RECURRENT AND DE NOVO RENAL DISEASES IN THE ALLOGRAFT

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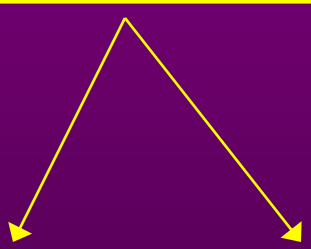
HISTOPATHOLOGIC DISORDERS AFFECTING THE ALLOGRAFT OTHER THAN REJECTION

RECURRENT DISEASE



Glomerular **Non-glomerular**

DE NOVO DISEASE

Glomerular

TRANSPLANT GLOMERULOPATHY

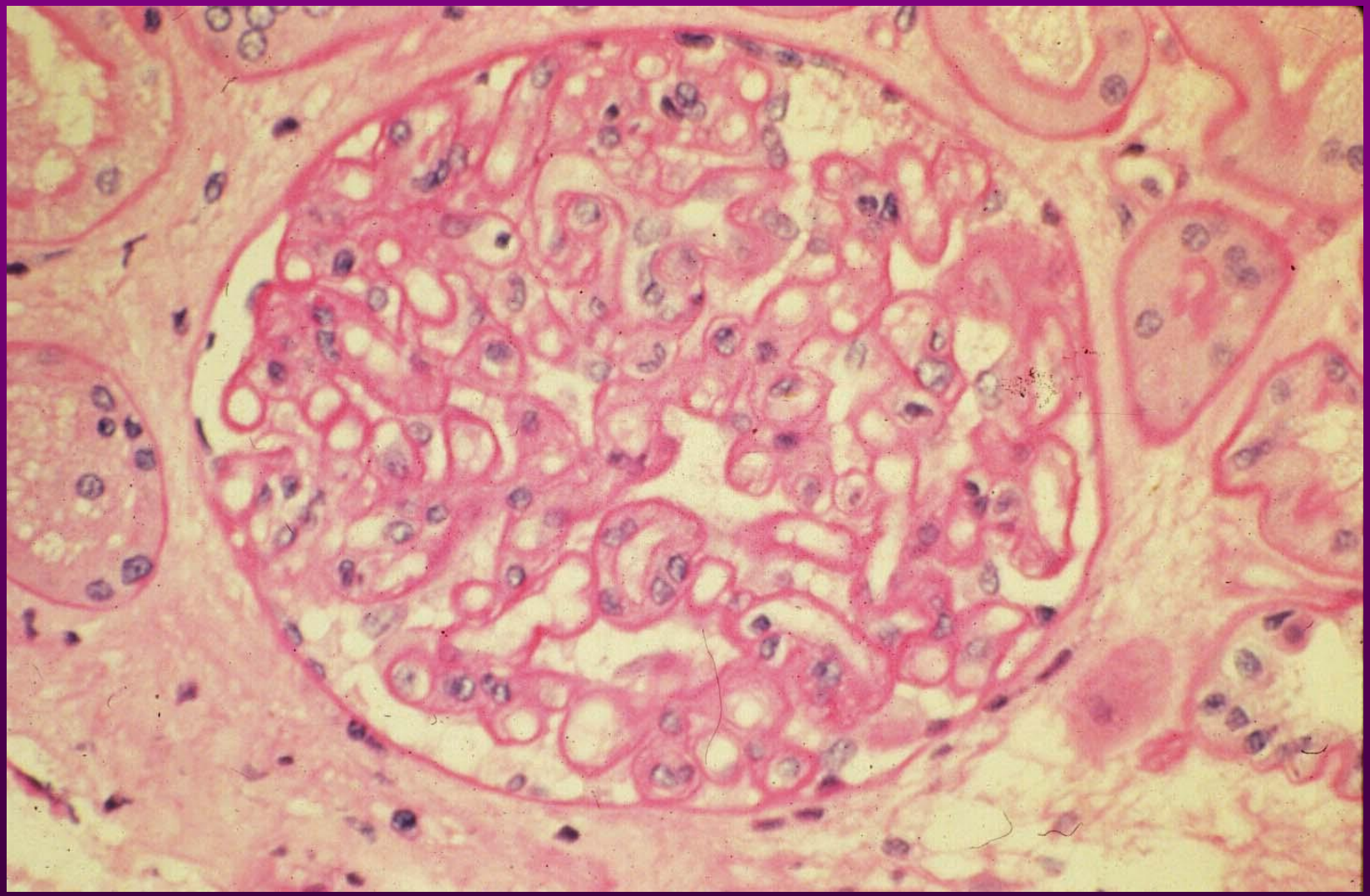
Chronic Rejection

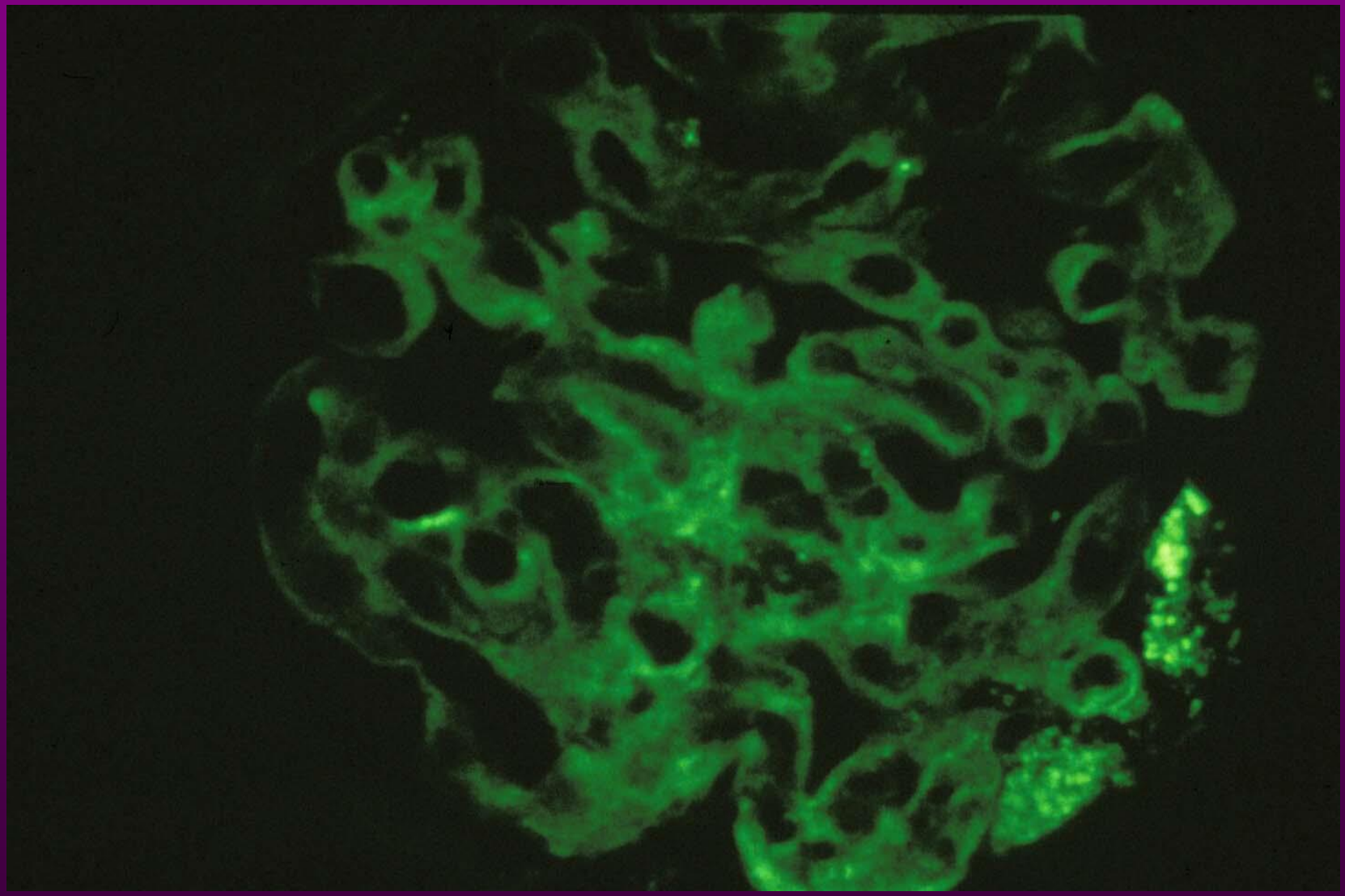
TRANSPLANT GLOMERULOPATHY

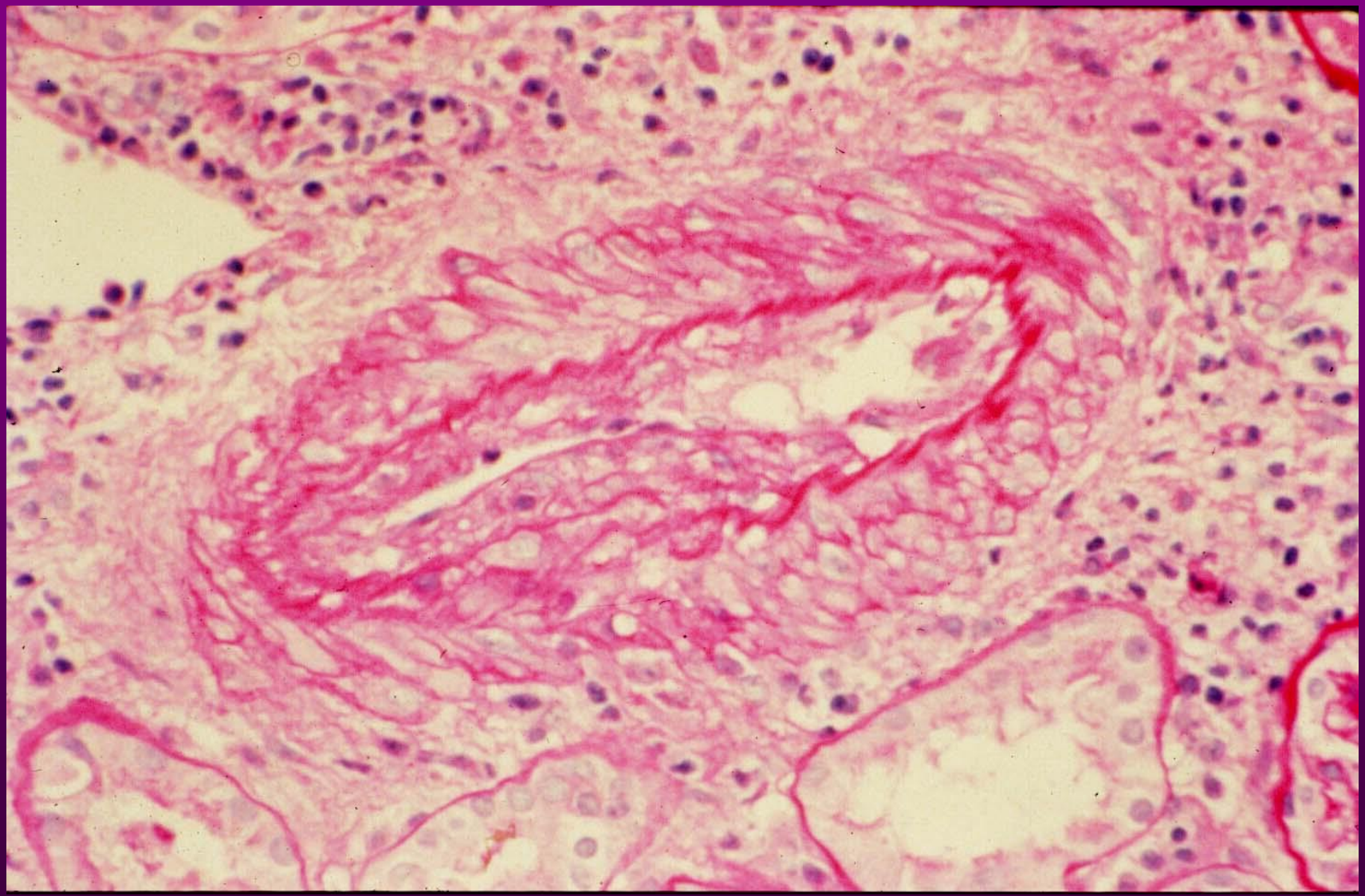
Pathogenesis: consequence of chronic rejection; inverse relation with donor an recipient compatibility; repetitive episodes of endothelial injury

Histology: endothelial and mesangial cell swelling; GBM reduplication; myointimal proliferation progressing to fibrosis leading to obliterative arteriopathy; IF- capillary wall lgM and C3; EM- subendothelial deposits, effacement of foot processes

Clinical: onset of nephrotic syndrome ~ 9 mos (1-48 mos) post-tx; 2 year graft survival of 67%







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Clinical: onset of nephrotic syndrome ~ 9 mos (1-48 mos) post-tx; 2 year graft survival of 67%

PROBLEMS WITH INTERPRETATION OF DATA

1. Nature of recipient's original disease must be well documented
2. Indications for allograft biopsy – usually based on an abnormality (renal dysfunction, abnormal U/A)
3. Recurrence - ? Histological or clinical
4. Interpretation of biopsy – differentiate recurrent changes from rejection or those already present in the grafted kidney

RECURRENCE OF DISEASE AFTER TRANSPLANTATION

Mathew TM; Am J Kid Dis 12:85; 1988

1. Overall incidence of recurrent disease ~ 10-20%
2. Recurrent disease accounts for < 2% of graft loss
3. Most frequent cause of recurrent disease is recurrent GN
4. GN recurs in 6-9 % of transplanted patients

GLOMERULONEPHRITIS IN RENAL ALLOGRAFTS: RESULTS OF 18 YEARS OF TRANSPLANTATIONS

Honkanen E et al; Clin Neph 21:210, 1984

Analyzed 1282 renal allograft recipients – found 13 cases of allograft GN of which 4 were recurrent GN – for a recurrence rate of < 1%

EVALUATION OF RECURRENT GLOMERULONEPHRITIS IN KIDNEY ALLOGRAFTS

Morzycka M et al; Am J Med 72:588, 1982

In patients with glomerulonephritis as their original disease, they found a 17.9% recurrence rate of glomerular disease

GLOMERULAR LESIONS IN THE TRANSPLANTED KIDNEY IN CHILDREN

Habib R et al; Am J Kid Dis 10:198, 1987

40/436 patients – 9% incidence of recurrent GN

40/120 patients – 33% recurrence rate of glomerular disease in patients whose original disease was a glomerulopathy

Epidemiology of recurrent glomerulonephritis reported through various registries

Registry	Prevalence of GN Recuurence (%)	FSGS (%)	IgAN (%)	MPGN (%)	MN (%)	SLE (%)	HUS/TTP (%)
NAPRTCS 2006	12.0	5.5	-	0.8	-	-	1.1
ANZDATA 1996 to 2005	4.0	-	-	-	-	-	-
RADR 1998 TO 2001	2.9	1.0	0.1	0.1	0.1	0.1	0.2

META - ANALYSIS

	Recurrence	Graft Loss 5-10 Yrs
IgA	10 – 25%	2 - 10%
FSGS	20 - 40%	10 - 20%
MPGN (C3diseases)	20 - 50%	10 - 30%
Dense Deposit	>80%	10 - 25%
Membranous	5 - 30%	5 - 20%
ANCA Vasculitis	20%	Unknown
SLE	5 - 30%	<10%

Floege J NDT 18:1260, 2003

PATHOGENESIS OF RECURRENT DISEASE

Nephritogenic factors:

1. Anti-GBM disease – circulating anti-GBM Abs
2. Recurrent FSGS – serum from patient injected into rats resulted in increased urinary protein excretion
3. Membranous- anti PLA2R antibodies
4. MPGN- genetic disorders of C3

RECURRENT DISEASES OF THE ALLOGRAFT

GLOMERULAR

PRIMARY

- FSGS
- Membranous Nephropathy
- MPGN I
- MPGN II
- lgA Nephropathy
- Anti-GBM

SECONDARY

- HSP
- HUS
- SLE
- DM
- Amyloidosis
- Wegener's
- Cryoglobulinemia (EMC)
- Monoclonal Gammopathy

NON-GLOMERULAR

- Oxalosis
- Fabry's Disease
- Cystinosis
- Sickle cell nephropathy
- Scleroderma
- Alport's Syndrome

RECURRENT FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

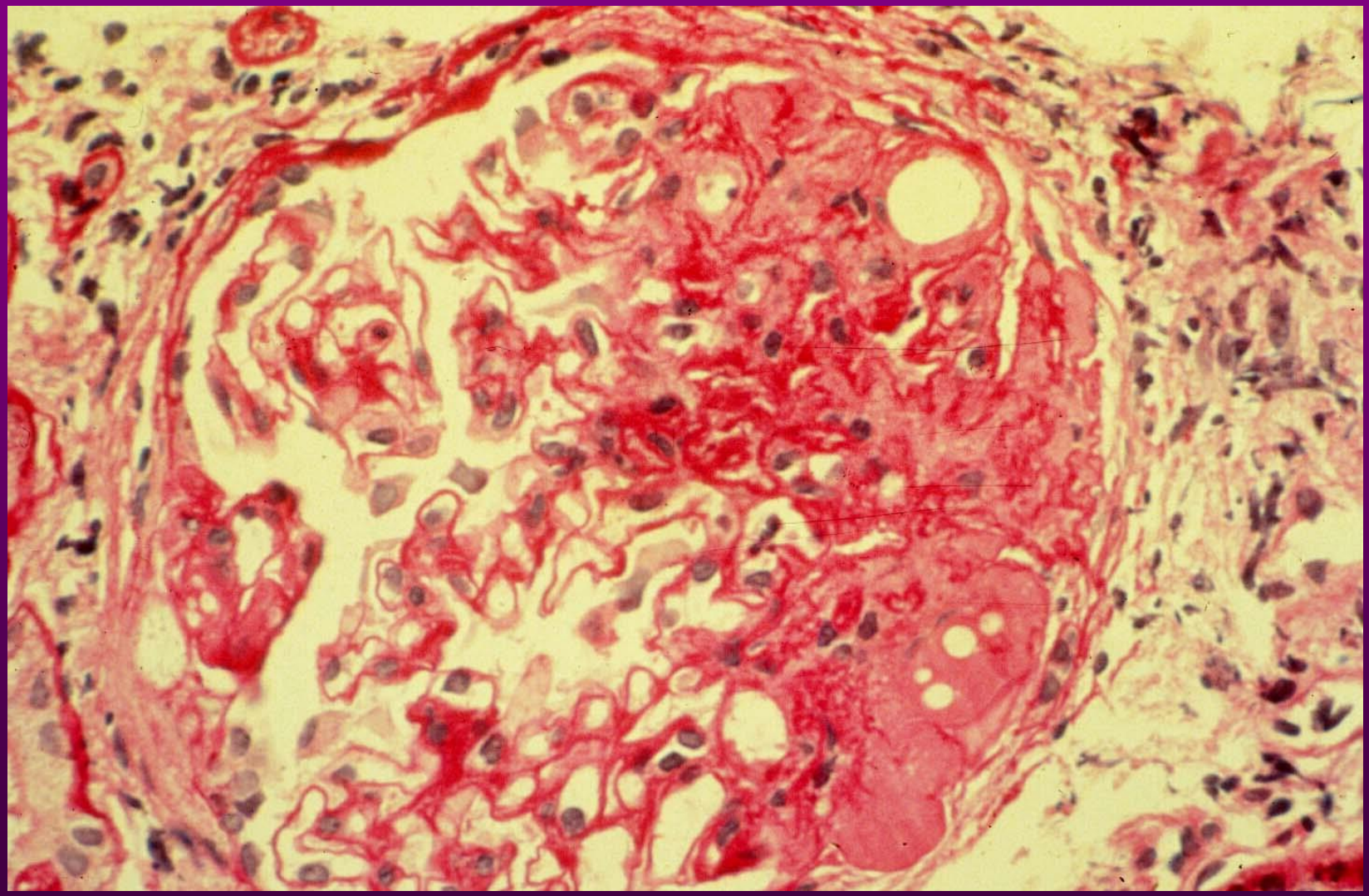
Recurrence rate: 20%-40%

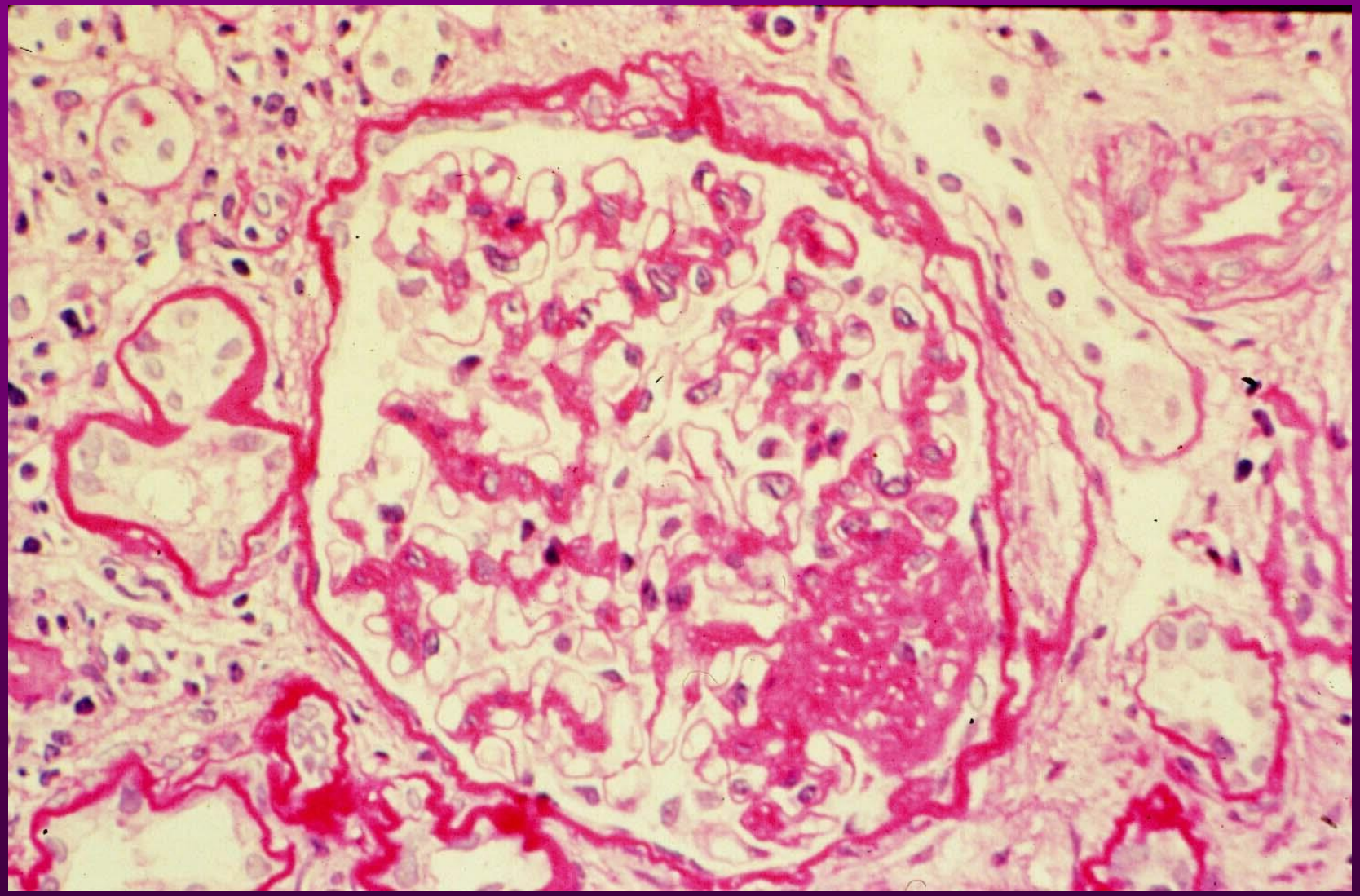
High risk group (recurrence rate of 50%)

- diagnosis to ESRD < 3 years
- younger patient (< 20 years of age)

Once recurrence in the first graft, subsequent graft with ~ 80% rate of recurrence

Histology: mesangial proliferation in the native kidney correlates with graft loss





RECURRENT FSGS

Clinical – most present with nephrotic range proteinuria; graft loss seen in 10-80% (highest in those with recurrence in earlier transplant);

Treatment – plasmapheresis, plasma exchange,MMF, high dose CSA, rituximab

Recommendations – living related transplants are those at high risk for recurrence or those with prior history of recurrence; wait 1-2 years between transplants; counseling for LRD

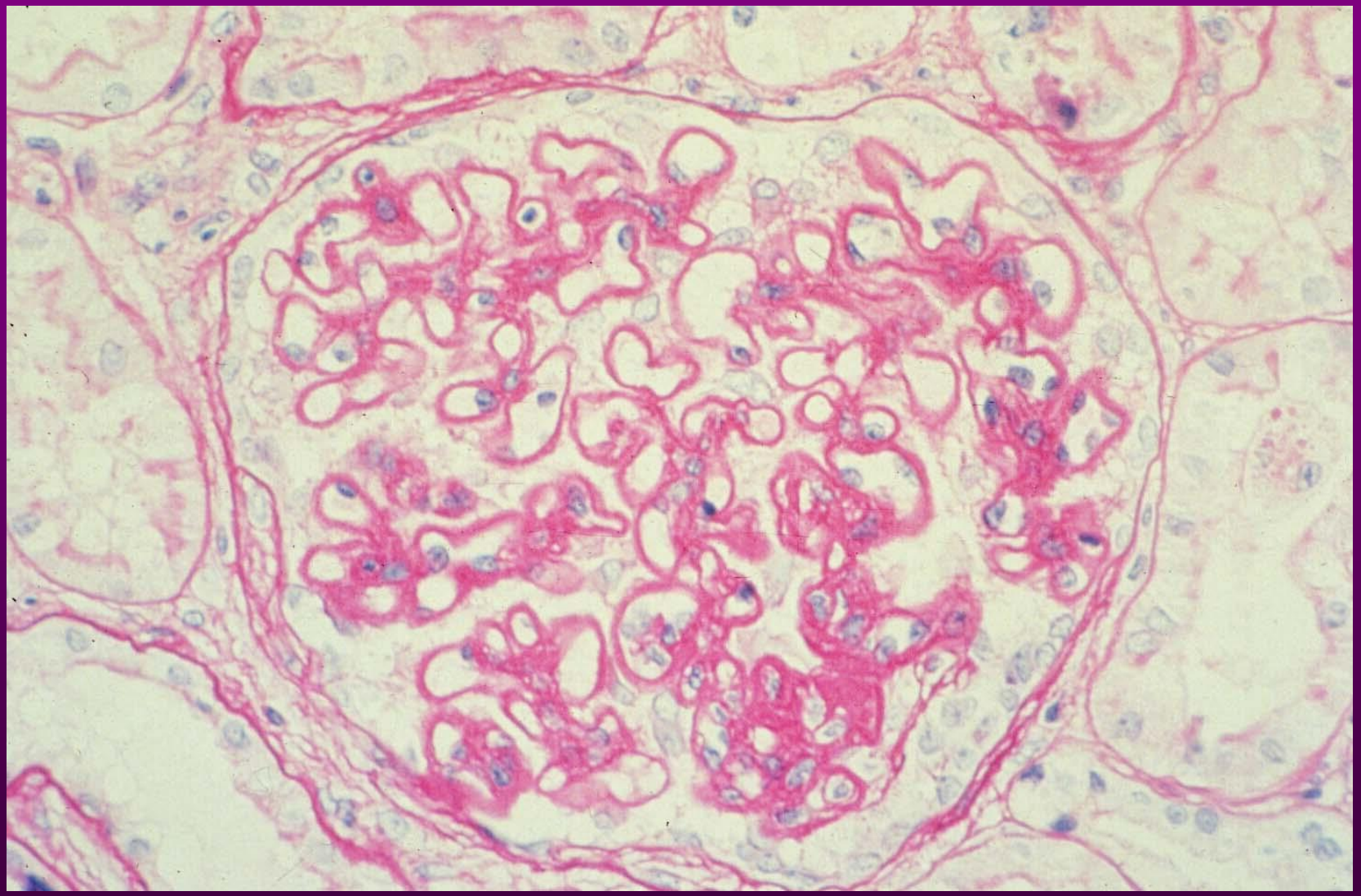
RECURRENT MEMBRANOUS NEPHROPATHY

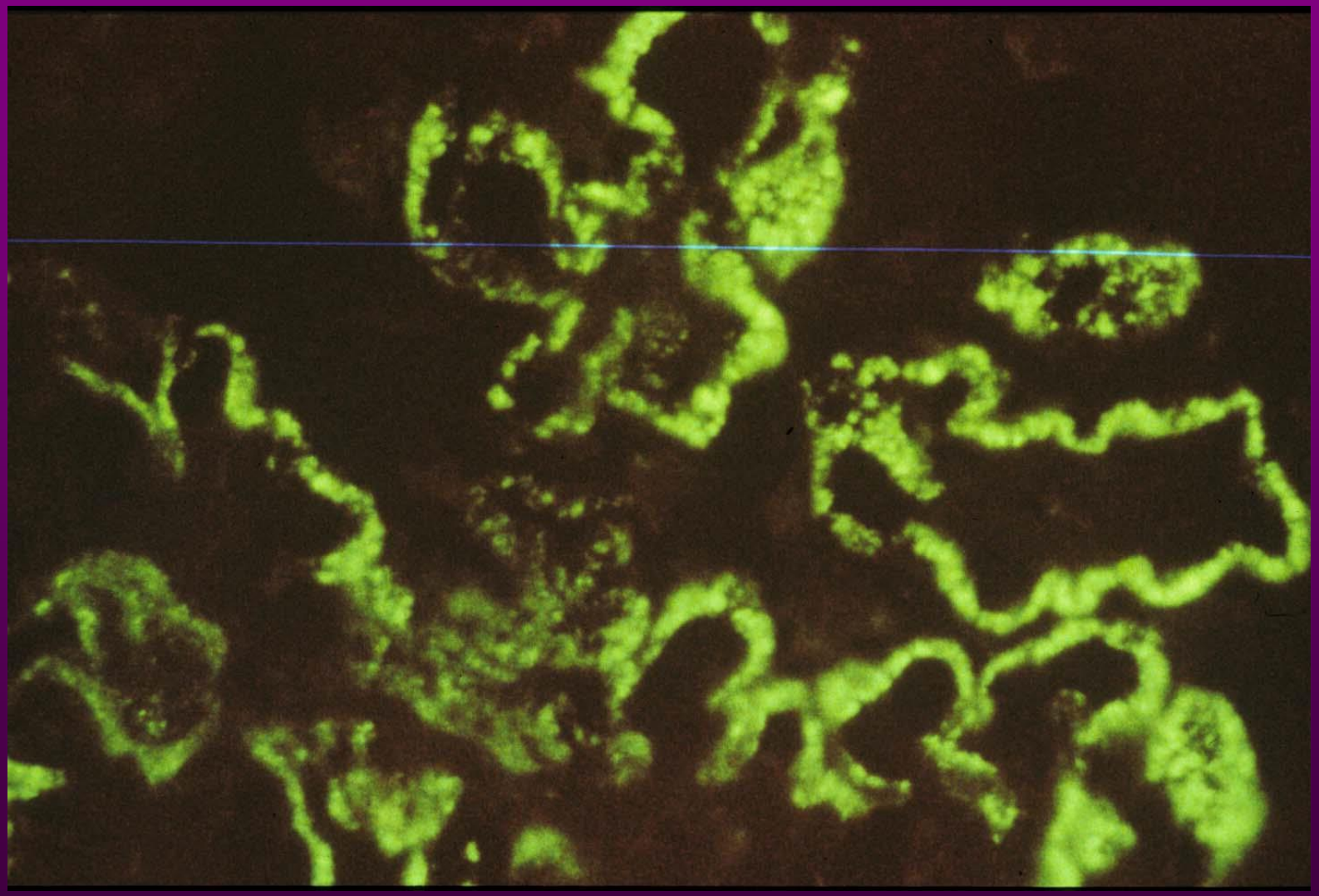
Recurrence rate – 5-30% accounts for < 25% of post-transplant membranous nephropathy

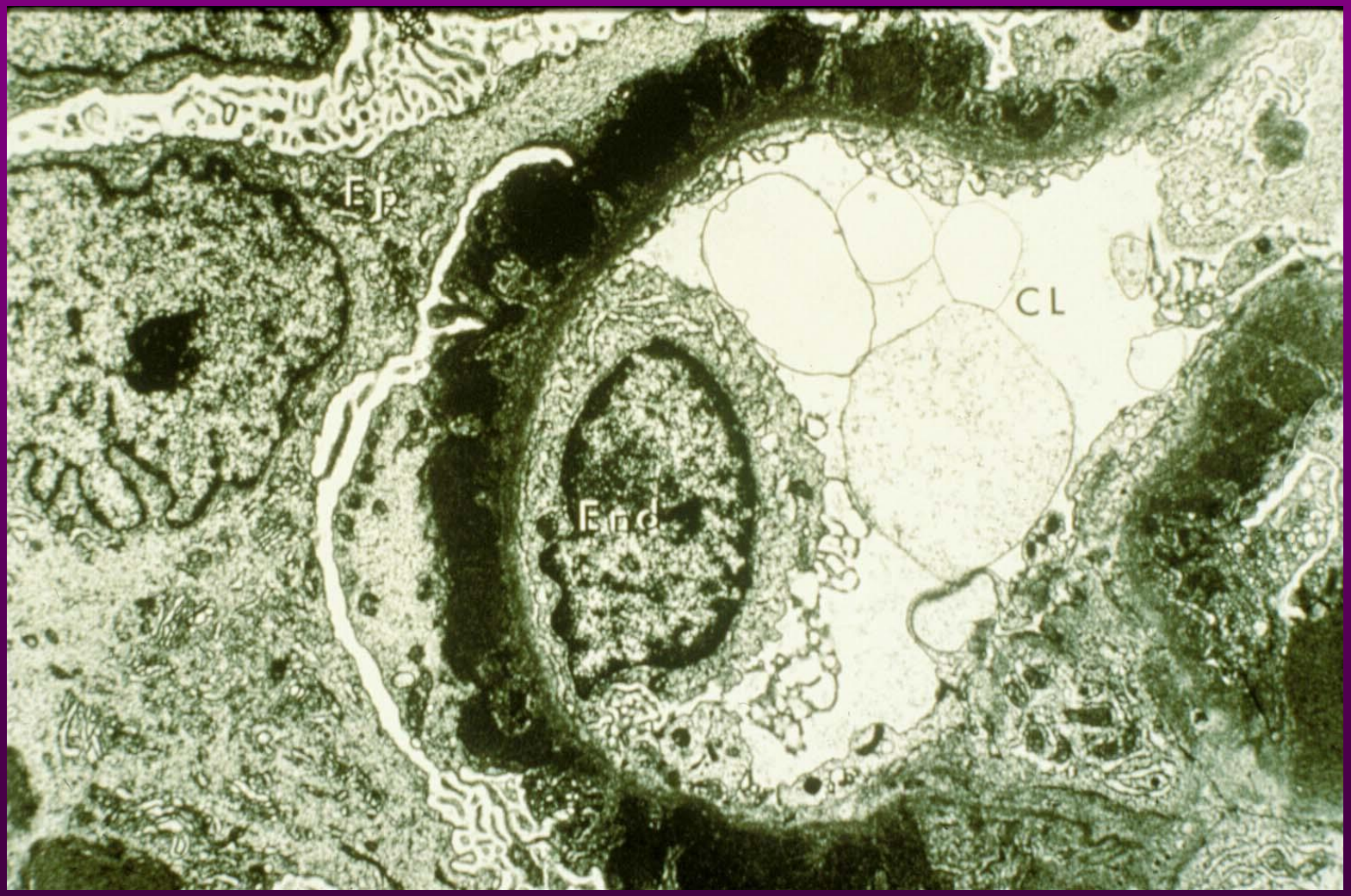
Clinical – most present early post transplant with nephrotic range proteinuria; graft loss – rare to 30% (± rejection); HLA-identical grafts at higher risk for recurrence

Pathophysiology- anti PLA2R antibodies

Treatment – no benefit with additional steroids; rituximab



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RECURRENT MPGN – TYPE I

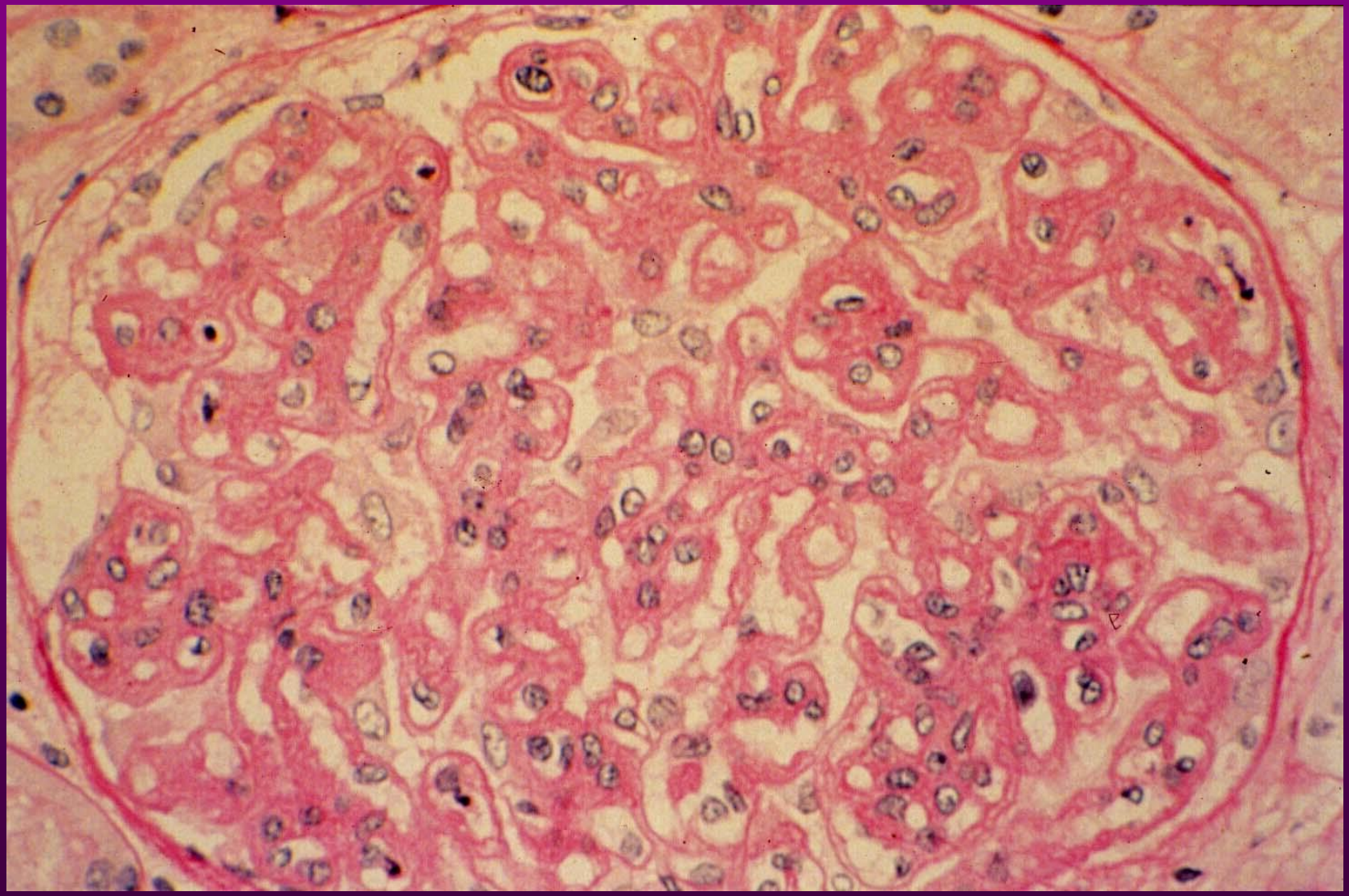
Recurrence rate - ~20-50%

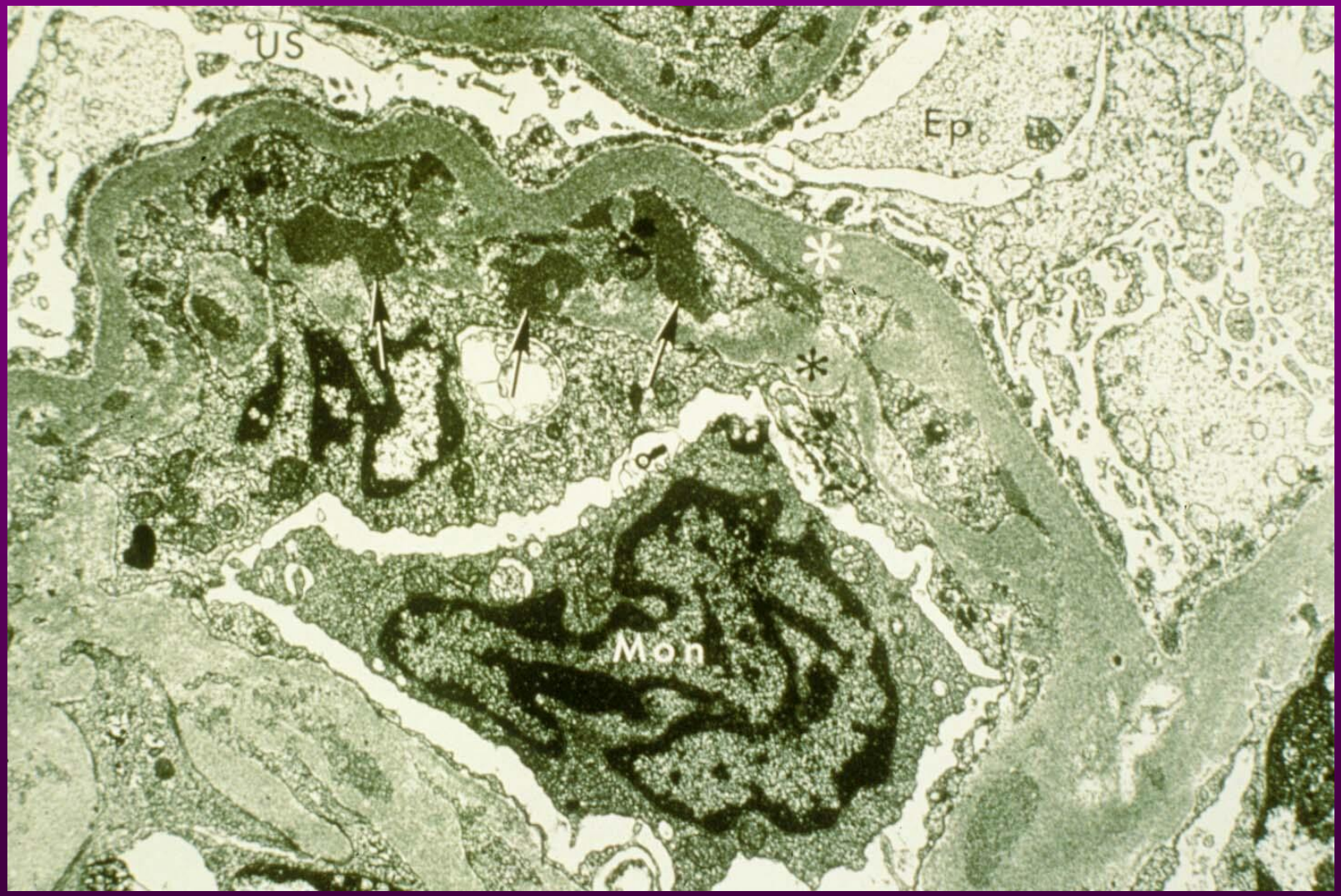
Histology- presence of subendothelial deposits and glomerular crescents may differentiate this from transplant glomerulopathy

Clinical – proteinuria, hematuria; serum C3 levels not helpful in diagnosis or prognosis; graft loss in 28-42%

Pathophysiology-genetic disorder of C3 regulation

Treatment – anti complement hybrid antibodies

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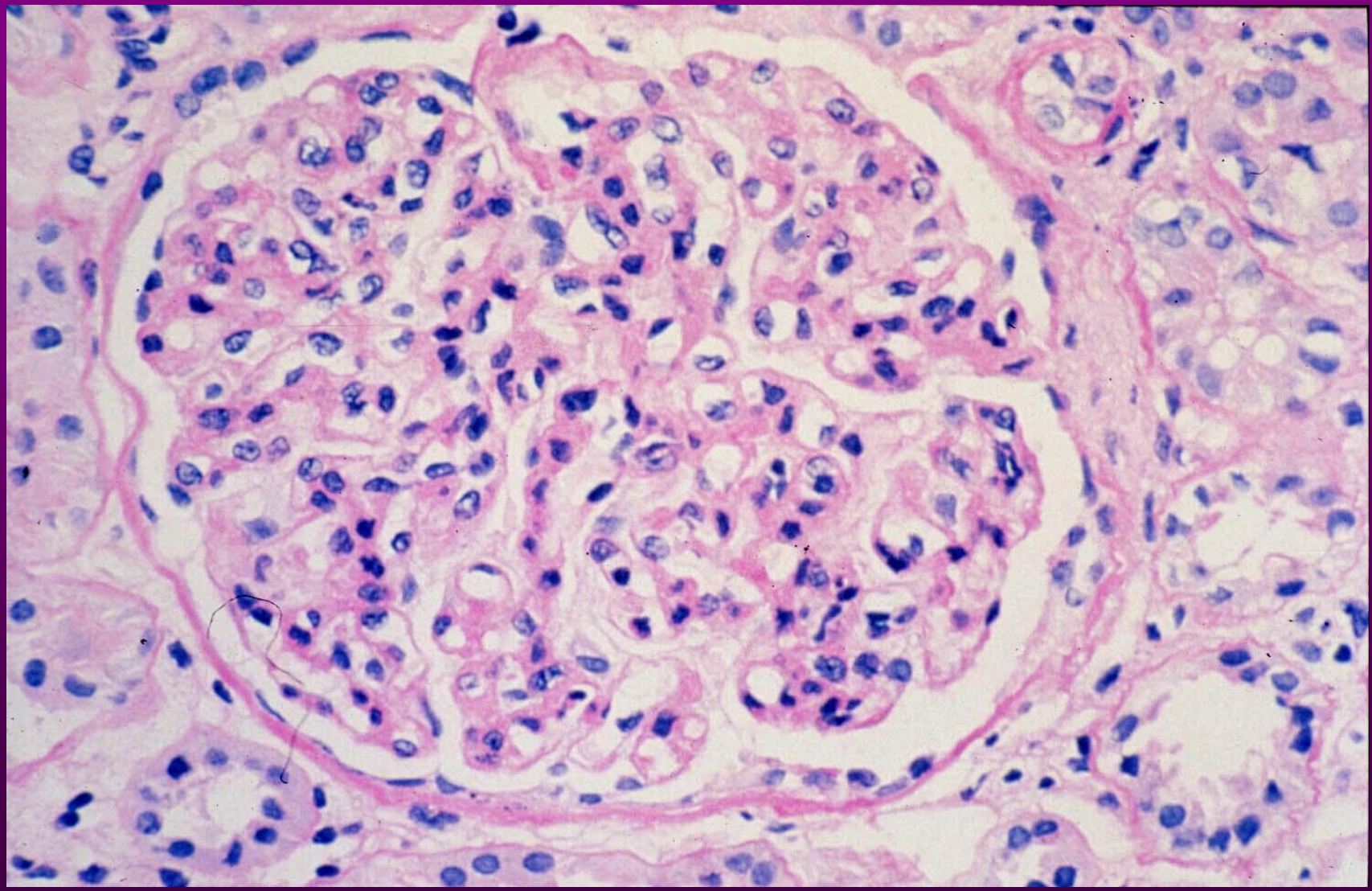
RECURRENT MPGN TYPE II

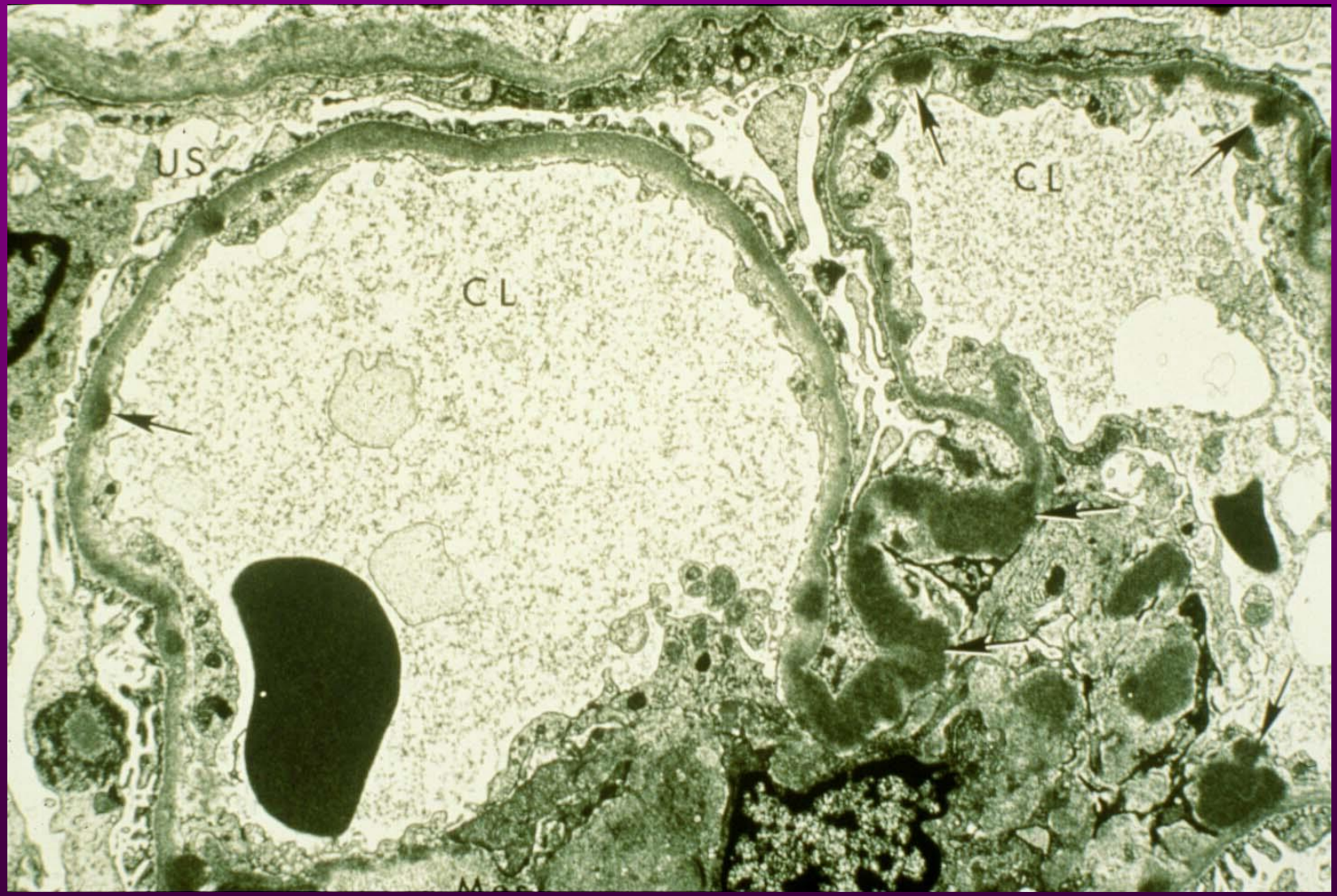
Recurrence rate – 50-100%

Histology – subendothelial dense deposits

Clinical – proteinuria, hematuria; graft loss 10-20%, up to 50% (risk factors – male sex, RPGN, recurrent nephrotic syndrome)

Treatment – plasma exchange (?)

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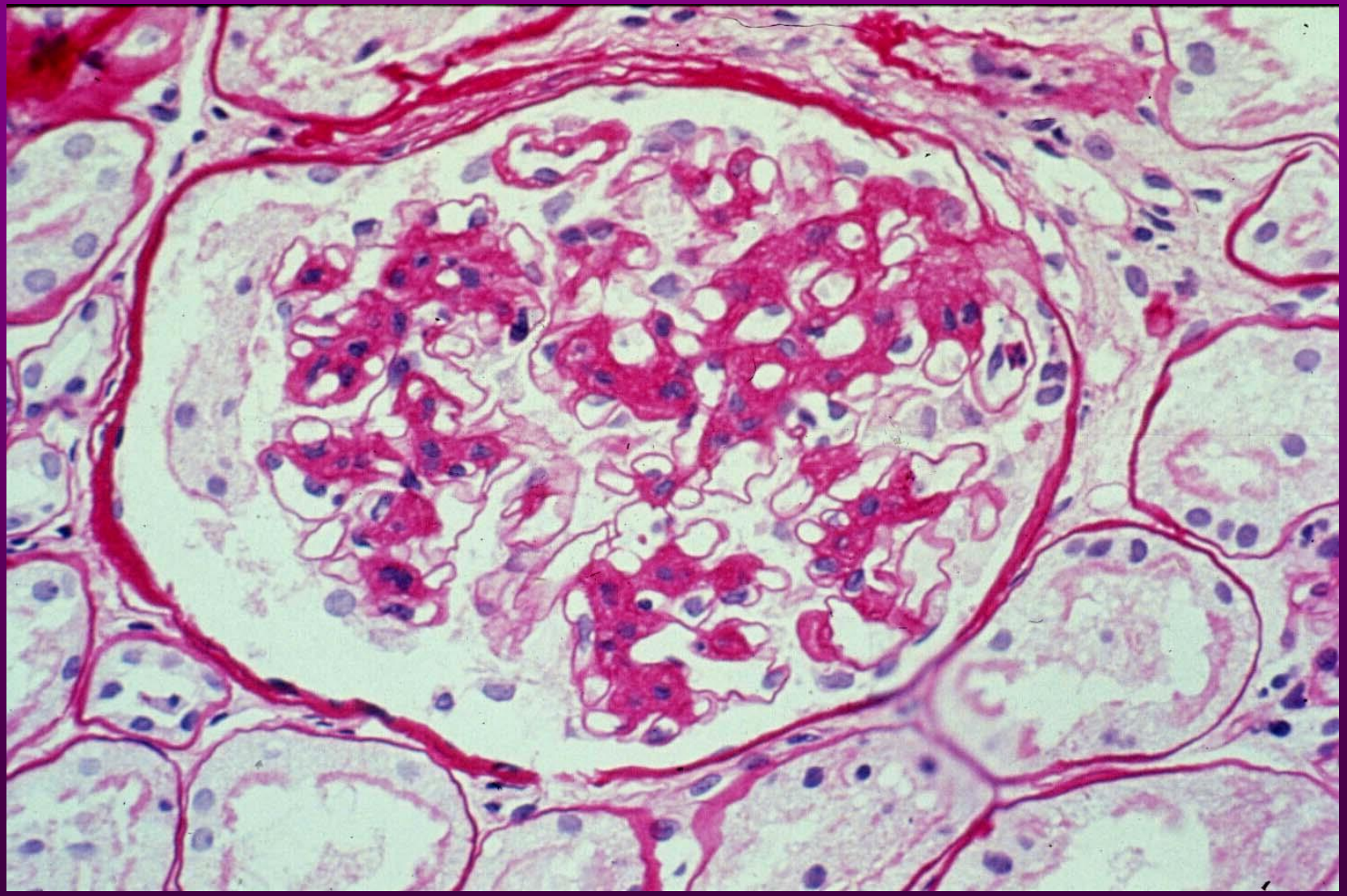
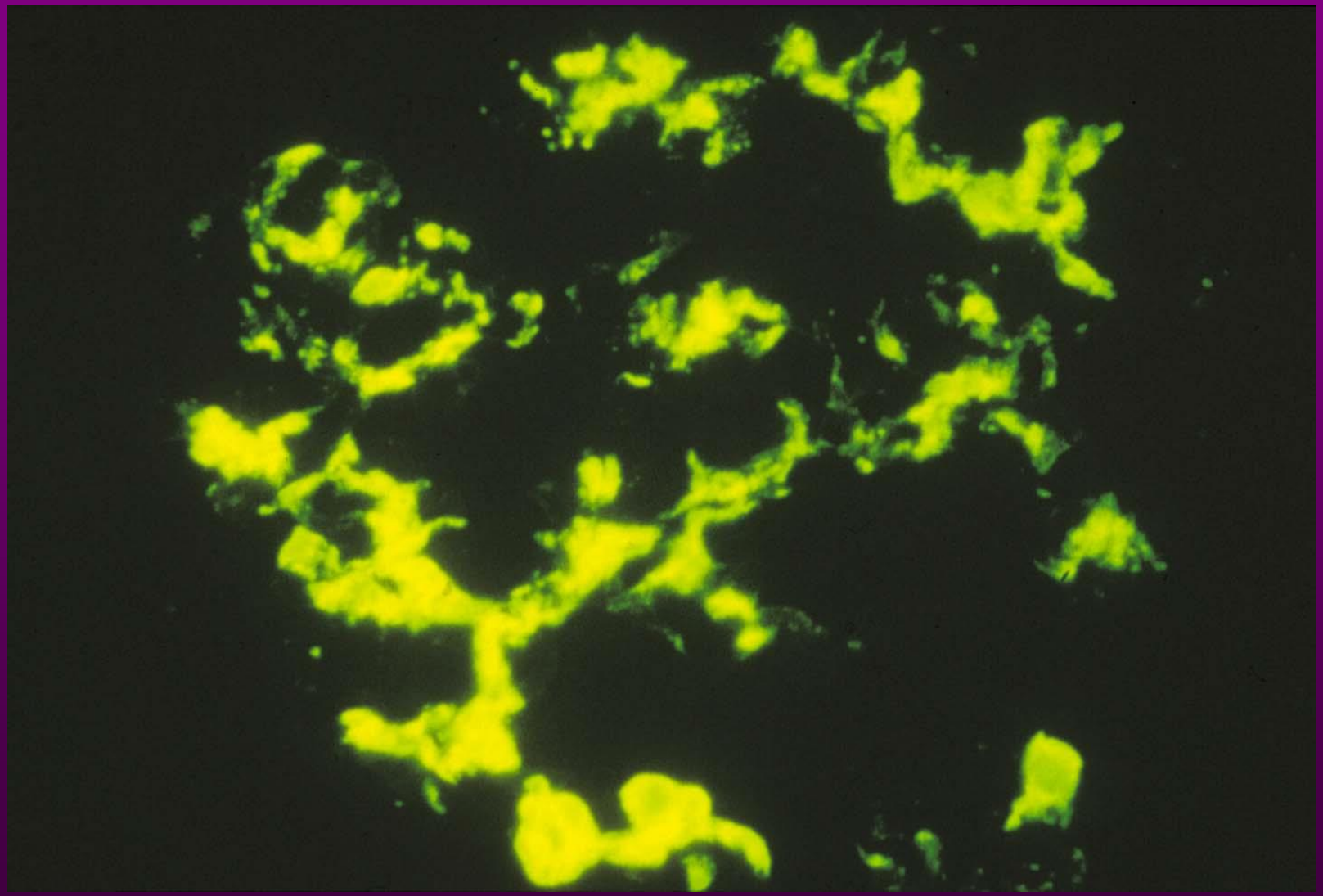
RECURRENT lgA NEPHROPATHY

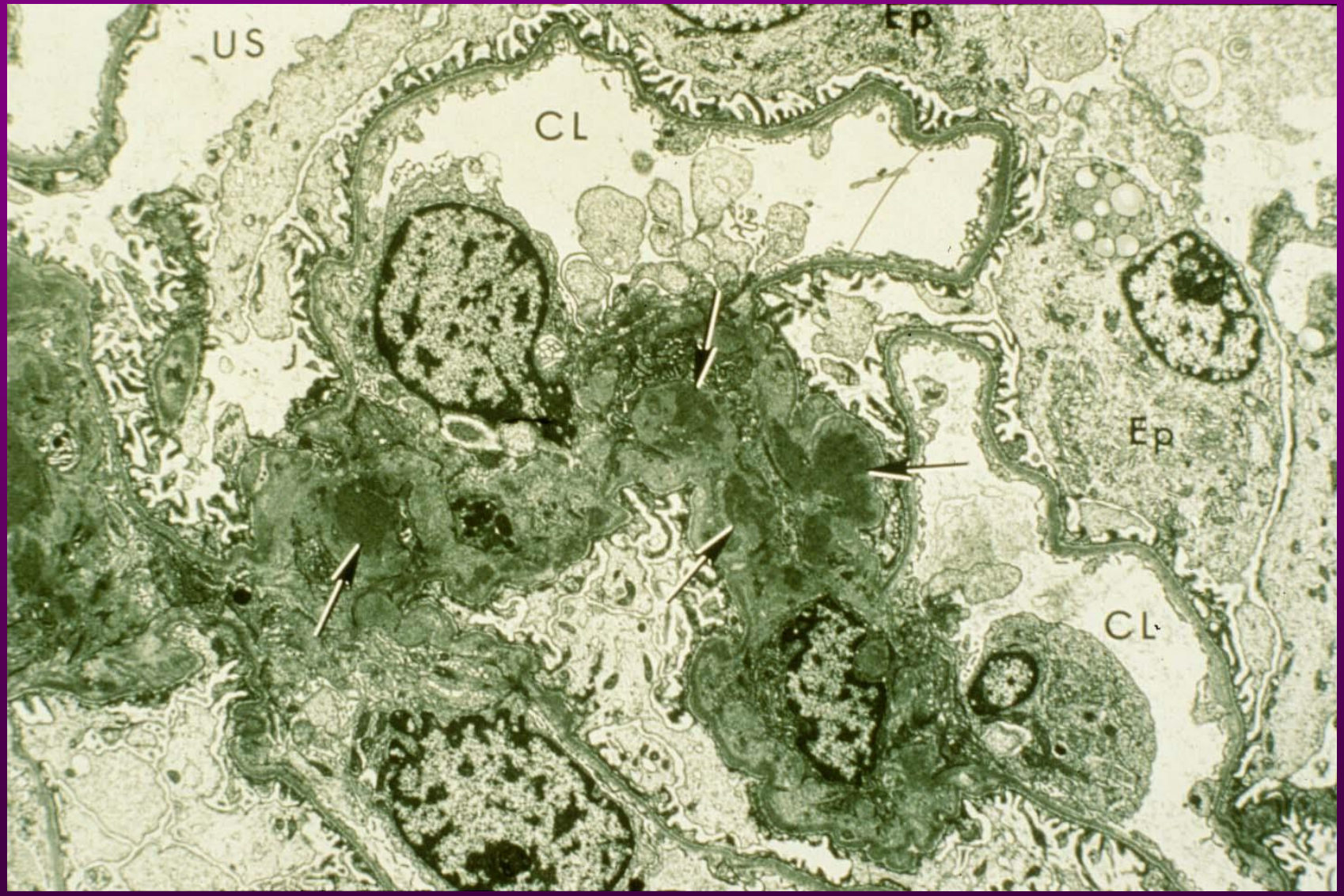
Recurrence rate – 10-25%

Histology – prominent mesangial lgA staining

Clinical – hematuria, proteinuria; recurrence more common in LRA (83%)/HLA B35, DR4; lgA rheumatoid factors may be elevated; graft loss is minimal (<10%)



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Recurrent MPGN

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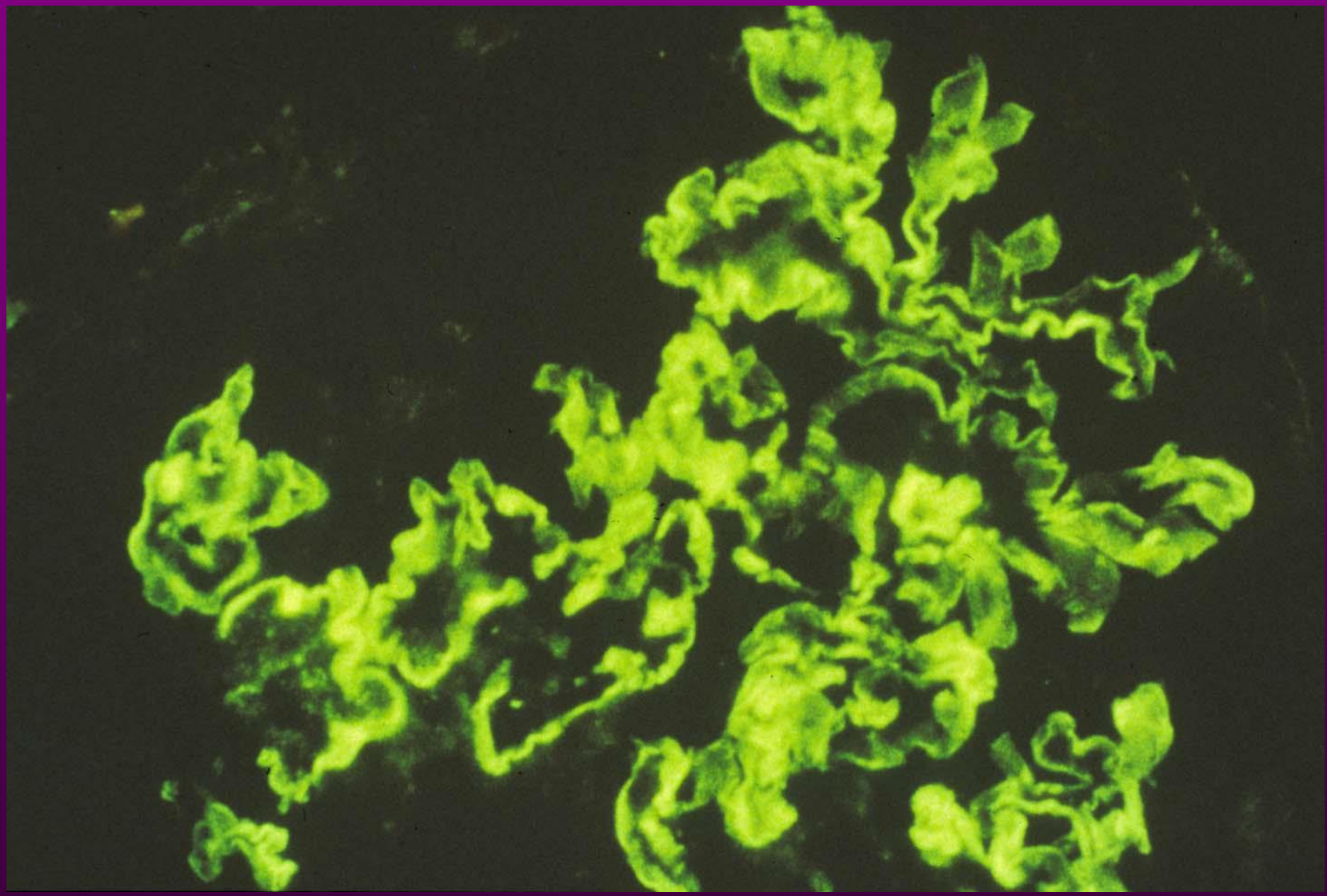
RECURRENT ANTI-GBM NEPHRITIS

Recurrence rate – clinical recurrence (nephritis) ~25%; histologic recurrence ~50% old data. Should be 0% now

Clinical – hematuria/proteinuria; some will resolve spontaneously; graft loss is rare

Recommendation: wait 6-12 months after loss of serum anti-GBM antibodies prior to transplantation



RECURRENT HENOCH-SCHOENLEIN PURPURA

Recurrence rate – clinical recurrence <10%; histologic recurrence (mesangial lgA) ~30%

Clinical – hematuria/proteinuria ± purpura; those with recurrence of purpura and renal involvement had active disease within 8-18 mos of tx; graft loss may approach 40-75% if both renal and skin involved

Recommendation – wait at least 6-12 mos, up to 2 years after disappearance of purpura before tx

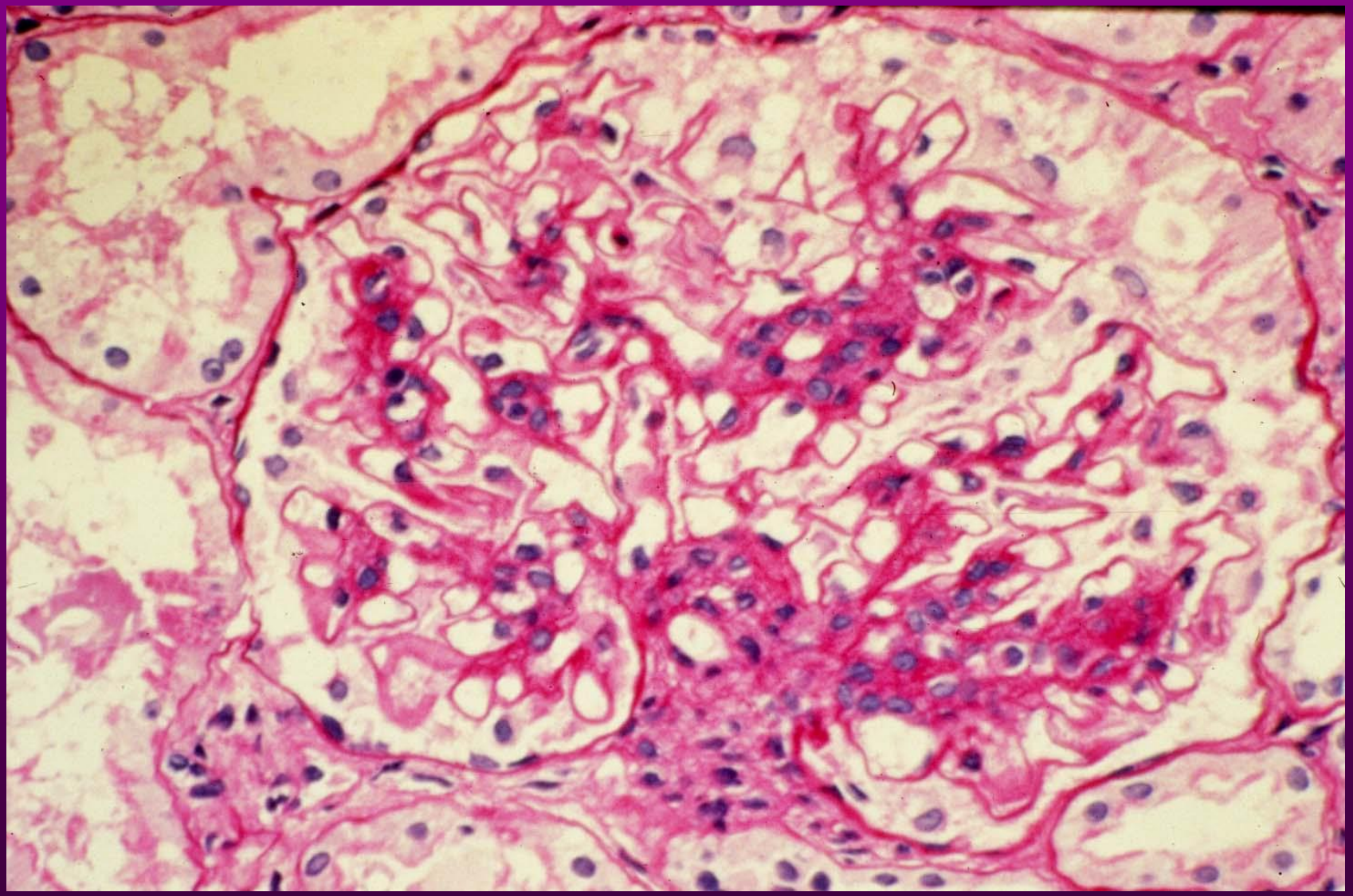
RECURRENT LUPUS NEPHRITIS

Recurrence rate – old view <1%; 5 cases documented; recent understanding 25% (Goral et al 2003)

Clinical – malar rash, Raynaud's, proteinuria (1-3gms), hematuria, pyuria; elevated anti-DNA titers and depressed complement levels; graft loss – none

Treatment – high dose steroids, chlorambucil, plasmapheresis

Recommendation – clinical and serologic quiescence prior to transplantation



RECURRENT HEMOLYTIC UREMIC SYNDROME

HUS associated with viral infections, pregnancy, oral contraceptives, chemoRx, CsA, malignant HTN, PSS< irradiation nephritis, severe acute vascular rejection, prograf

Recurrence rate - ~25-50%

Pathogenesis – lack of plasma factors leading to endothelial prostacyclin synthesis; CsA effect on prostaglandin synthesis

Histology – microvascular thrombosis

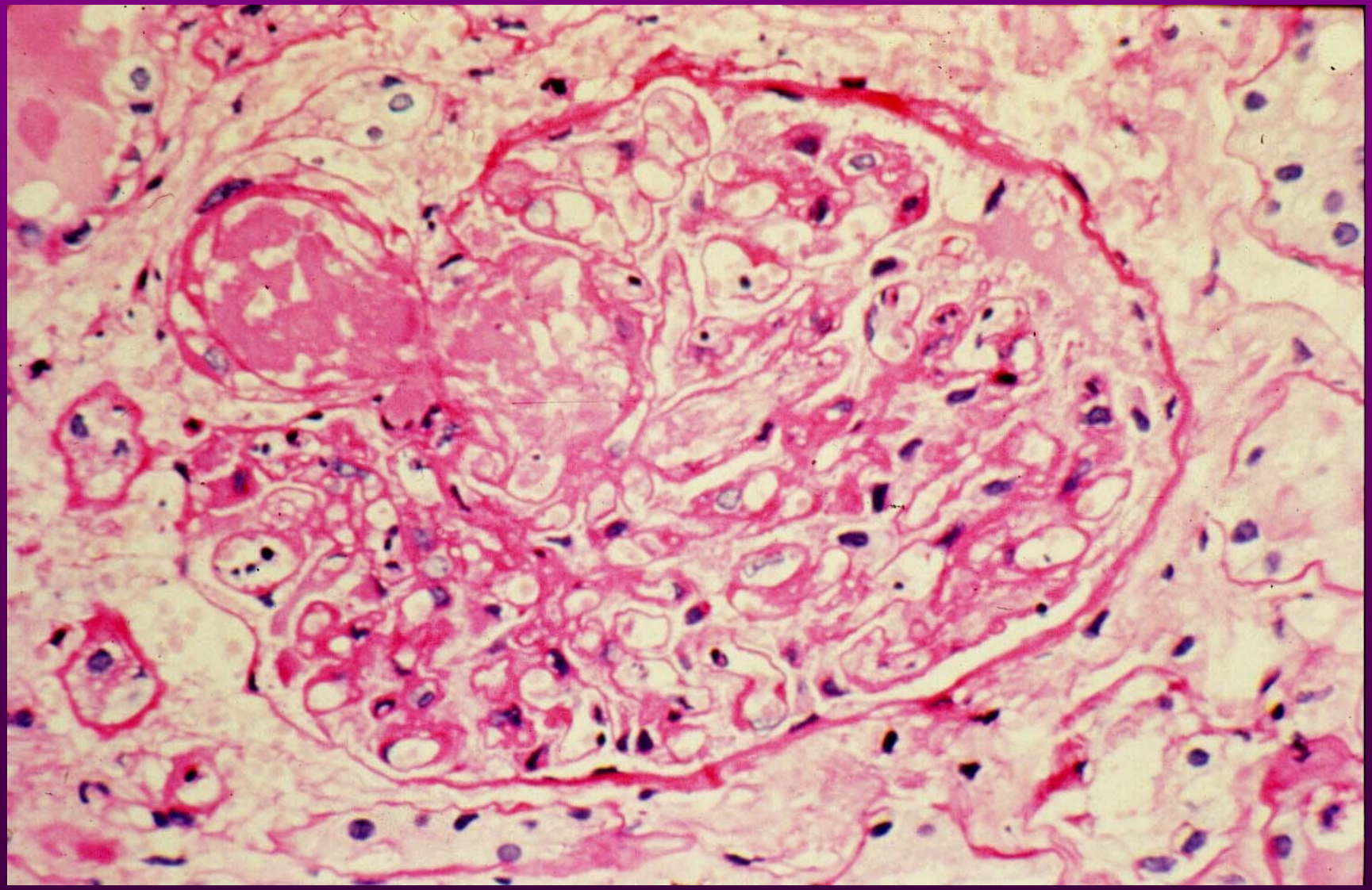
RECURRENT HUS

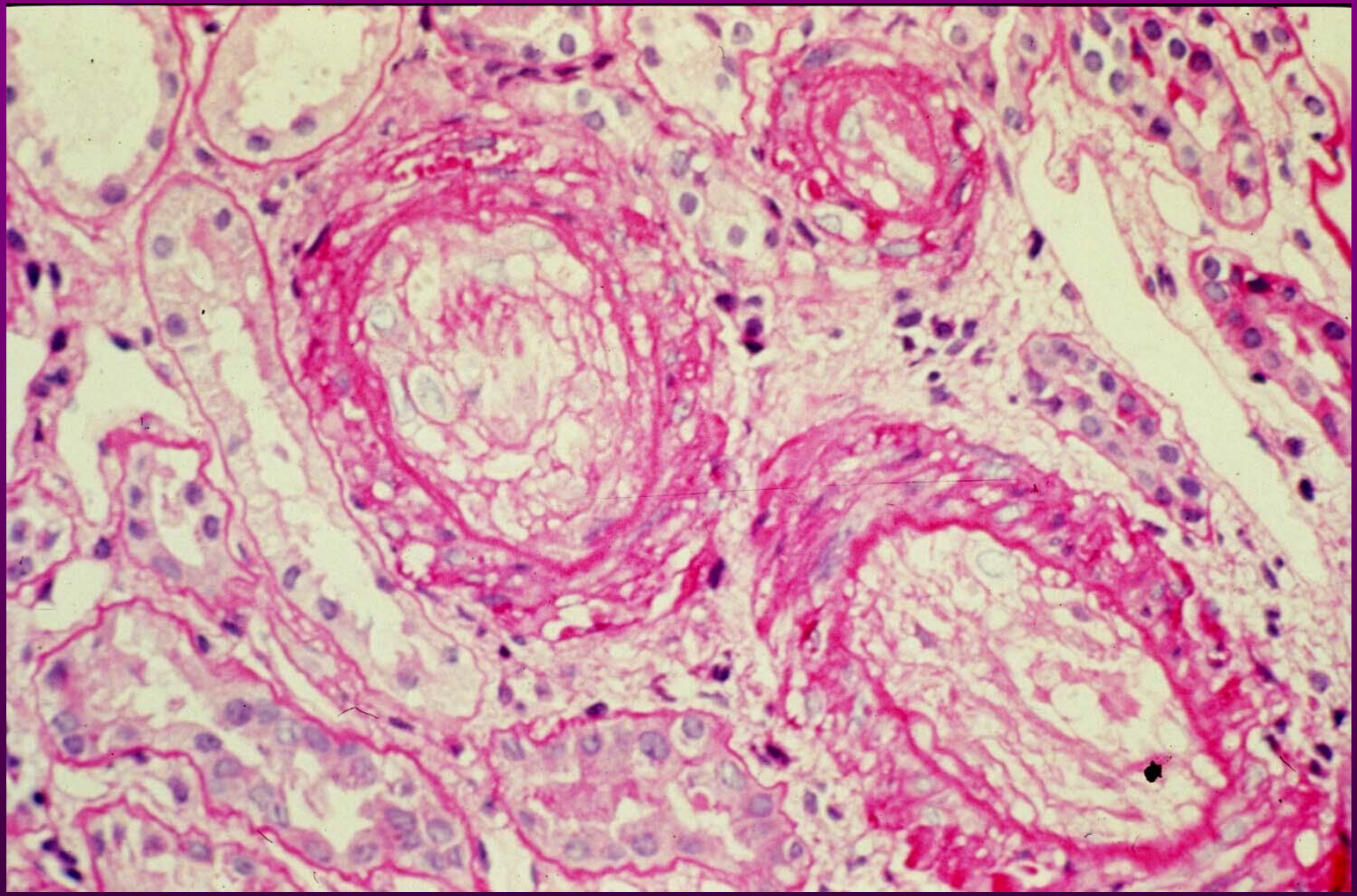
Clinical – microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure; graft loss – 10-40%

Treatment –

1. **Prophylactic – low dose salicylate, dipyridamole**
2. **Acute – plasma infusions, plasma exchange**

Recommendations – avoid CsA, ALG and living related transplants



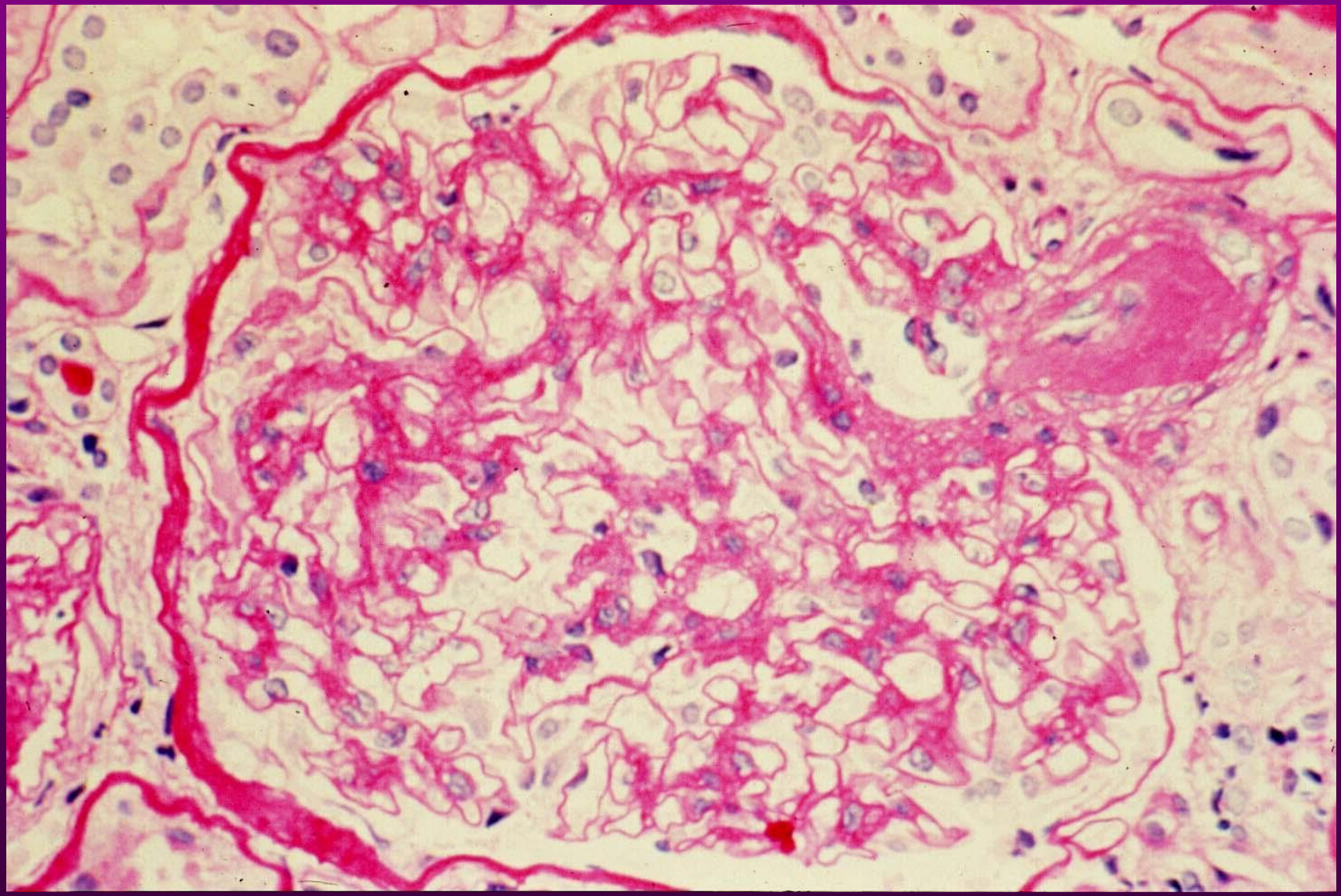


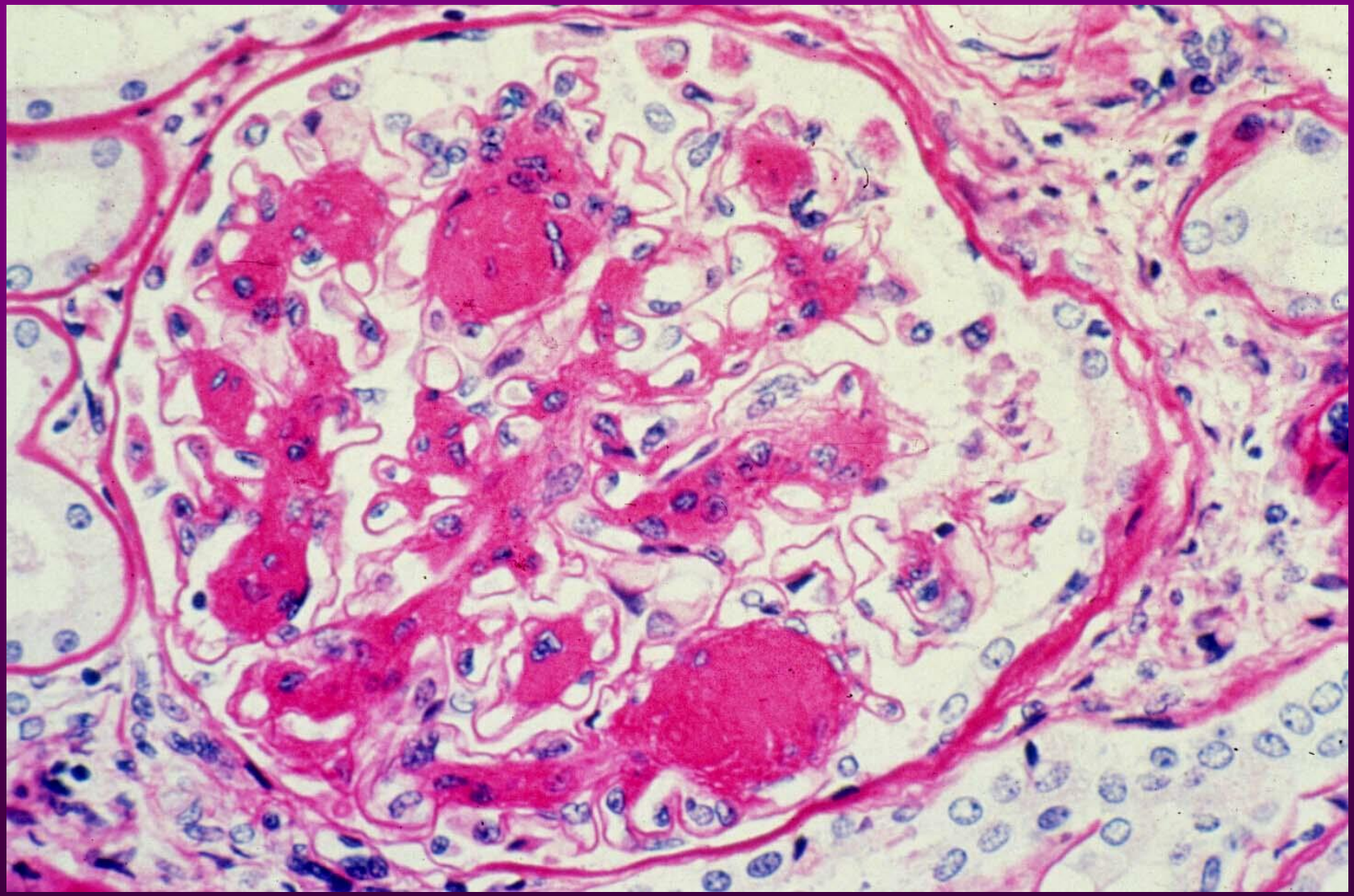
RECURRENT DIABETIC NEPHROPATHY

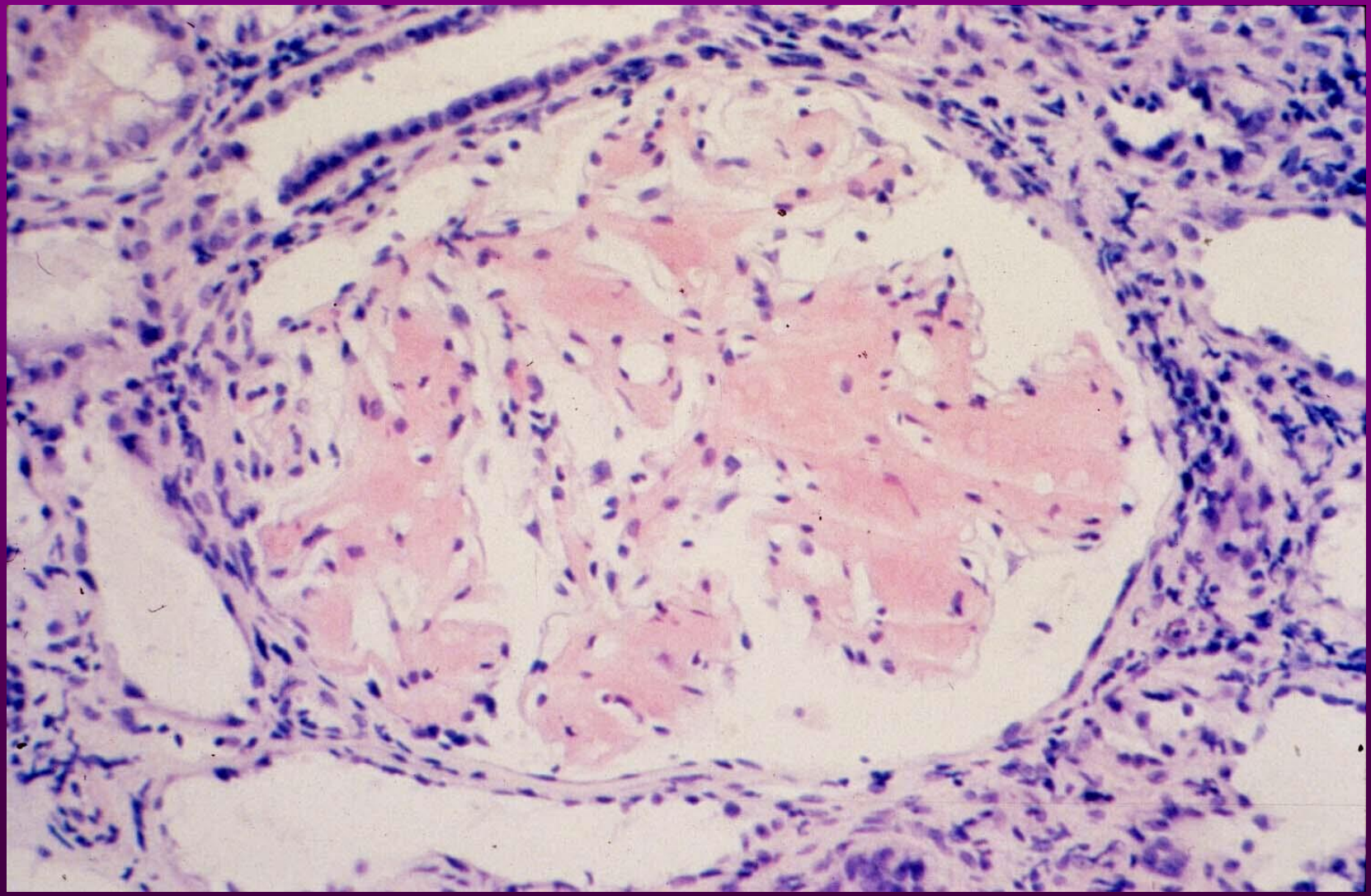
Recurrence rate – 100%

Histology – GBM thickening (2years); hyalinization of afferent and efferent arterioles (4 years); related to glycemic control (lesions not observed in renal/pancreas transplants)

Clinical – proteinuria; decline in renal function much faster than diabetic nephropathy in native kidneys





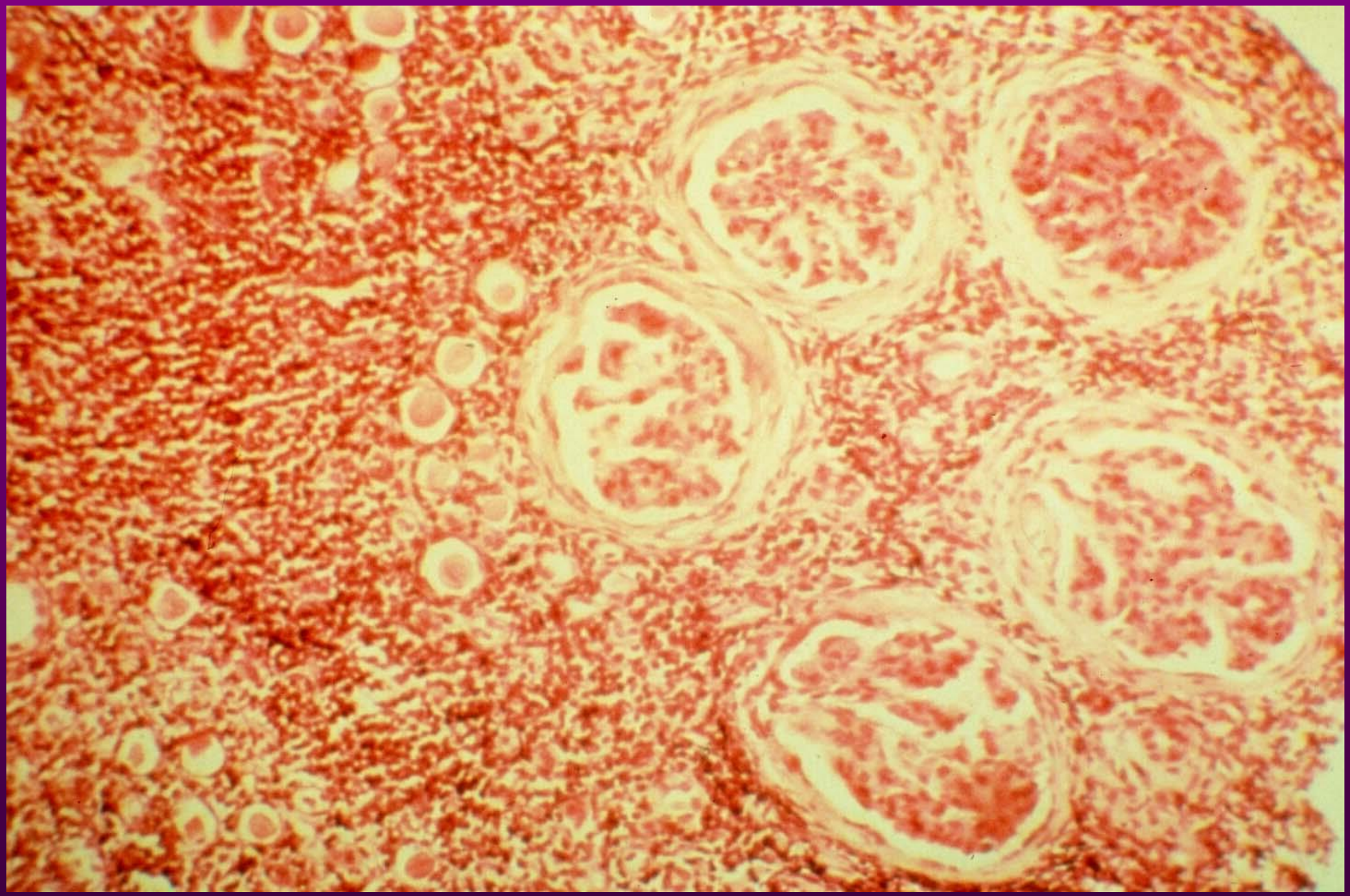


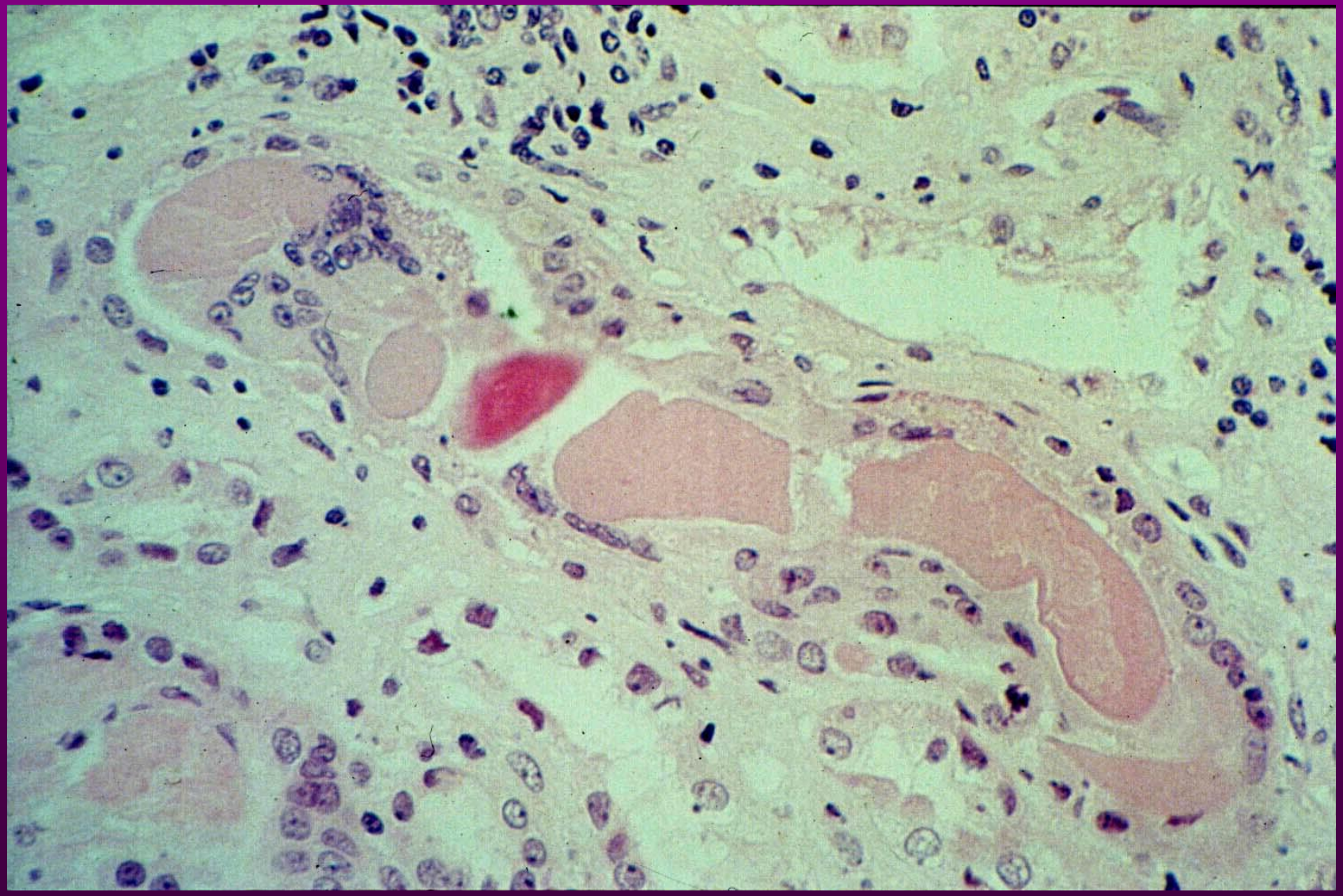
ESSENTIAL MIXED CRYOGLOBULINEMIA

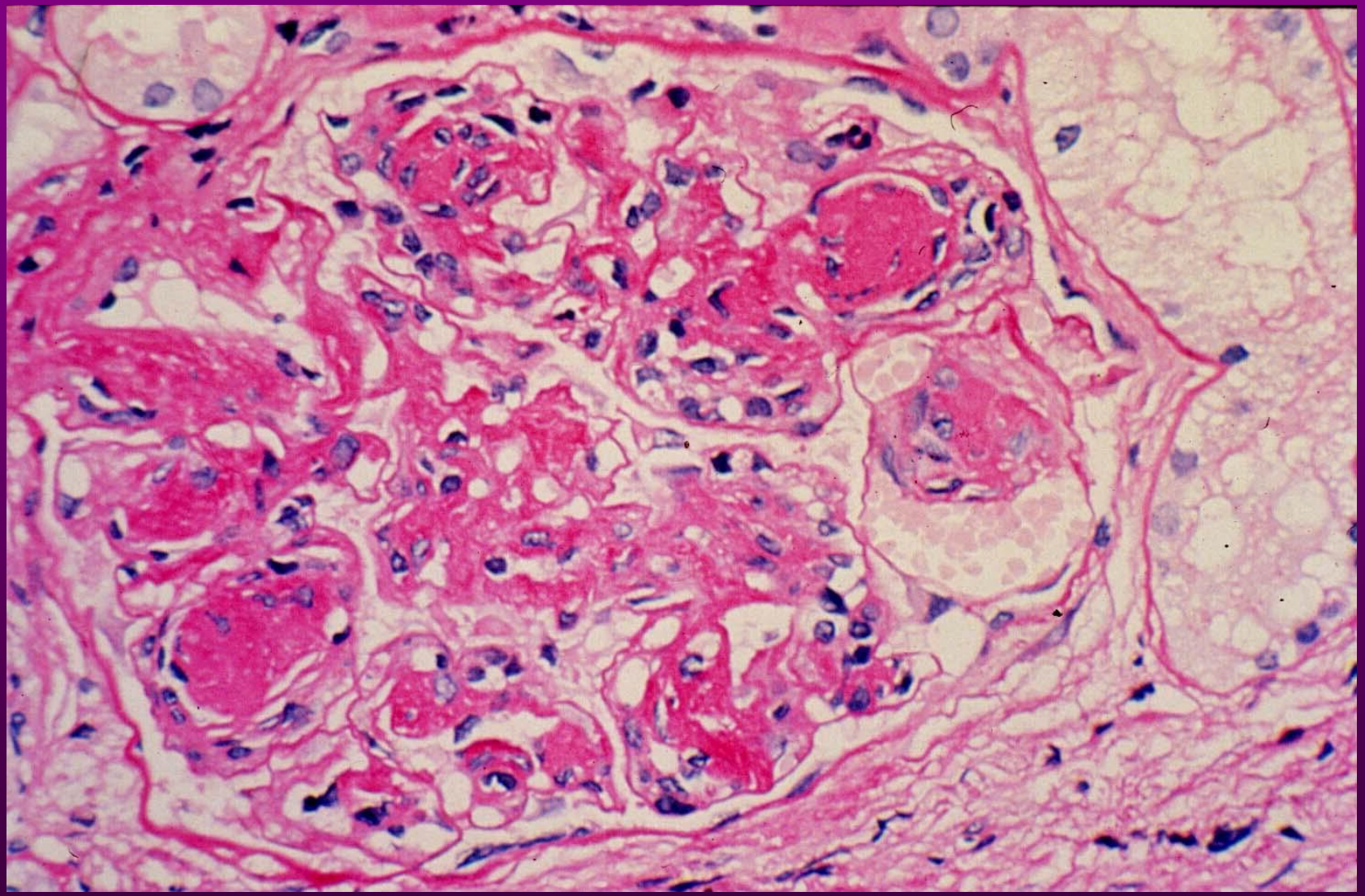
Recurrence rate - ~50%

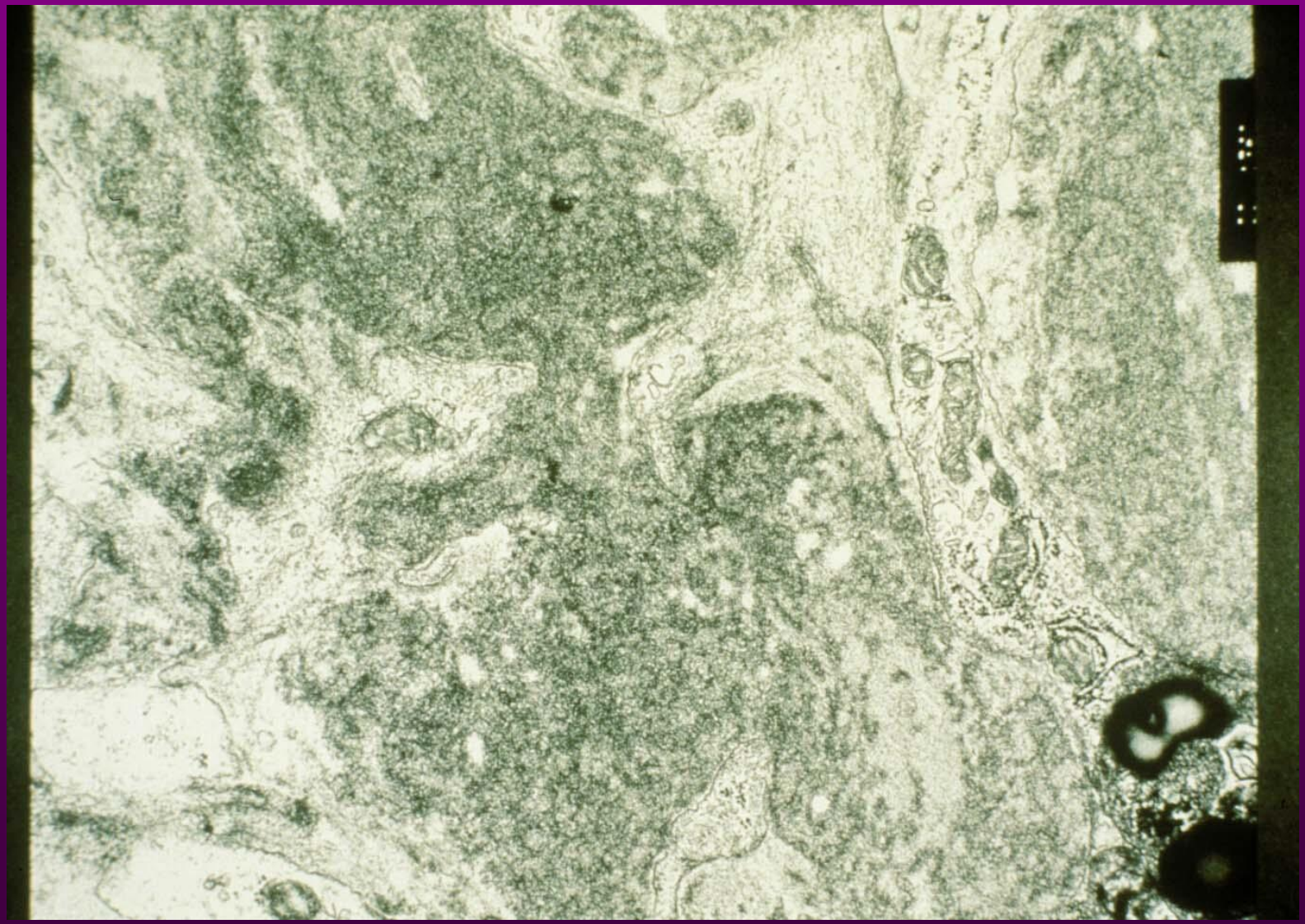
Clinical – renal (proteinuria, hematuria) and extrarenal (purpura, arthraigias) manifestations; cryoglobulins, rheumatoid factor and decreased C3 and C4 levels in the serum

Recurrence may occur despite clinical and serologic quiescence; may lead to graft loss









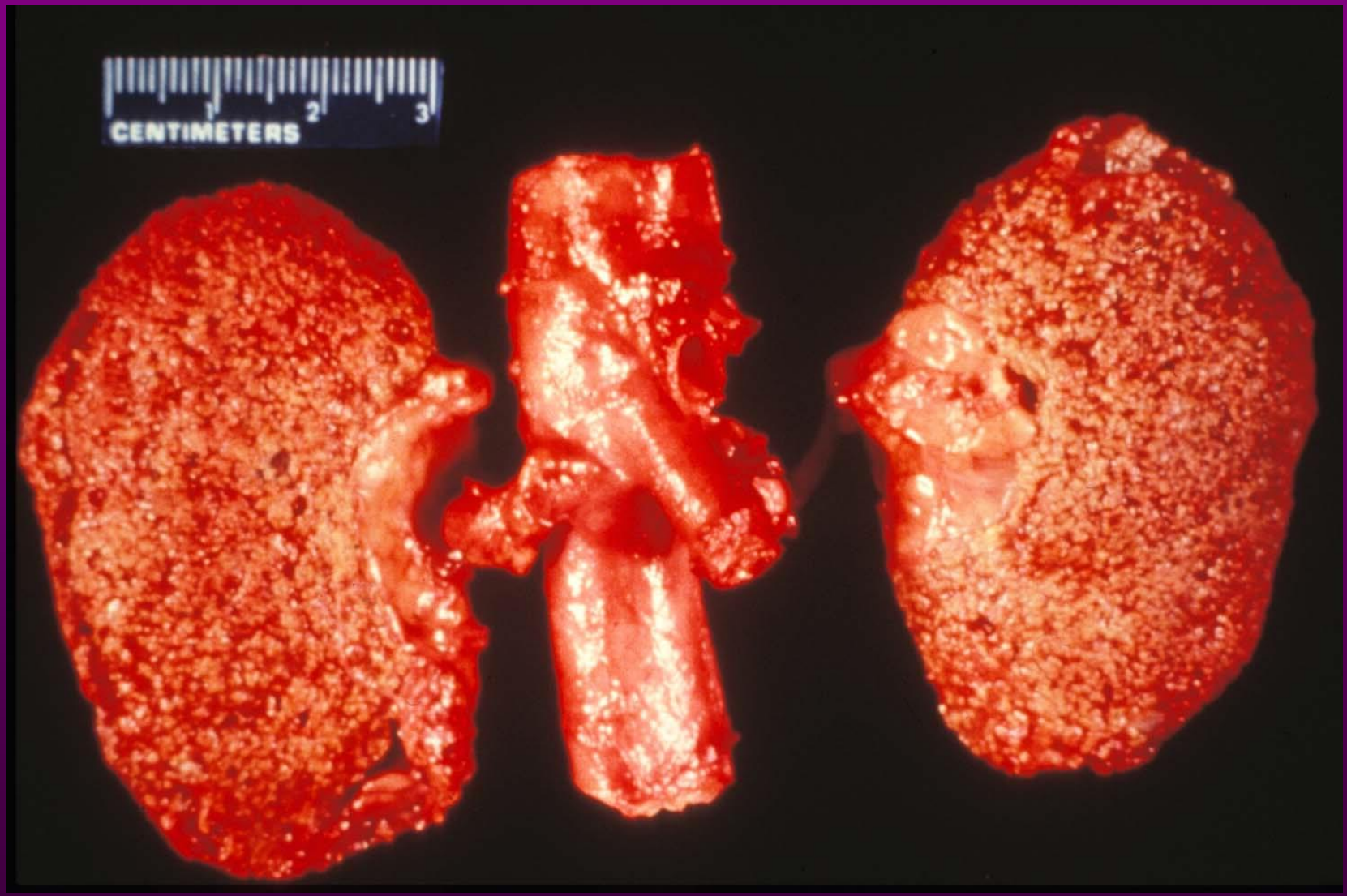
OXALOSIS

Inborn error in glyoxalate metabolism – oxalate accumulation

Recurrence rate – 90%

Clinical – Success more likely if:

1. Early tx – GFR ~20 ml/min1.73 meter squared
2. Aggressive pre-op dialysis to deplete oxalate pool
3. Maintenance of high rates of urine flow; avoid allograft non-function and rejection
4. Simultaneous renal-liver transplant (enzyme replacement)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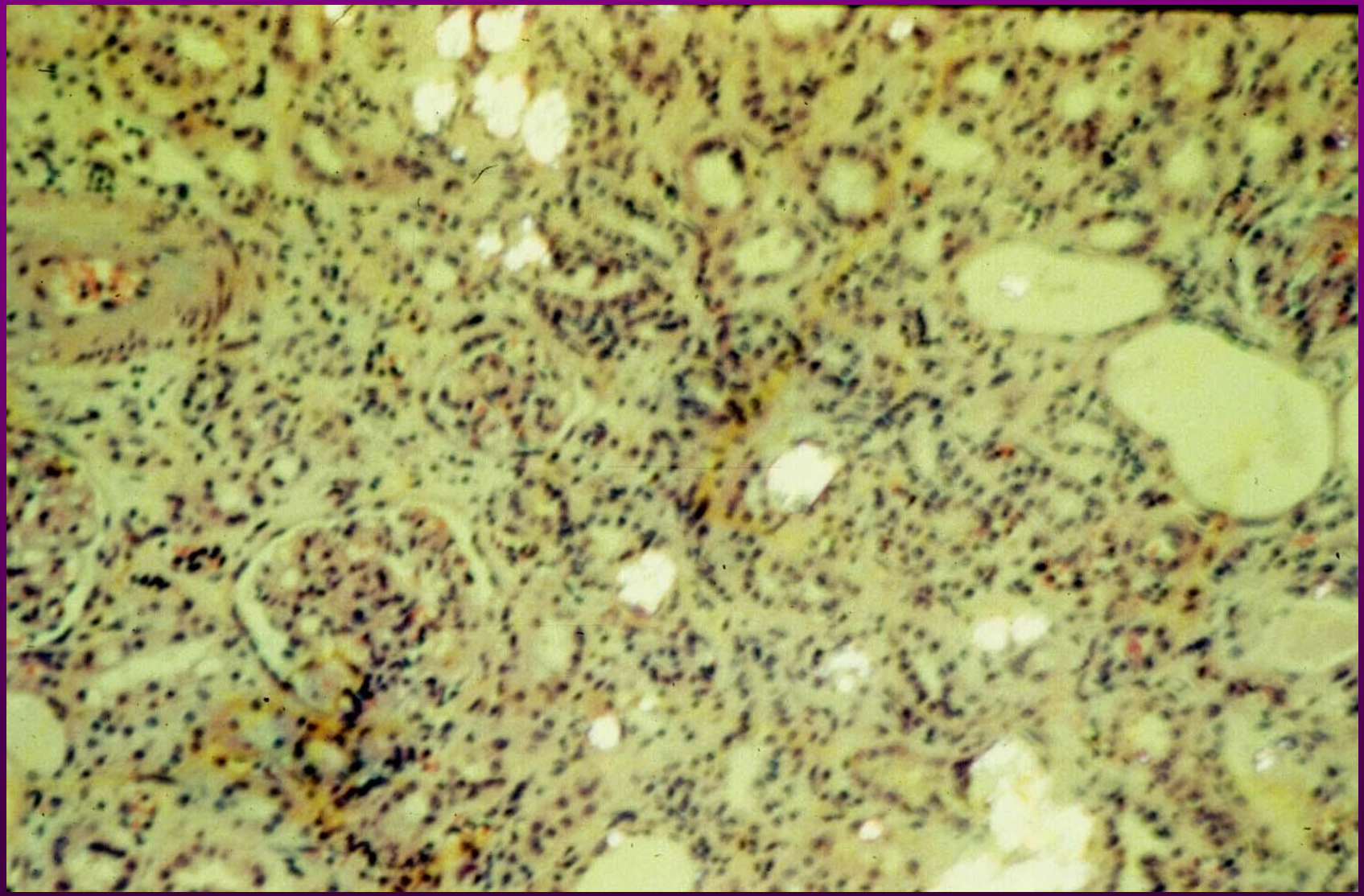

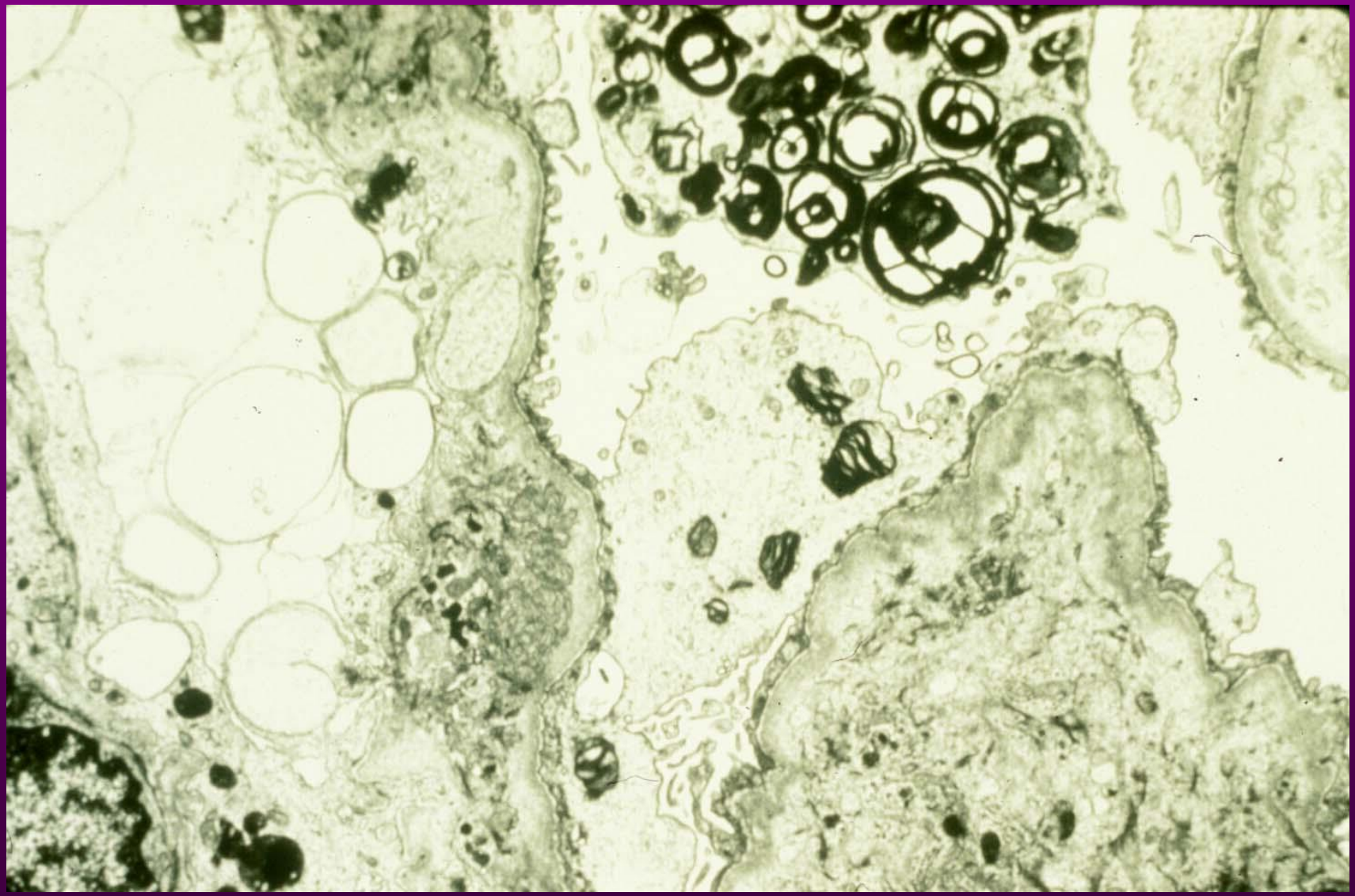

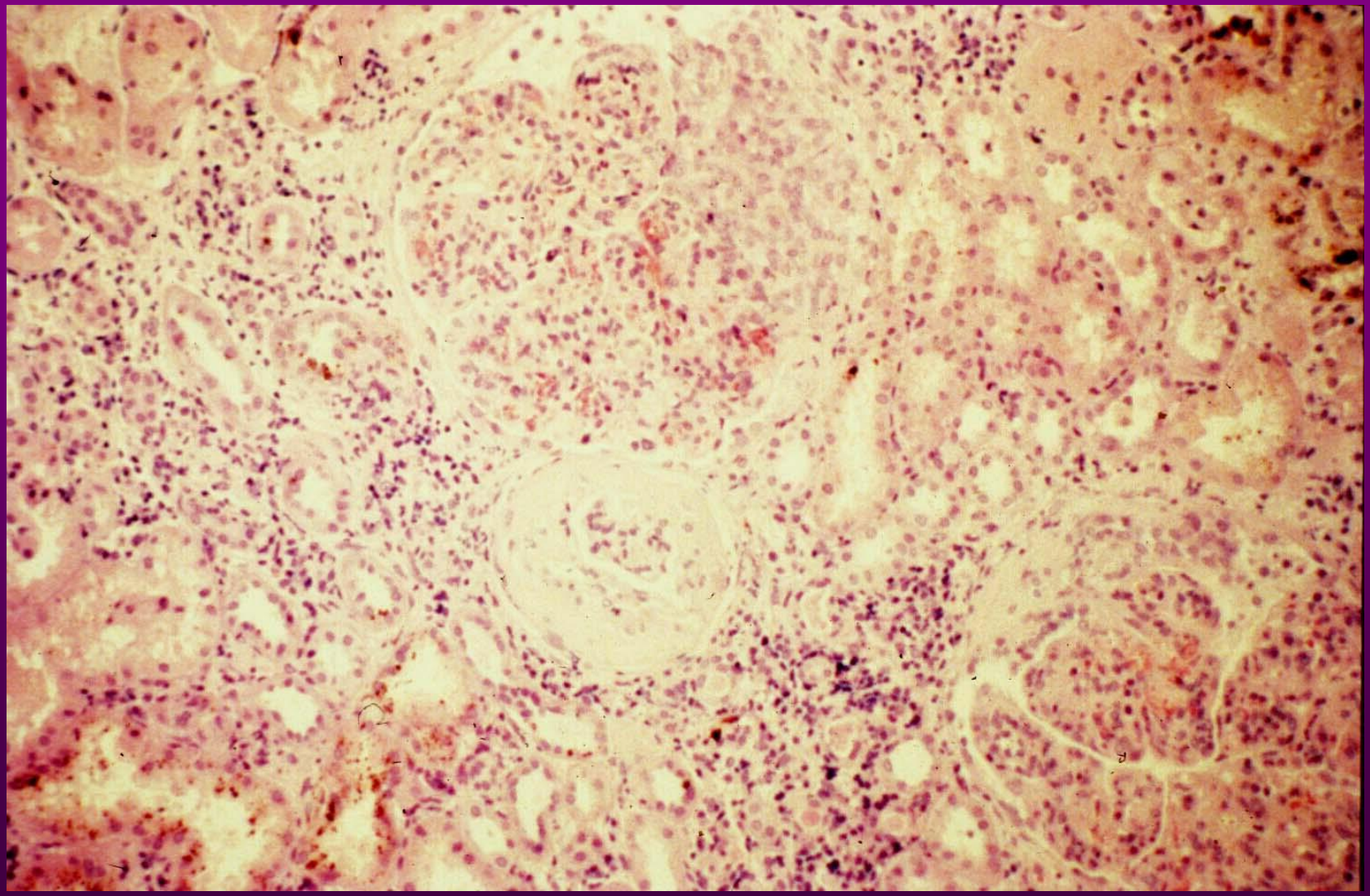

ALPORT'S SYNDROME

Recurrence – rare, only one reported case

Clinical – patients are at small risk to develop anti-GBM nephritis due to exposure to "normal" GBM antigens present in the allograft (lack a domain of type IV collagen)

May have serum anti-GBM Abs, abnormal U/A, linear lgG staining, GN; crescentic GN associated with graft loss

CONCLUSION

- THE TRANSPLANTED KIDNEY IS NOT IMMUNE FROM DE NOVO OR RECURRENT RENAL DISEASE
- INCREASINGLY IMPORTANT CAUSE OF GRAFT LOSS
- A REGISTRY IS NOW IN PLACE TO AIDE IN OUR UNDERSTANDING