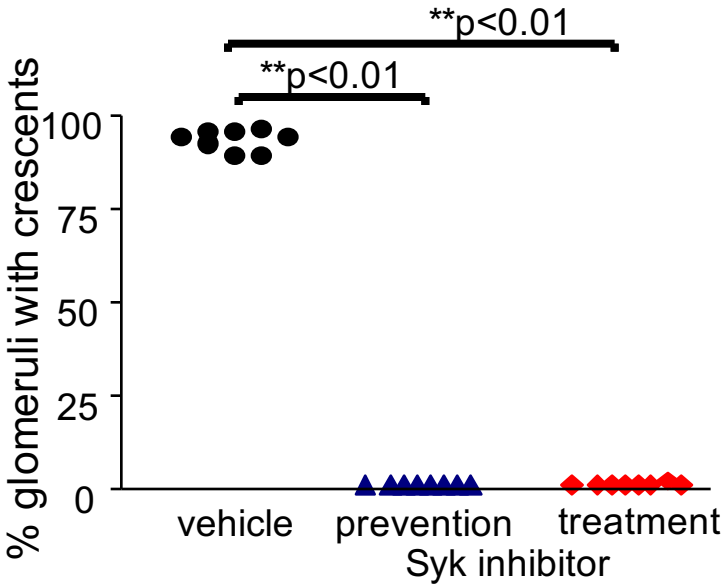
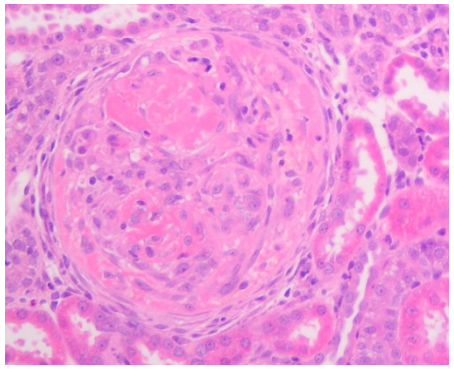
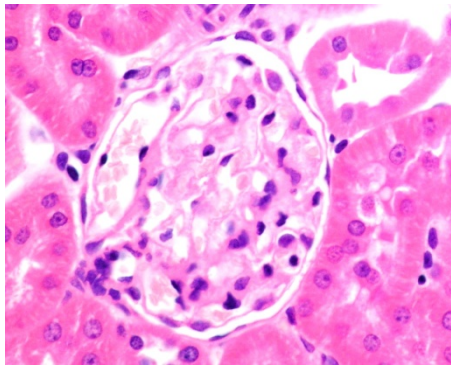
SYK inhibition in NTN

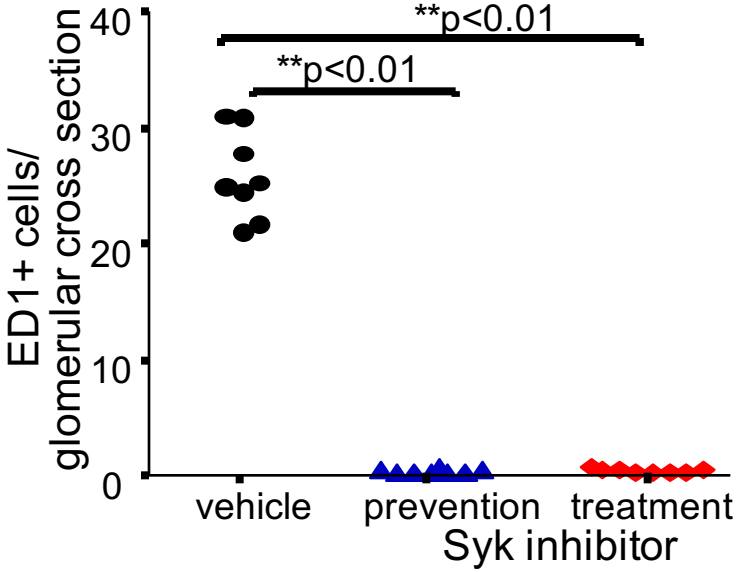


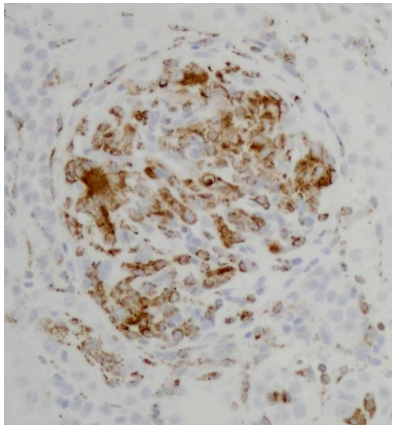


Positive control

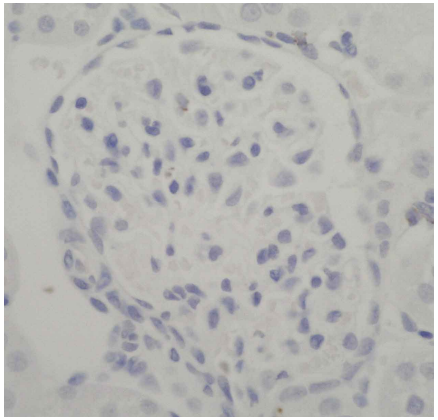


Syk inhibitor





Positive control



Syk inhibitor

Tam, J Am Soc Nephrol 2010

Case 2

- 23 year old Turkish woman; 1 child age 3
- Diagnosed with SLE 6 months previously- arthralgias, rash; SCr 60 μmol/l
- Developed pericarditis and pleuritis started on prednisolone and azathioprine, later MMF
- Initial improvement then recurrent pericardial effusion; dsDNA ++, v. low C3/C4; negative ANCA
- Unkeen on CYP, RTX added

- Rapid decline in renal function, HT, oedema
- Admitted to poor compliance
- Eurolupus CYP 6x 500mg
- Continued decline in renal function
- Renal biopsy
- Severe crescentic glomerulonephritis little Ig deposition; ANCA /anti-GBM negative
- Increased dose of CYP, PEx x 7
- Reached end stage

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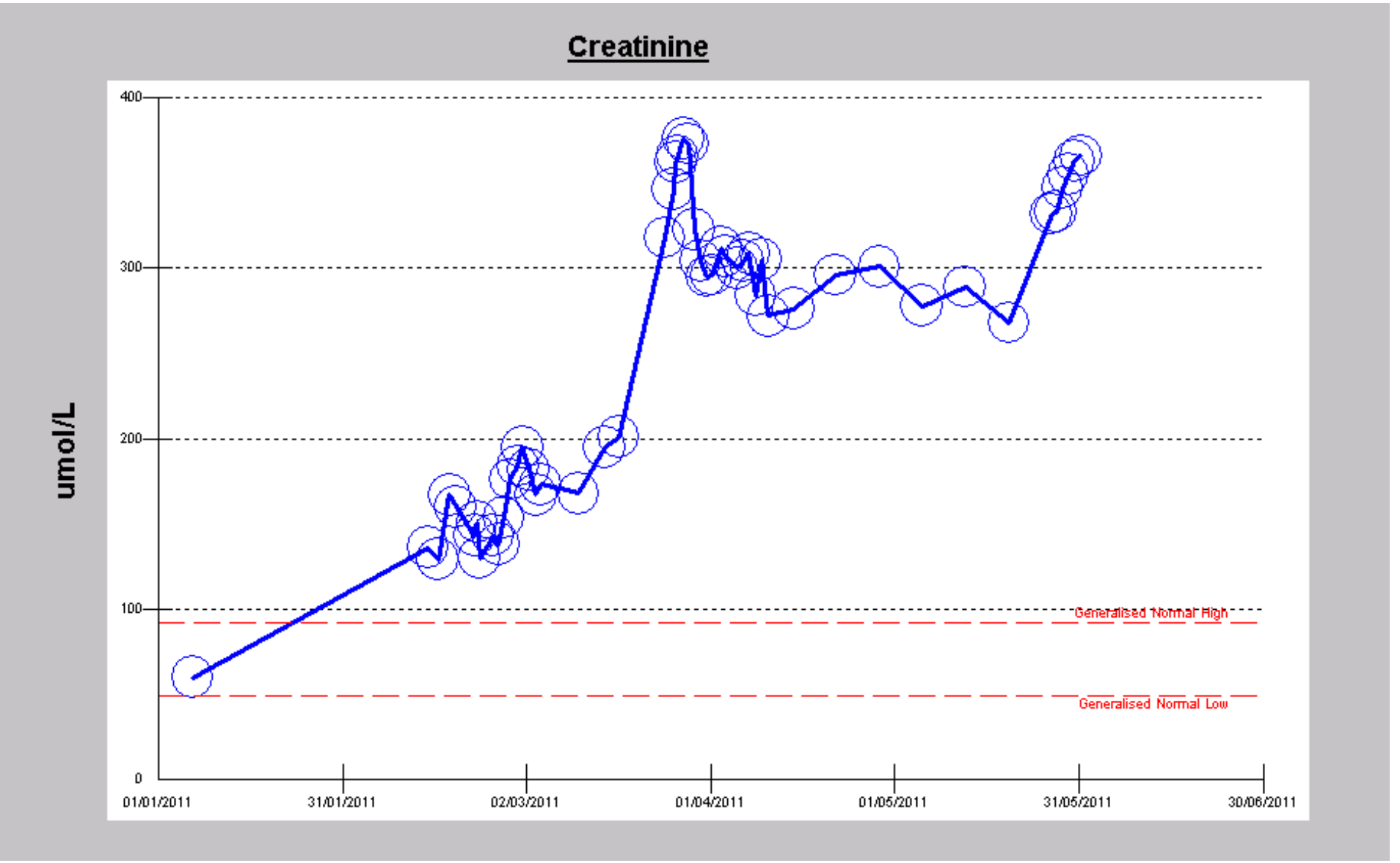

AKI in SLE

- Kidney involvement is common
  - 25-50% of patients have abnormalities of urine or renal function early in their course
  - Up to 60% of adults and 80% of children will develop renal abnormalities at some time
- Zhu et al 2011
  - 322 patients with LN; 66 with AKI (20.5 %)
  - Significant differences between groups with/without AKI

	With AKI	**Without AKI**
Male:female	1:2.7	1:8.8
Class III	0 %	20.7 %
Class IV	92.4 %	46.9 %
Class V	1.5 %	25.4 %
Crescents	2 (1-6)	0 (0-2)
Proteinuria g/24 hours	6.6±4.4	4.7±3.2

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Eurolupus trial

n=90

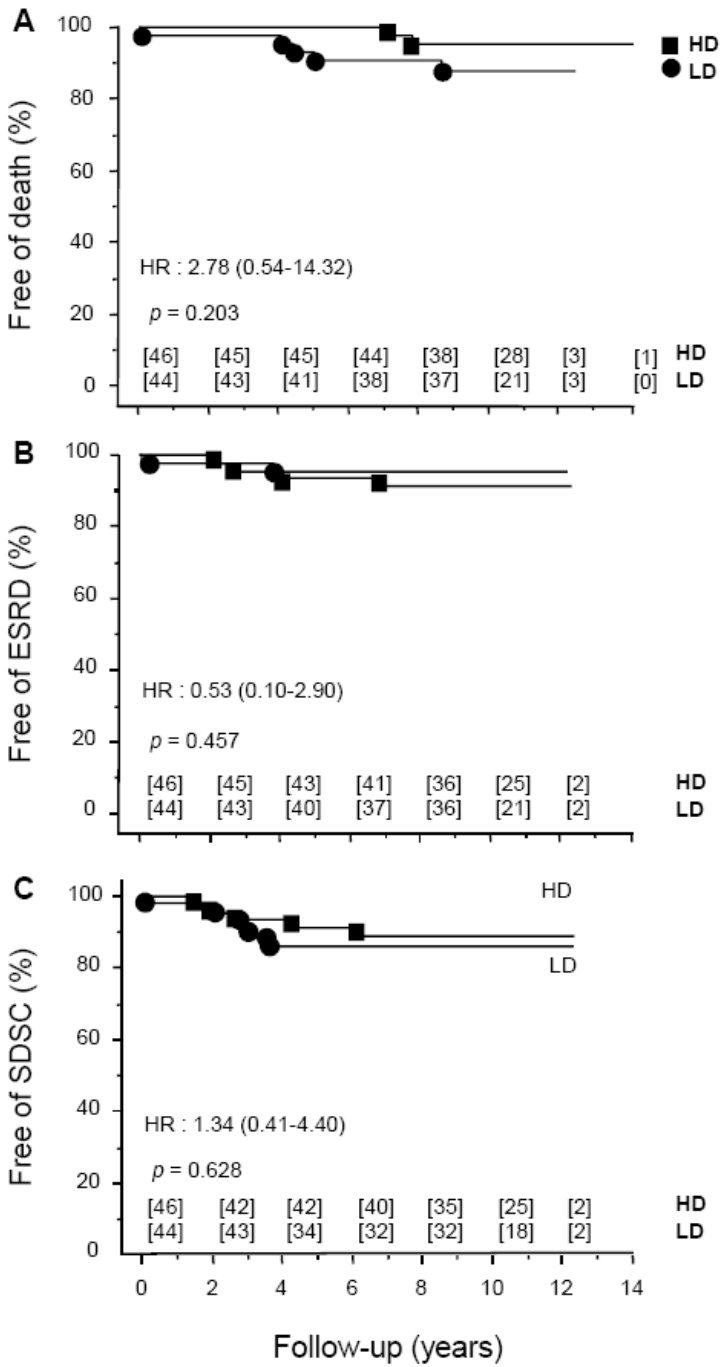
Class III and IV (83 pts) or V (7pts)

Treated: Low dose (6 x 500mg)

CYC vs High Dose (8 x 0.5g/m^2) CYC

	LD	HD
ESRD	5%	9%
Doubing of SCr	14%	11%

Houssiau FA et al 2010



MMF rather than CYC in LN

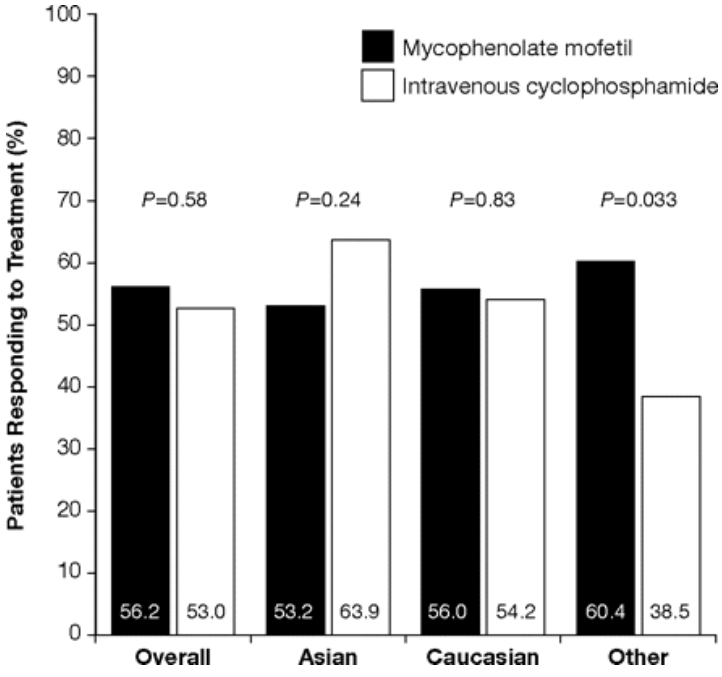
- ALMS study

185 MMF vs 185 IVC

Median dose 2.6 g MMF v 6 doses IVC(0.75 g/m^2)

Primary endpoint reduction of proteinuria and stabilisation of Scr

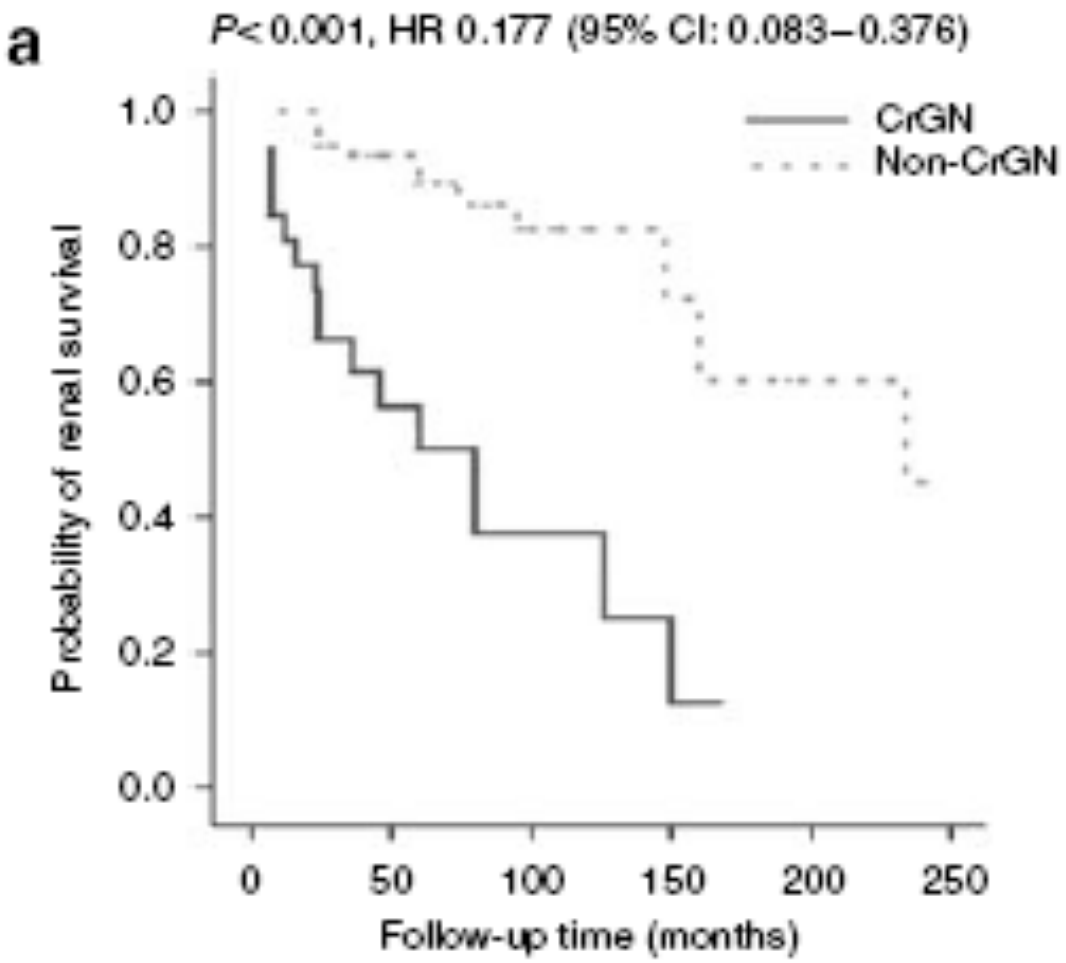
- 56% vs 53% reached endpoint (p=NS)
- Effect of region and ethnicity on response



SLE and crescentic nephritis

- Yu et al 2009
- 33/327 (10%) LN patients had crescentic GN
- All presented with RPGN; SCr 330± 235(vs 141±138)
  - All treated with MP/steroids and 6/12 CYP in 30 and MMF in 3
  - 8(24 %) CR, 16(49 %) PR, 9 (27 %)no response
  - 30% of pts had concurrent p-ANCA/anti-MPO Ab vs 2.5 % in those without crescentic nephritis
  - 1 patient had anti-GBM Ab

Outcome in crescentic LN



Treatment of crescentic LN

- No specific trials of RPGN or crescentic disease
- Trial of adjunctive PEx showed no benefit
  - 86 pts with LN (class III-V), excluded if SCr >530 μmol/l
- Retrospective Chinese study suggested more CR with MMF (n=27) vs CYP (n=25) treated pts (Tang 2008)

- Test for ANCA/anti-GBM
- Treatment escalation as for AAV; role for MMF ?
- Impact of non-compliance ?

AKI in IgA

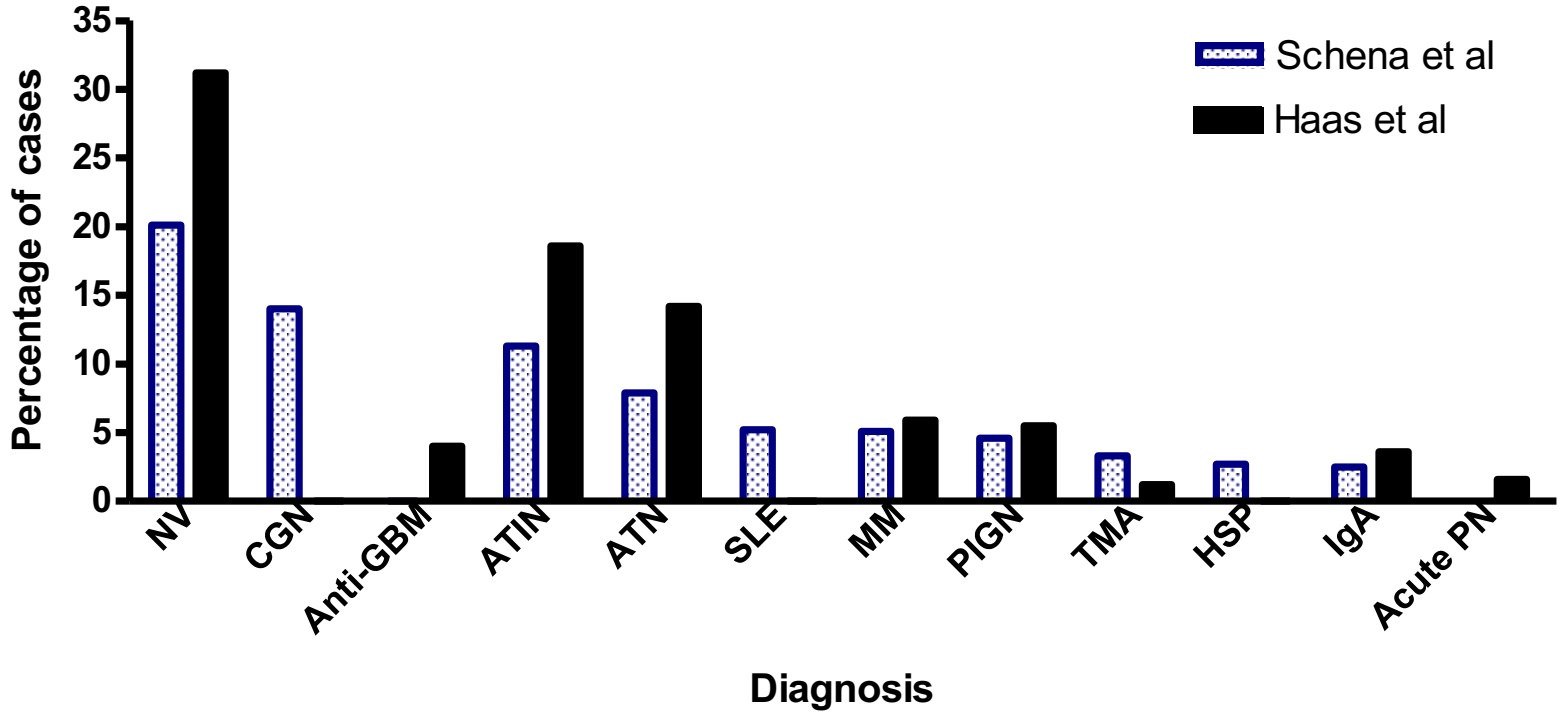
- AKI may be due to glomerular or tubular disease
- 20 pts with IgA and AKI (Wen 2010)
  - 55% crescentic GN, 55% ATN, 20% AIN
  - 7(35%) reached end stage, 11(55%) remission, 2 (10%) died

RPGN in IgA disease

- Crescentic IgA may be characterized by HT, oedema, rapid renal function decline
- Retrospective analyses suggest benefit from steroid/CYP based regimen
- No controlled trials

Biopsy diagnoses in AKI

Patients without obvious clinical cause of ATN
Haas n=259; pts >60 years
Schena n=1273; all adult pts



Renal biopsy in the elderly

- Brown et al 2011
  - Ireland
  - 1372 native biopsies, 236 in patients >65 years(17%)
  - Commonly for AKI or nephrotic syndrome
  - Commonest diagnosis pauci immune crescentic GN
- Moutzouris et al 2009
  - USA
  - 235 patients >80 years
  - 46% for AKI; commonest diagnosis pauci immune GN (19% cases), greater than in those 60-61 yrs

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ANCA associated vasculitis

- Prolonged prodrome with extrarenal symptoms, but remember…
- In small percentage may be limited to kidney (renal limited vasculitis)
- Characterized by ANCA in 90-95%
- ANCA negative disease recognised
- Crescents may be of different ages suggesting waves of inflammation

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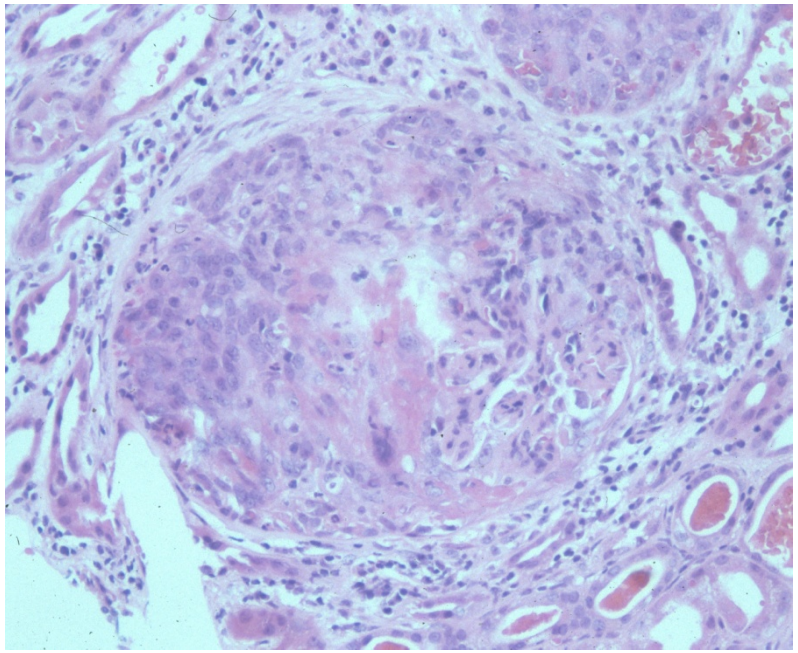
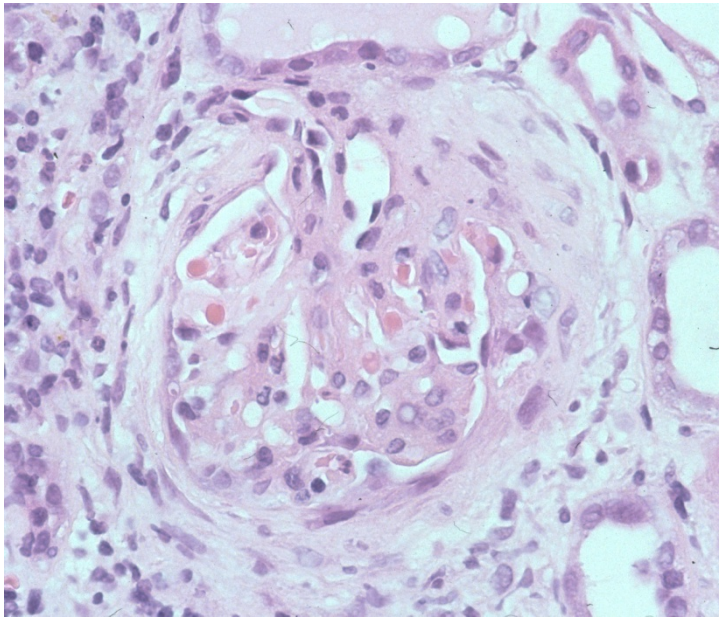
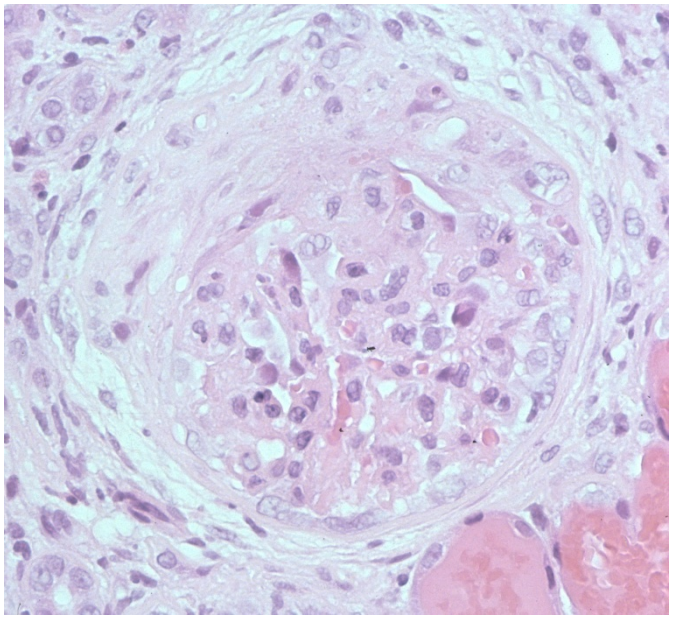


Cellular crescent

Fibrous Crescents





ANCA associated vasculitis

- Recovery of dialysis dependent renal failure in up to 60% patients
- Treatment regimens with steroids, cyclophosphamide, RTX, plasmapheresis
- High morbidity and mortality from treatment
- Rituximab in recent clinical trials is efficacious but not better with regards adverse effects

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Case 3:Negative serology

- 47 year old woman
- Diagnosed with lymphoma 18 months prior to presentation
- Decided on homeopathy rather than chemotherapy
- Various agents including selenium and silver therapy
- Presented to UCH with Cr 900
- Immunolgy screen negative (ANCA, ANA, dsDNA, ant-GBM, Ig's, normal complement)

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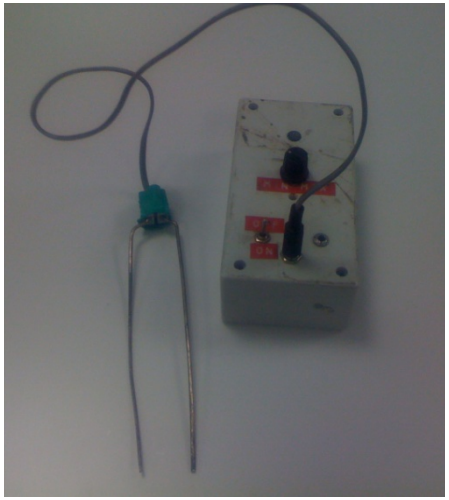
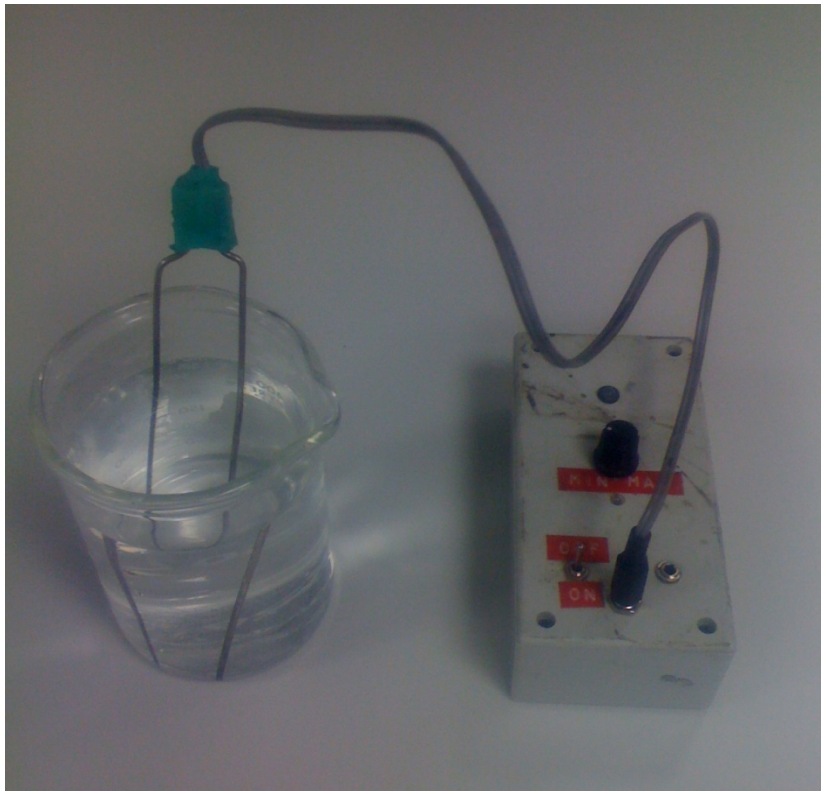
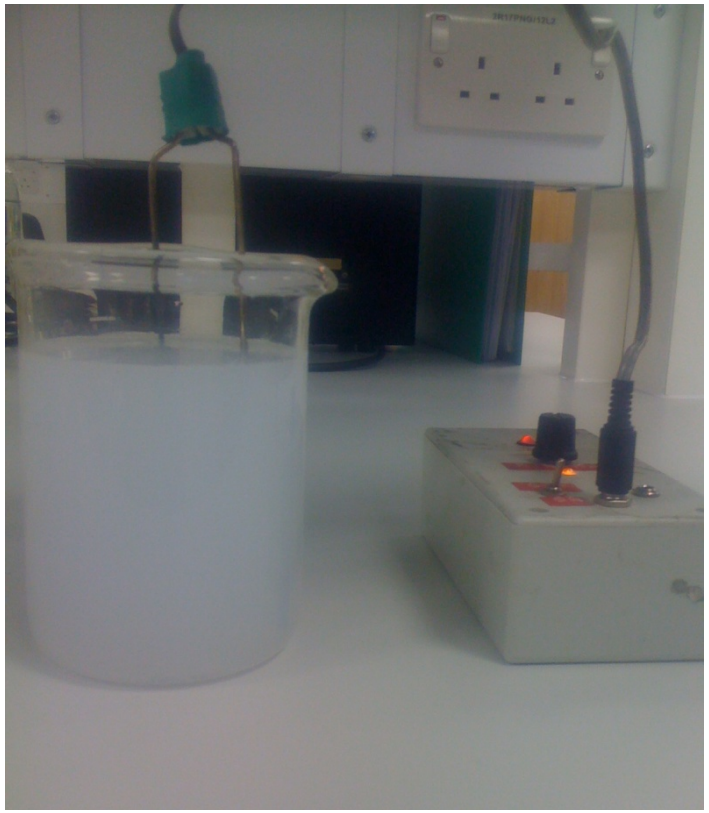
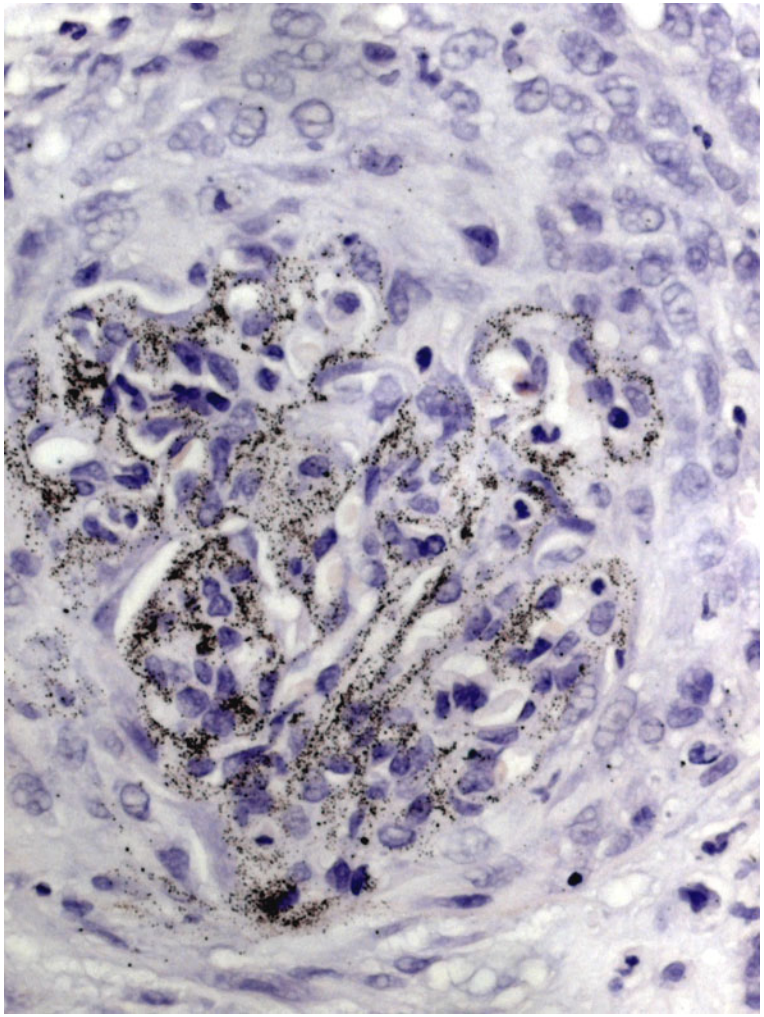
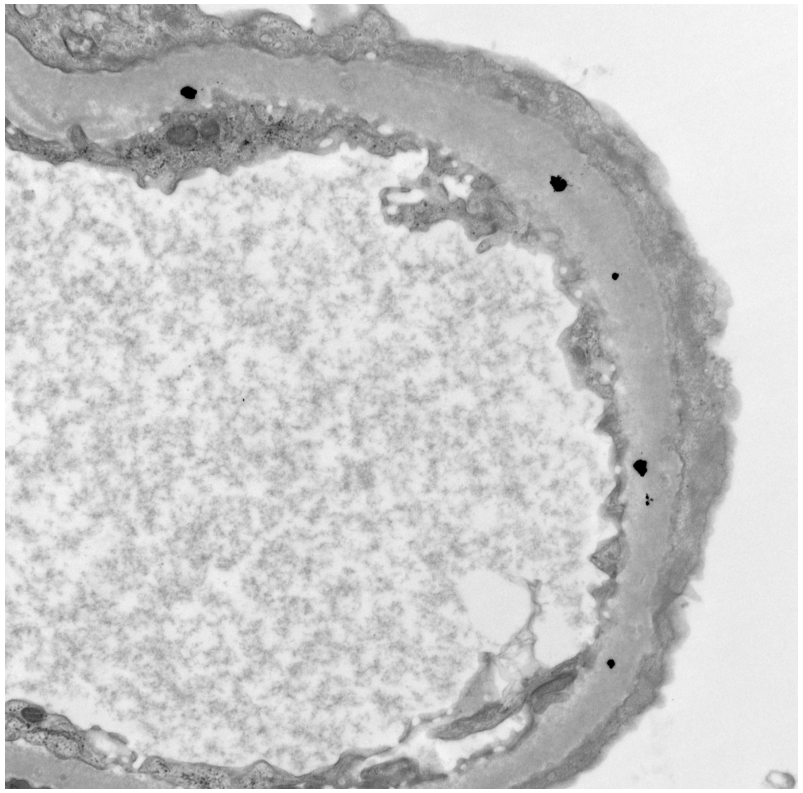






Severe crescentic glomerulonephritis





Exposure of neoepitope??

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Conclusions

- RPGN common cause of AKI
- Timely diagnosis required to maximise renal recovery
- Renal biopsy invaluable especially if serological tests delayed
- Treatment regimens still associated with significant morbidity
- New strategies are required to improve short and long term outcome