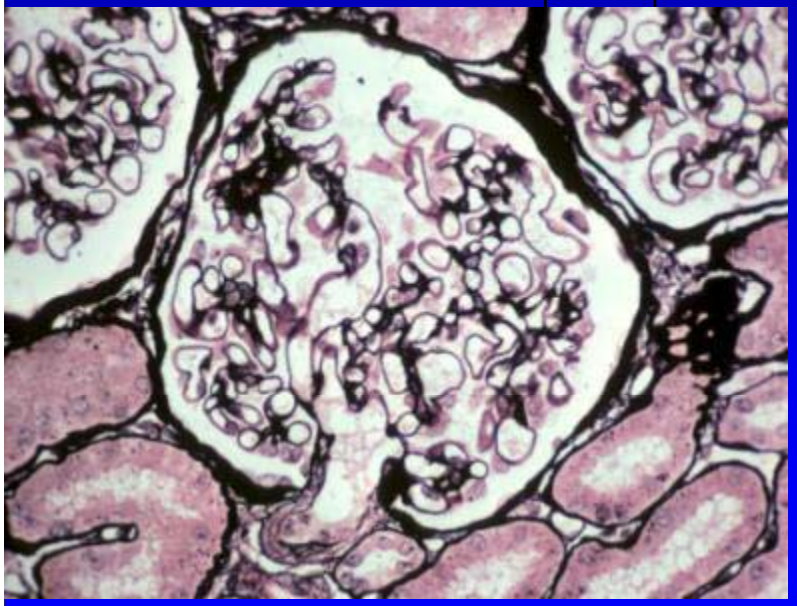
The Nephrotic Syndrome



Gerald B Appel, MD

Vivette D'Agati, MD

Objectives –Nephrotic Syndrome

- Define the nephrotic syndrome.
- Review the mechanism of proteinuria.
- Discuss the mechanisms of the major manifestations of the NS – edema, hyperlipidemia, thrombotic tendency
- Discuss the clinical features and pathology of major clinical forms of the NS .

The Nephrotic Syndrome

Glomerular Disease associated with heavy albuminuria (> 3-3.5 g/day)

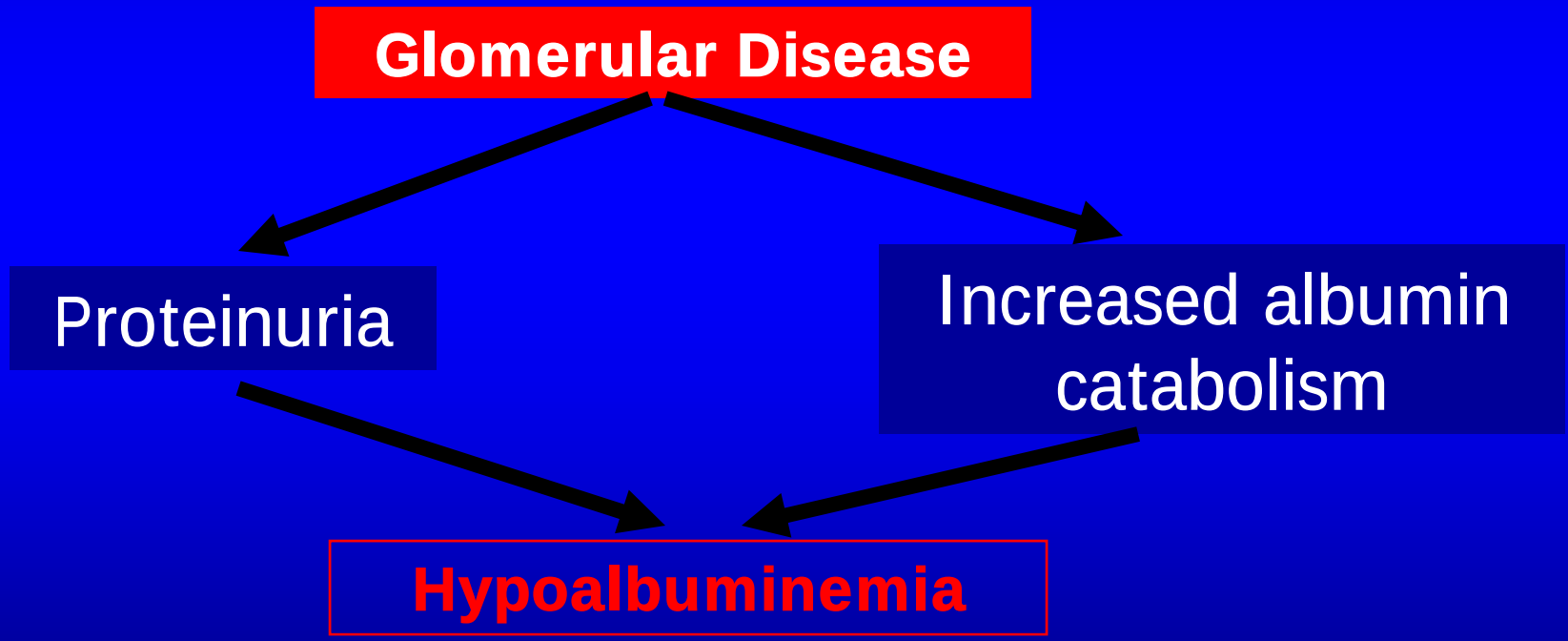
Hypoalbuminemia

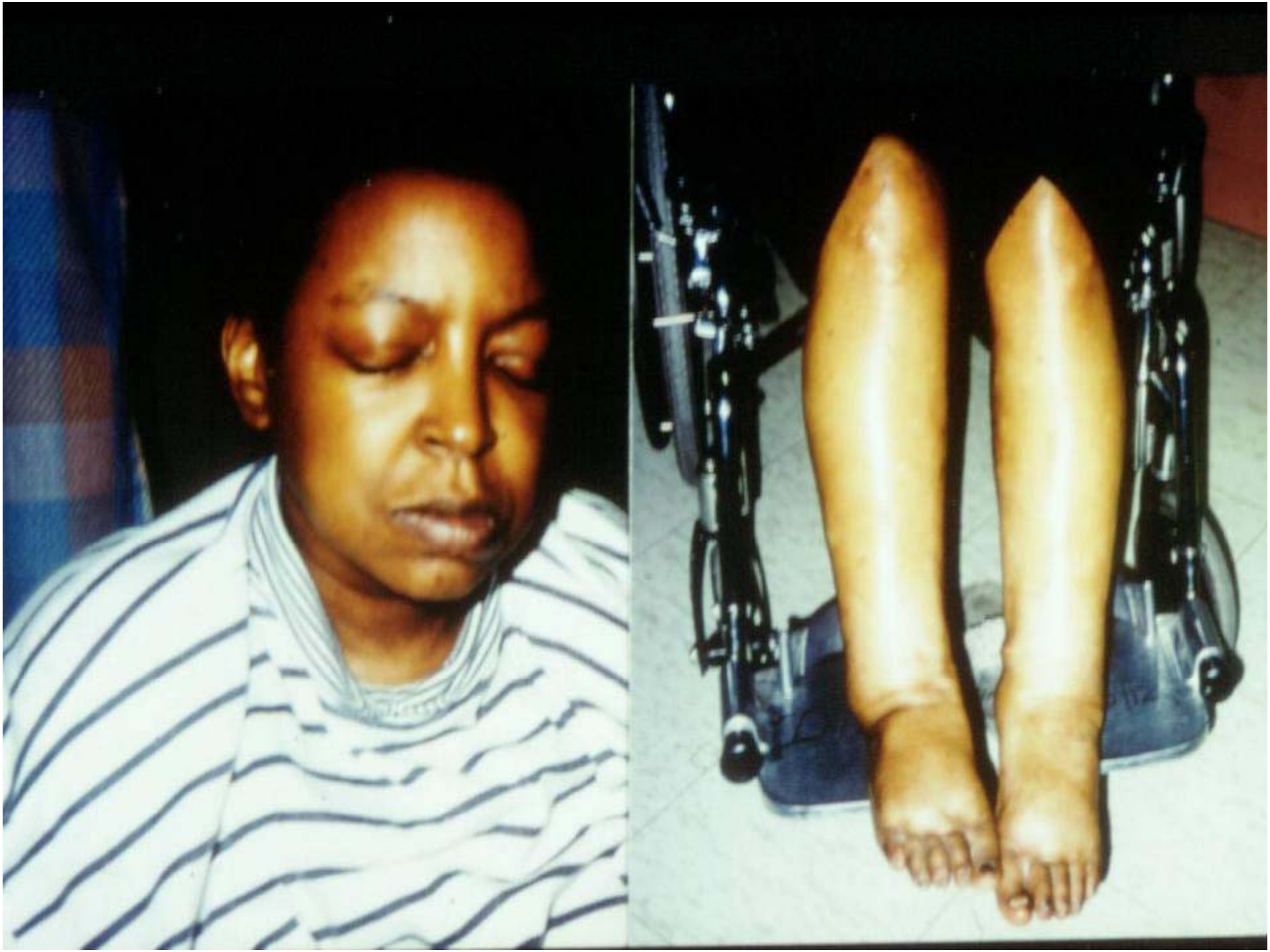
Edema

Hyperlipidemia

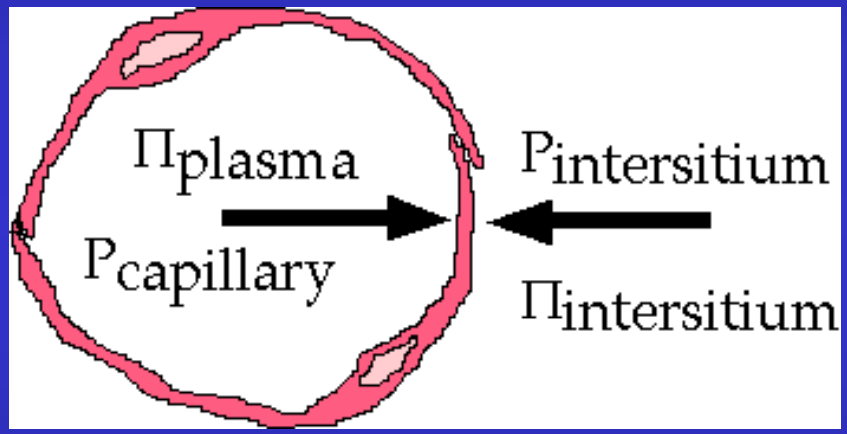
Thrombotic tendency

Genesis of Hypoalbuminemia





Pathogenesis of Nephrotic Edema



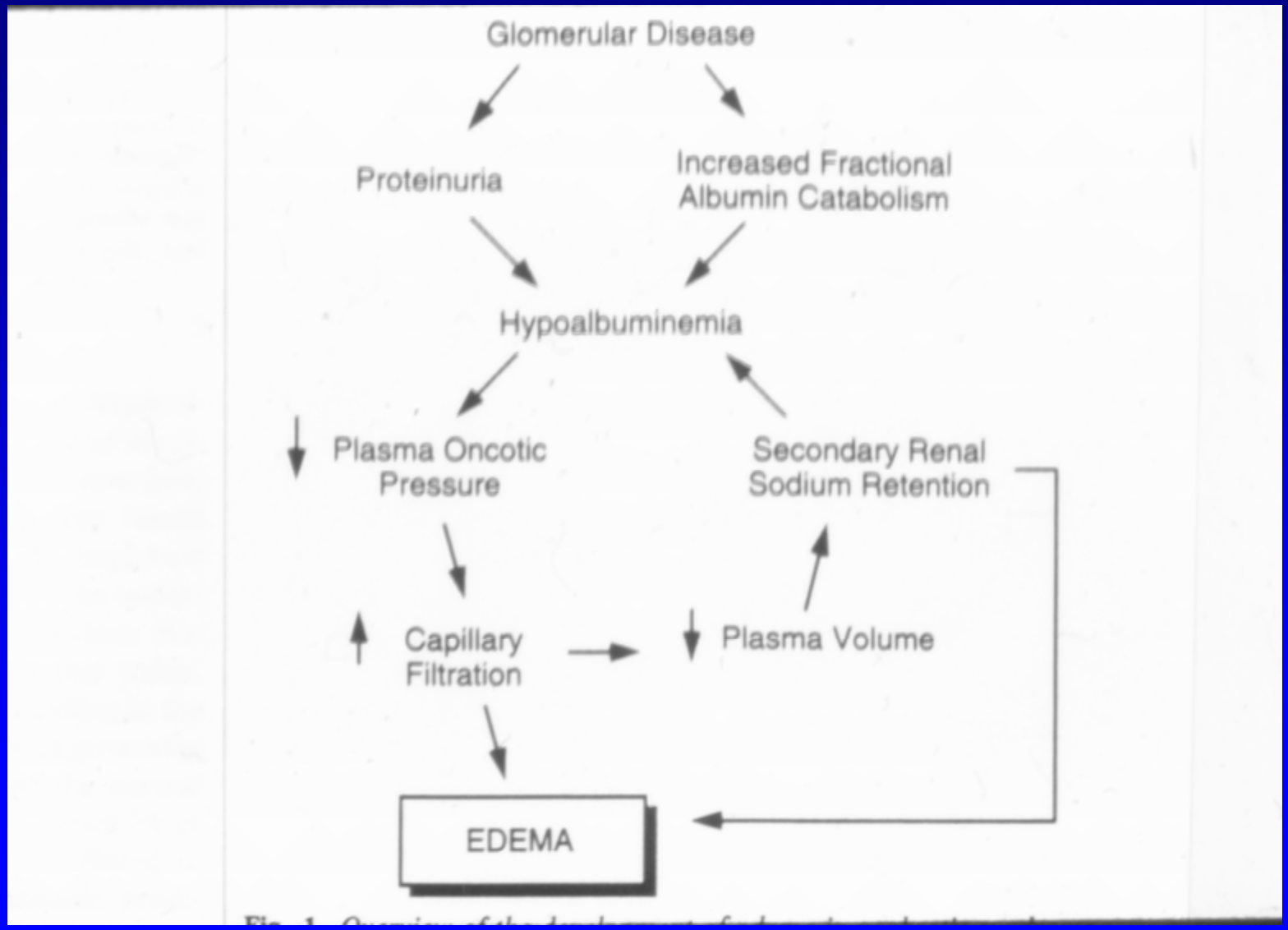
(Starling forces)

- Hypoalbuminemia:
  - Low oncotic pressure

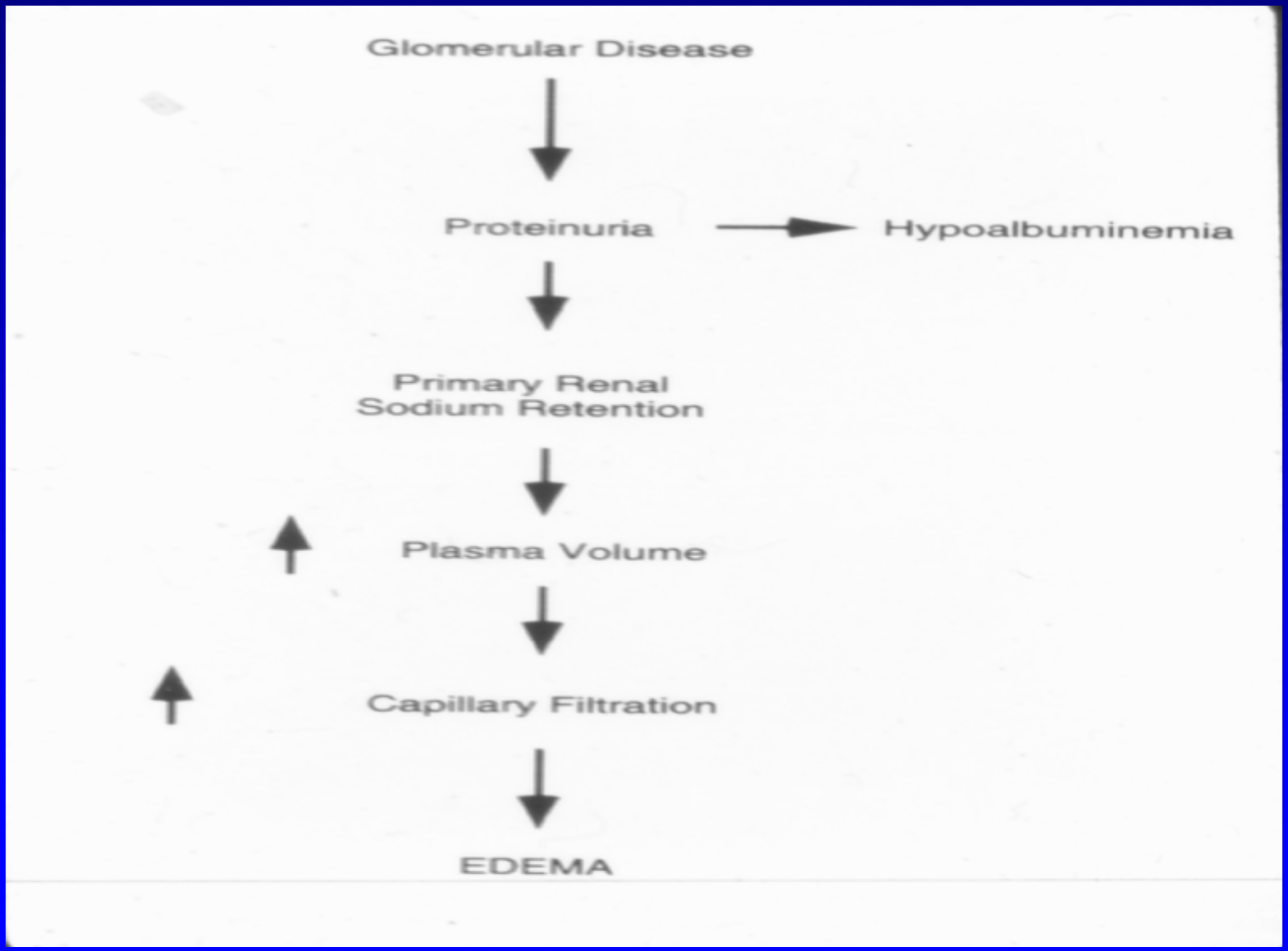
Na and Water retention:

- High hydrostatic pressure

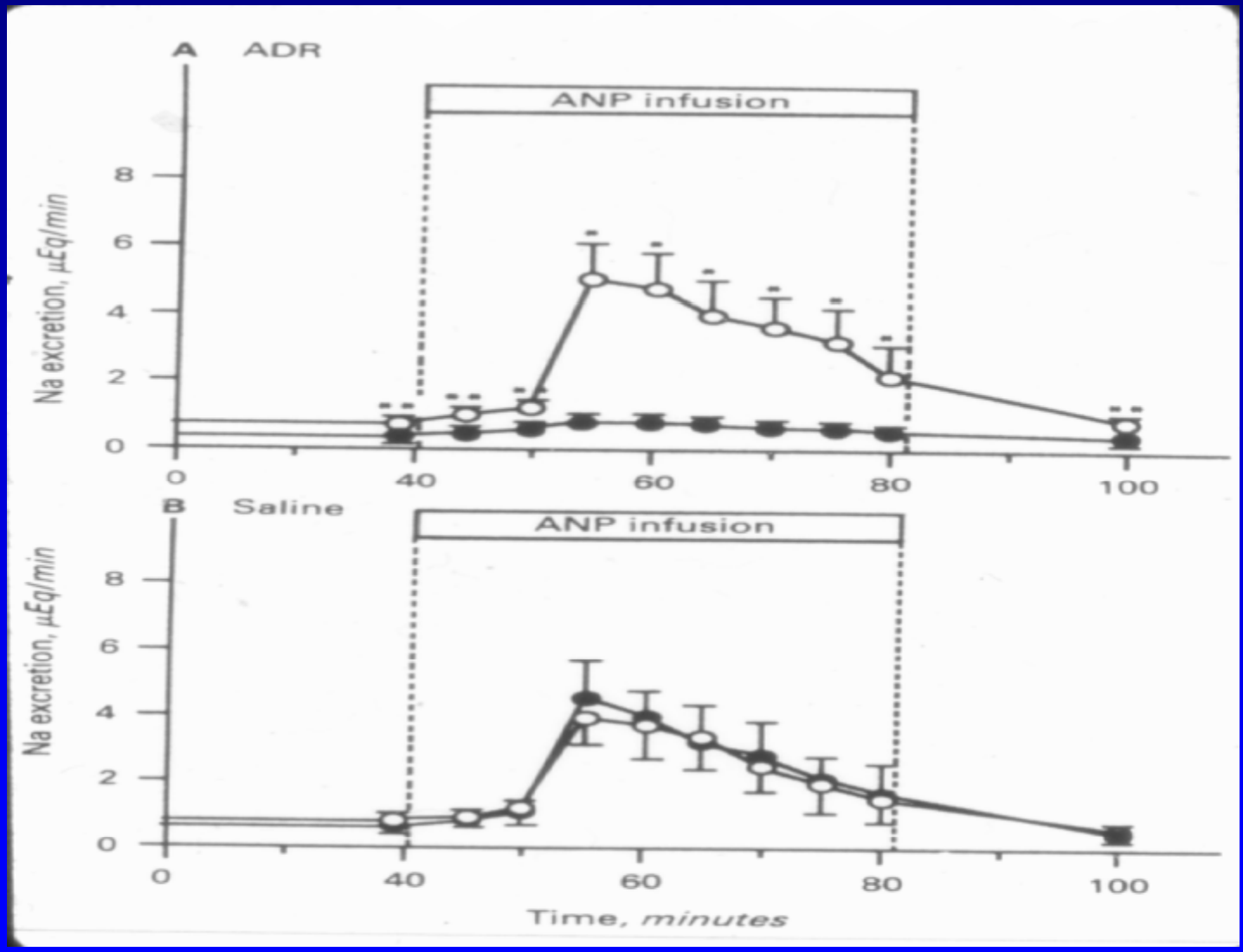
Pathogenesis of Edema



Pathogenesis of Edema



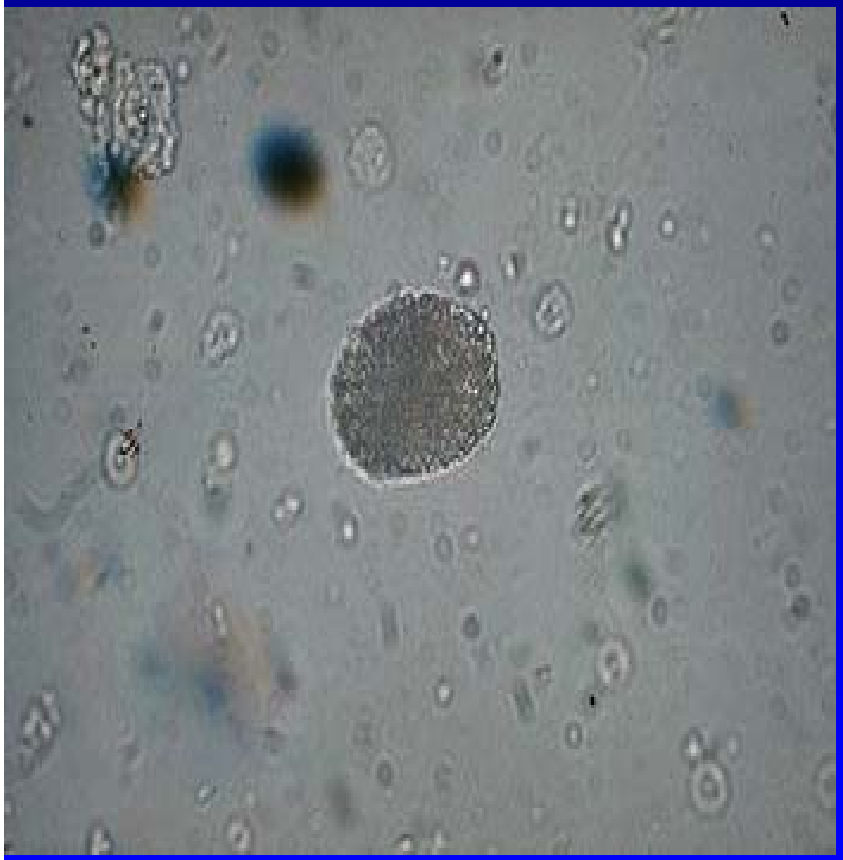
Pathogenesis of Edema

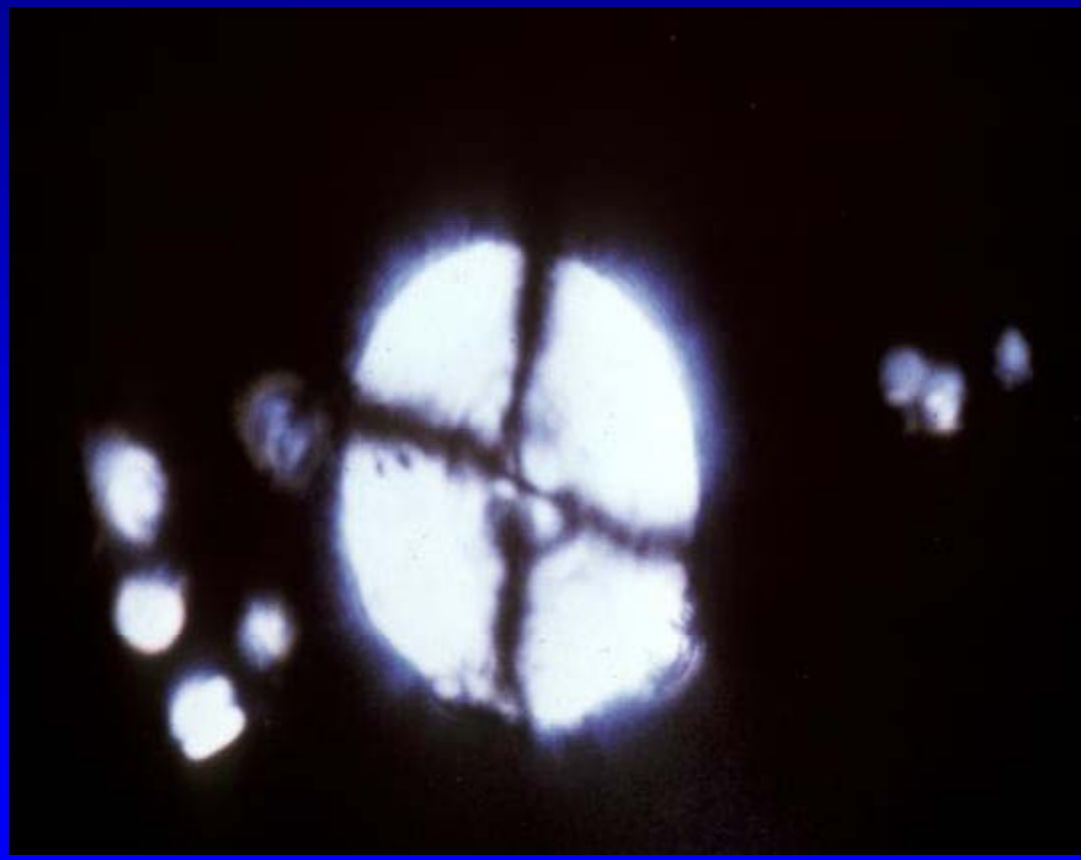


Therapy of Edema in NS

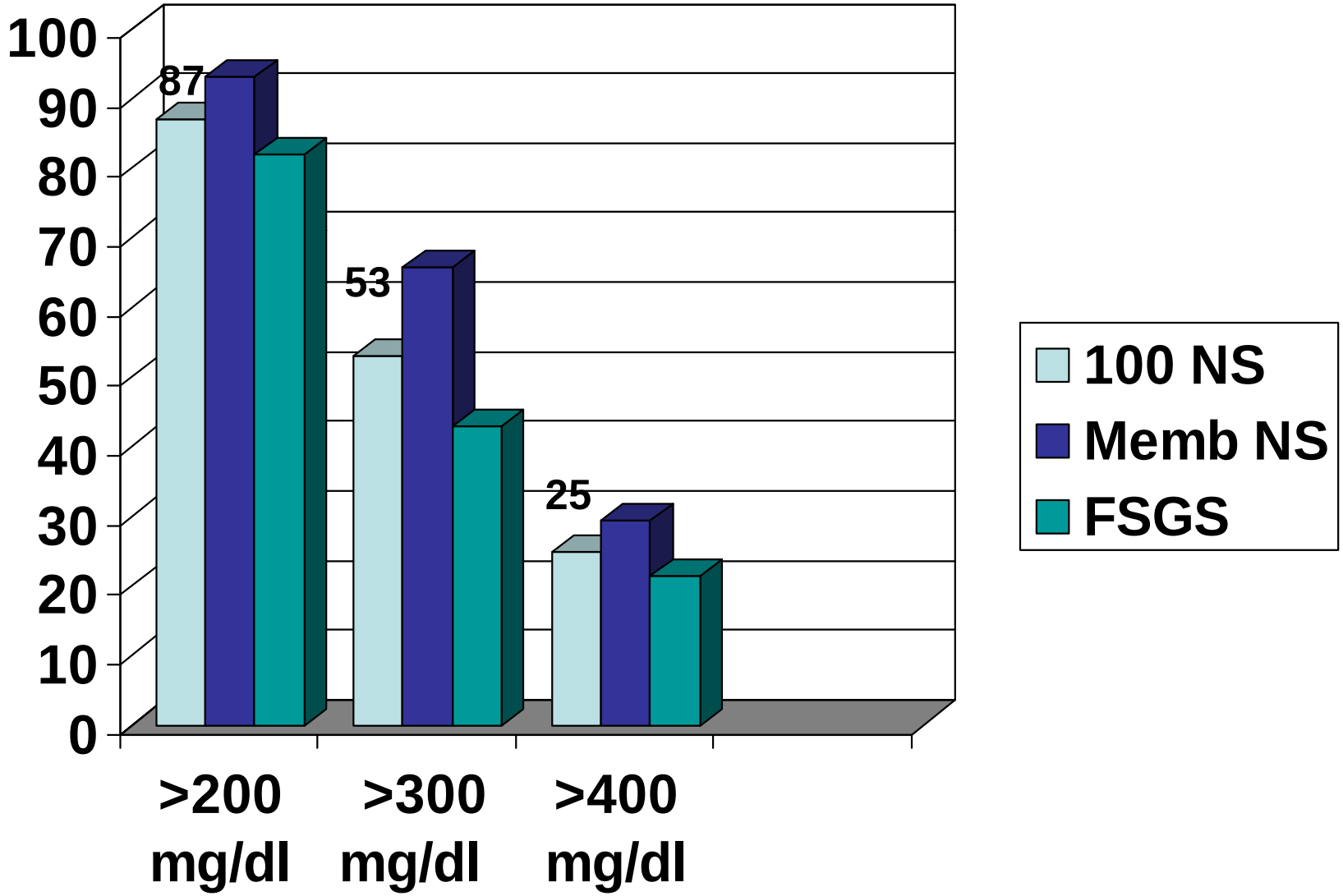
- Put pt on low Na+ diet
- Use oral loop diuretics
- Start w low dose - double doses
  - add zaroxolyn
  - +/- high BID doses
- IV diuretics and colloid rarely needed
- Goal is 1-2 # edema loss/ day

Lipiduria and Oval Fat Bodies

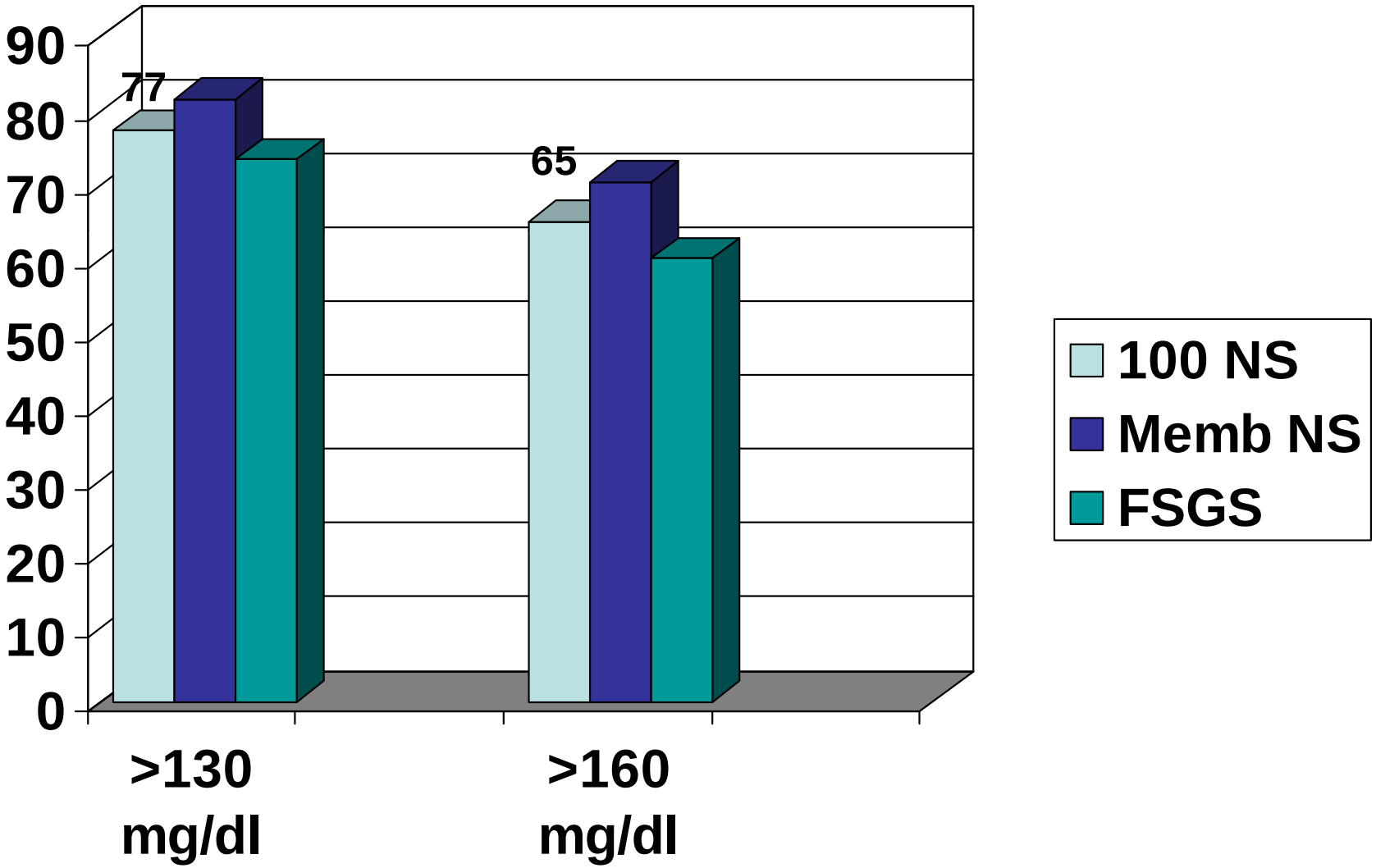




Total Cholesterol Levels in 100 Consecutive Nephrotic Synd. Pts

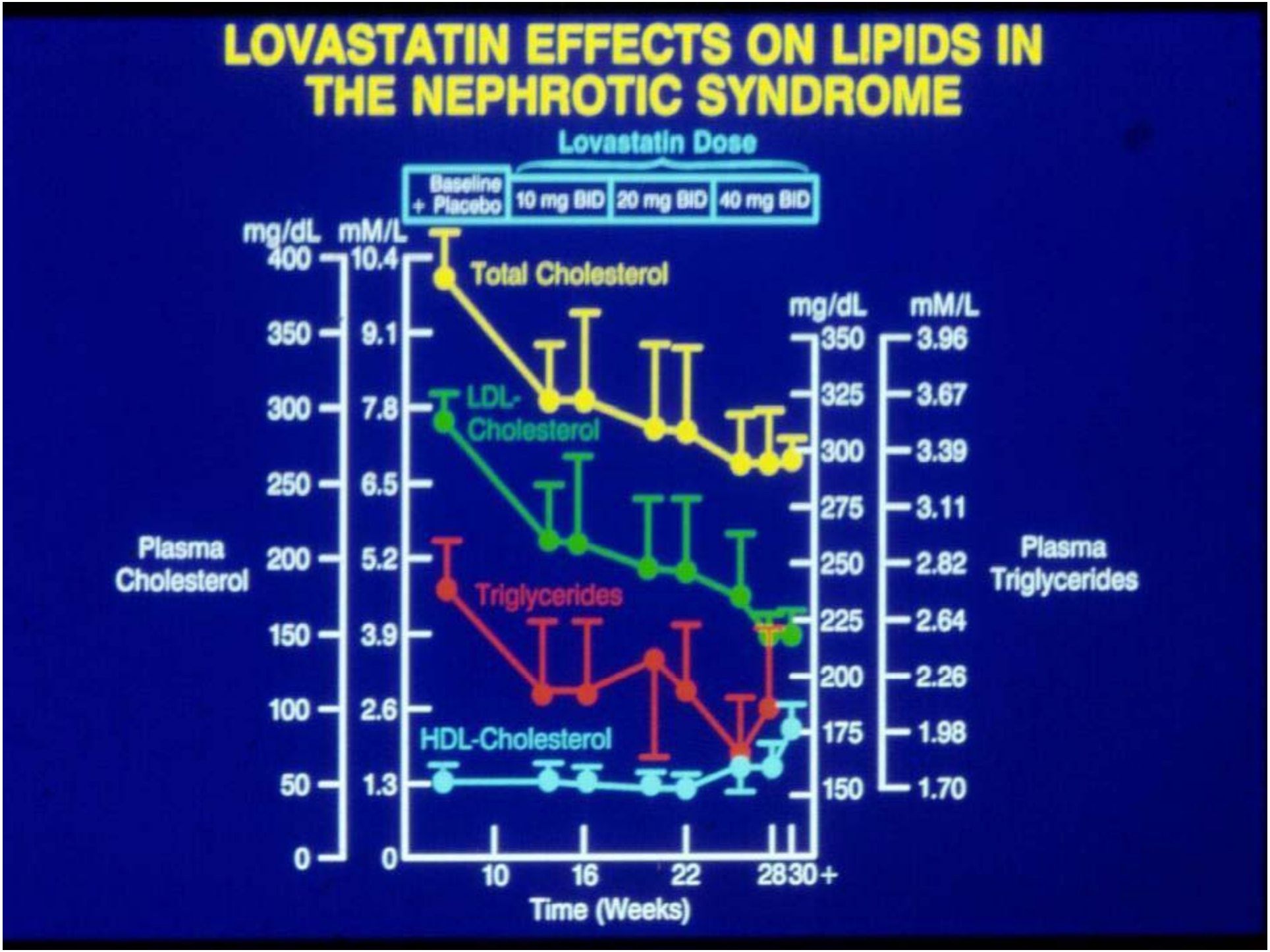


LDL Cholesterol Levels in 100 Consecutive Nephrotic Synd. Pts



Treatment of Hyperlipidemia of the Nephrotic Syndrome

- Select high risk pt (high LDL, low HDL, unlikely to rapidly remit)
- Attempt to induce a remission of the proteinuria (ACEi/ARBs , specific immunosuppressives, etc.)
- Dietary Therapy
- Medical Therapy (statins +)


LOVASTATIN EFFECTS ON LIPIDS IN THE NEPHROTIC SYNDROME
Lovastatin Dose
Baseline + Placebo
10 mg BID
20 mg BID
40 mg BID
mg/dL
mM/L
400
10.4
350
9.1
300
7.8
250
6.5
200
5.2
150
3.9
100
2.6
50
1.3
0
Total Cholesterol
LDL-Cholesterol
Triglycerides
HDL-Cholesterol
Plasma Cholesterol
mg/dL
mM/L
350
3.96
325
3.67
300
3.39
275
3.11
250
2.82
225
2.64
200
2.26
175
1.98
150
1.70
Plasma Triglycerides
10
16
22
28
30+
Time (Weeks)

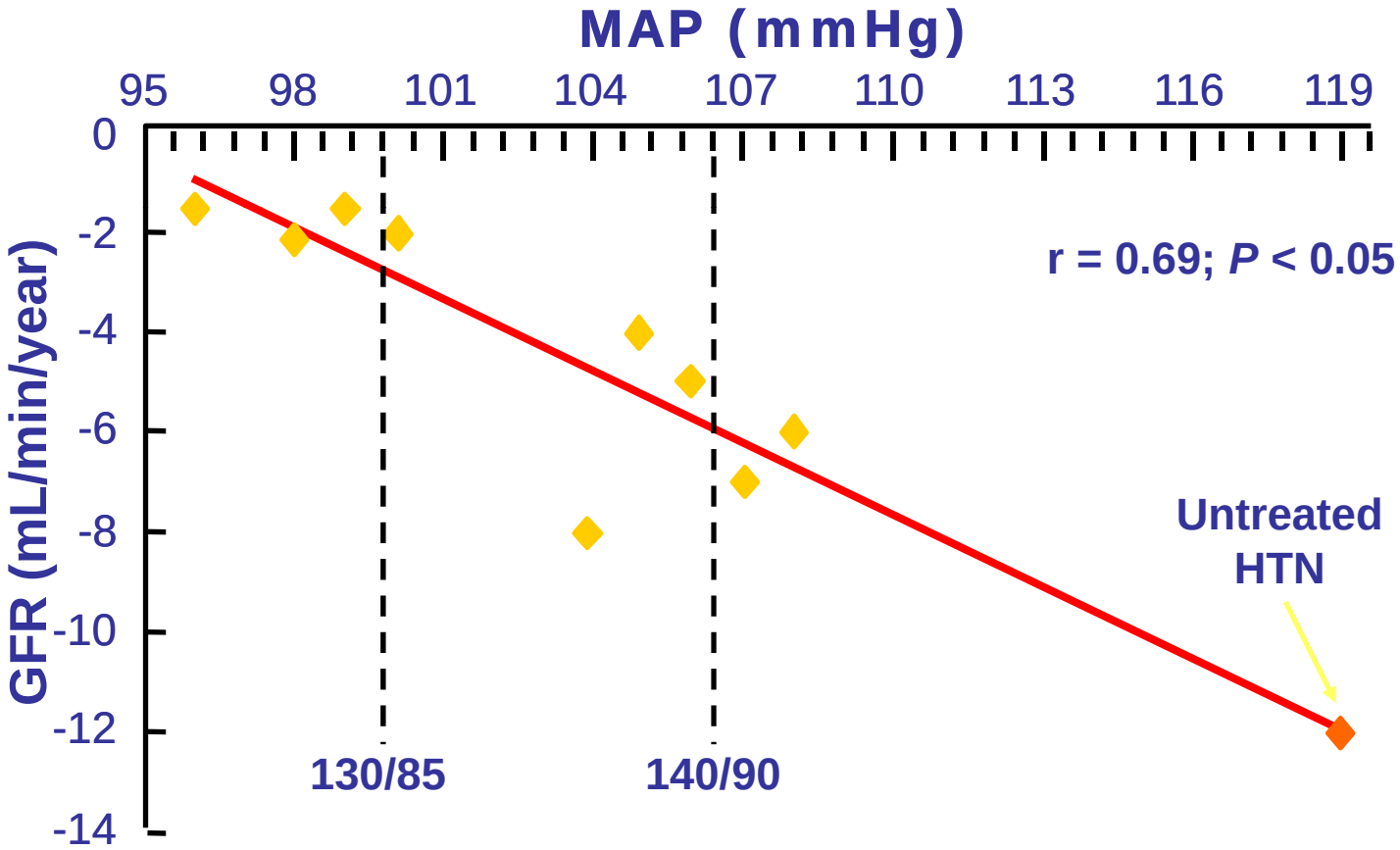
Treatment Principles

- Treatment of Primary Disease- Often immune modulating medications
- Symptomatic Treatment – Diuretics, statins, diet, in some anticoagulation
- Reduction of Proteinuria/Slowing Progression

Reduction of Proteinuria and Slowing Progression

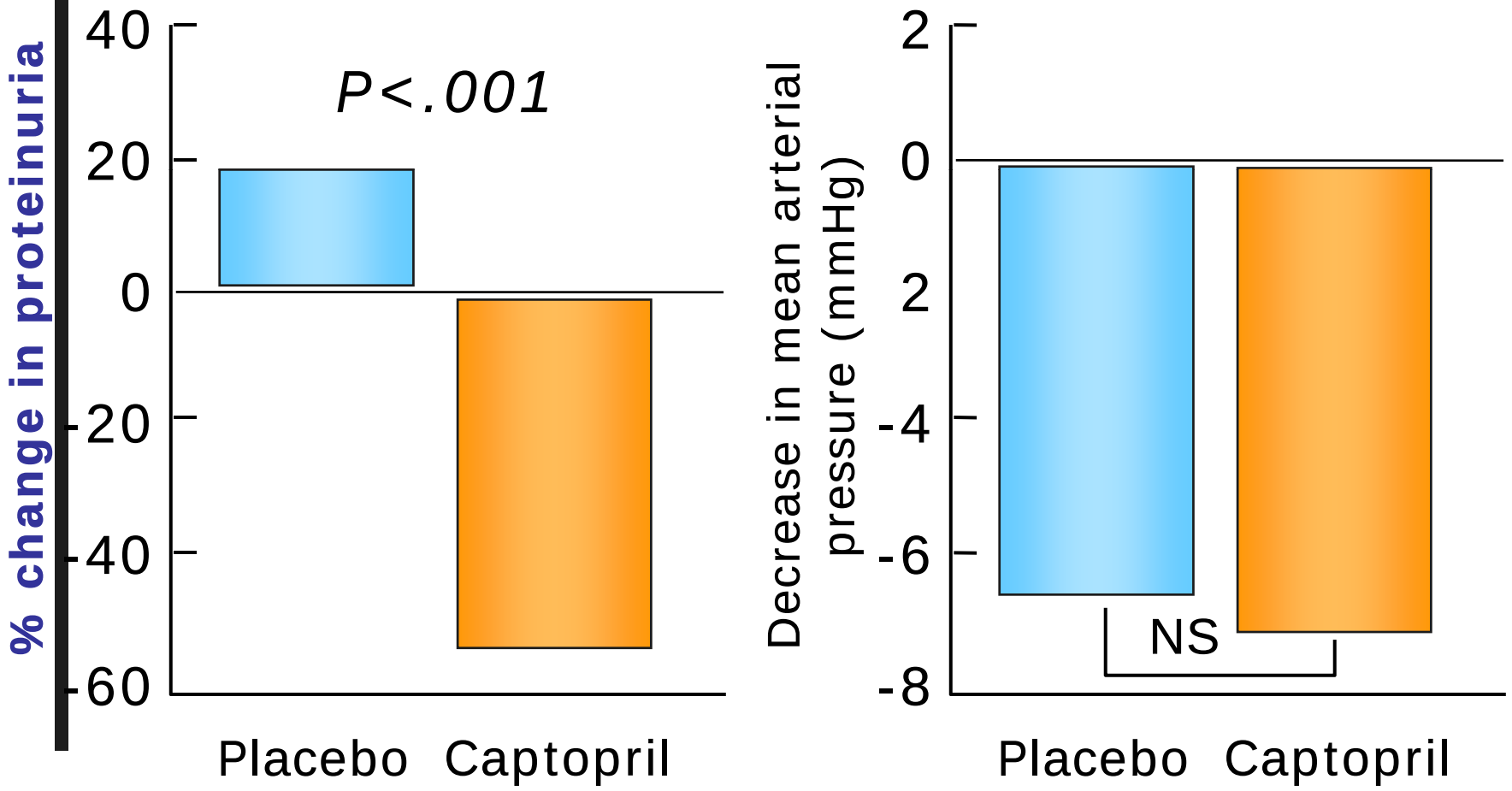
- Blood pressure reduction
- Inhibition of the renin-angiotensin-aldosterone axis

Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics



Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

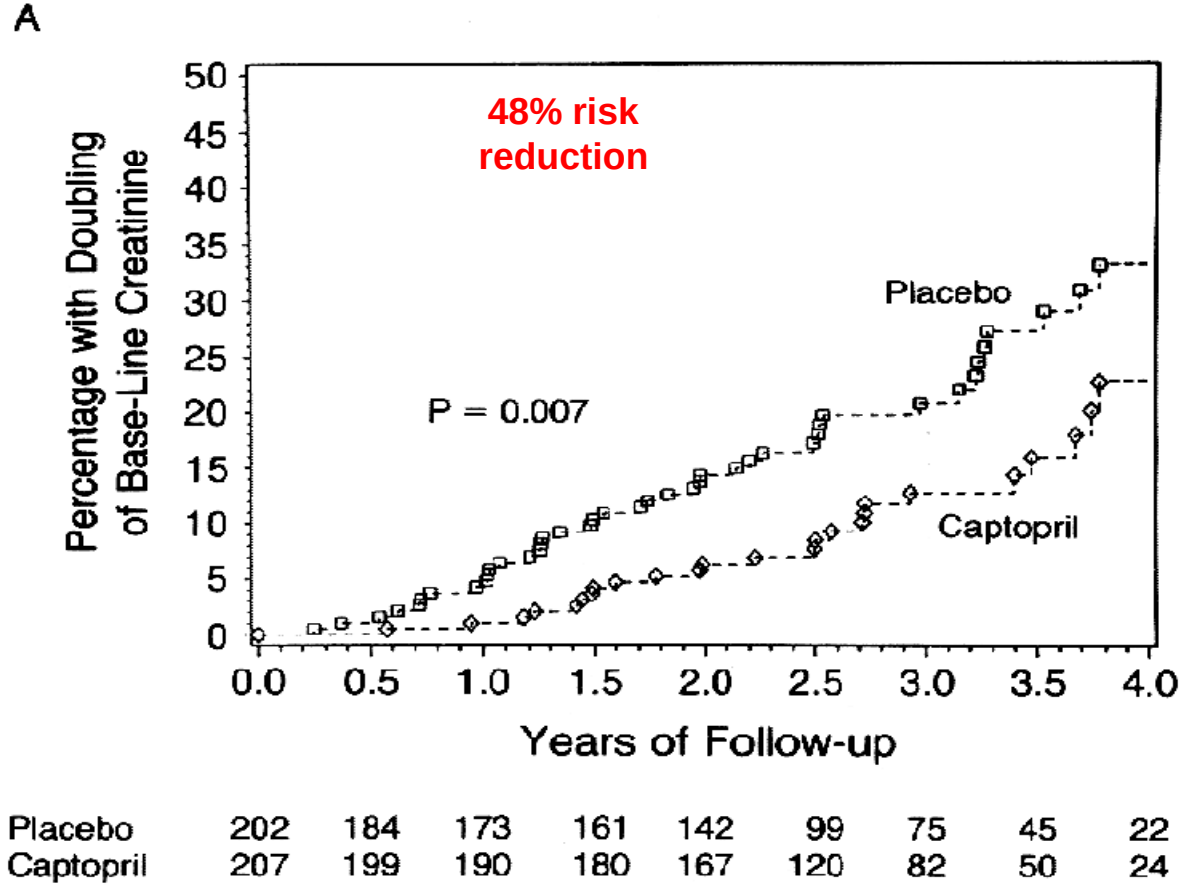
ACE-I Is More Renoprotective than Conventional Therapy in Type 1 Diabetes



Lewis EJ, et al. N Engl J Med. 1993;329(20):1456-1462.

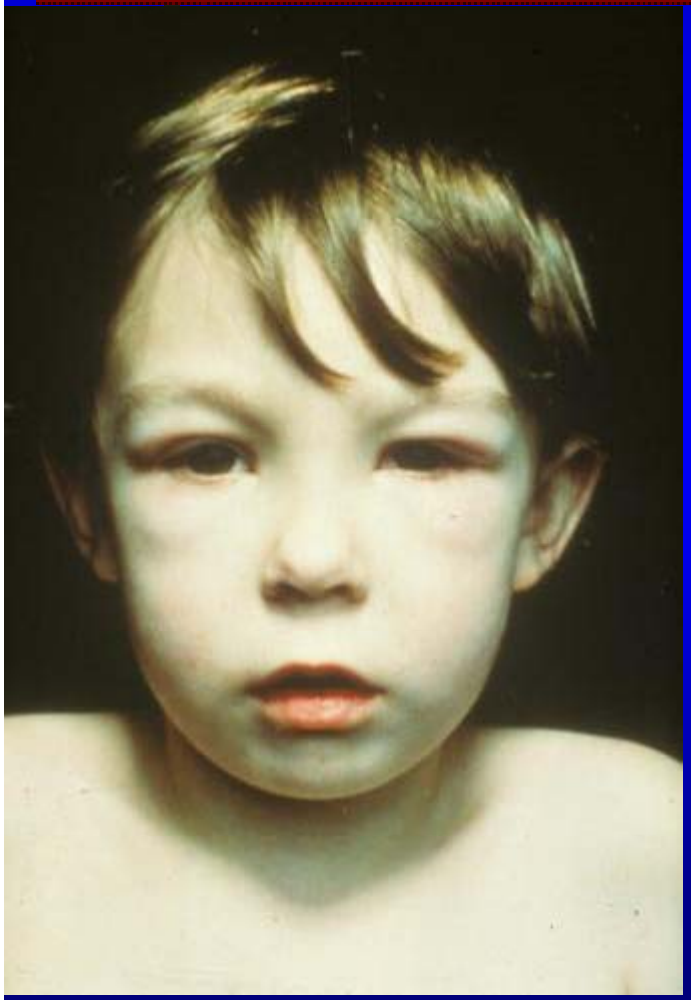
The Effect of ACE-I on Diabetic Nephropathy: The Collaborative Study Group

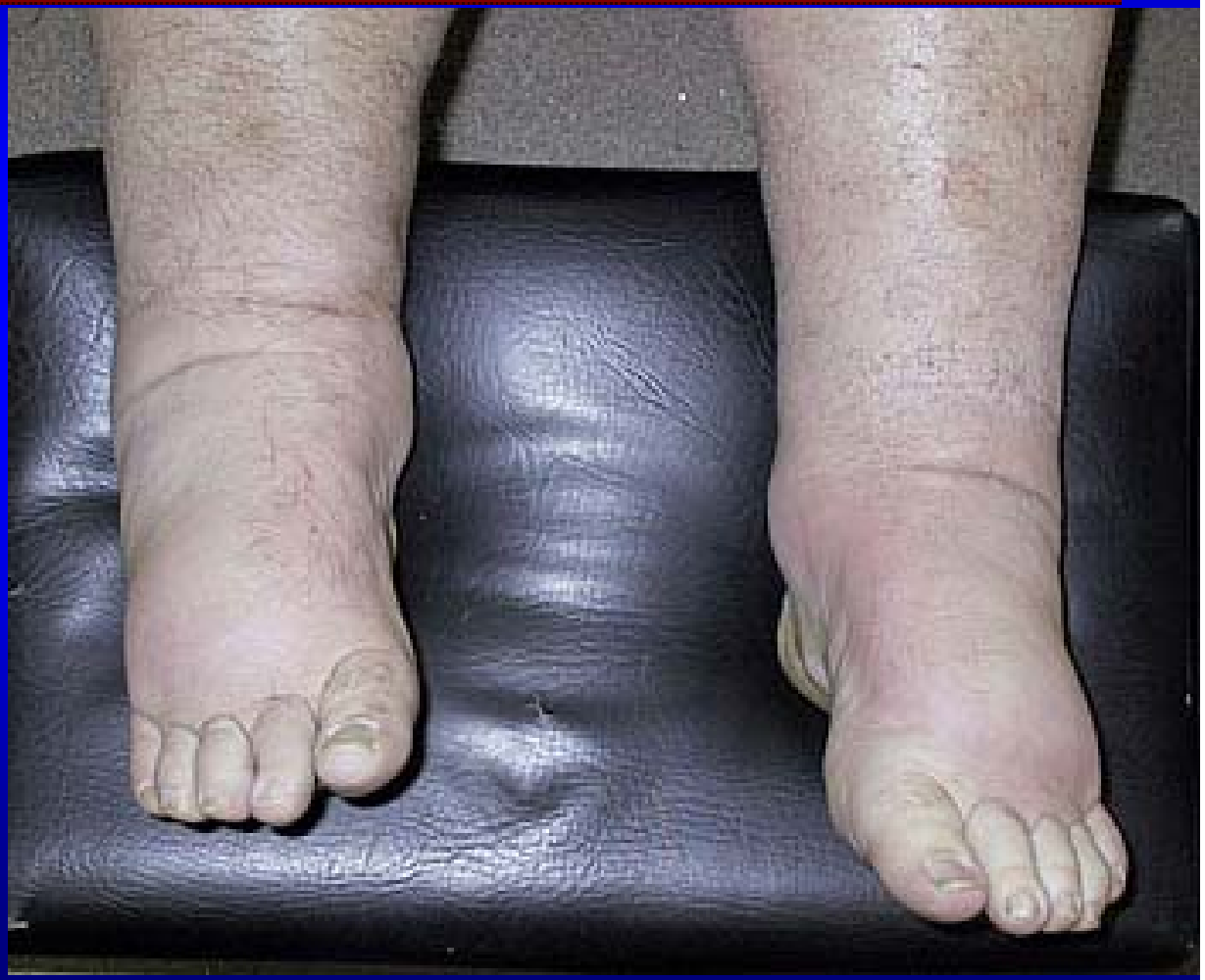
- Type 1 DM with Urine Alb>500mg/d



Lewis EJ, et al. N Engl J Med. 1993 Nov 11;329(20):1456-62.

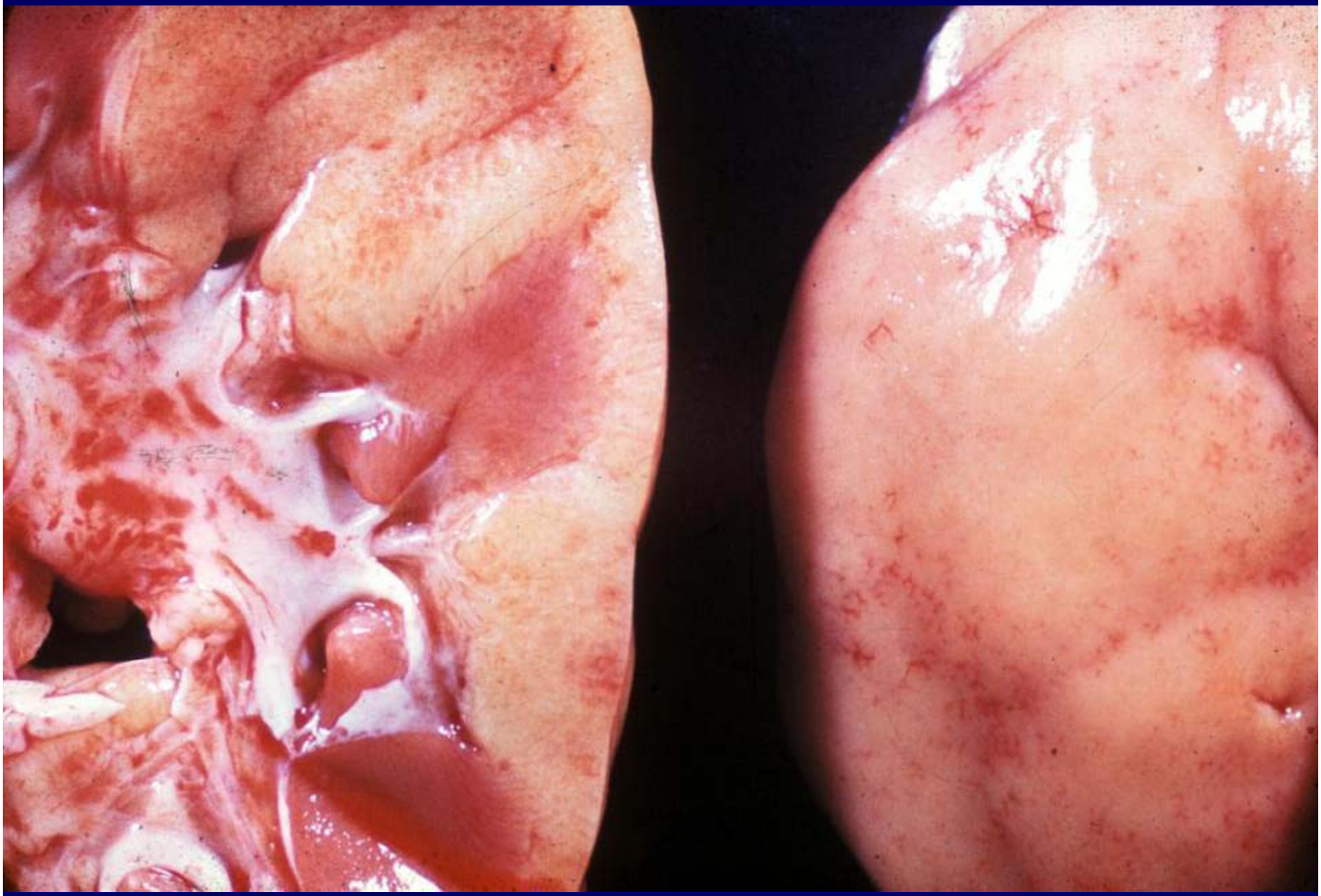
Case 1 – 8 year old child

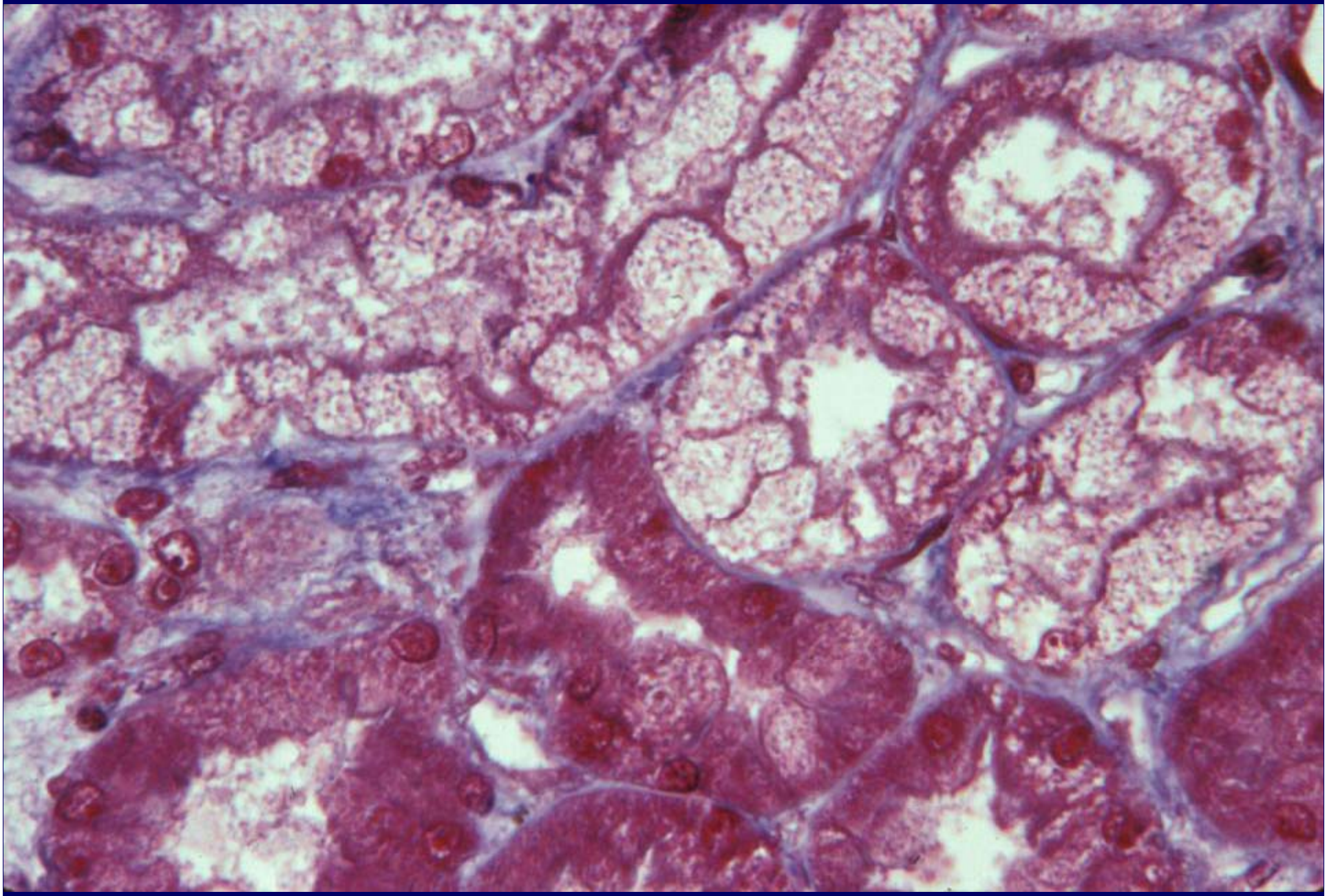


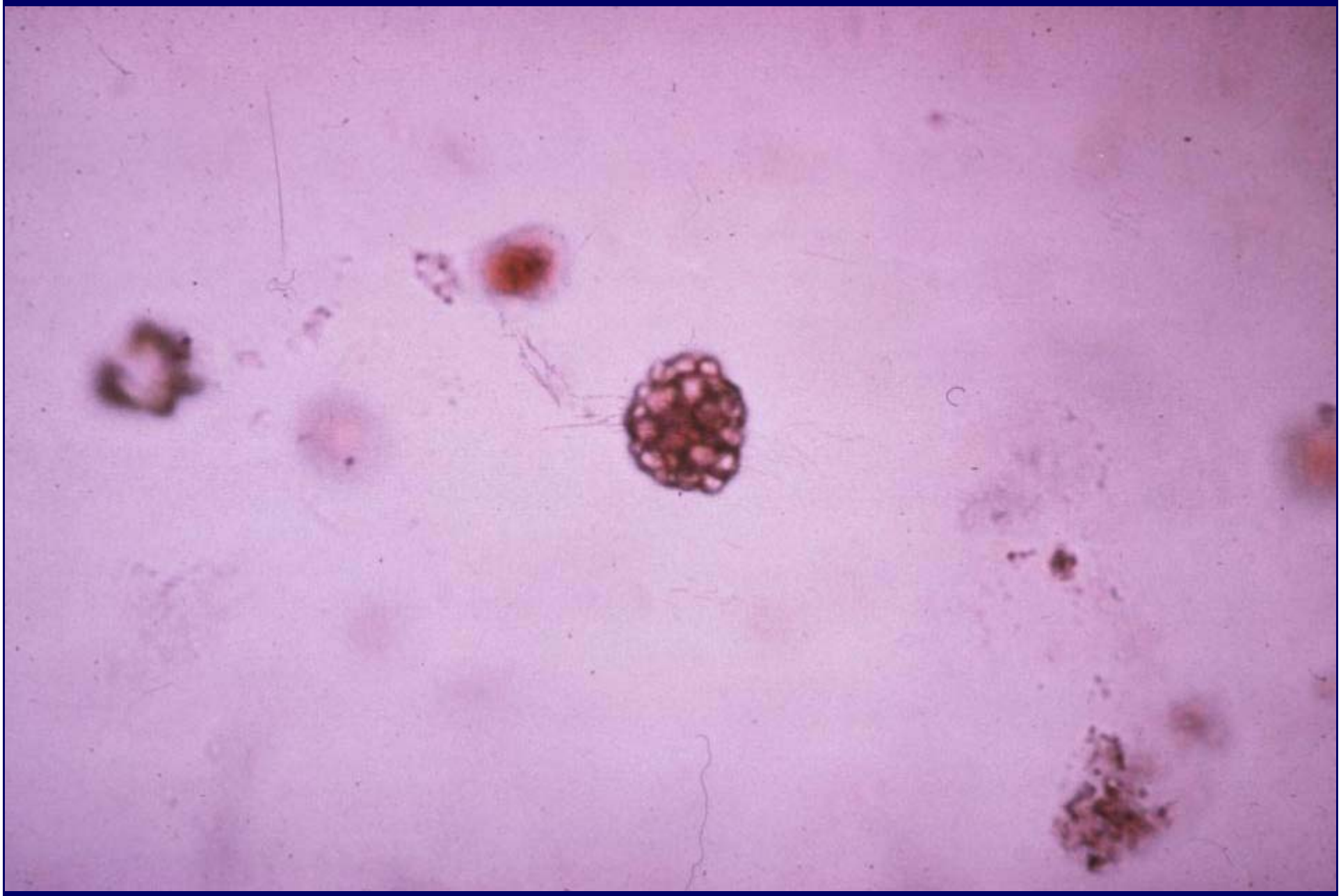


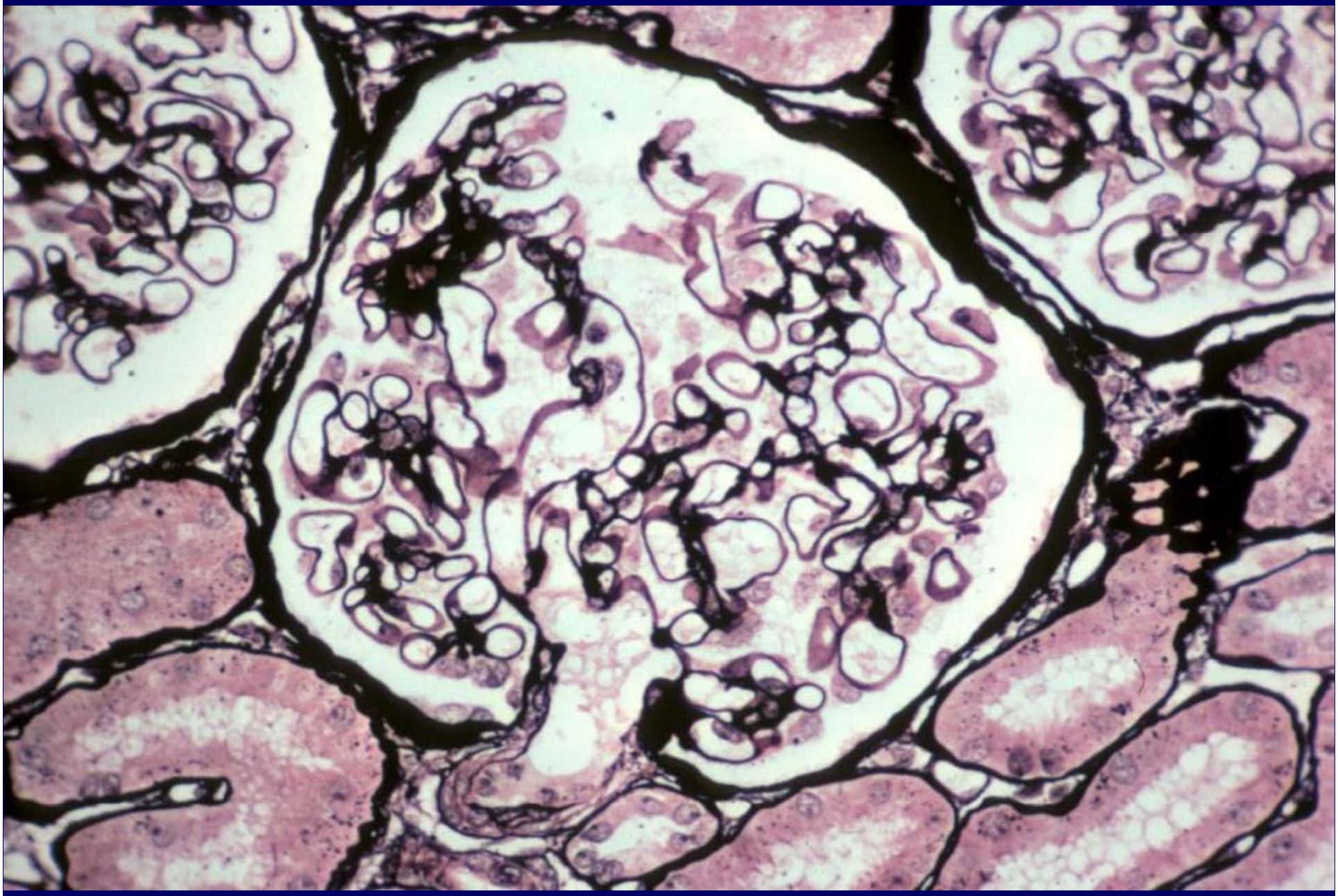
Case 1

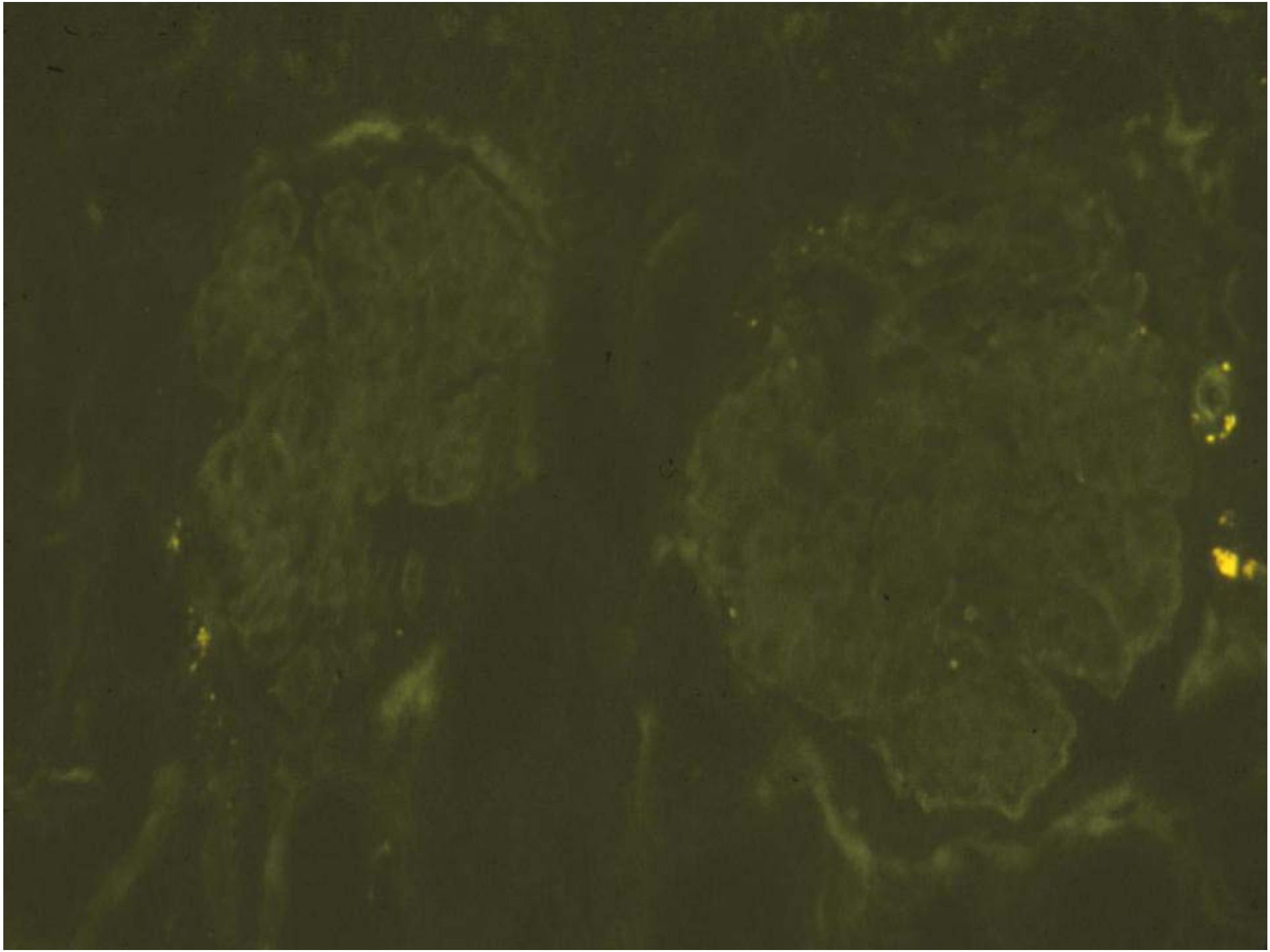
- **An 8 year old child presents with swelling of his eyes and ankles. He has 4+ proteinuria on urine dipstick**
- **Other labs:**
  - **BUN 8 mg/dl**
  - **Creatinine 0.5 mg/dl**
  - **Albumin 2.2 g/dl, serum cholesterol 400mg/dL**
  - **24 hour urine protein 6.0 g/day (normal <150mg)**
- **Serologic tests are negative or normal**

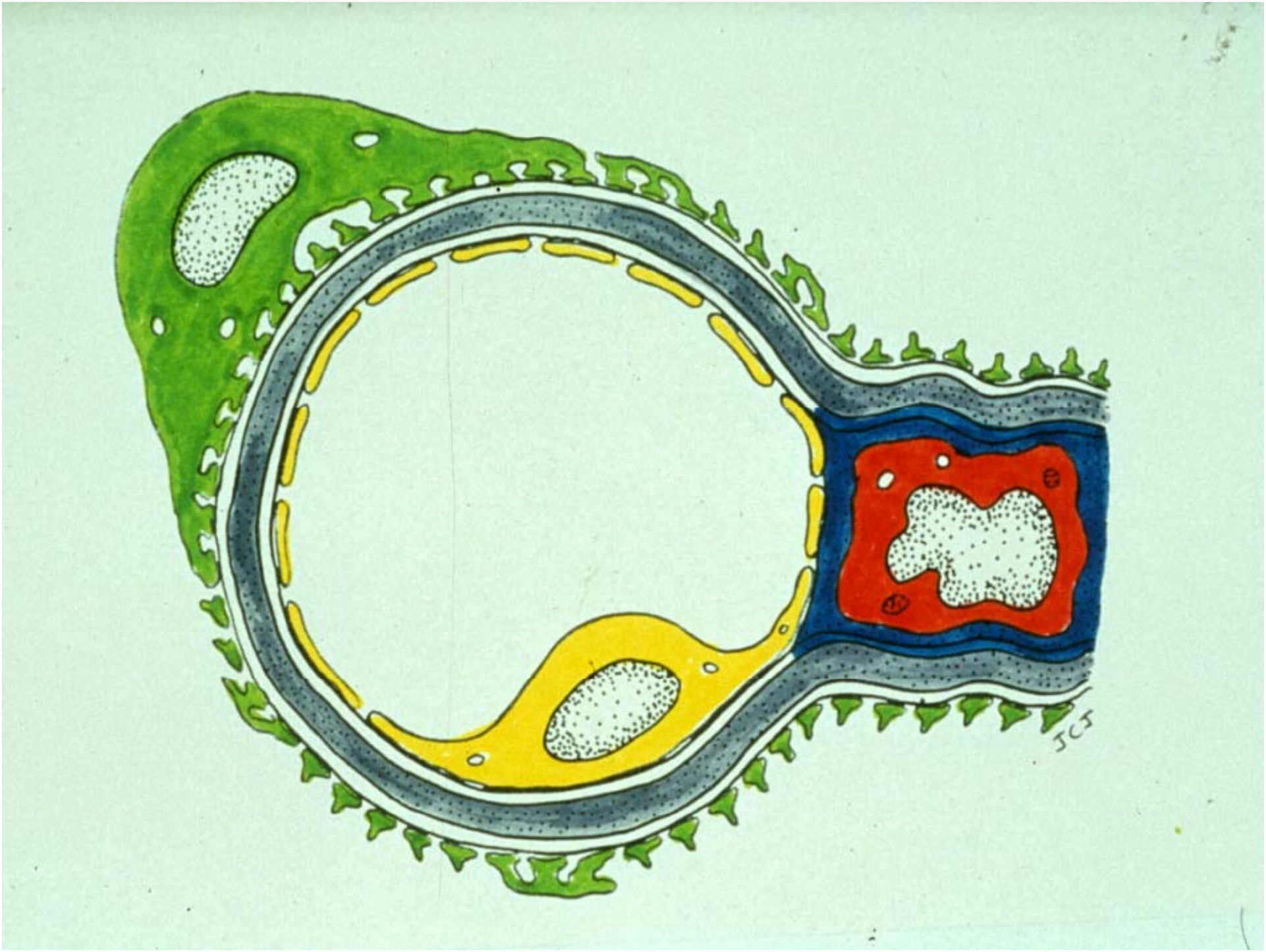


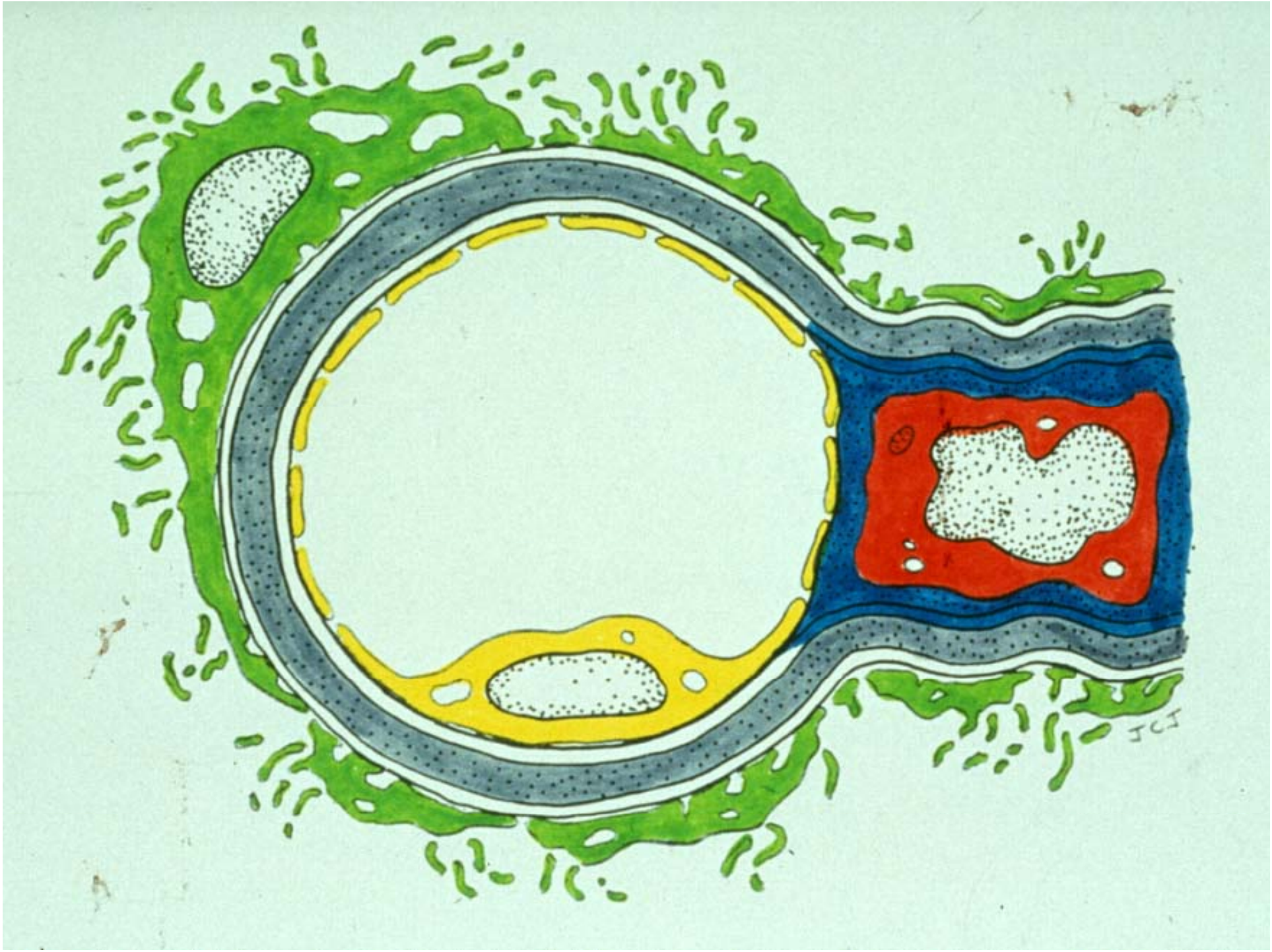


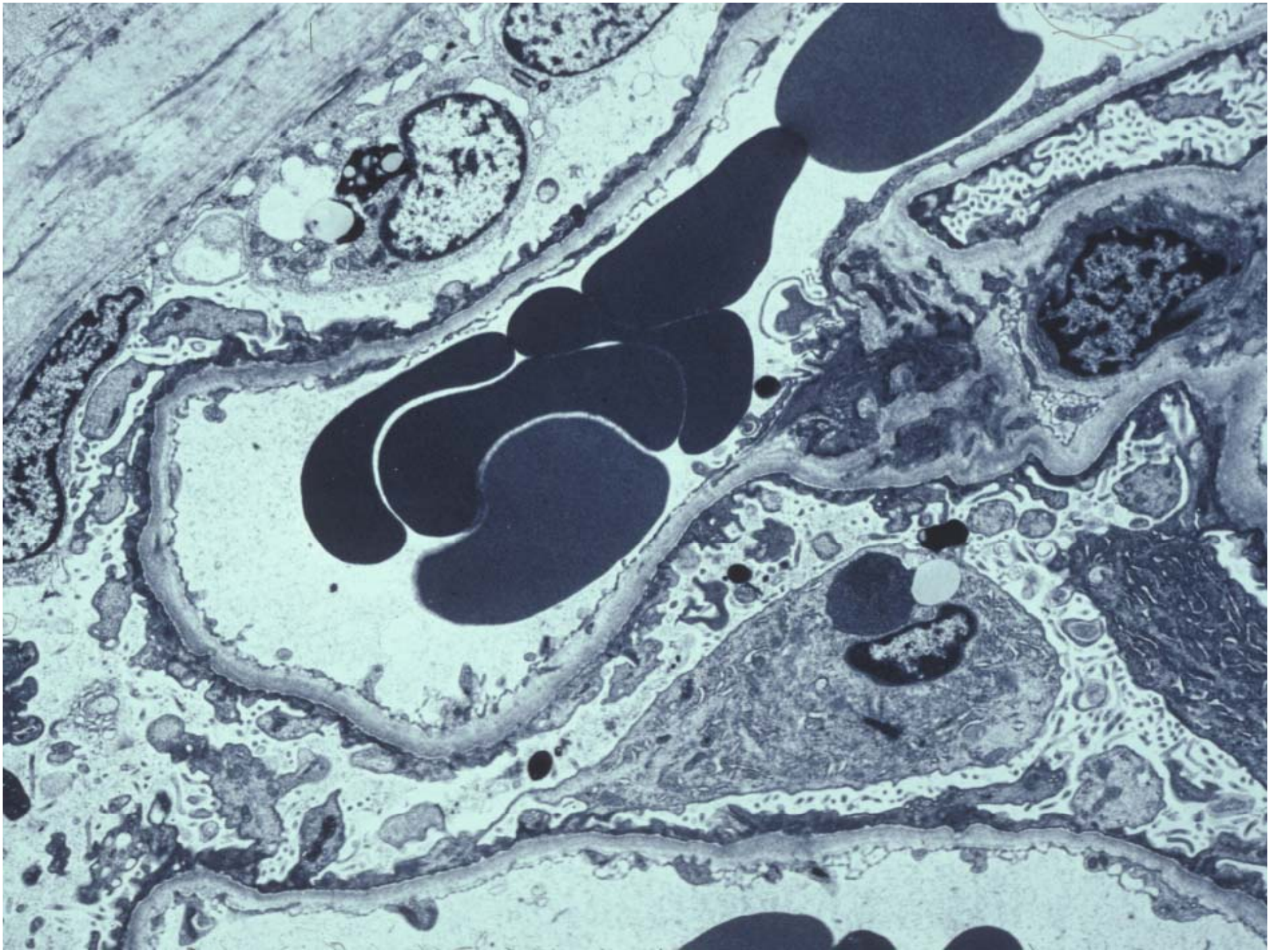


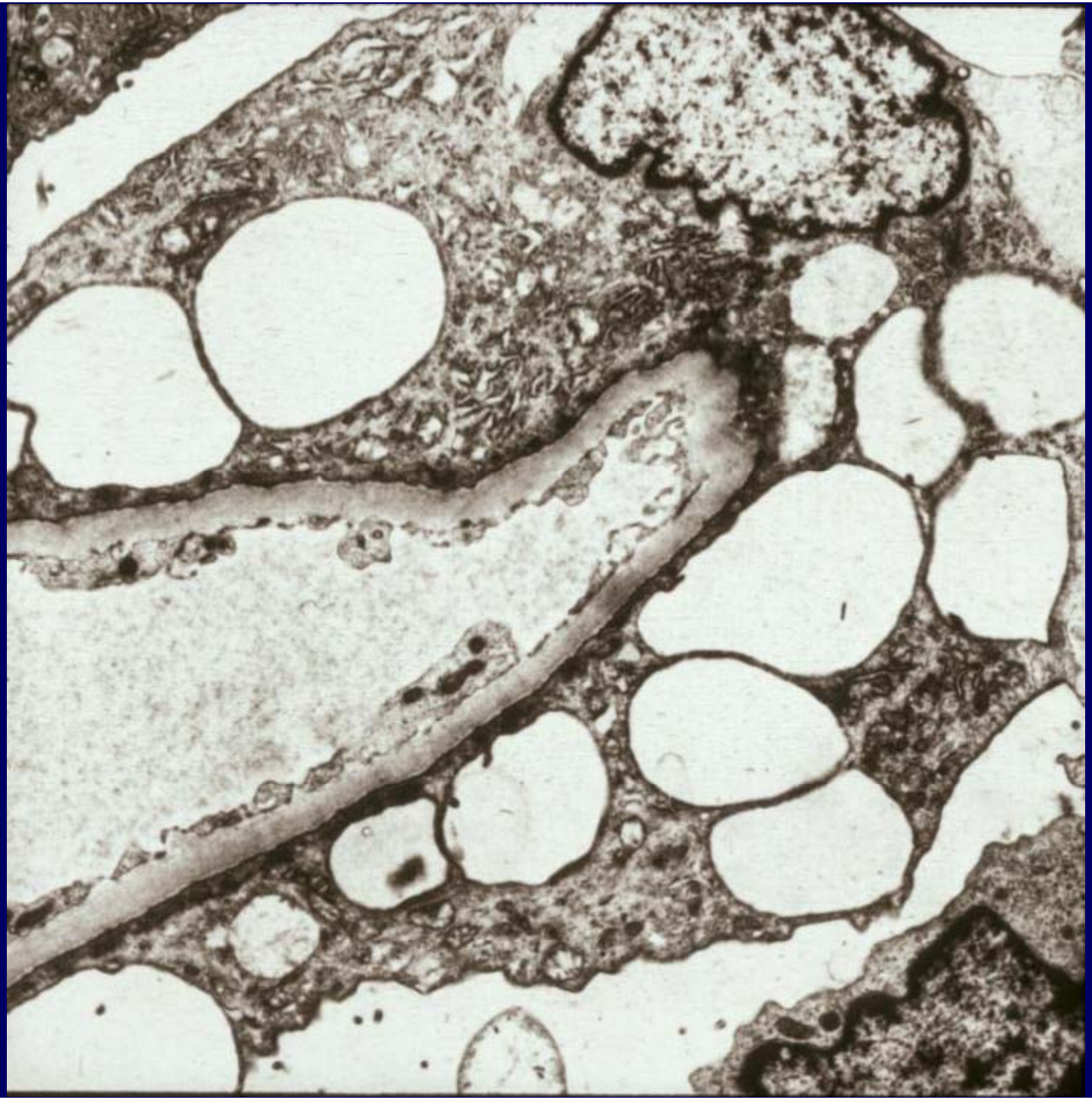












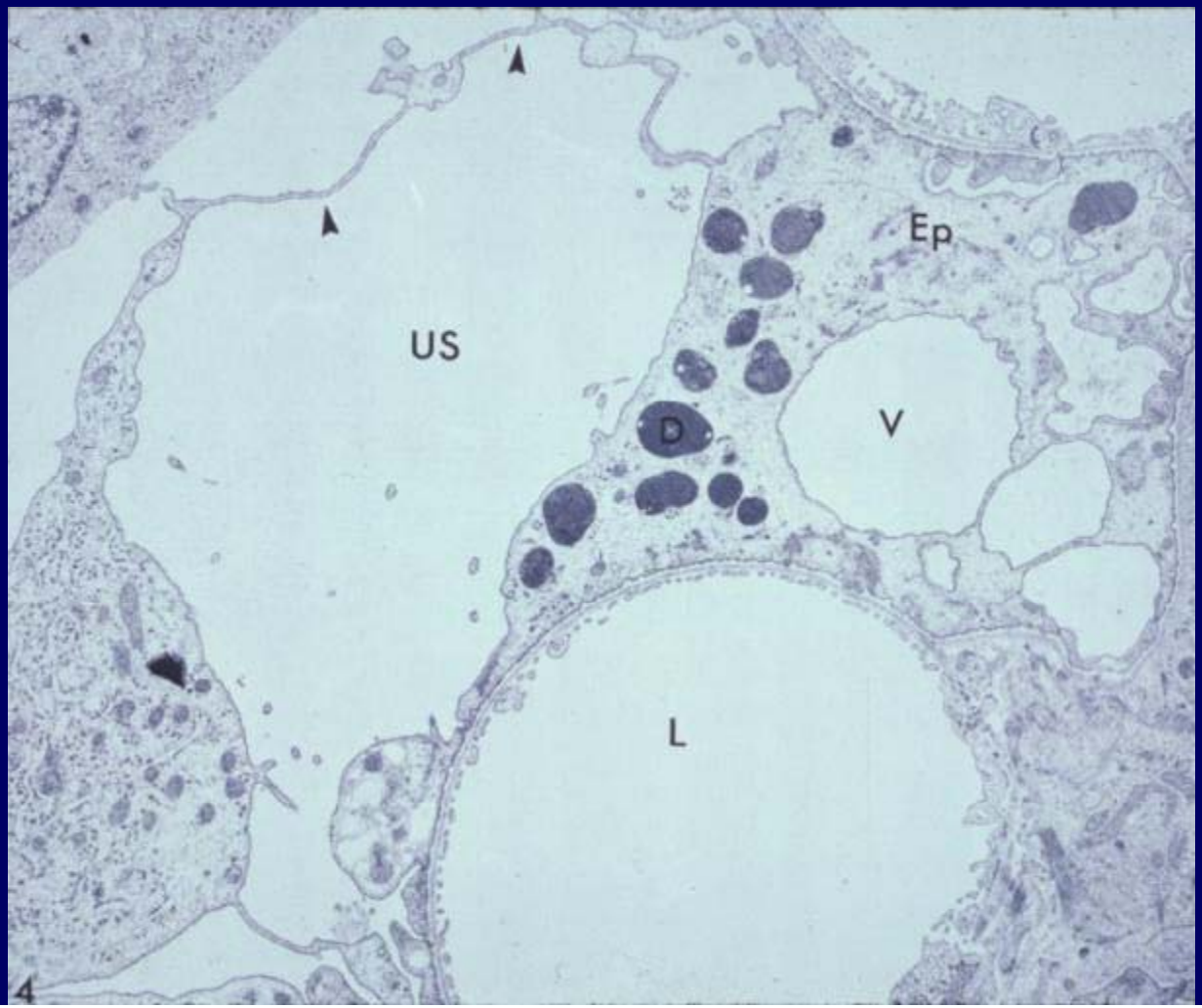
Synonyms

- Minimal Change Disease
- Nil Disease
- Lipoid Nephrosis
- Childhood Nephrosis

Evidence for Immunologic Derangements in Nil Disease

- Viral infections may precede onset or recrudescences.
- May follow recent immunizations.
- Altered in vitro response to mitogens.
- Circulating lymphocytotoxins.
- Association with Hodgkin's Disease and other lymphoproliferative disease

Animal Model
Puromycin Aminonucleoside Nephrosis



Minimal Change Disease

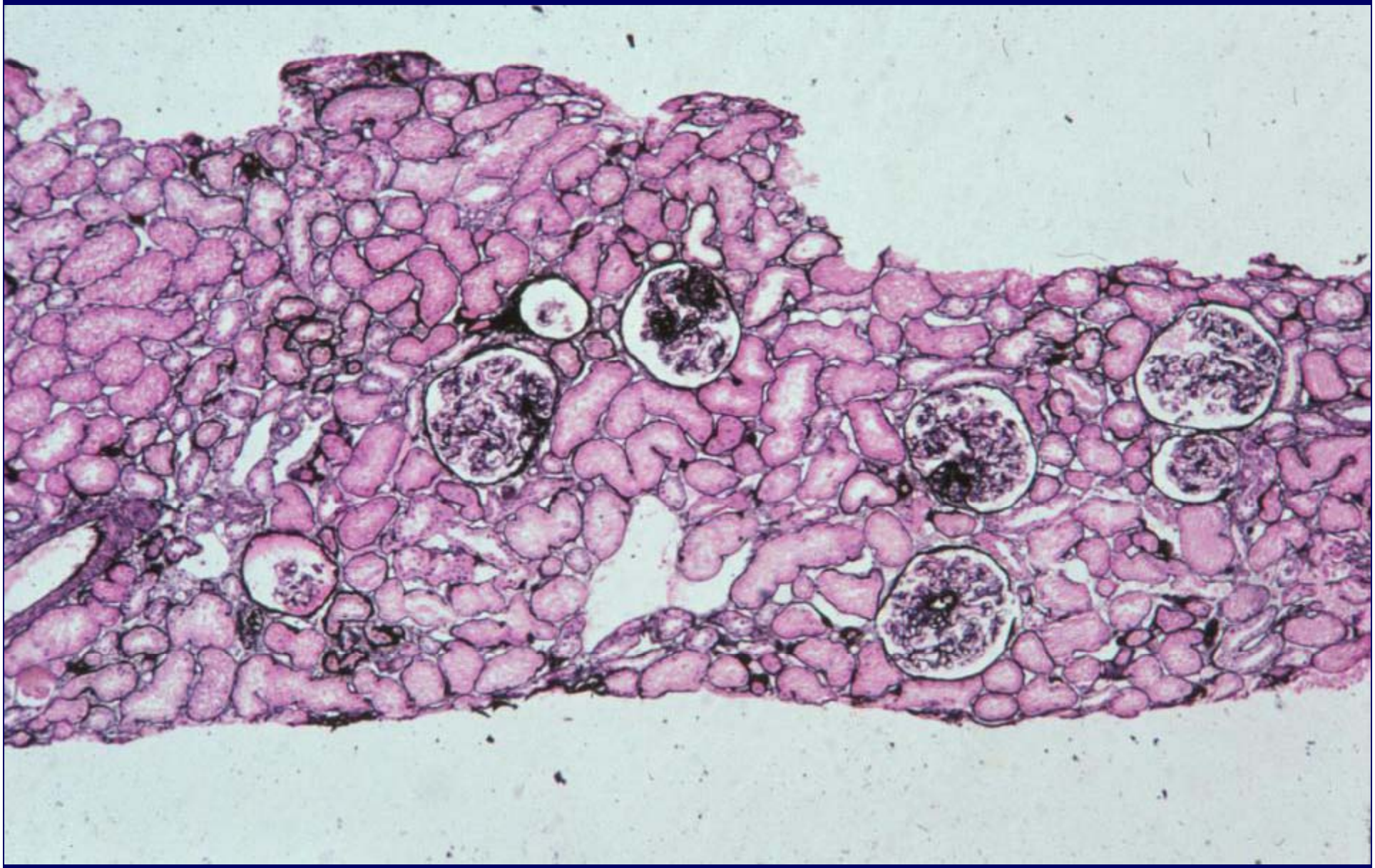
- 5-10% Adults with NS, >85% children
- Usually sudden onset, heavy proteinuria, and edema
- HBP 30%, Microhem 30 %,+/- Low GFR
  (volume depletion)
- Pathology: LM-Normal, IF-Neg, EM-FPF
- Course : Respond to Steroids, Relapse, No RF

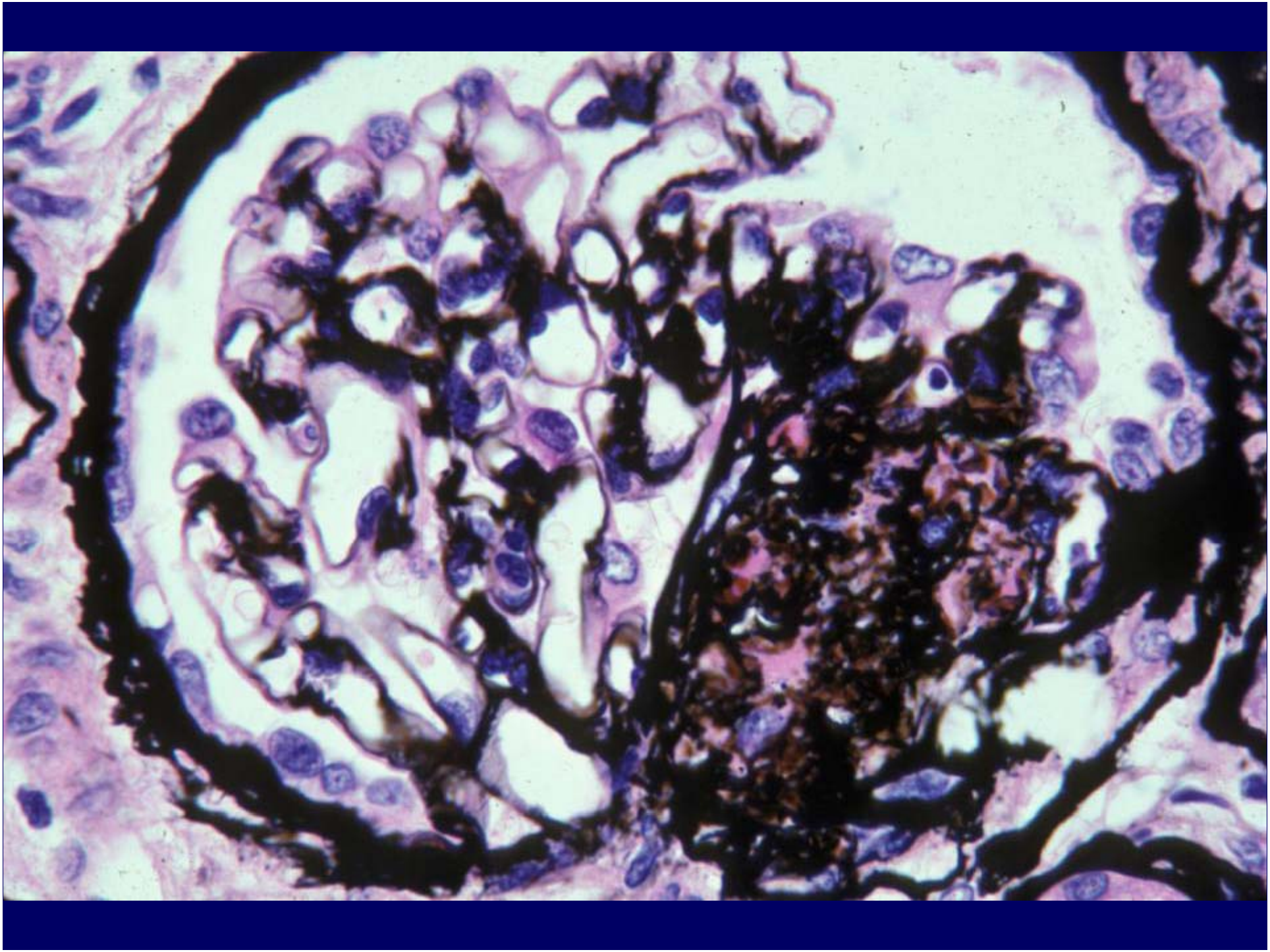
Case 1: Treatment and Course

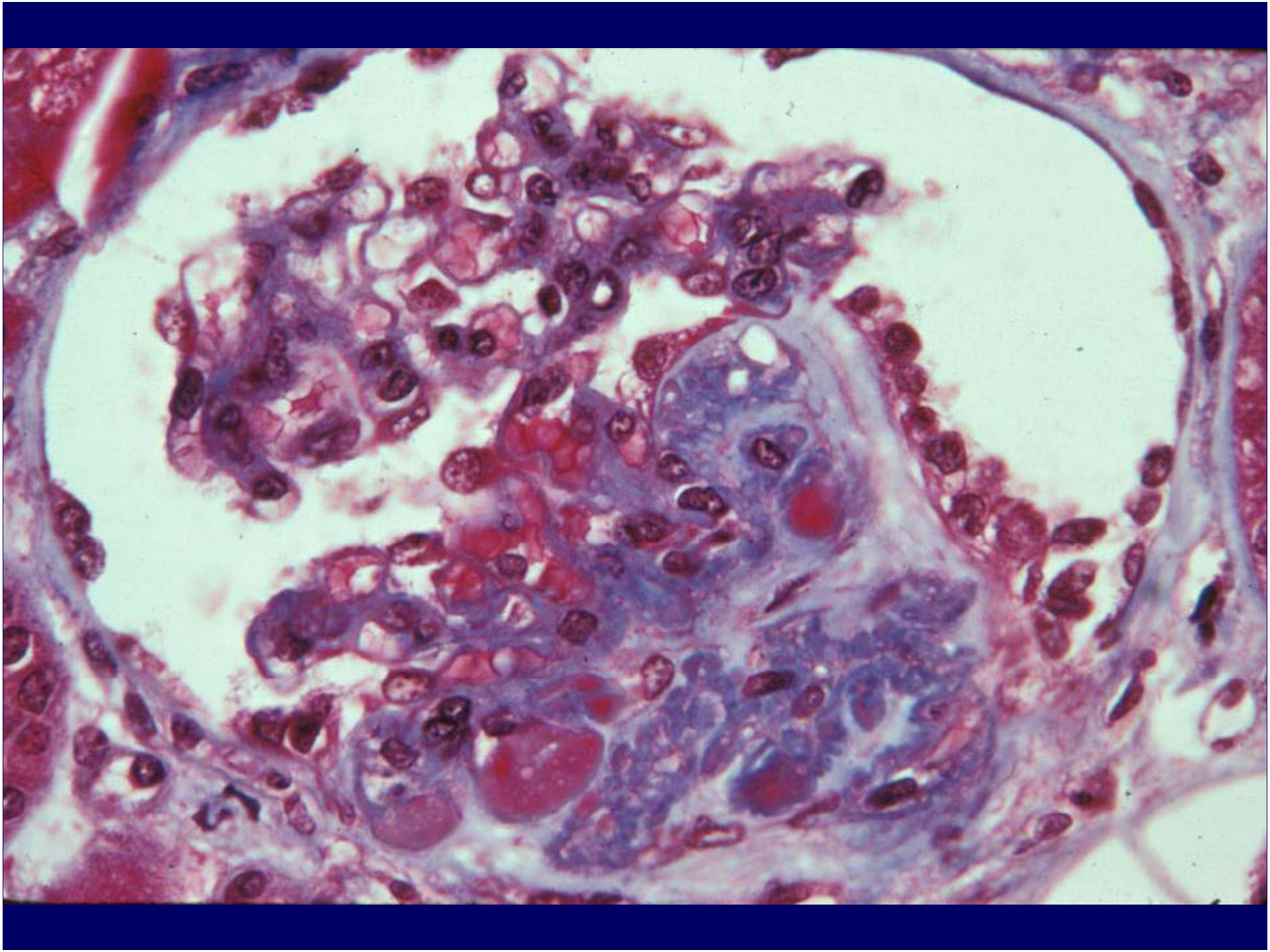
- Prednisone 1mg/kg was started
- Furosemide was prescribed for edema
- 3 weeks later the patient was edema-free.
- Urine dipstick tests for protein were negative.
- Prednisone was tapered and stopped by the third month

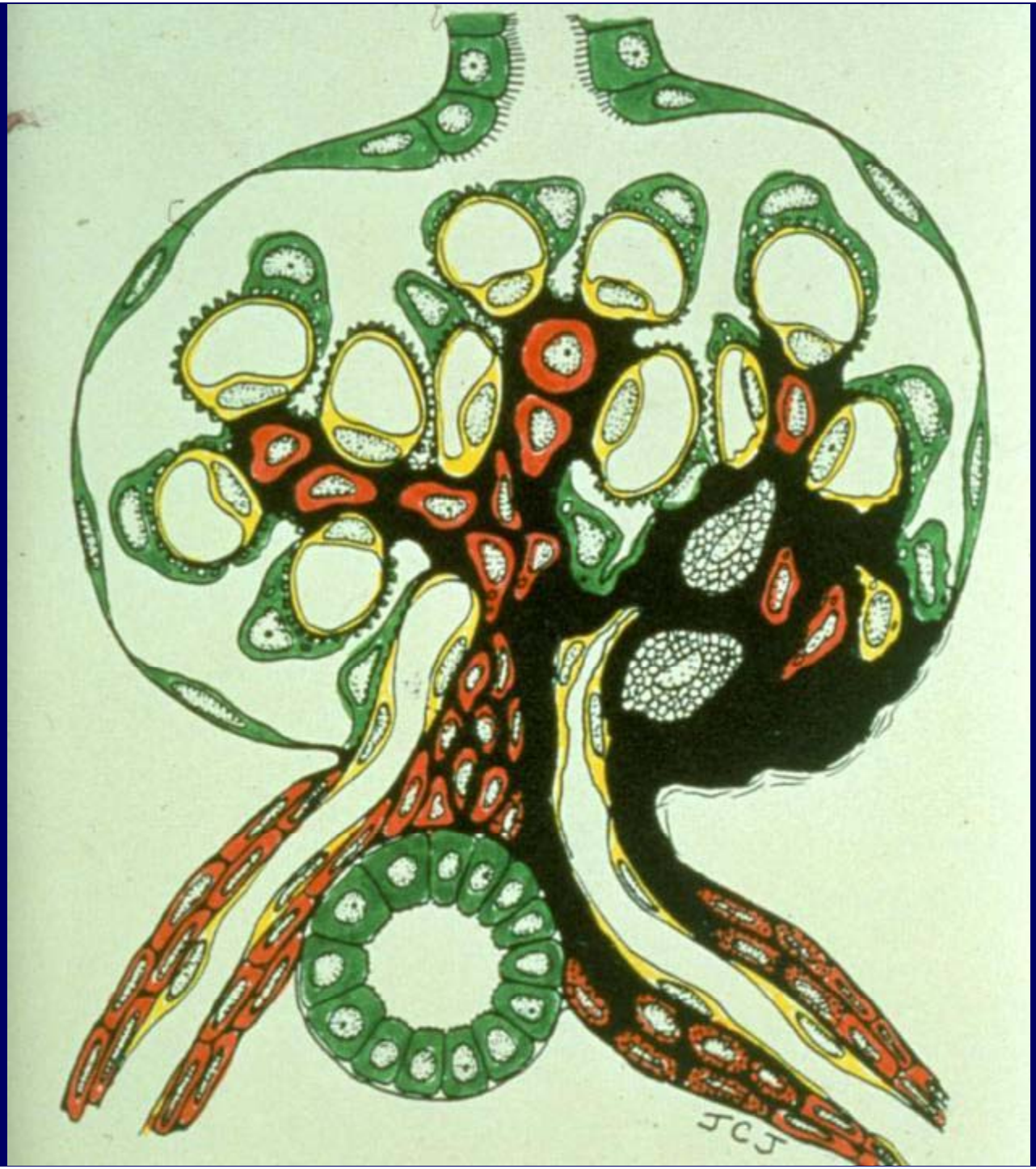
Case 2

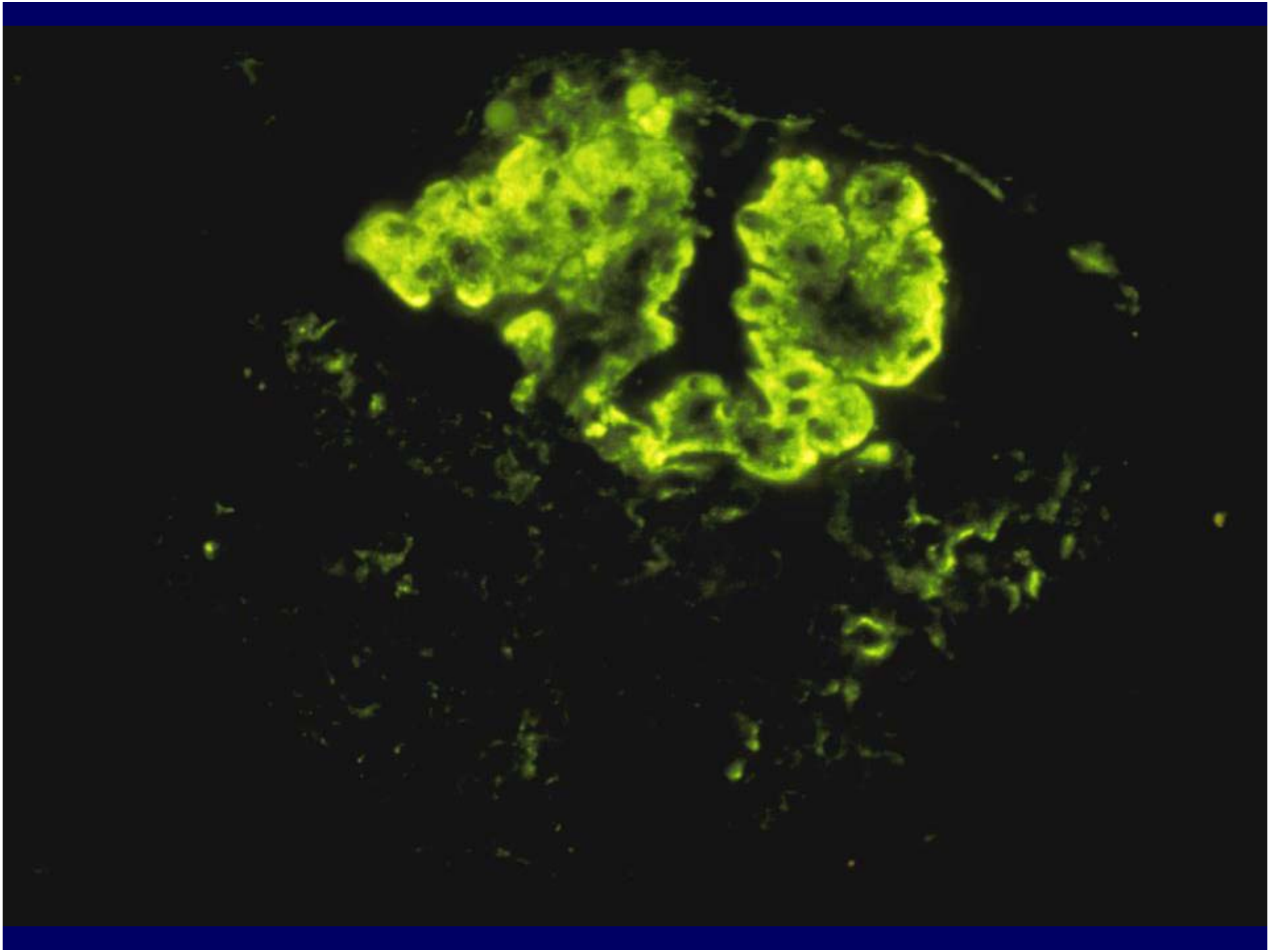
- A 19 year old female college student gains 12 pounds and has lower extremity edema. Her physician finds 4+ albuminuria.
- Labs:
  - Creatinine 1.0 mg/dl
  - Albumin is 2.0 g/dl
  - Cholesterol 425 mg/dl
  - 18g proteinuria/day
  - Serologic tests are negative
- Corticosteroid treatment is without improvement.

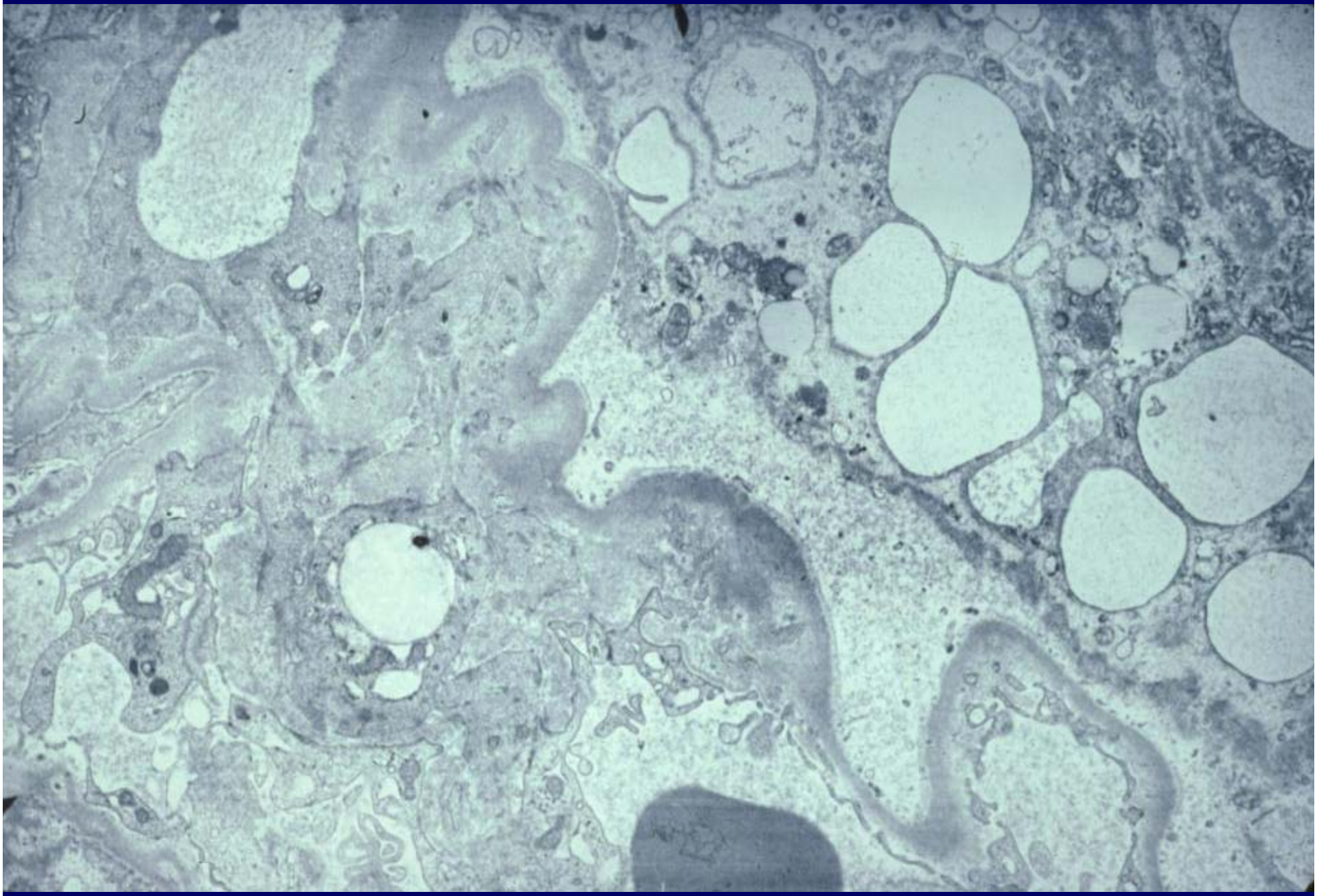


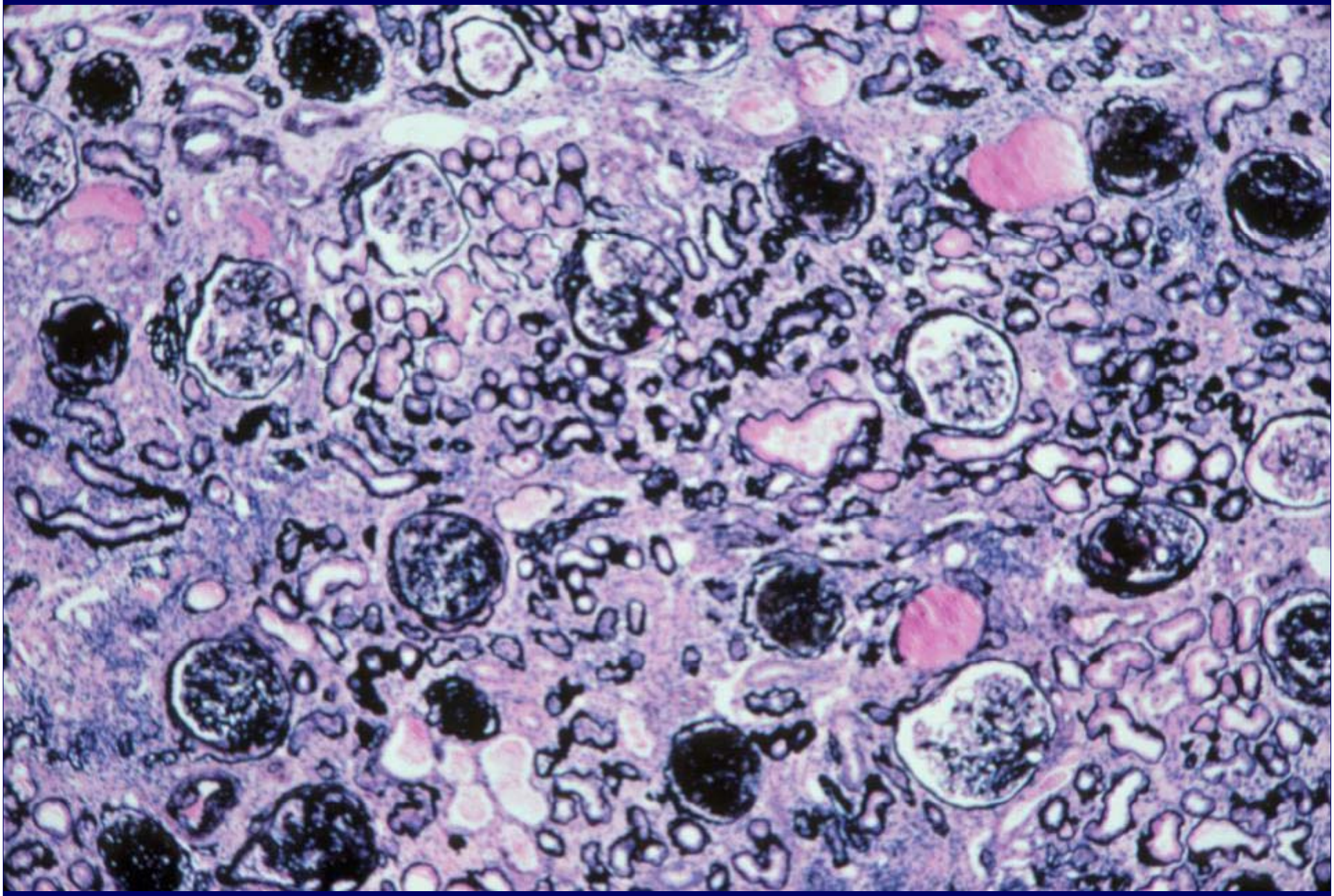





JCJ

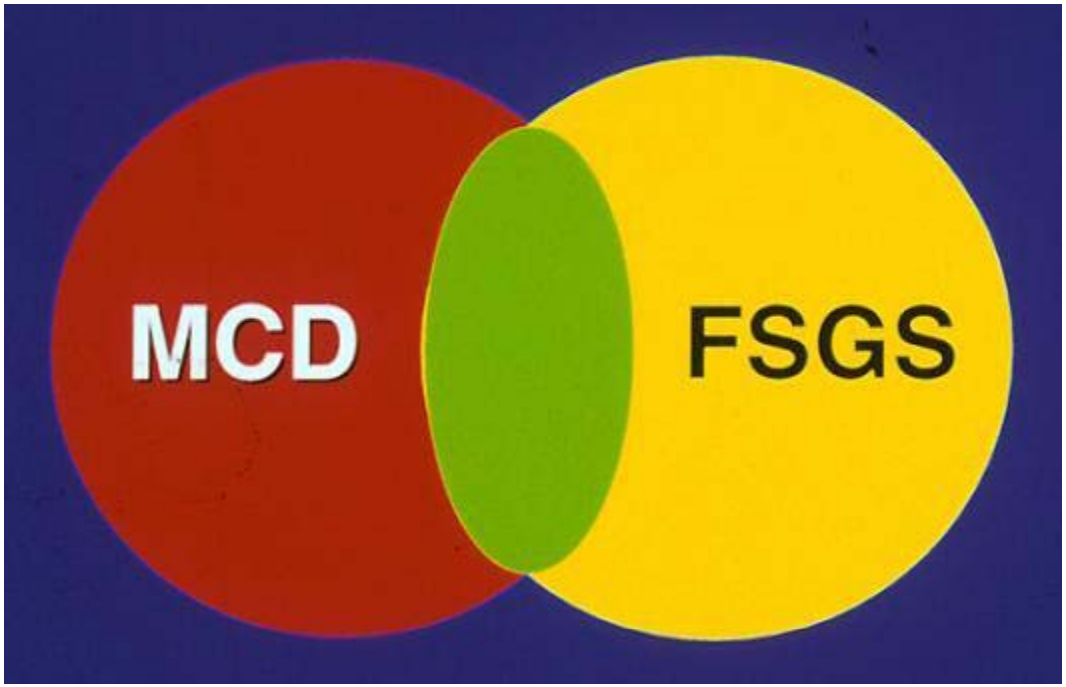






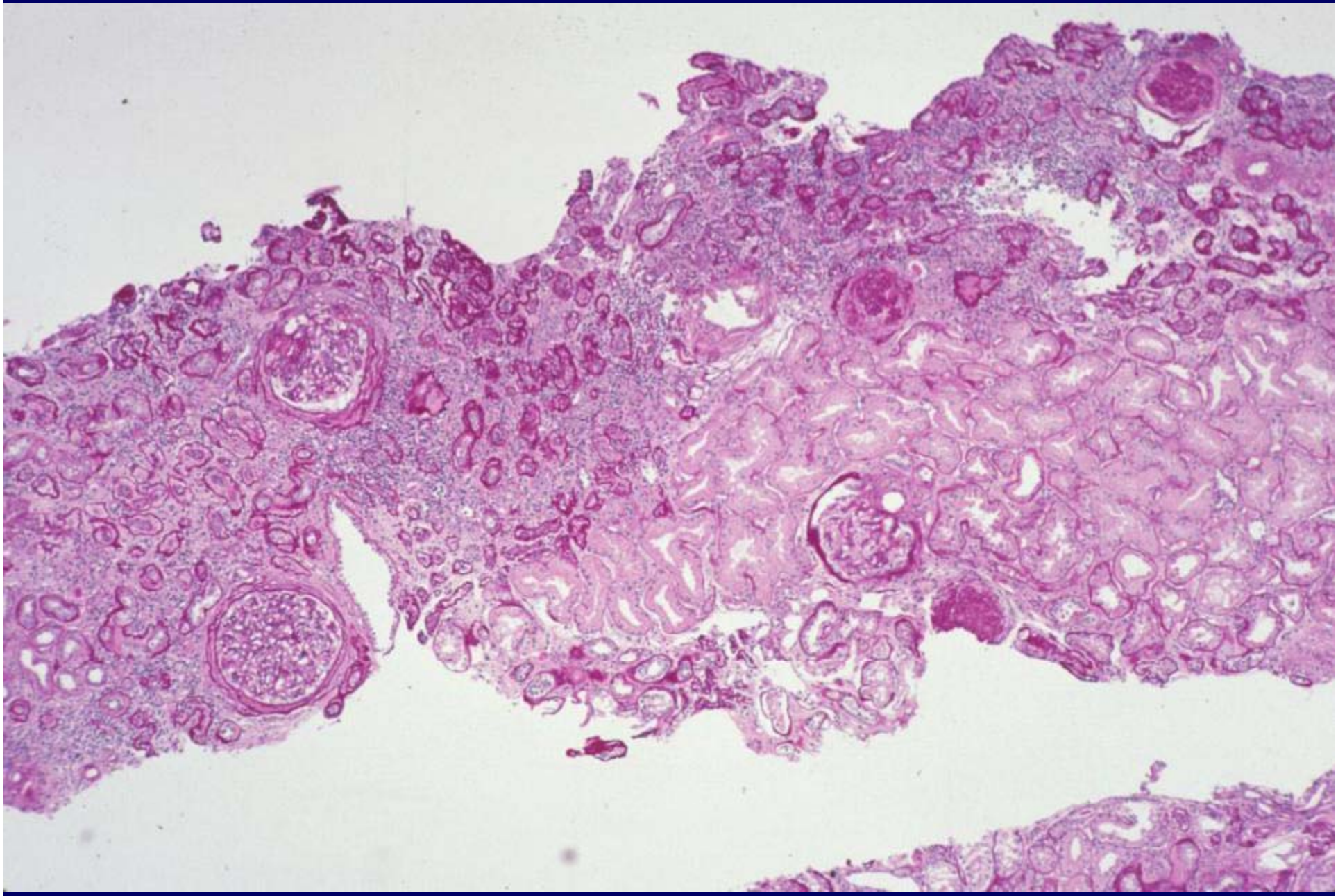
MCD and FSGS

- Separate or related entities?



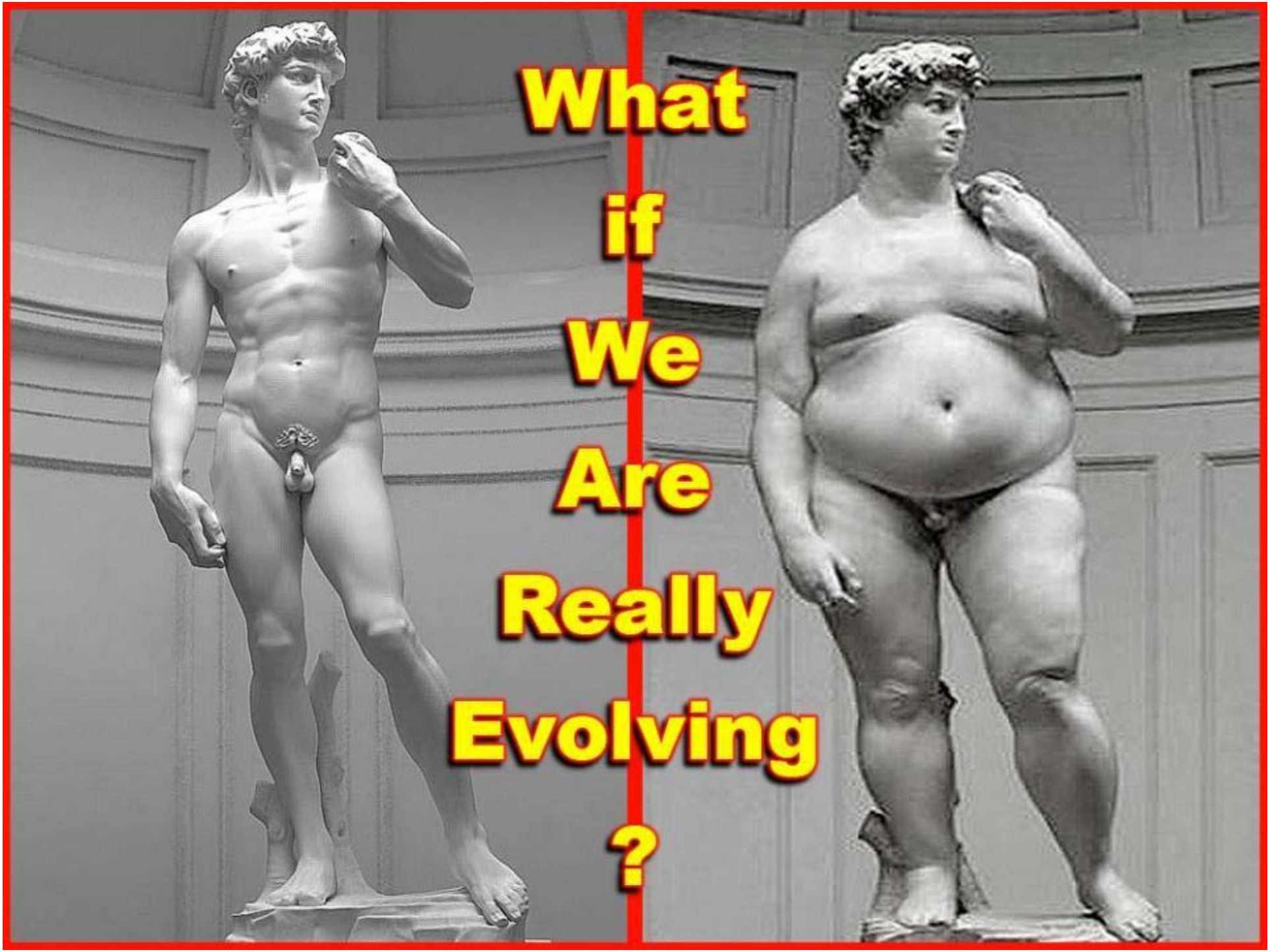
Circulating Factors in MCD and FSGS:

Ref	Source	Biologic Activity	Biochemical Characteristics
Bakker 1986	Serum or mononuclear cells of MCD	Increases vasc. permeability Binds anionic sites	~ 120 Kd Kallikrein-like
Koyama 1991	T cell hybridoma from MCD	Causes proteinuria and foot process fusion in rats	60-160 Kd Not an Ig
Savin 1996	Serum or plasma of FSGS (initial, collapsing, recurrent) and steroid-resistant MCD	Increases glom permeability in vitro	50 Kd Binds protein A Not Ig Not Cationic
Dantal 1994	Plasma of recurrent FSGS in txp	Causes proteinuria and foot process fusion in rats	< 100,000 Kd Binds protein A Not Ig



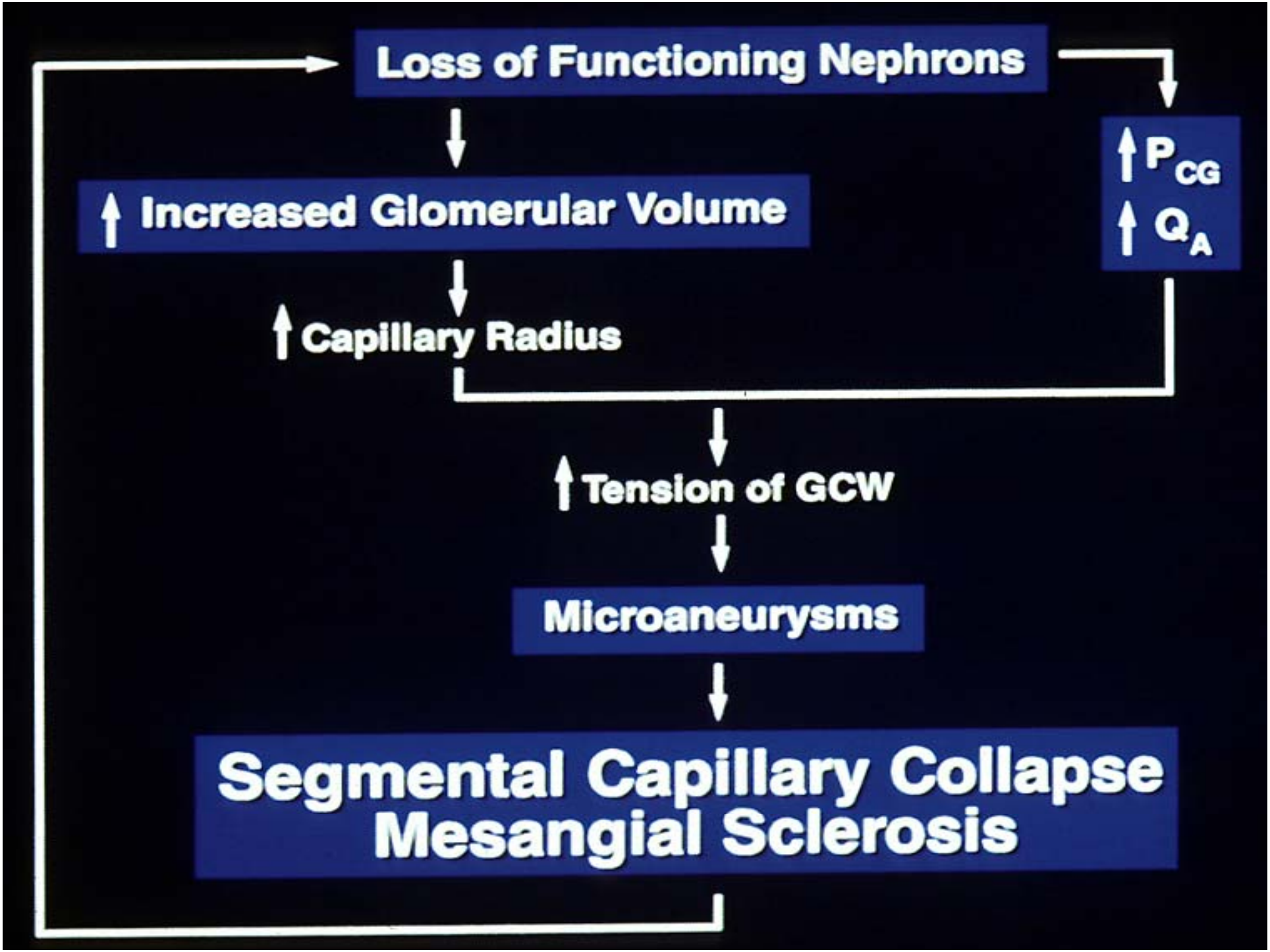
Secondary FSGS due to Adaptive Responses

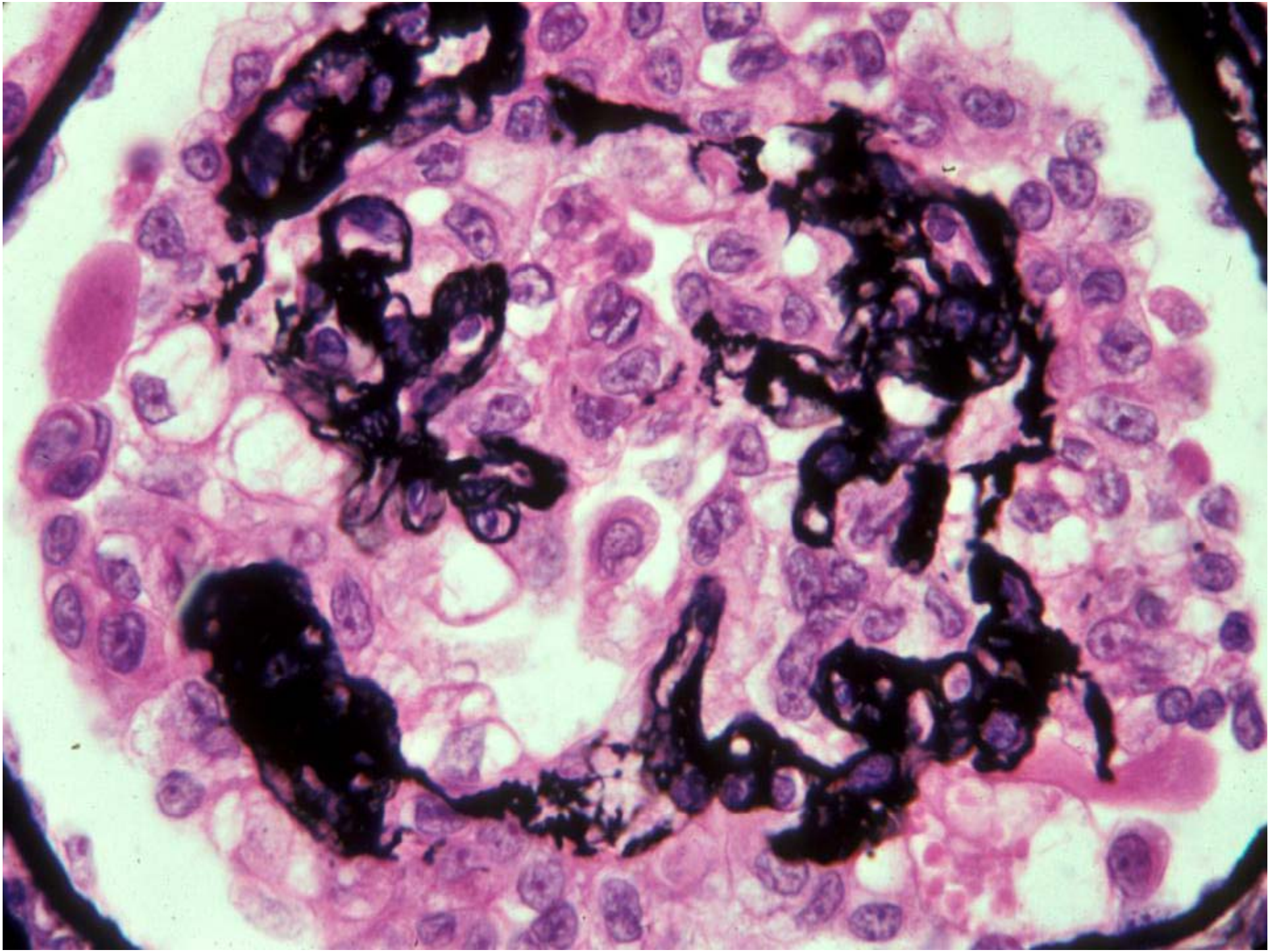
- Reflux nephropathy
- Renal agenesis (solitary functioning kidney)
- Any Chronic Renal Disease
- Obesity

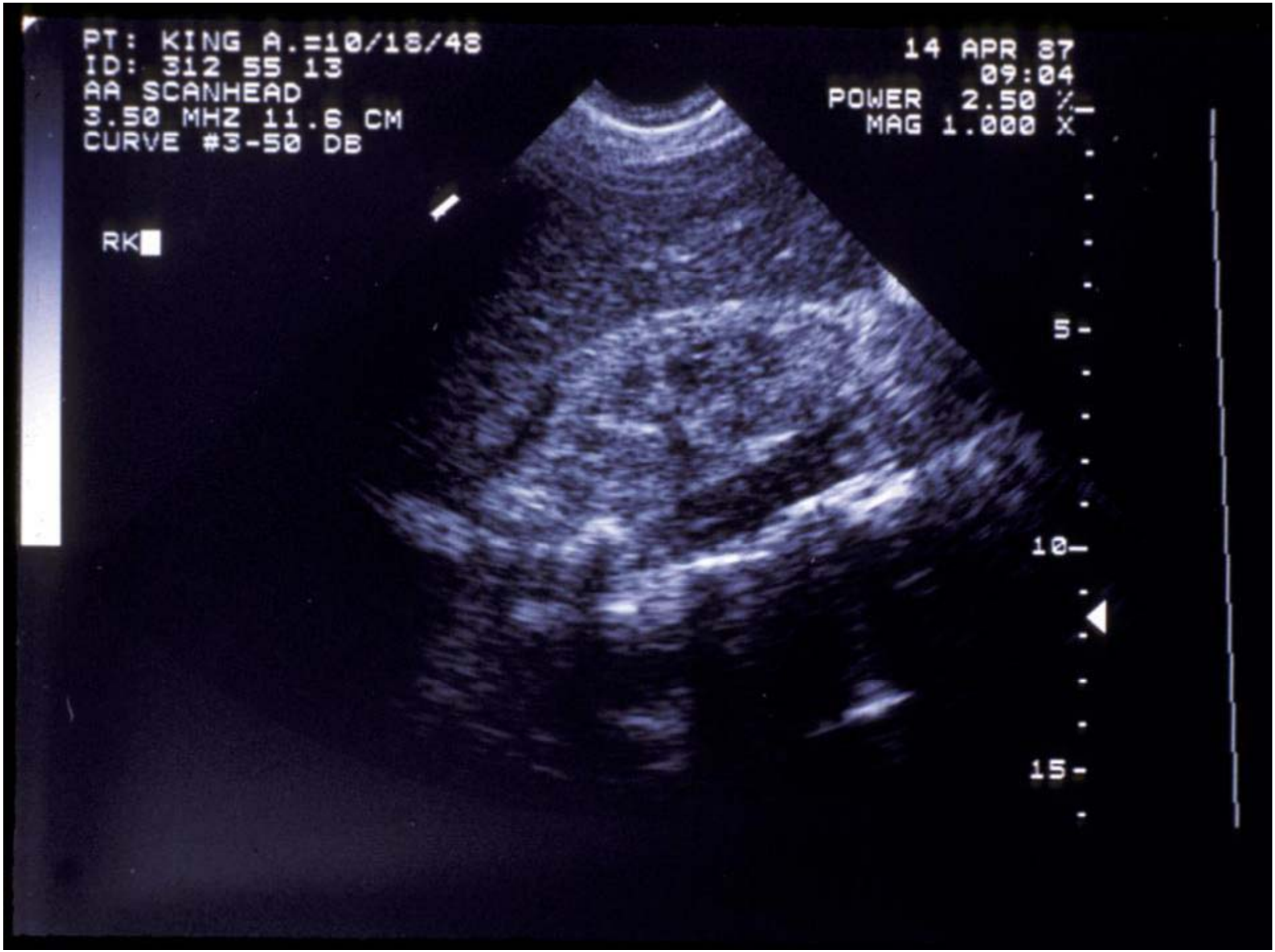

What
if
We
Are
Really
Evolving
?

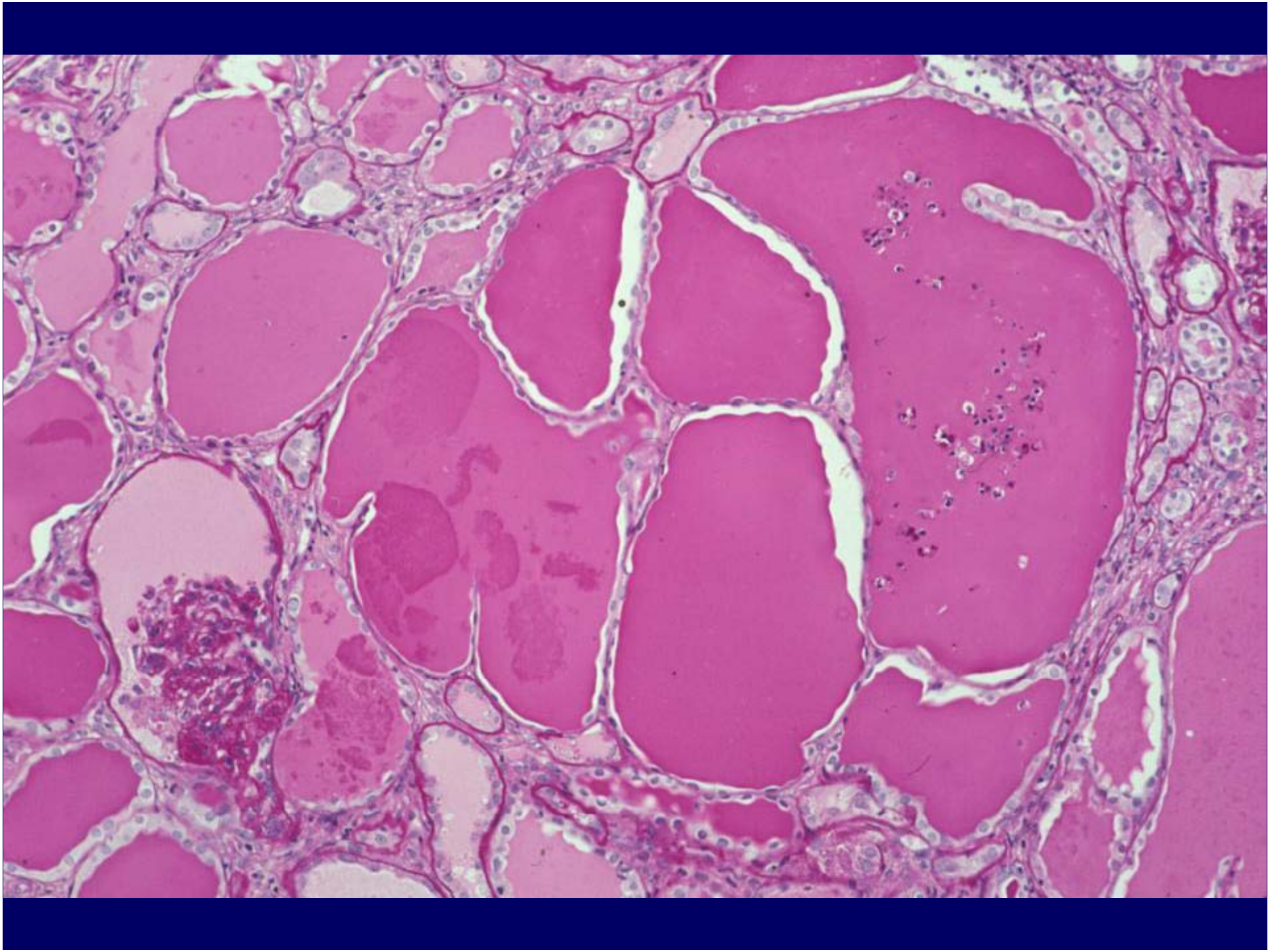
Obesity-Glomerular “Stress”

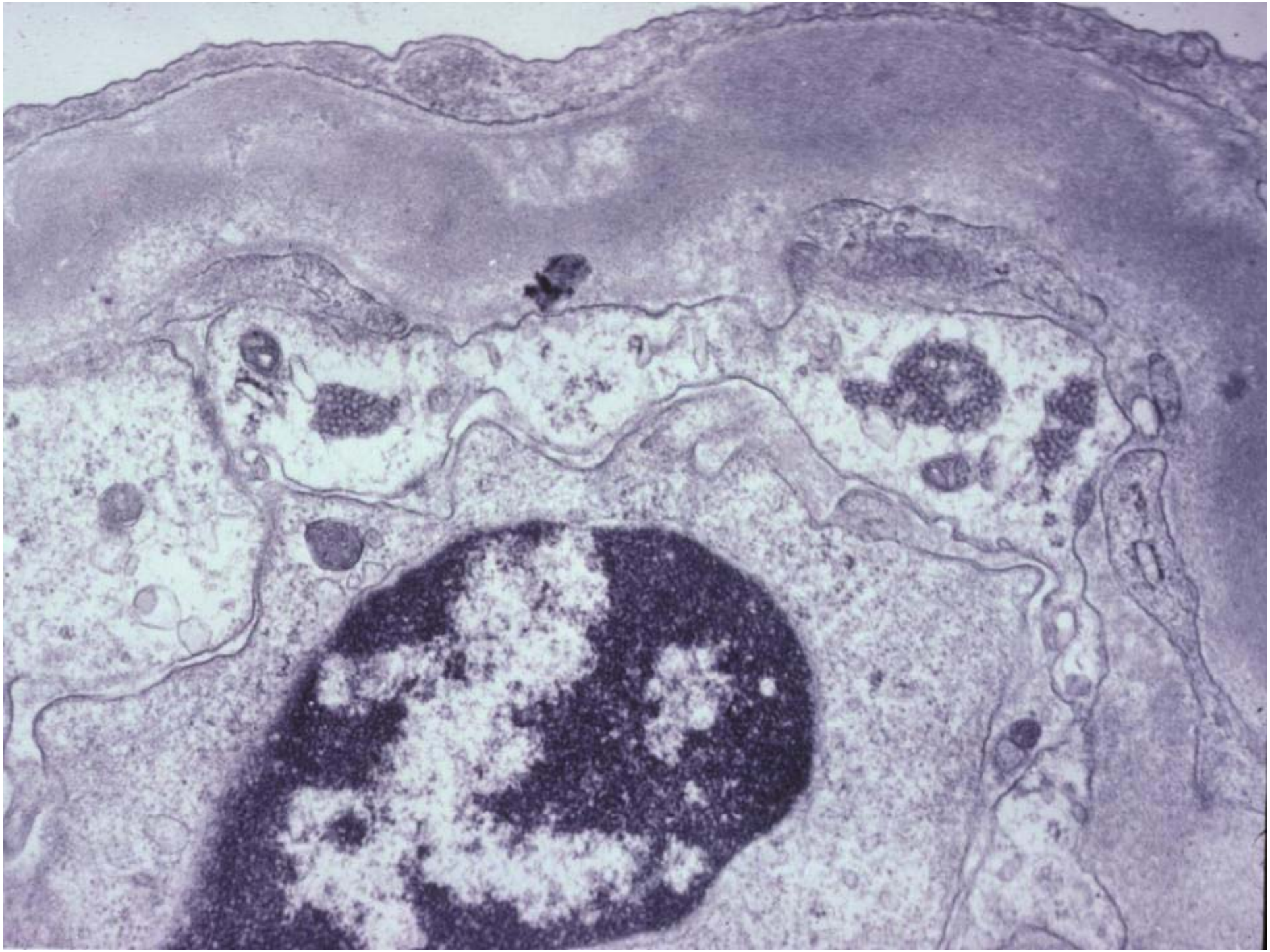
...AND YOU THINK YOU HAVE STRESS..


Loss of Functioning Nephrons
↑ Increased Glomerular Volume
↑ Capillary Radius
↑ P_{CG}
↑ Q_A
↑ Tension of GCW
Microaneurysms
Segmental Capillary Collapse
Mesangial Sclerosis

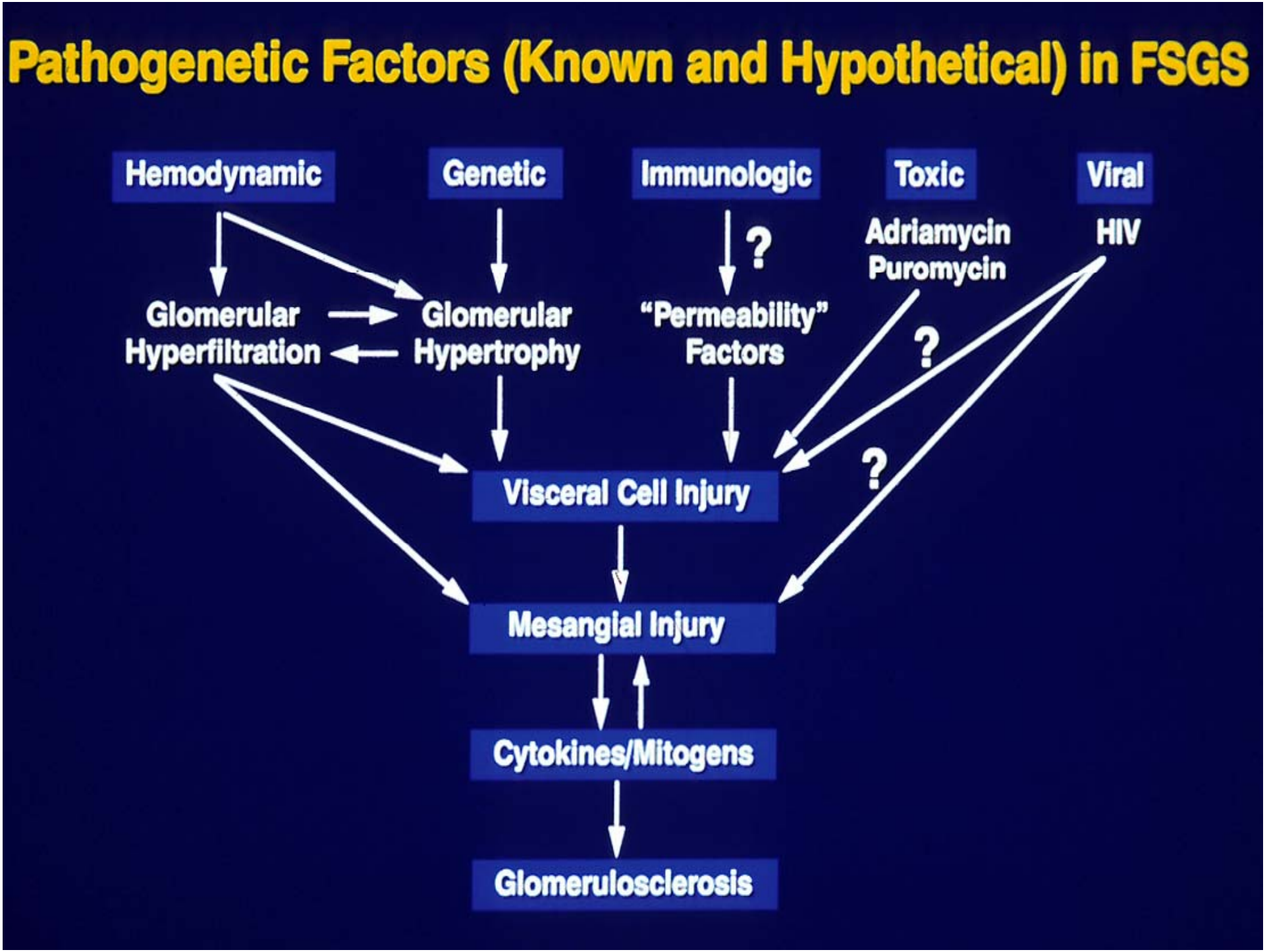



PT: KING A.=10/18/48
ID: 312 55 13
AA SCANHEAD
3.50 MHZ 11.6 CM
CURVE #3-50 DB
RK
14 APR 87
09:04
POWER 2.50 %
MAG 1.000 X
5
10
15





Pathogenetic Factors (Known and Hypothetical) in FSGS

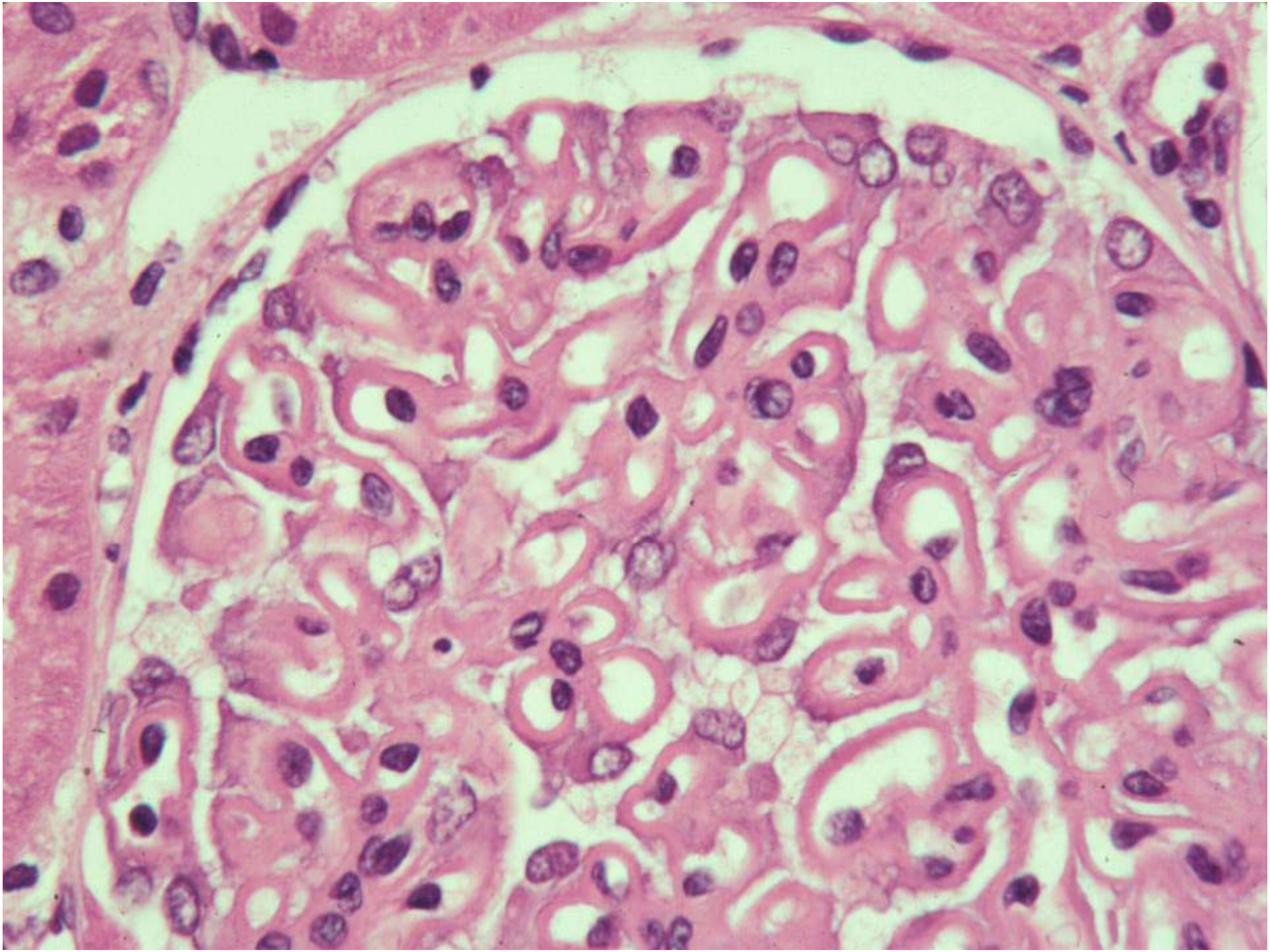


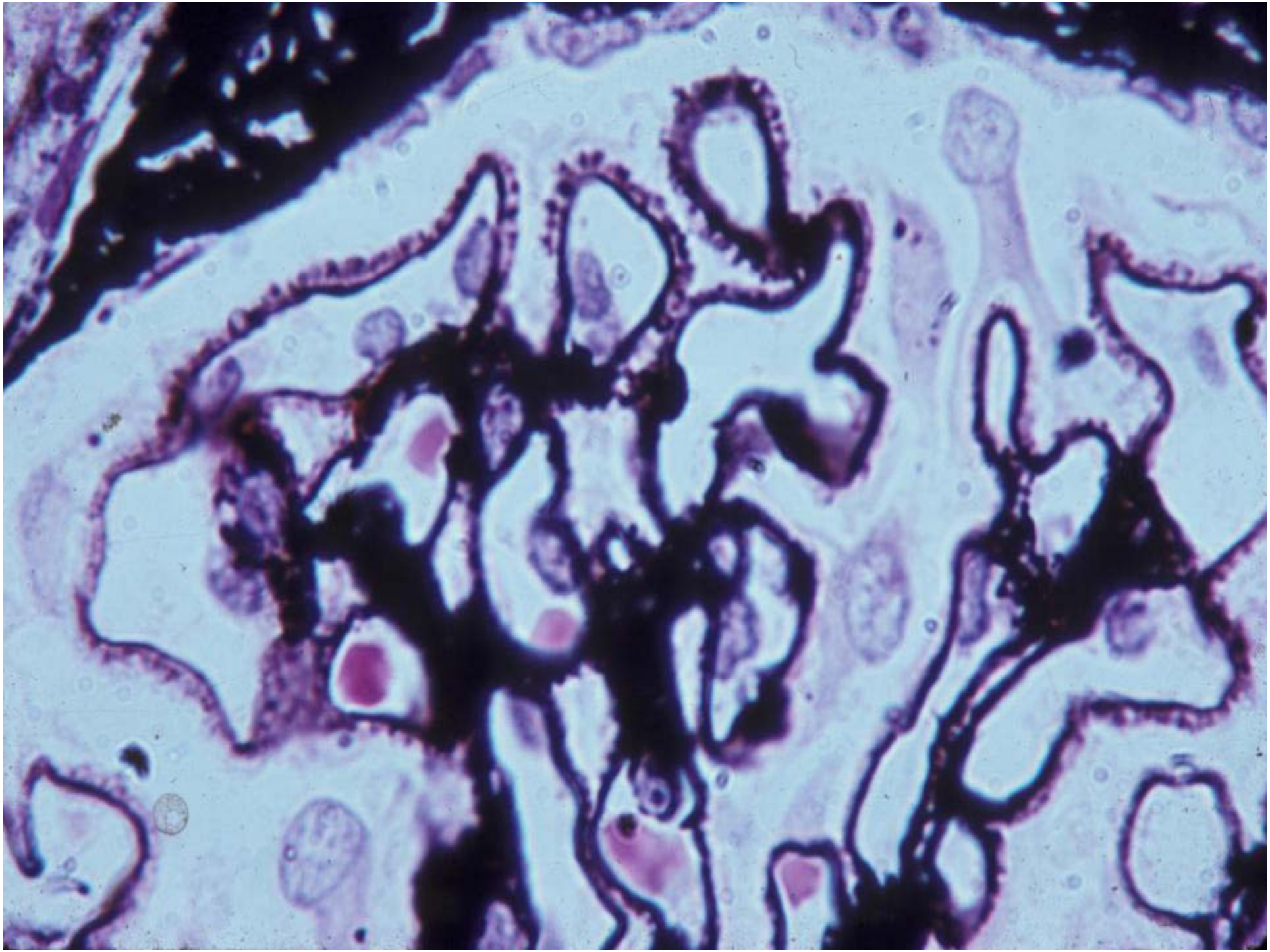
Focal Segmental Glomerulosclerosis

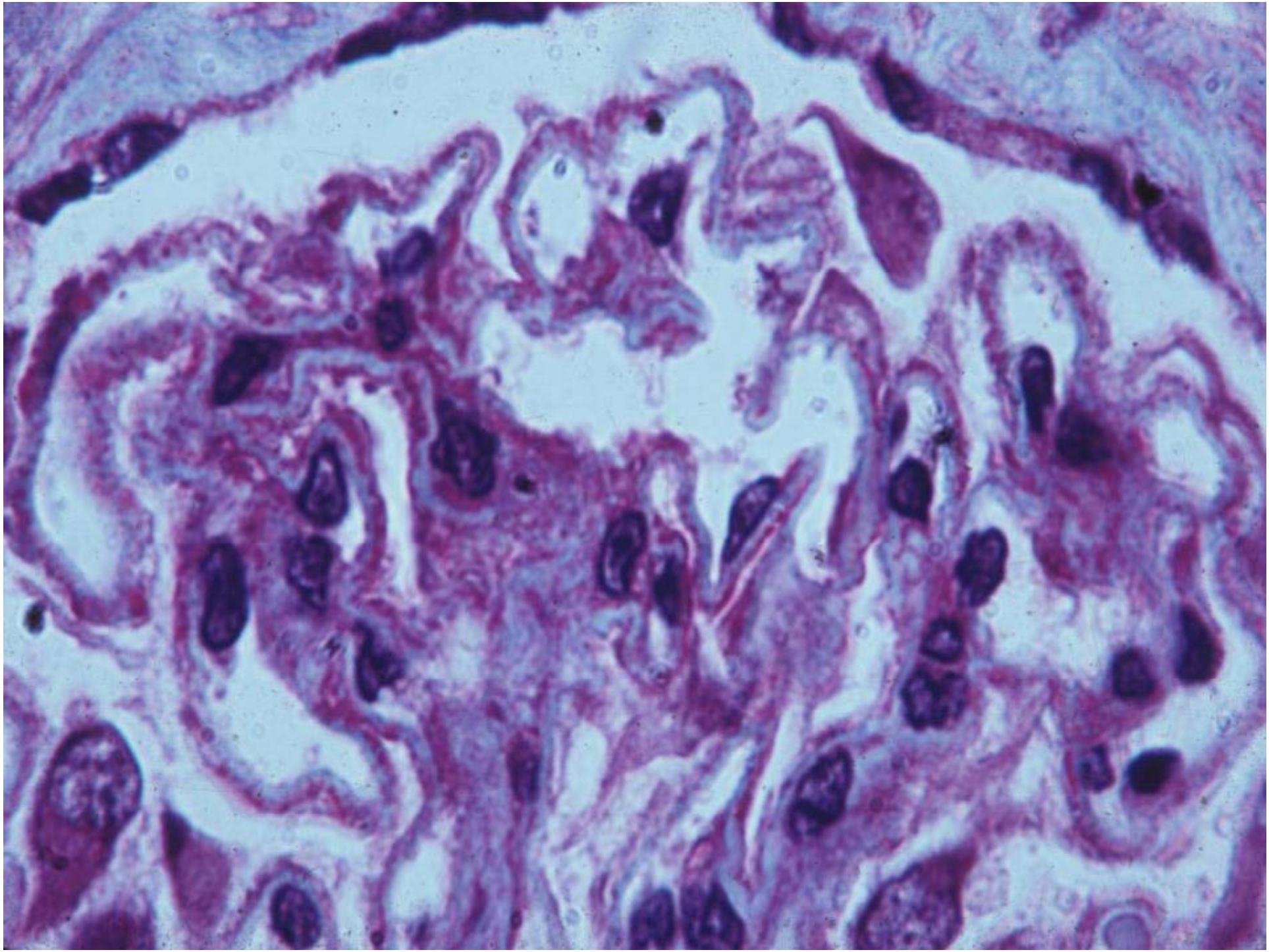
- **Increased frequency > 20% NS – Blacks!**
- **In adults onset 2/3 NS, 1/3 proteinuria**
- **HBP > 30 %, Microhematuria >30 %, renal dysfunction 50 %**
- **Predictors of ESRD: hvy prot.,Blks, high creatinine, on BX – int fibrosis & Collapse**
- **Strds >50% respsond, cytoxan, cyA, MMF**
- **Recurs 1/3 Txps-**

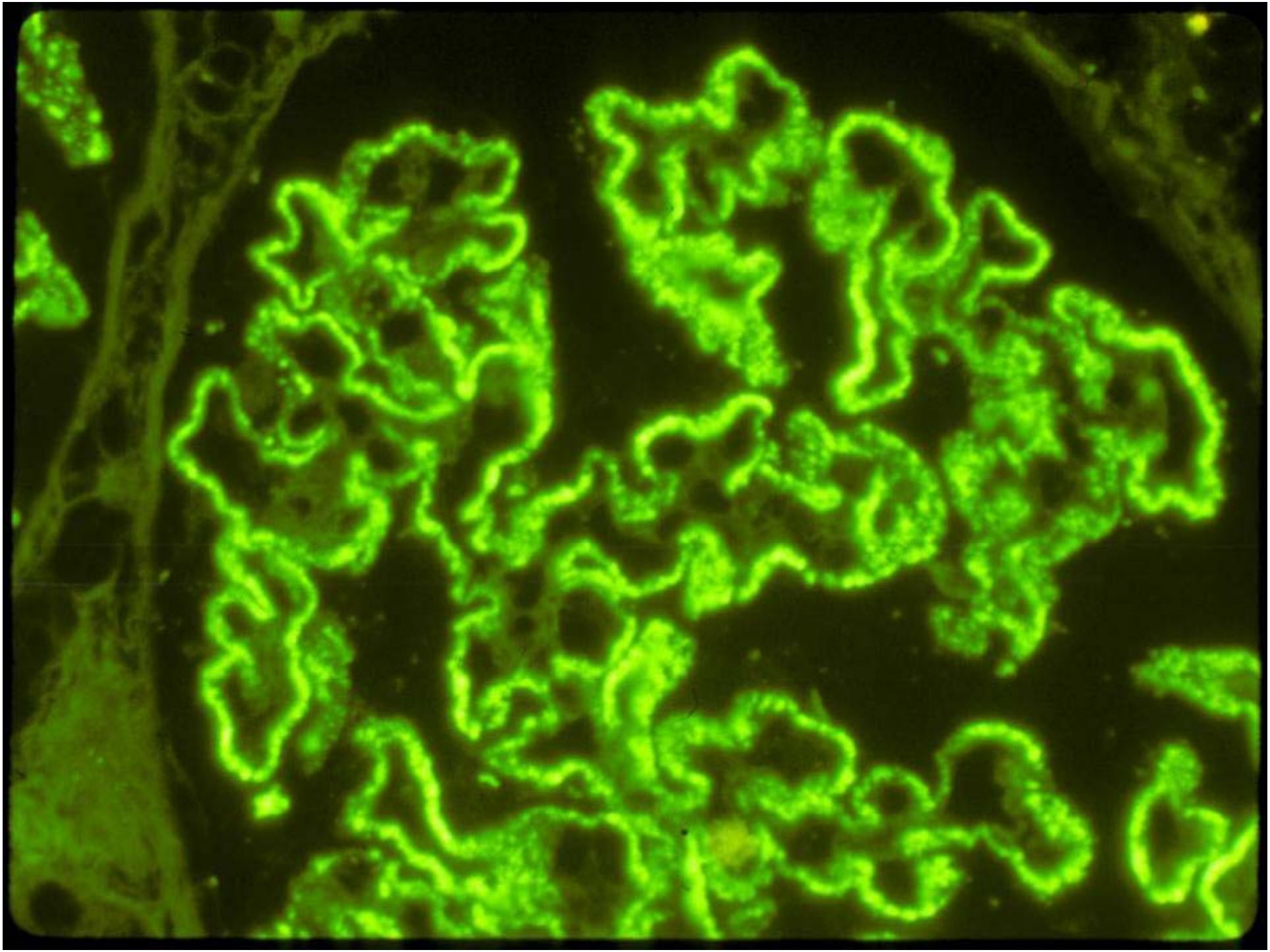
Case 3

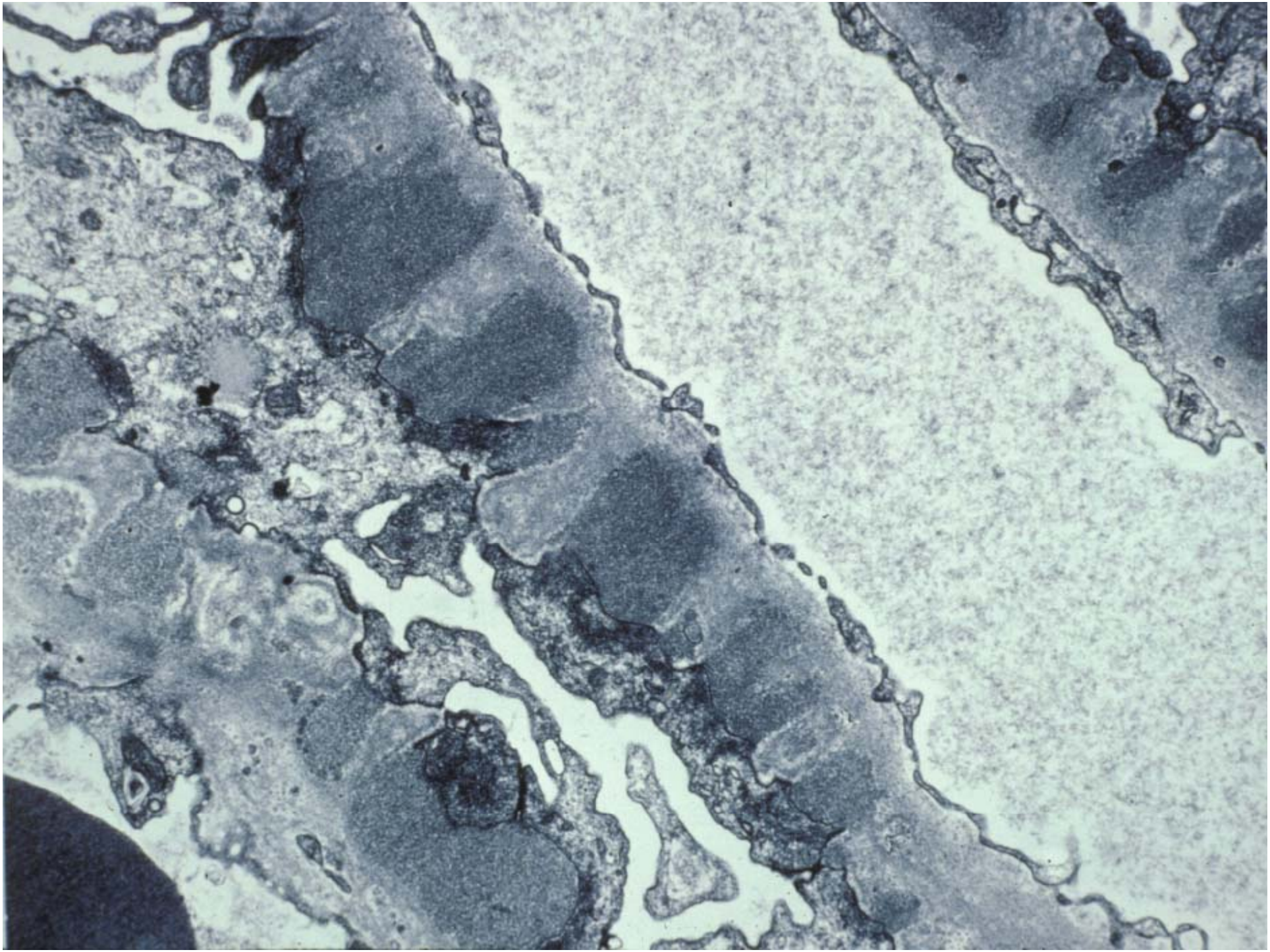
- A 67 year old Caucasian Male develops ankle edema and weight gain.
- Labs:
  - 12 g proteinuria/day
  - GFR normal (creatinine 1.1 mg/dl)
  - Albumin of 1.4 g/dl
  - Cholesterol 635 mg/dl

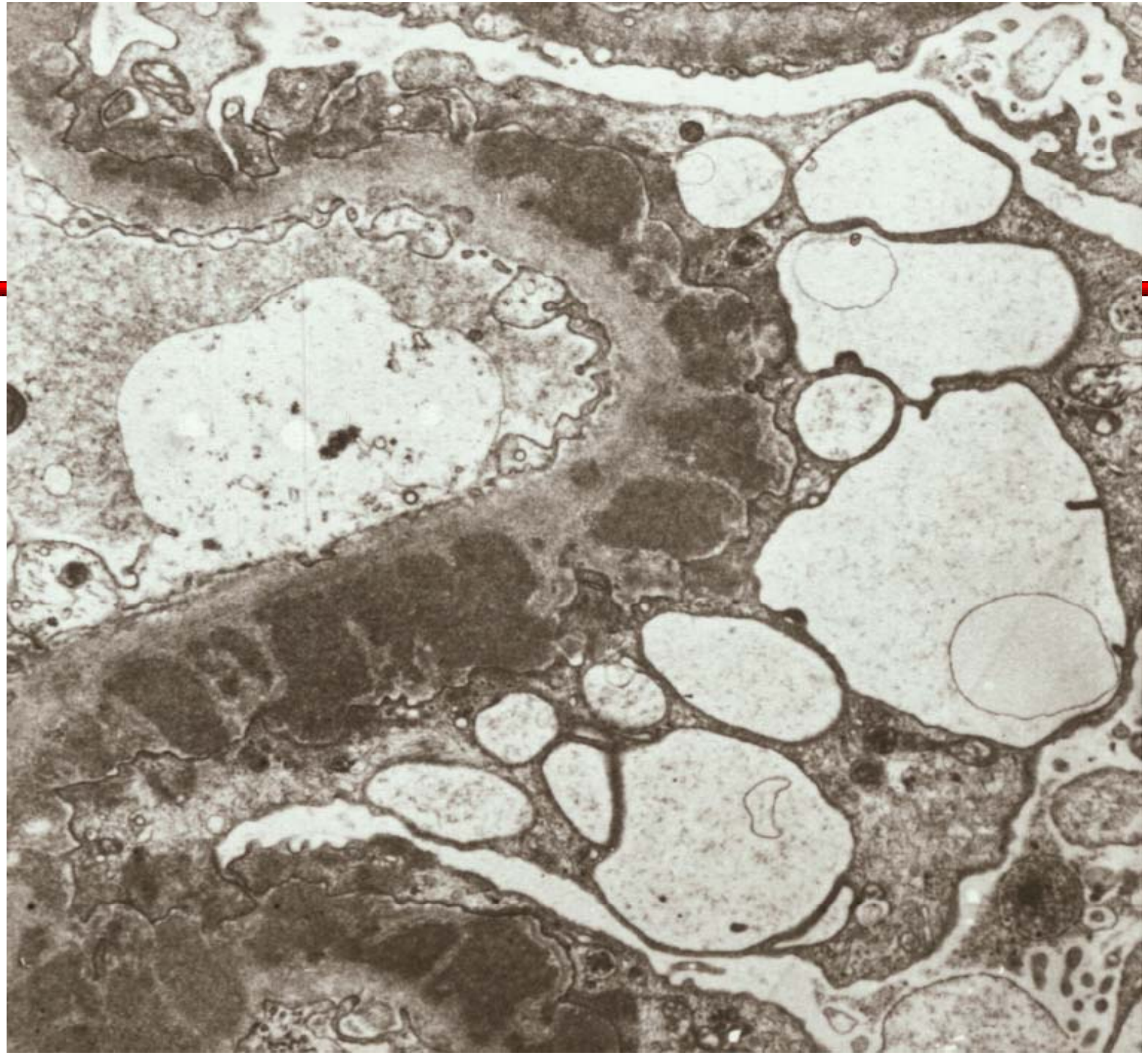












B

Conditions Associated with Membranous Glomerulopathy

- Infections

  Hepatitis B, Hepatitis C, secondary and congenital syphilis, malaria, schistosomiasis
- Drugs

  Gold, penicillamine, captopril
- Collagen vascular disease

  SLE, Hashimoto's thyroiditis, Rheumatoid Arthritis
- Neoplasia

  Carcinoma (lung, breast, colon, stomach)

GENERATION OF HEYMANN NEPHRITIS

FX1A (fractioned material from renal cortex)

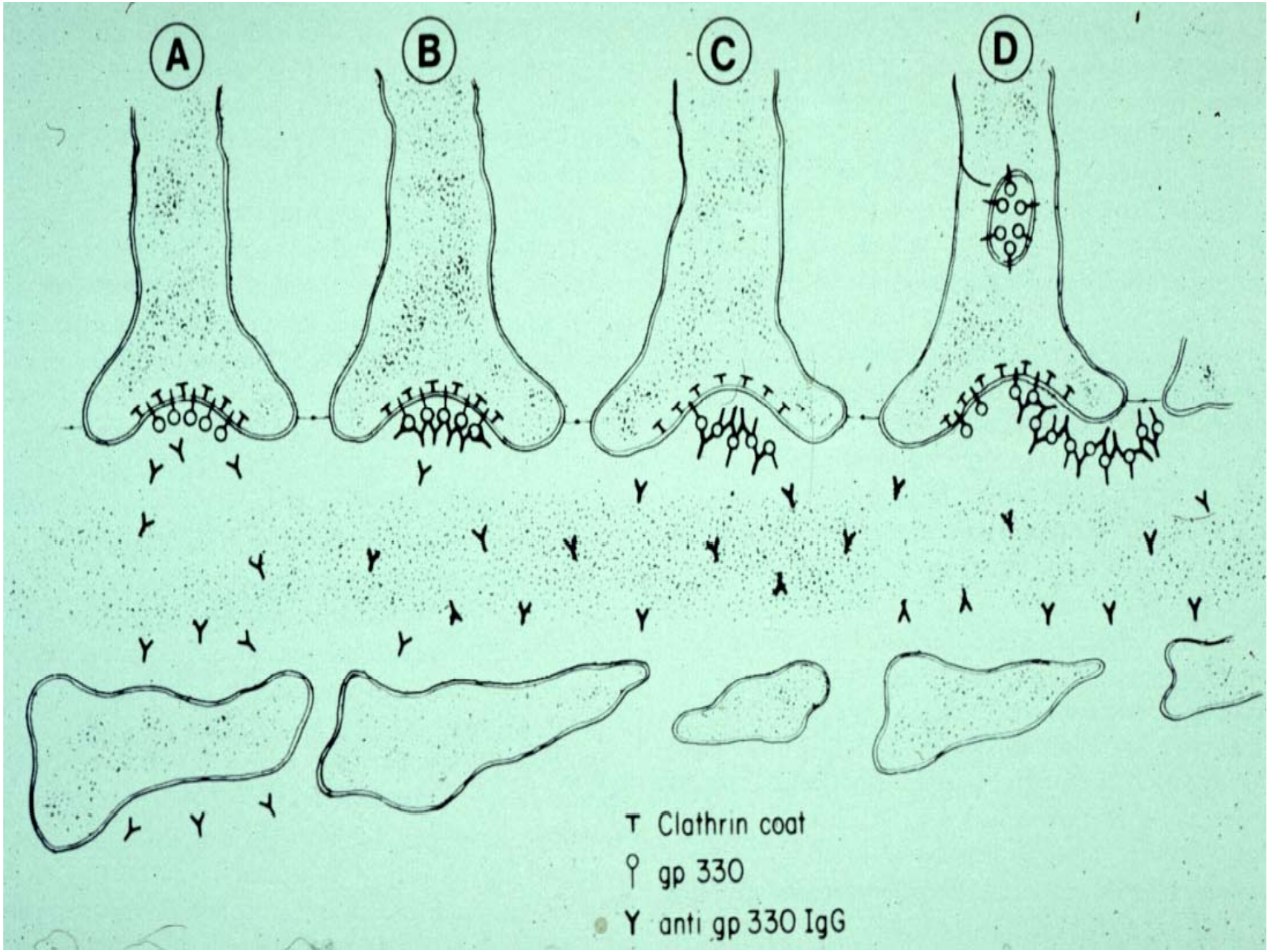
RAT

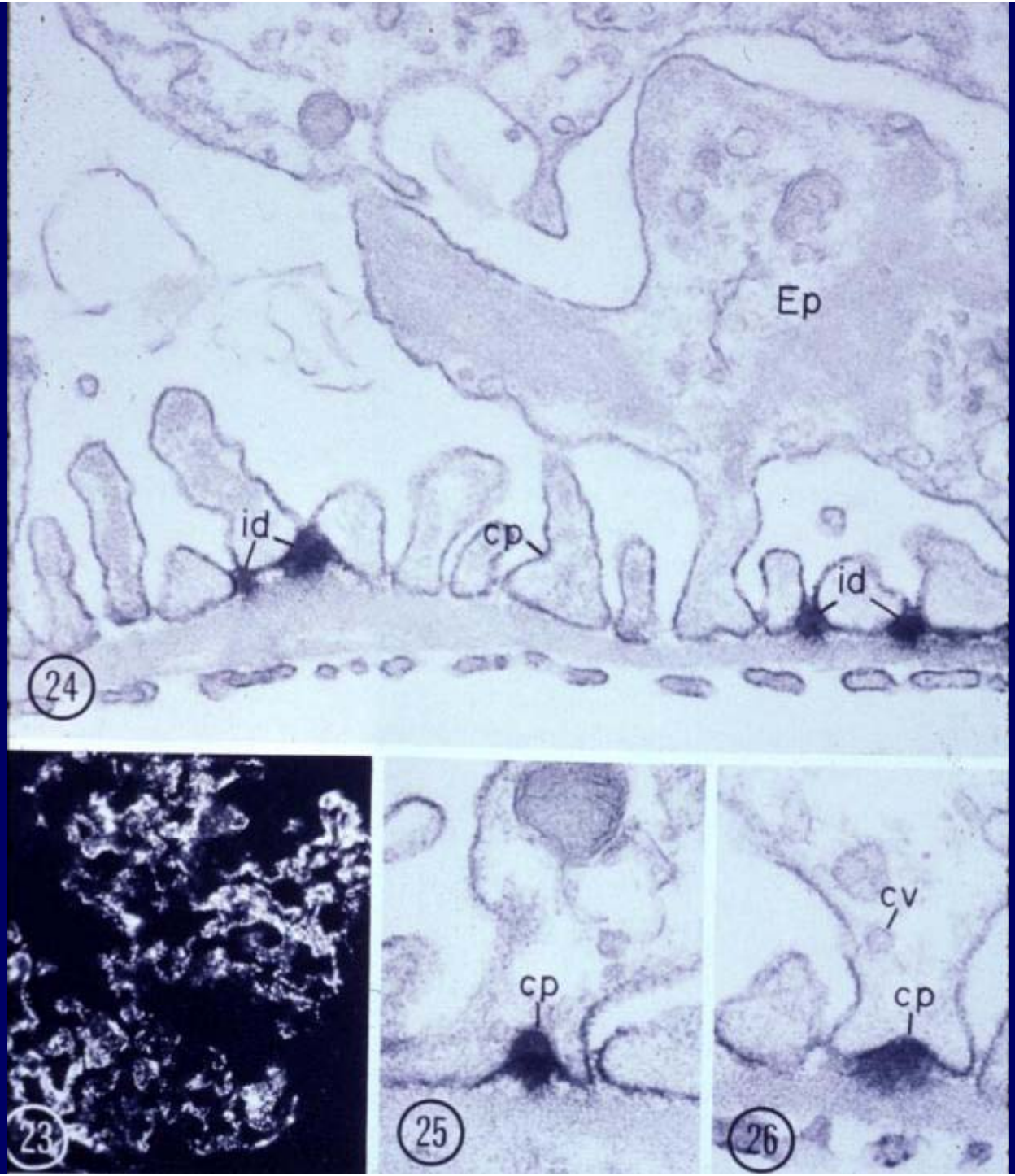
SERUM

RAT

ACTIVE HEYMANN NEPHRITIS

PASSIVE HEYMANN NEPHRITIS


A
B
C
D
T Clathrin coat
gp 330
Y anti gp 330 IgG


Ep
id
cp
id
24
23
25
cv
cp
26

CONSEQUENCES OF IMMUNE DEPOSIT FORMATION

BINDING OF COMPLEMENT → FORMATION OF THE C5b-9 COMPLEX

↓

ACTIVATION OF GVEC
Scavenging of C5b-9
Increased expresion of cytochrome b_{558}

FORMATION OF REACTIVE OXIGEN SPECIES (ROS) → DEPOSITION OF ROS IN GBM

↓

PROTEINURIA

Discovery of the Target Antigen in Human Membranous Glomerulopathy!!!!! (Salant et al. NEJM 2009)

- PHOSPHOLIPASE A2 RECEPTOR (PLA2R)

Antibody to PLA2R has been eluted from glomerular deposits of human MGN

Antibody to PLA2R is detected in serum of 70% of patients with primary MGN

Membranous Nephropathy

- The most common etiology of nephrotic syndrome in white adults
- Course variable
- Renal survival at 10 y: 65%-85%
- Renal survival at 15 y: 60%
- Spontaneous remission rate: 20%-30%

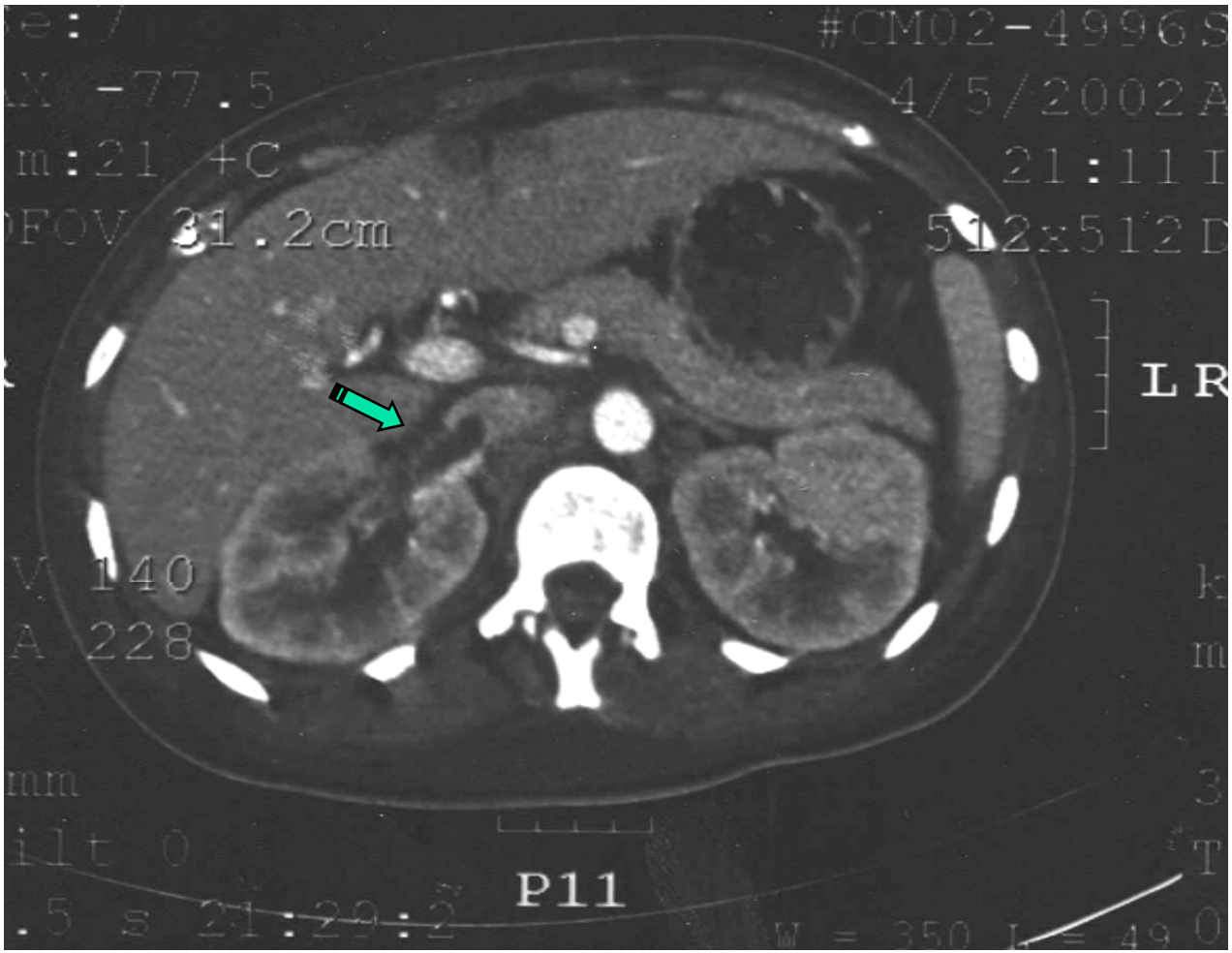
Treatment of Membranous Nephropathy

- Conservative Therapy
- Corticosteroids
- Alternating Steroids –Cytotoxics
- Cyclosporine
- Mycophenolate
- Anti C5 Ab, Rituximab

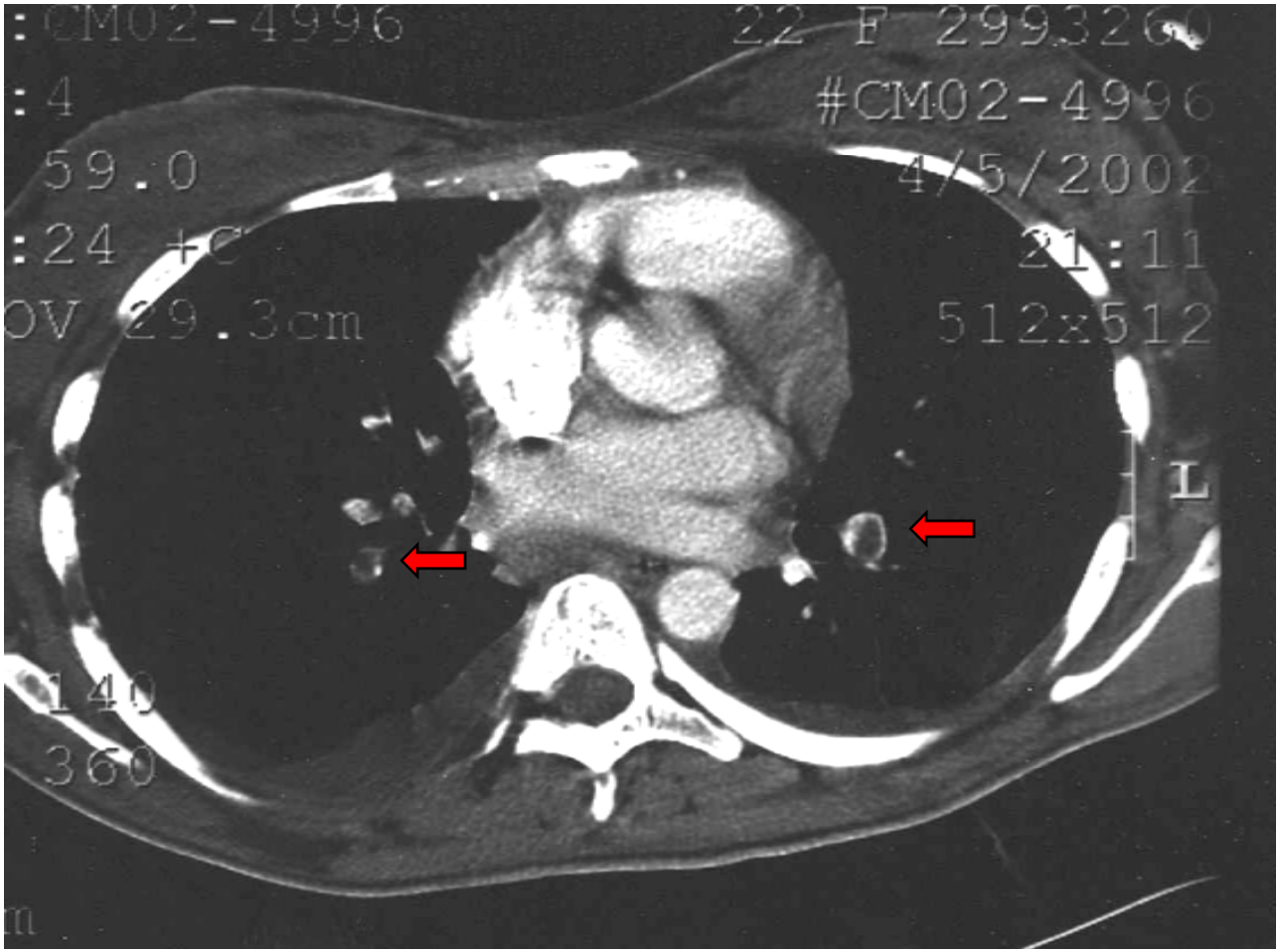
Case 3: Post Biopsy Course

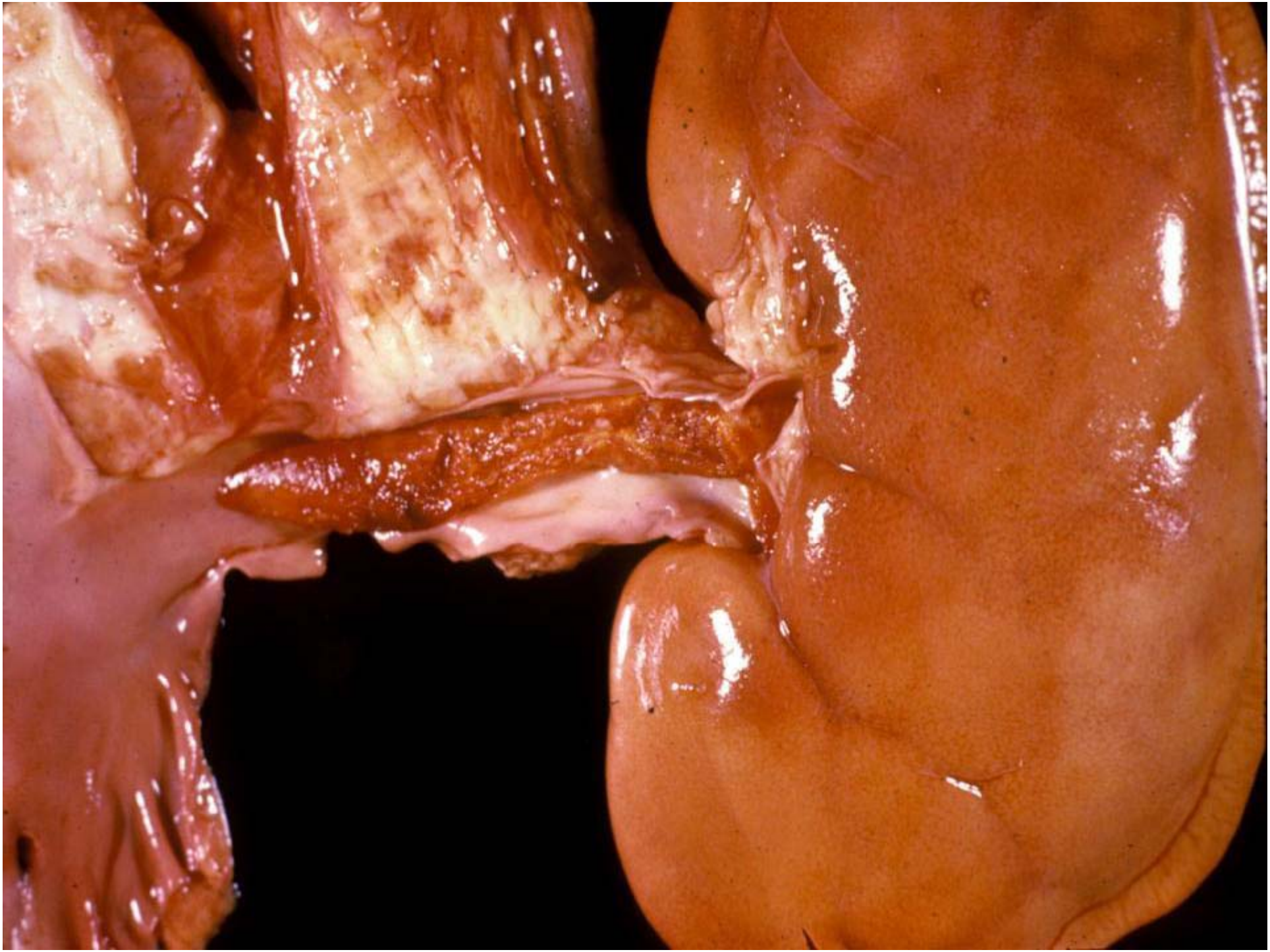
- All serologic tests are normal
- Normal Colonoscopy and CT abdomen/chest
- 3 days after admission, he develops a dull back ache and then becomes acutely short of breath.
- Chest X-ray is normal
- ABG: pH=7.45 pCO_2=30, pO_2 =60 on room air
- CT angiogram is requested

CT angiogram: Abdomen



CT angiogram: Chest





Thrombotic Abnormalities in the Nephrotic Syndrome

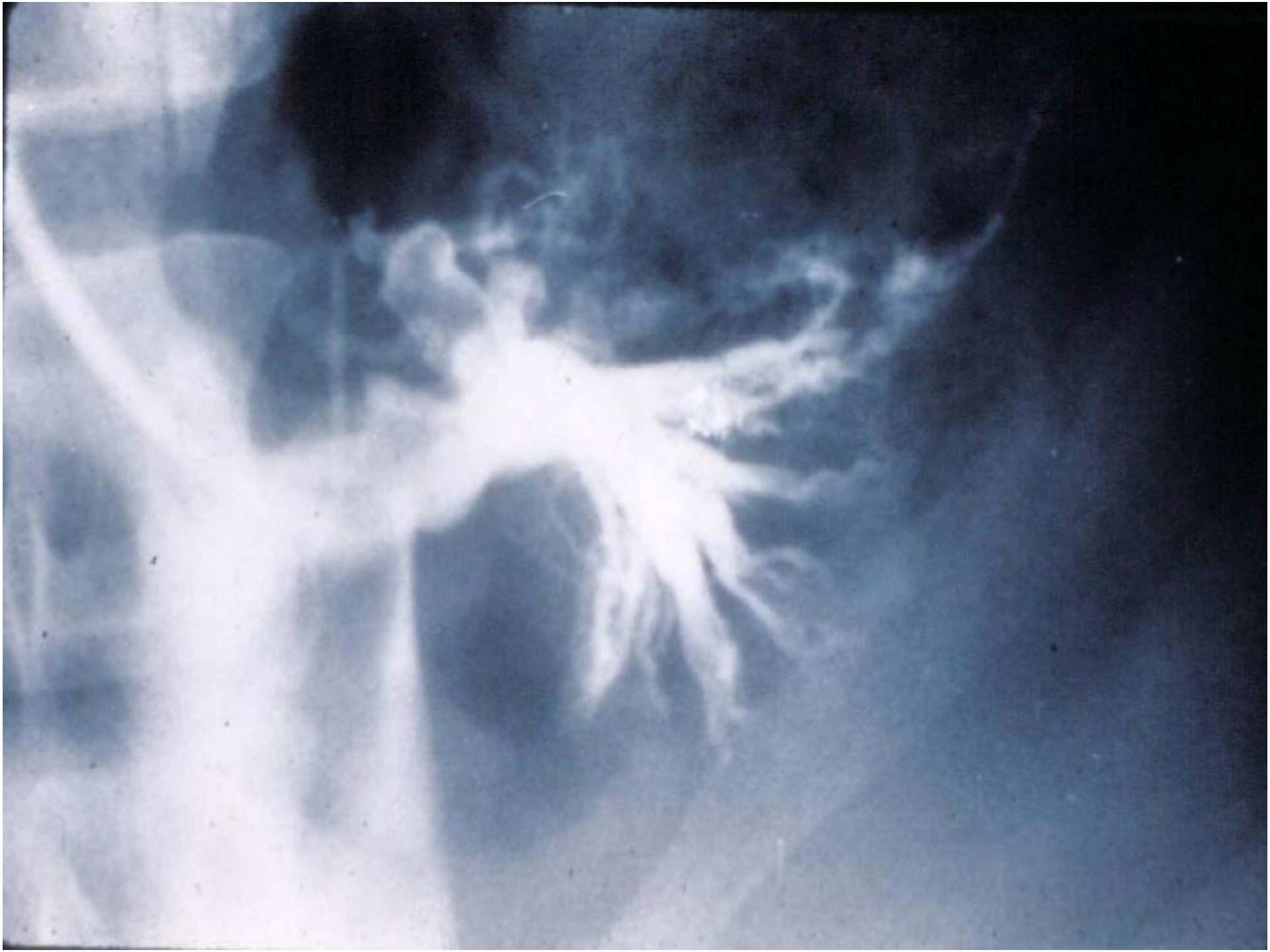
Increased coagulation tendency

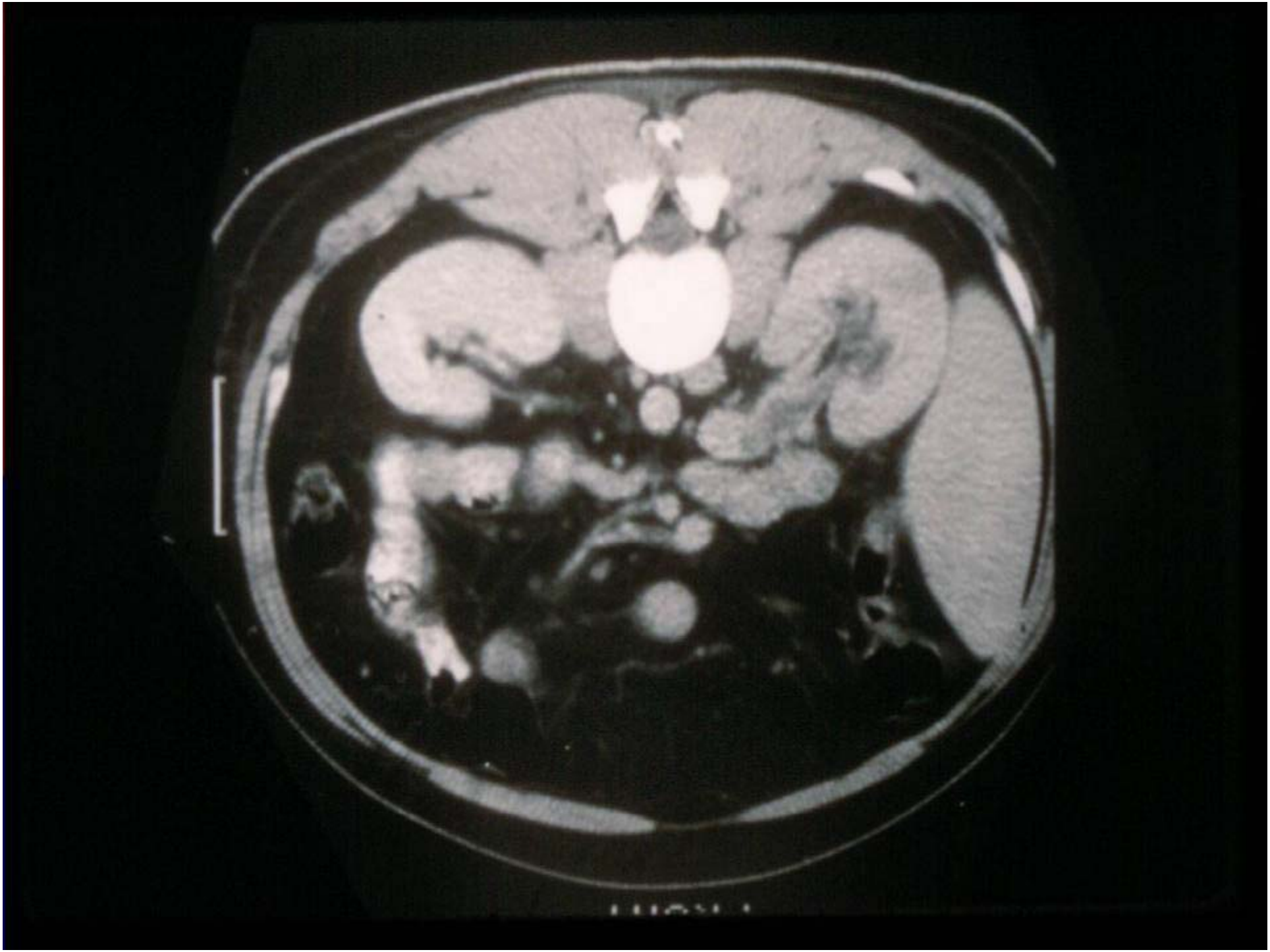
(plat. hyperaggregability, high fibrinogen and fibrinogen-fibrin transfer, decreased fibrinolysis, low anti-thrombin III)

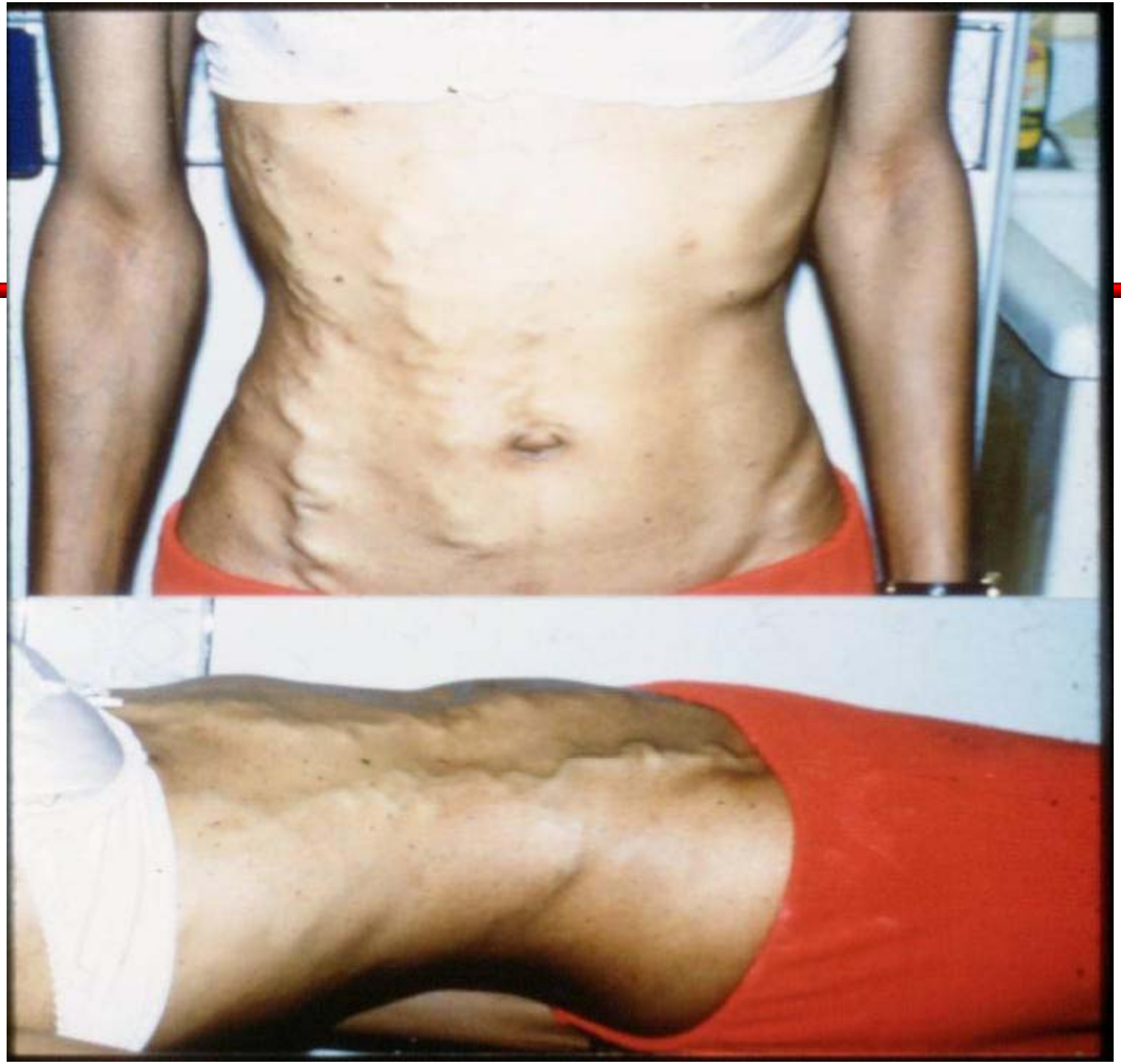
DVT, RVT, pulmonary emboli

Membranous NS greatest risk (up to 35%)

Most RVT asymptomatic , but flank pain, microhematuria, low GFR



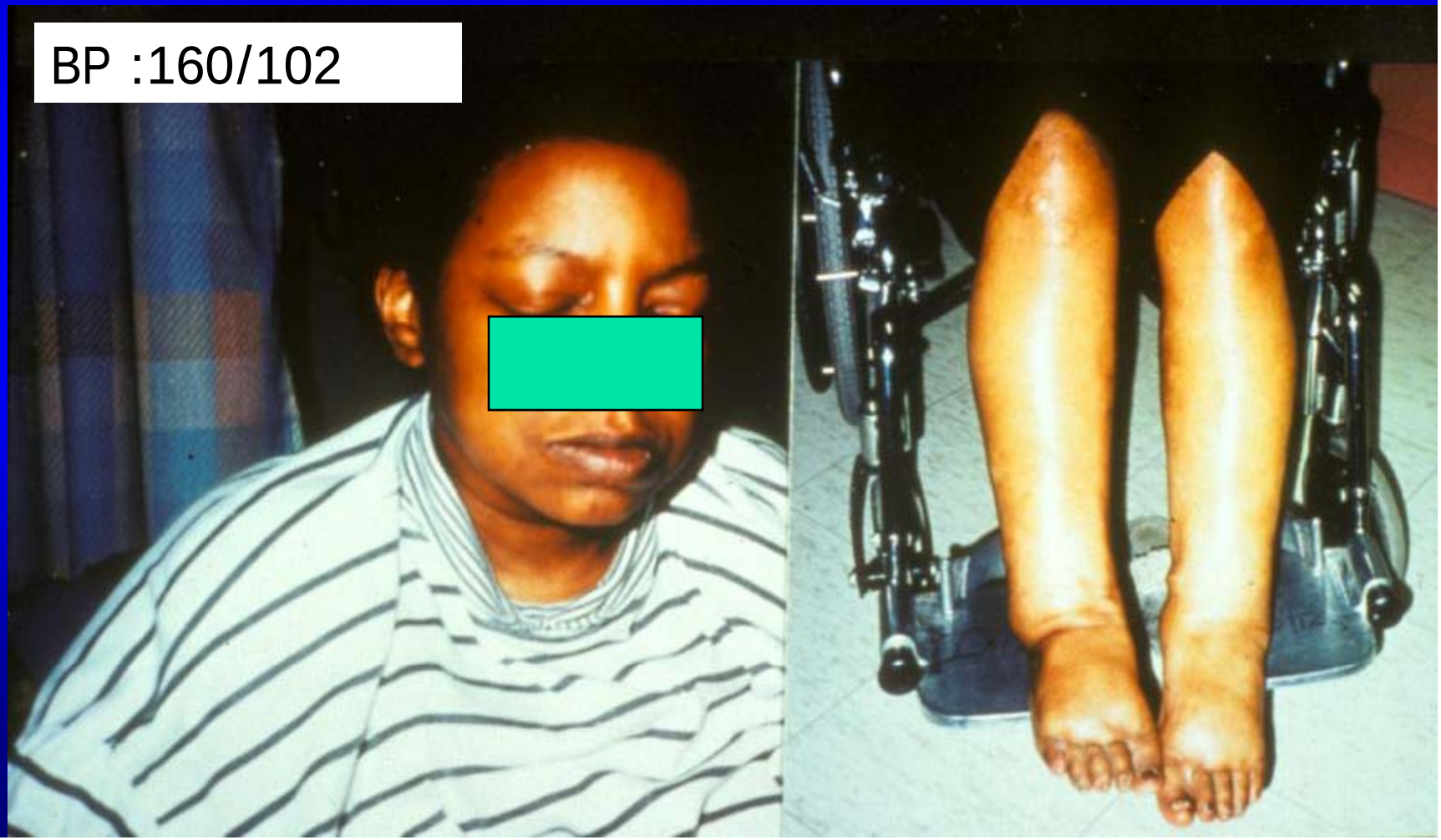




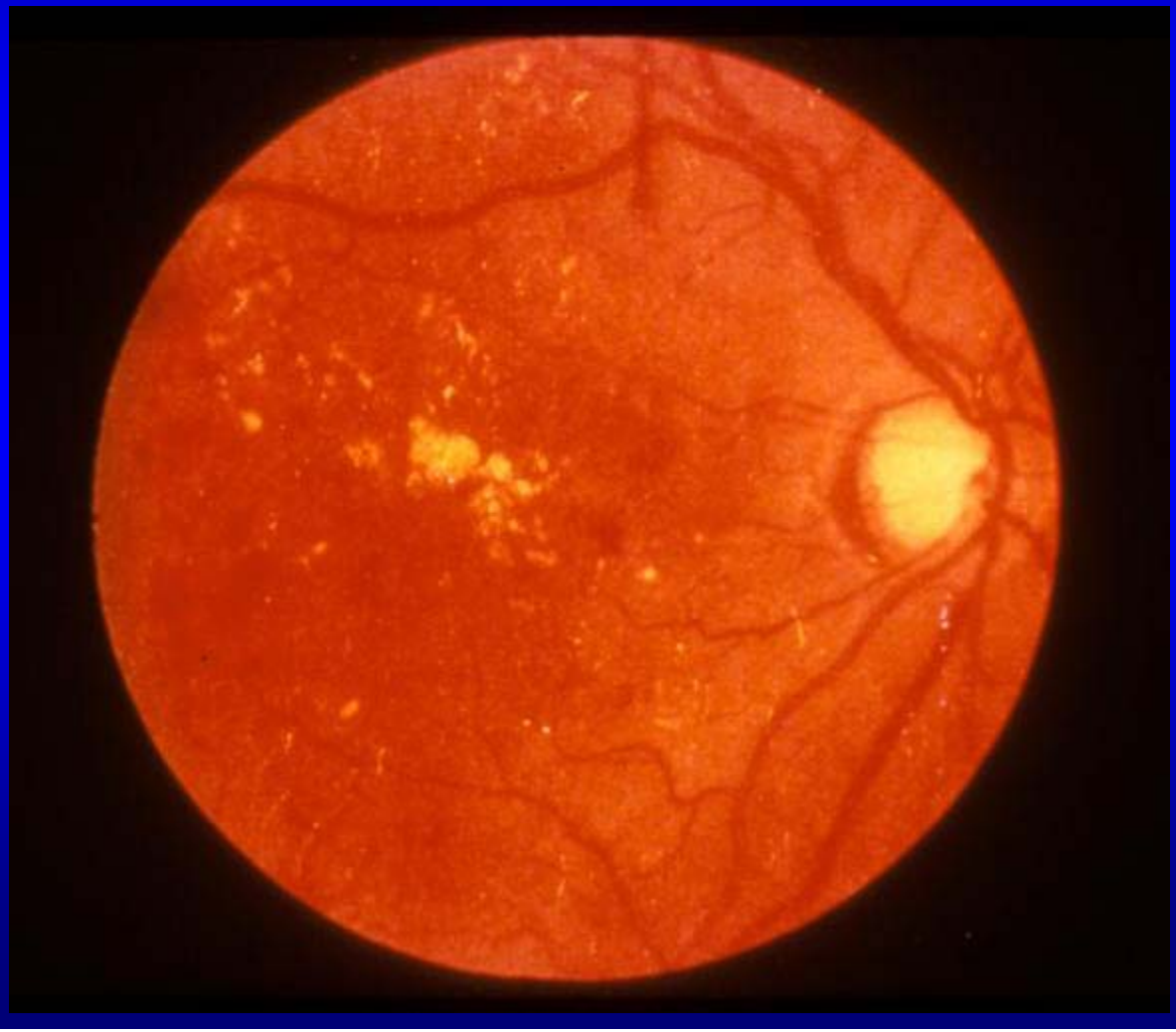
Case 4

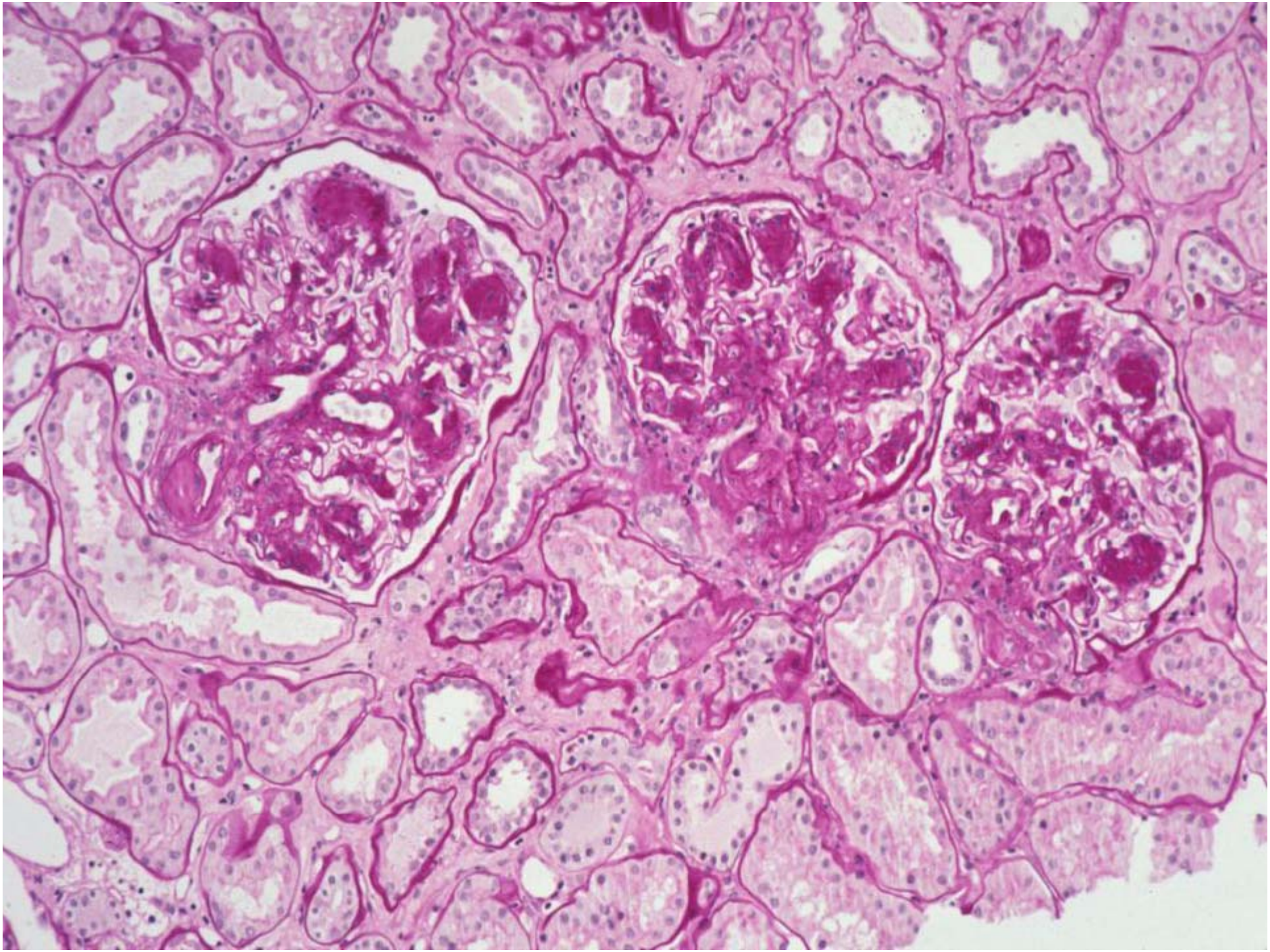
- A 38 year AA female has had Type 1 diabetes since the age of 19.
- She has severe retinopathy and multiple admissions for labile blood sugars.
- Her internist refers her for proteinuria which has gone up from 200mg/day to 3.2 grams. Her serum creatinine is 1.5mg/dL
- She has experienced a 22 pound weight gain and pitting edema to her thighs.
- She is on twice/daily insulin and Diltiazem

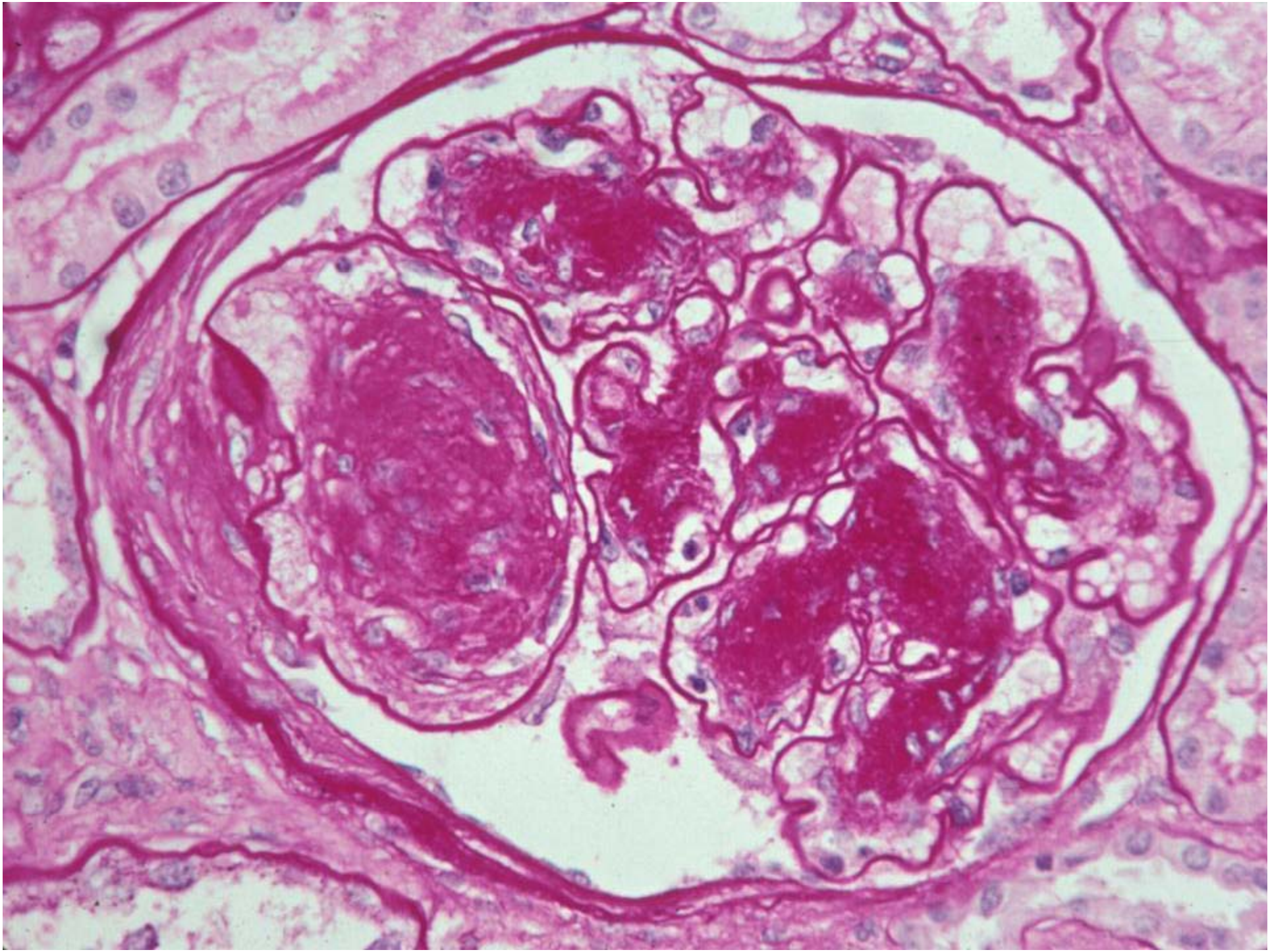
Case 4: Physical Exam

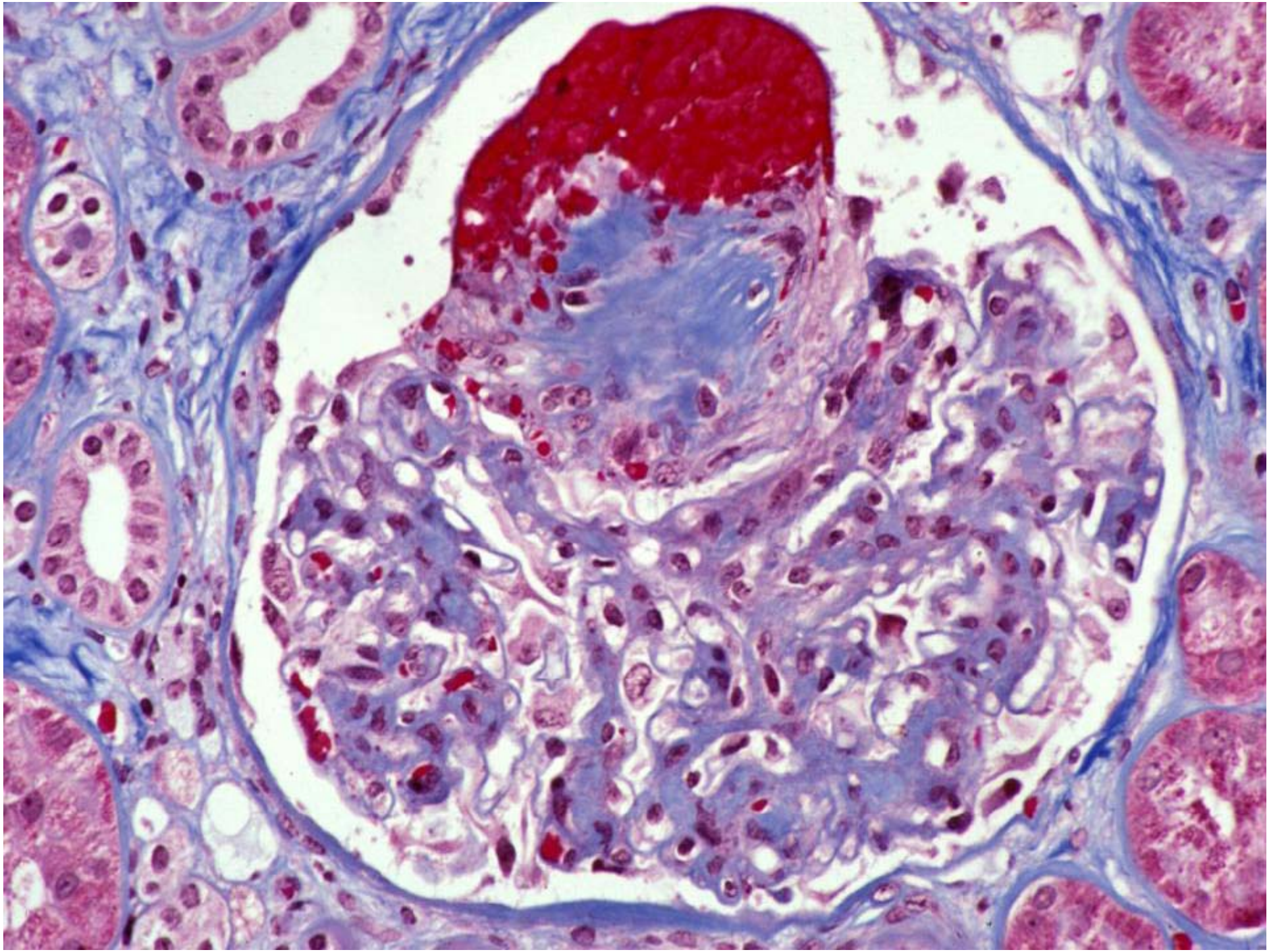


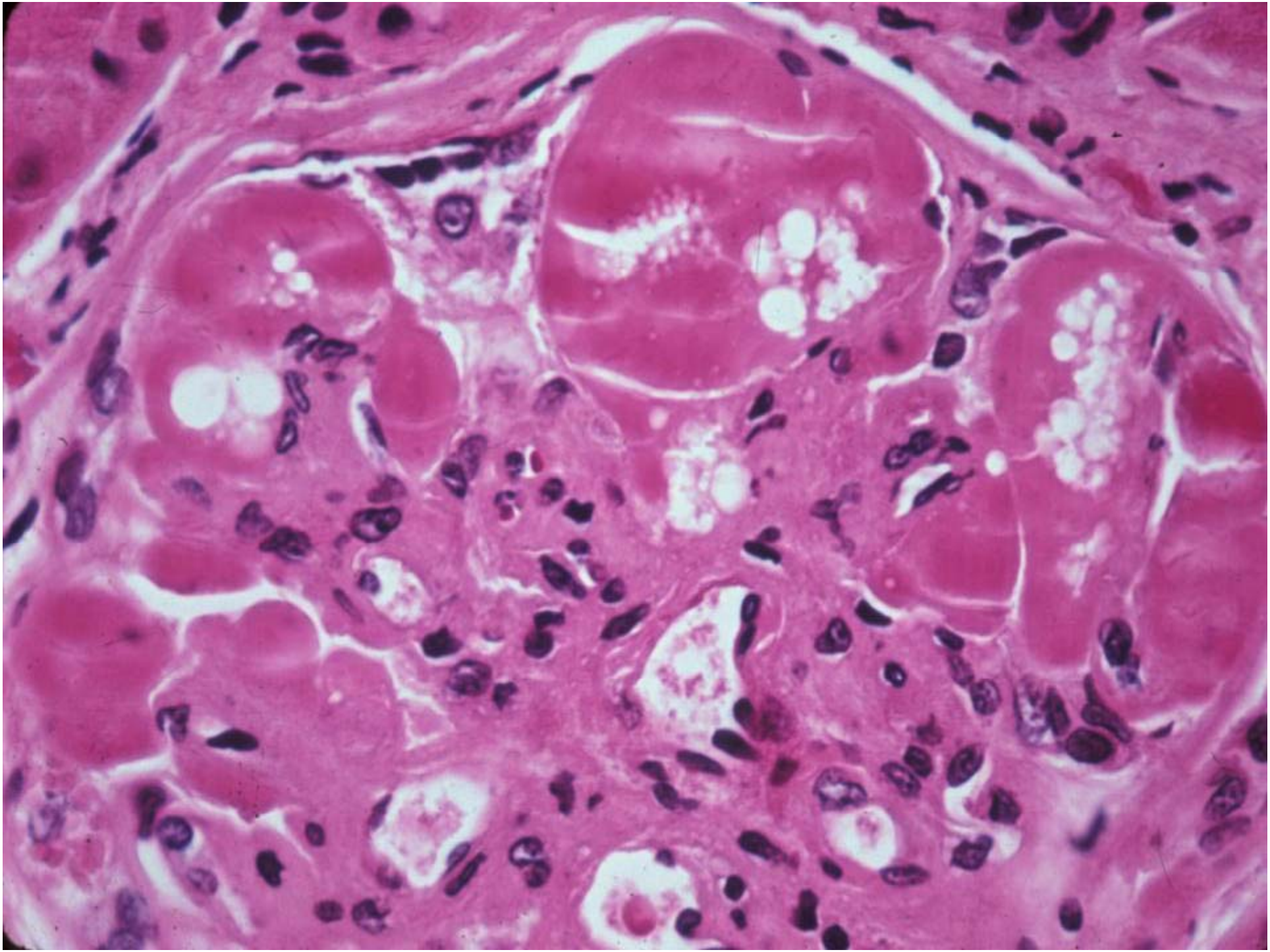
Case 4: Opthalmologic Exam

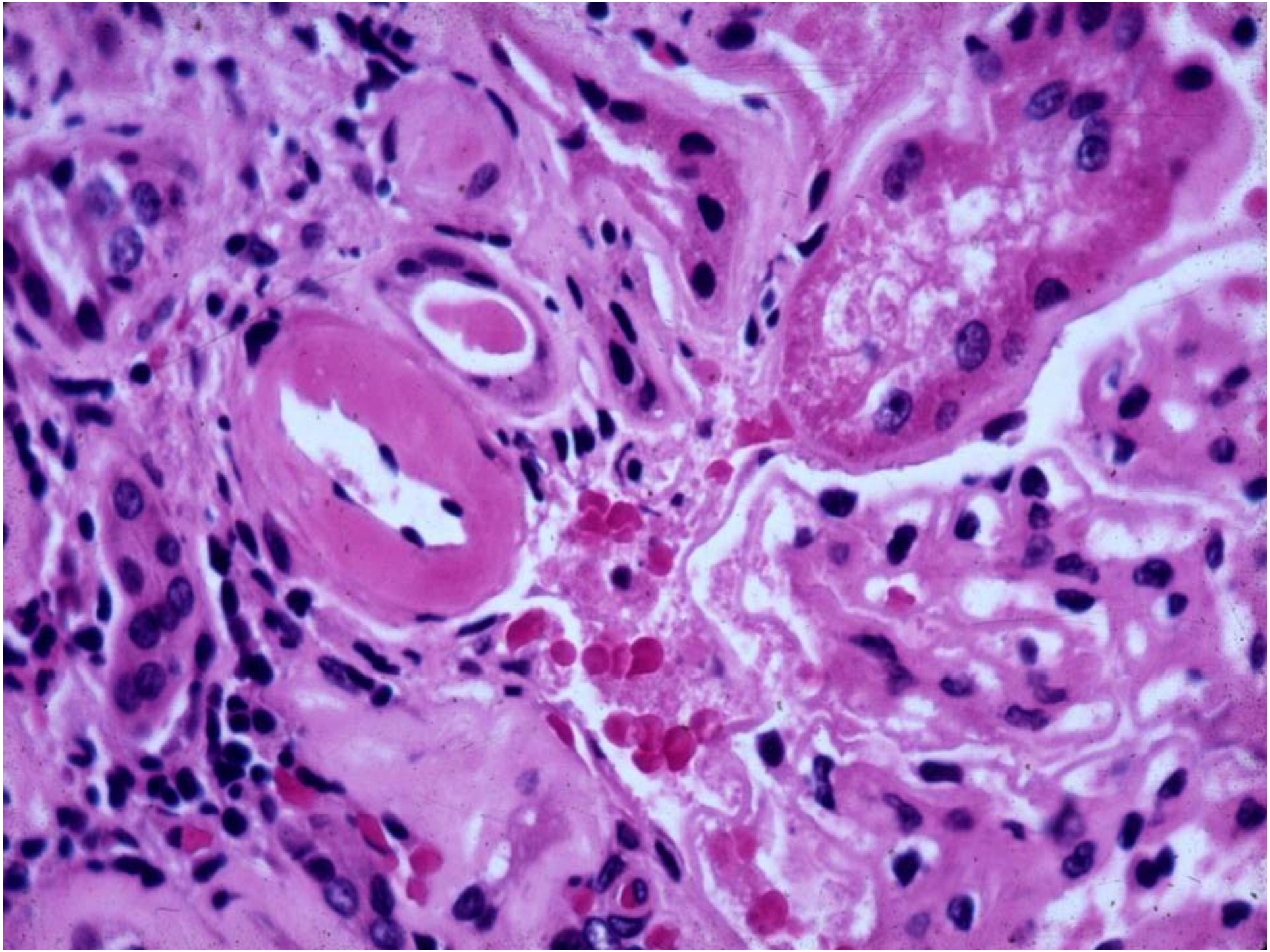


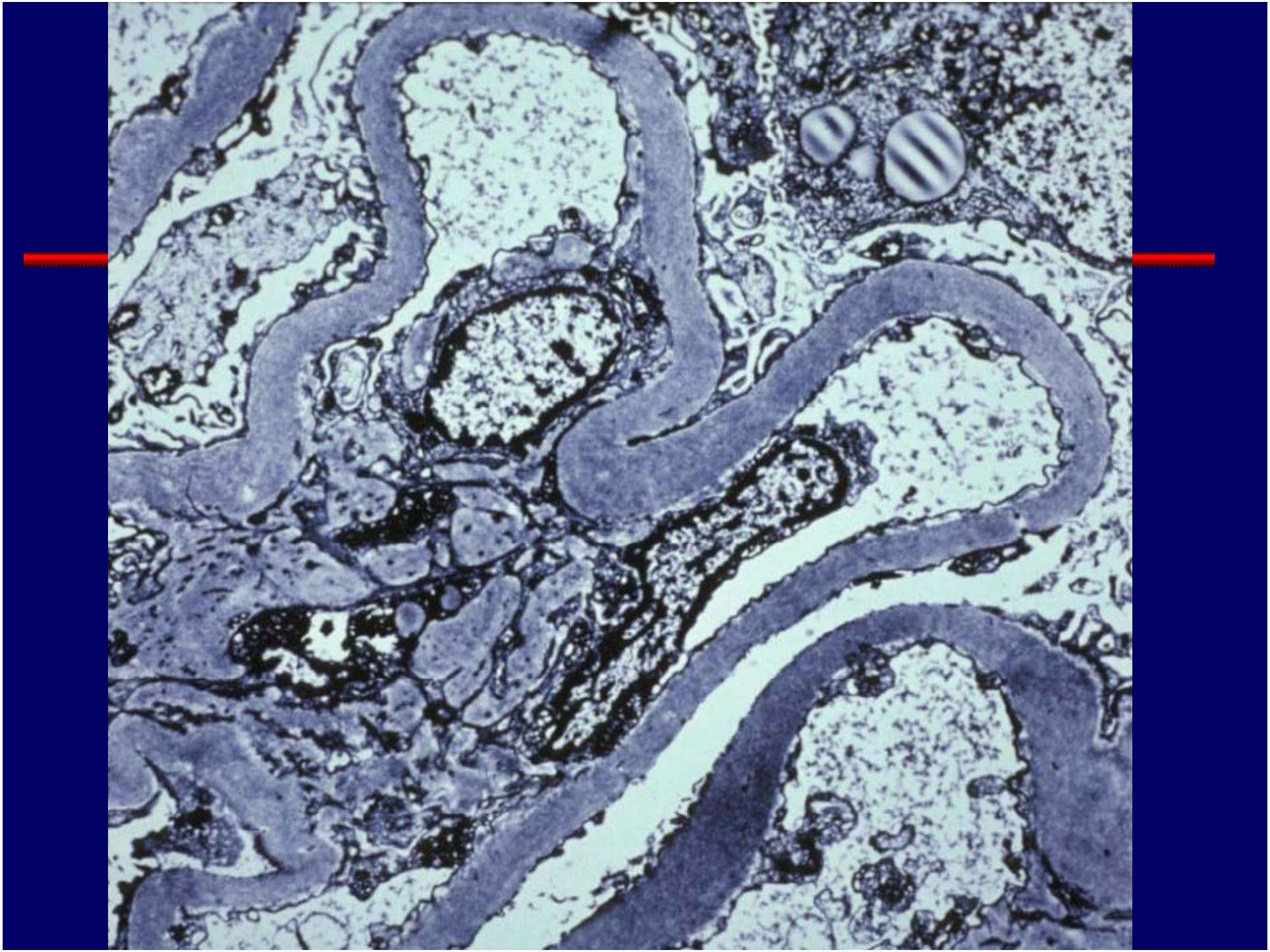


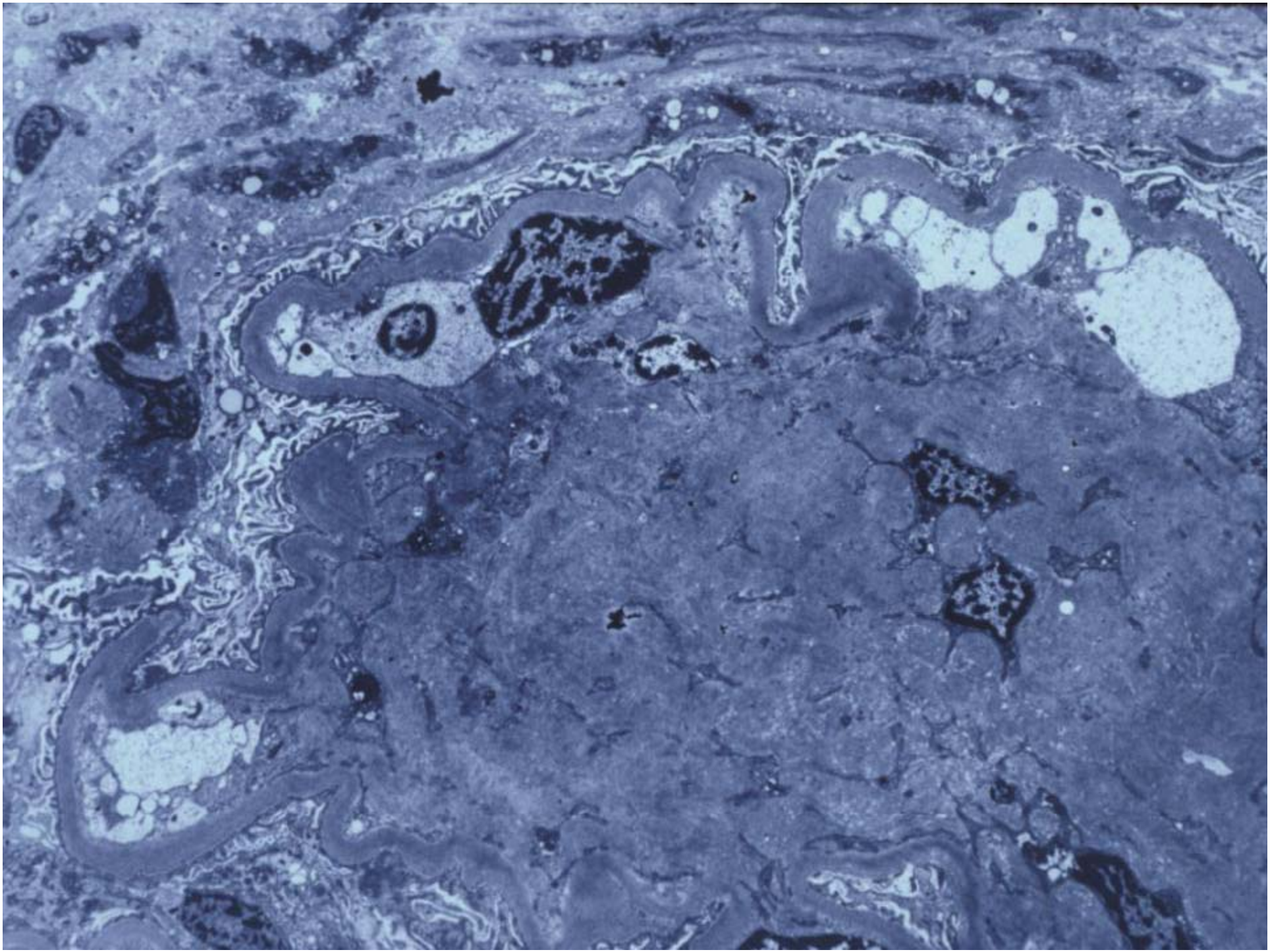








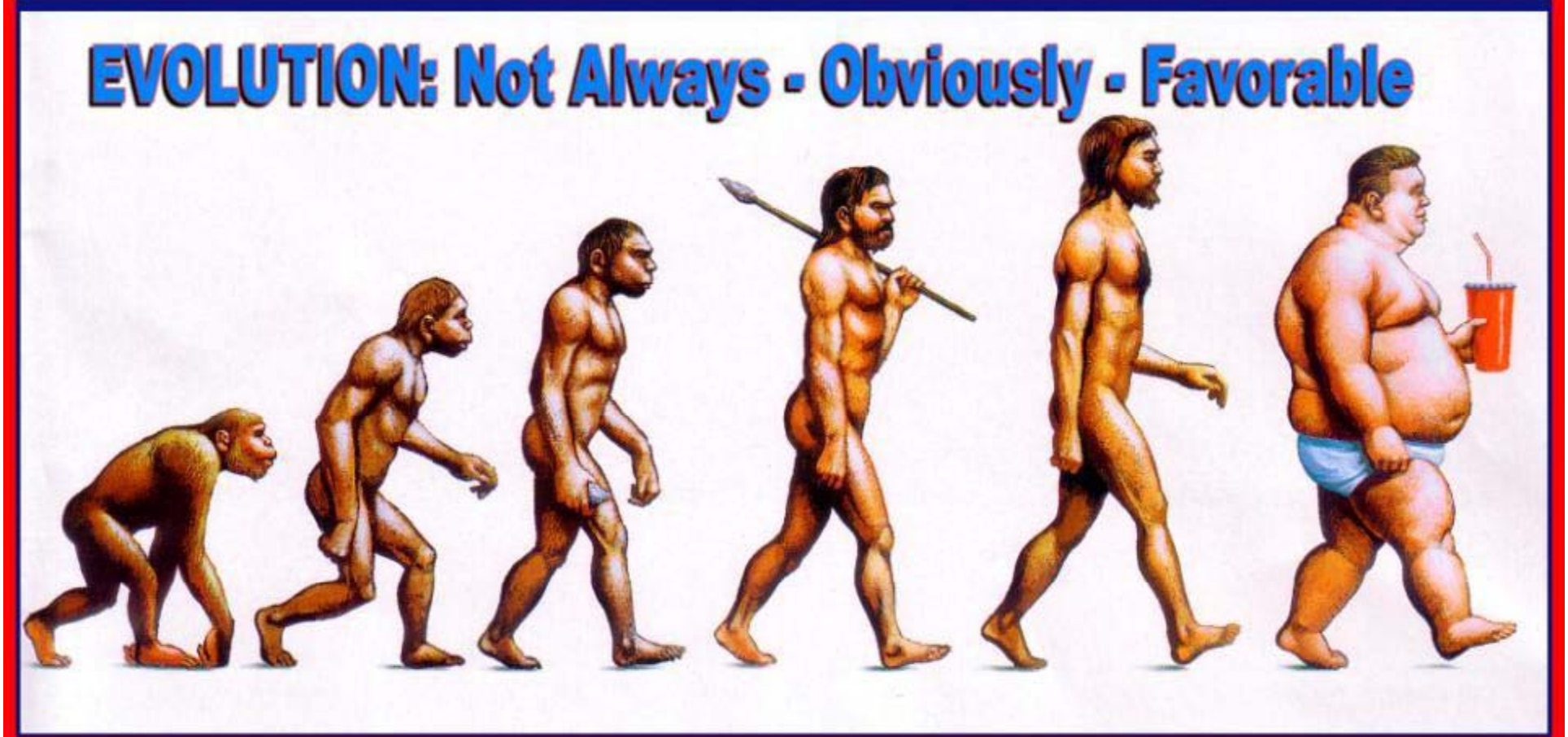




Types of Diabetes Mellitus

- Type I - Insulin Dependent (hypoinsulinemic, ketotic, juvenile onset)
- Type II - Non-Insulin Dependent (Normoinsulinemic, non-ketotic, maturity onset)

MUTATION: SURVIVE FAMINE
THEN: ADEQUATE FOOD
TODAY: SUPERABUNDANT FOOD



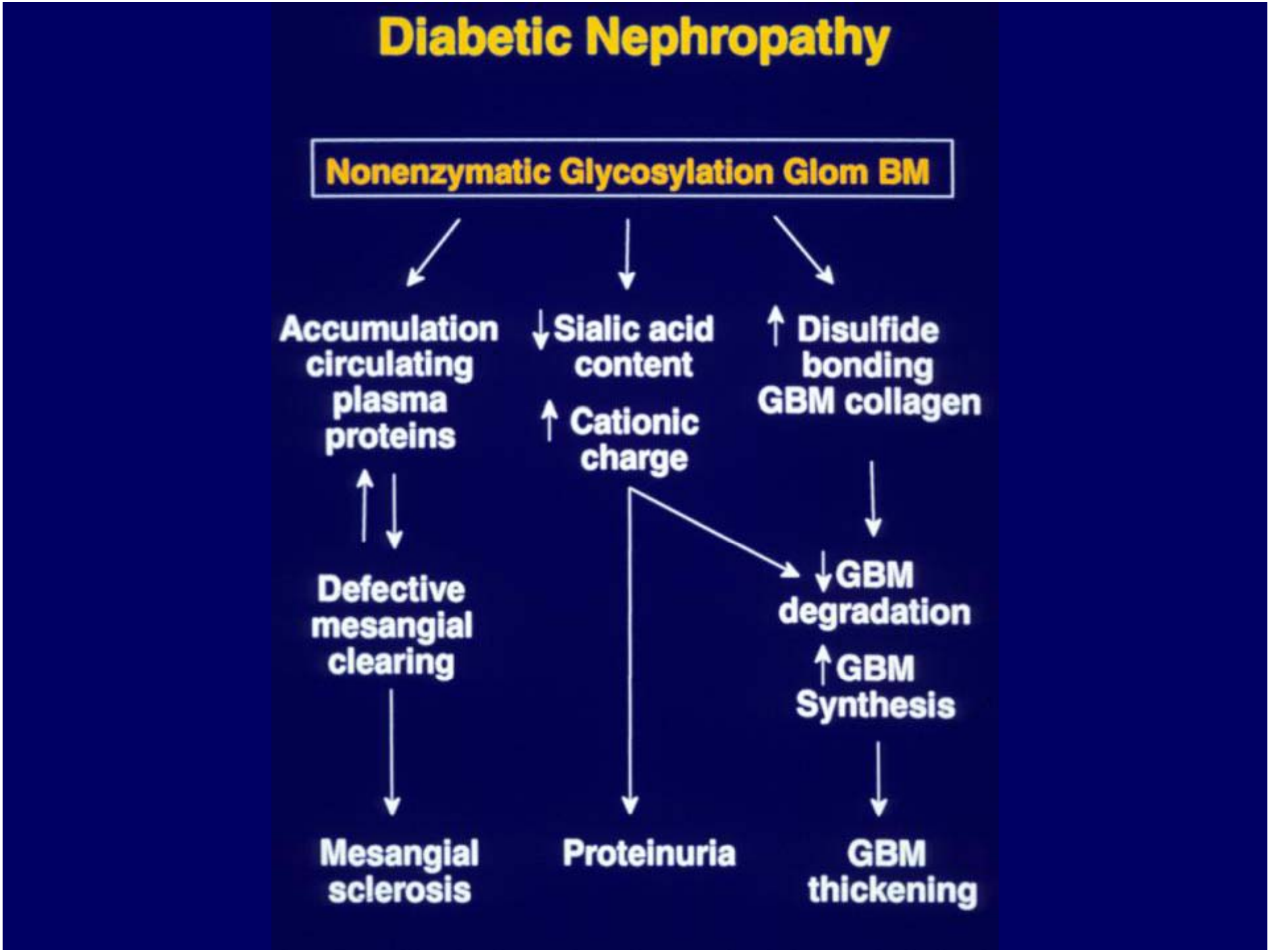
Basement Membrane Thickening in Diabetes Mellitus

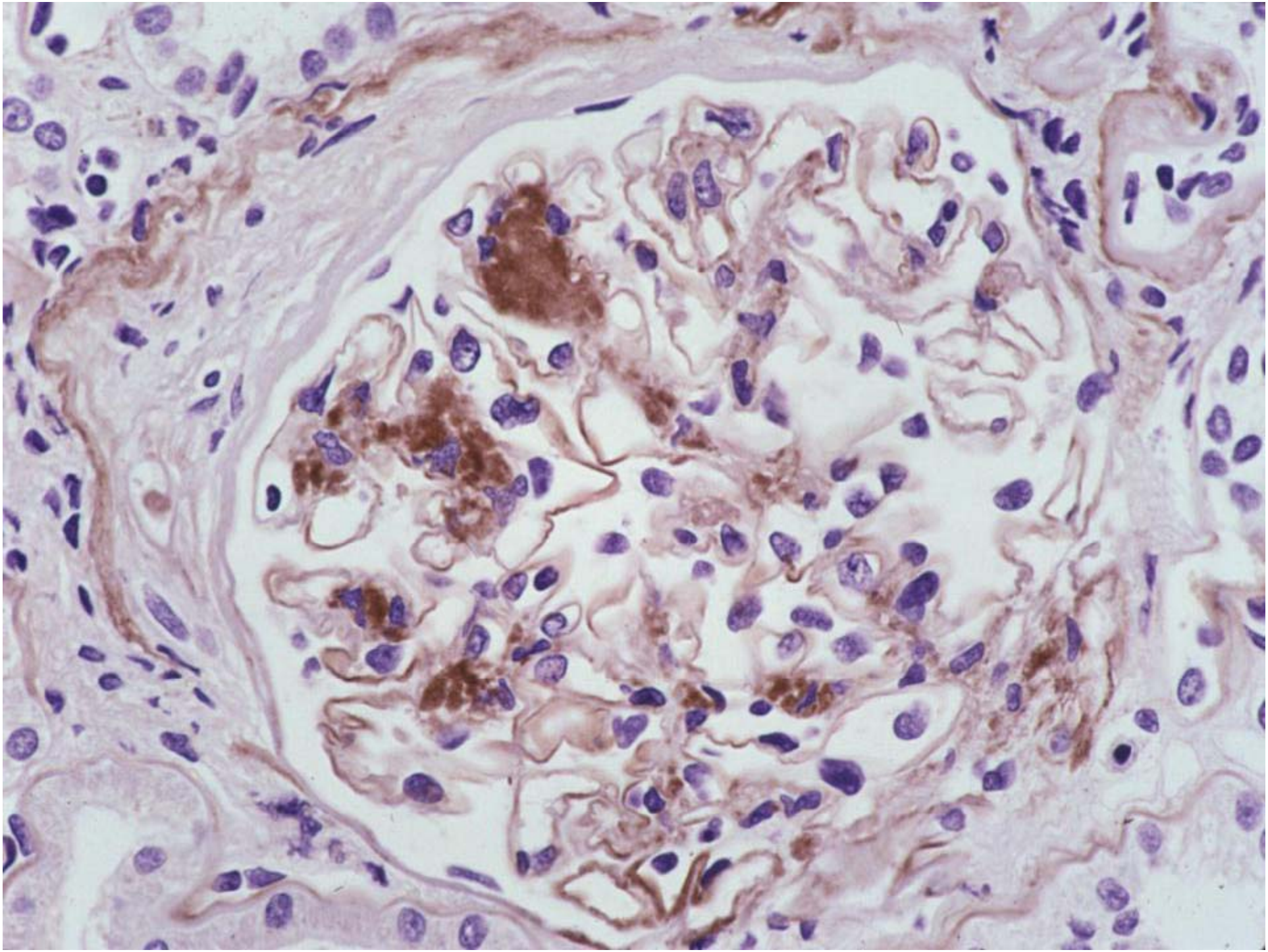
Vascular BM

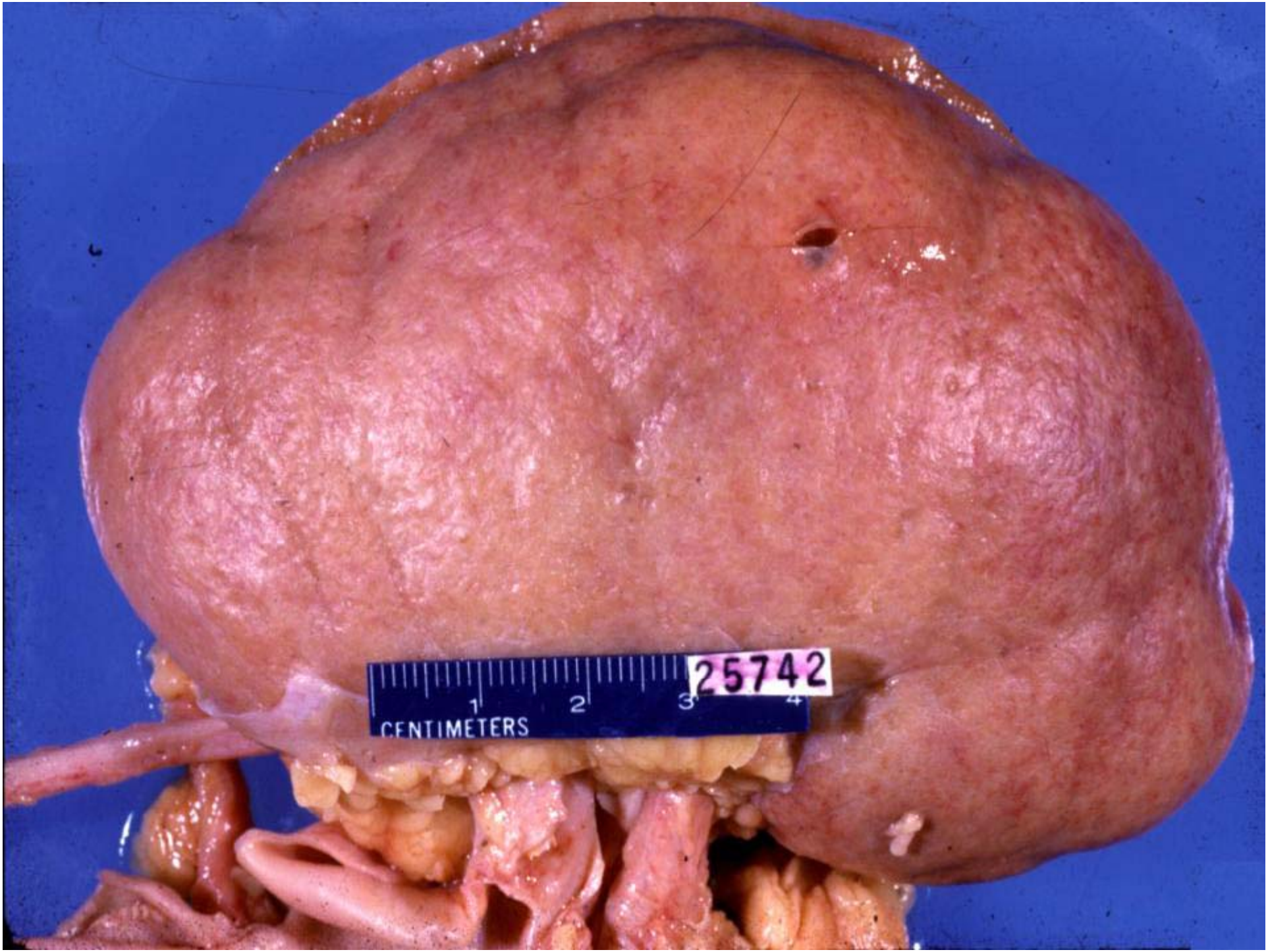
- Glomerular Capillaries
- Muscle Capillaries
- Retinal Capillaries
- Arterioles

Other BM

- Renal Tubules
- Mammary Ducts
- Schwann Cells

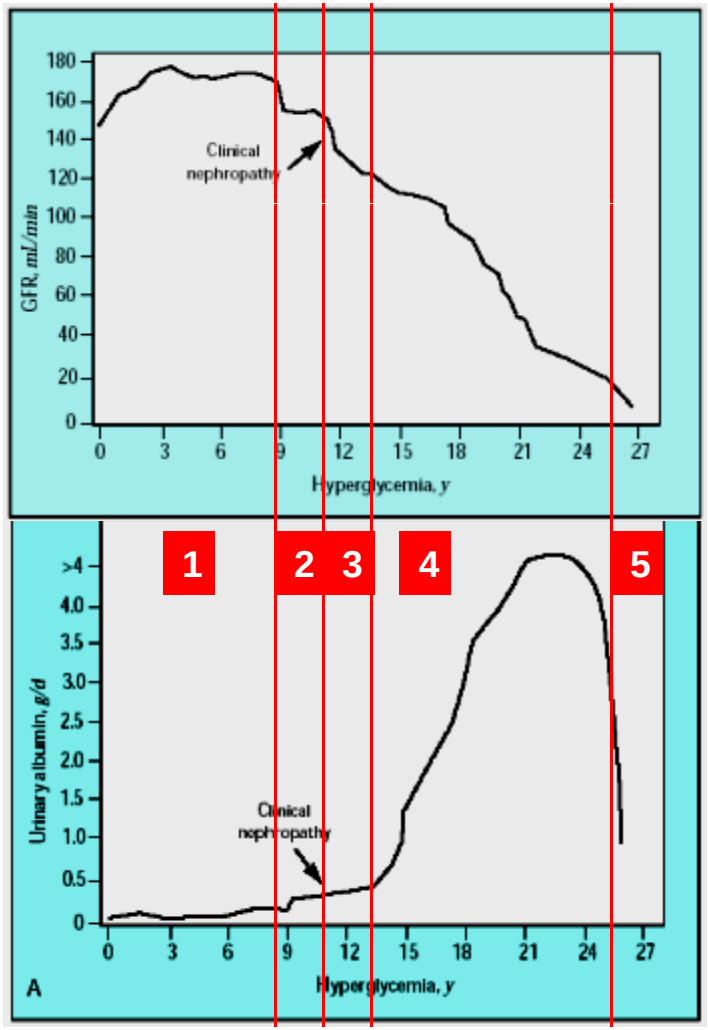

Diabetic Nephropathy
Nonenzymatic Glycosylation Glom BM
Accumulation circulating plasma proteins
↓Sialic acid content
↑Cationic charge
↑Disulfide bonding GBM collagen
Defective mesangial clearing
↓GBM degradation
↑GBM Synthesis
Mesangial sclerosis
Proteinuria
GBM thickening

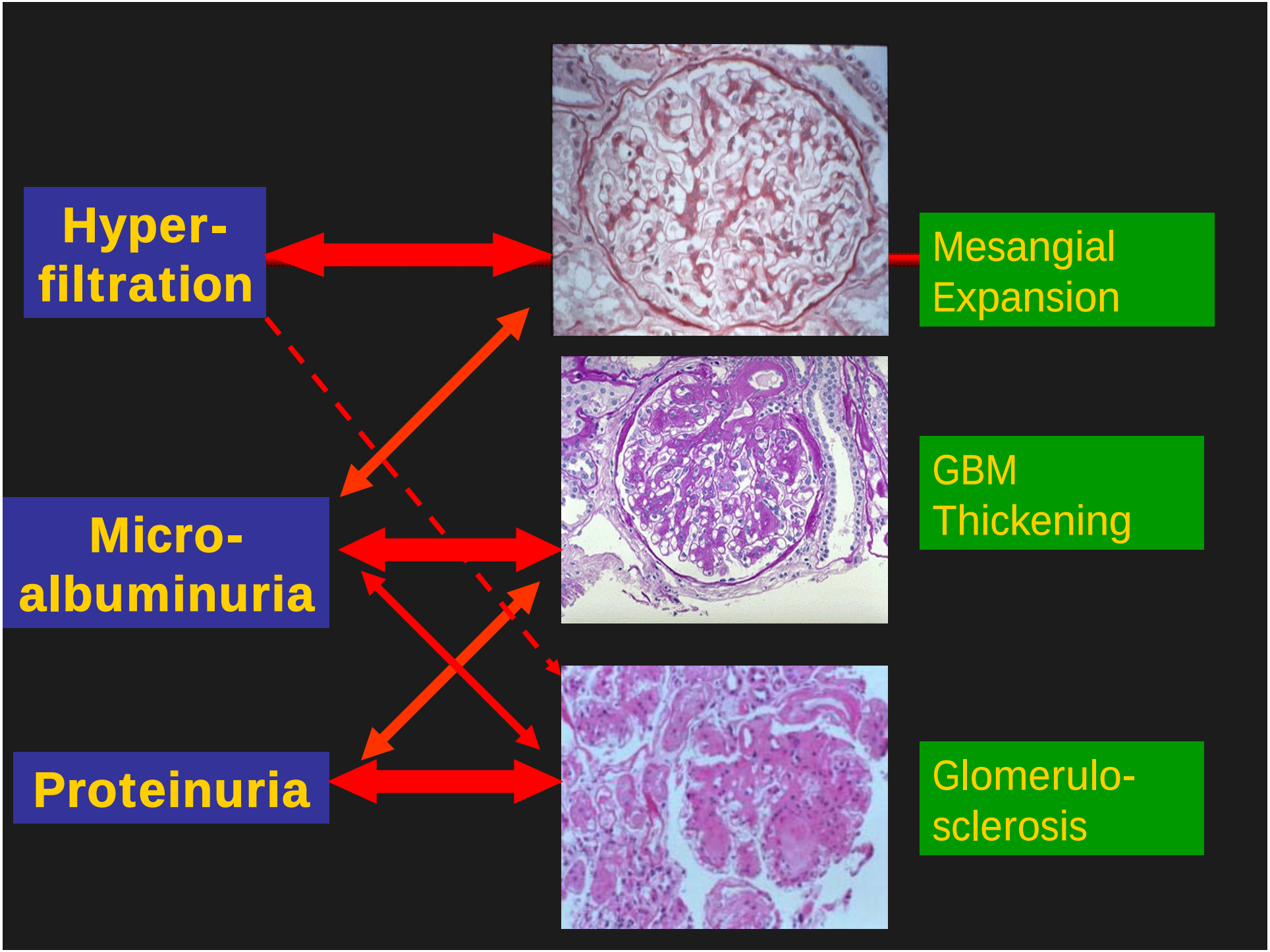



25742
1
2
3
4
CENTIMETERS

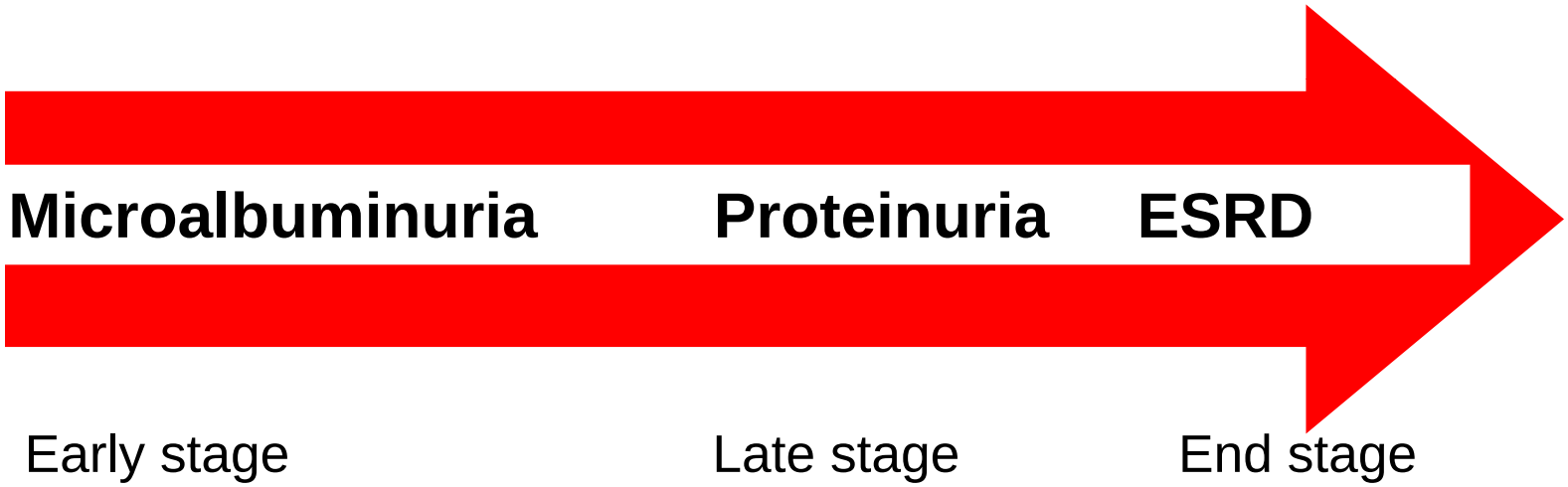
Stages of Diabetic Renal Disease Type 1 Diabetes

- Stage 1
  Hyperfiltration
- Stage 2
  Clinically silent
- Stage 3 (AER: 20-200ug/min)
  Incipient Nephropathy
- Stage 4
  Overt Nephropathy
- Stage 5
  ESRD




Hyper-
filtration
Micro-
albuminuria
Proteinuria
Mesangial
Expansion
GBM
Thickening
Glomerulo-
sclerosis

Progression of Diabetic Nephropathy



Current Strategies to Limit Renal Injury in Diabetic Nephropathy

- Blood pressure reduction
- Inhibition of the renin-angiotensin-aldosterone axis

- Blood sugar control
- Metabolic manipulation

Blood Pressure Targets

Clinical Status	BP Goal
Hypertension (no diabetes or renal disease)	**<140/90 mmHg** **(JNC 7)**
Diabetes Mellitus	**<130/80 mmHg** **(ADA, JNC 7)**
Renal Disease with proteinuria >1 gram/day or diabetic kidney disease	**<130/80 mmHg** **<125/75 mmHg** **(NKF)**

Case 4:Follow up

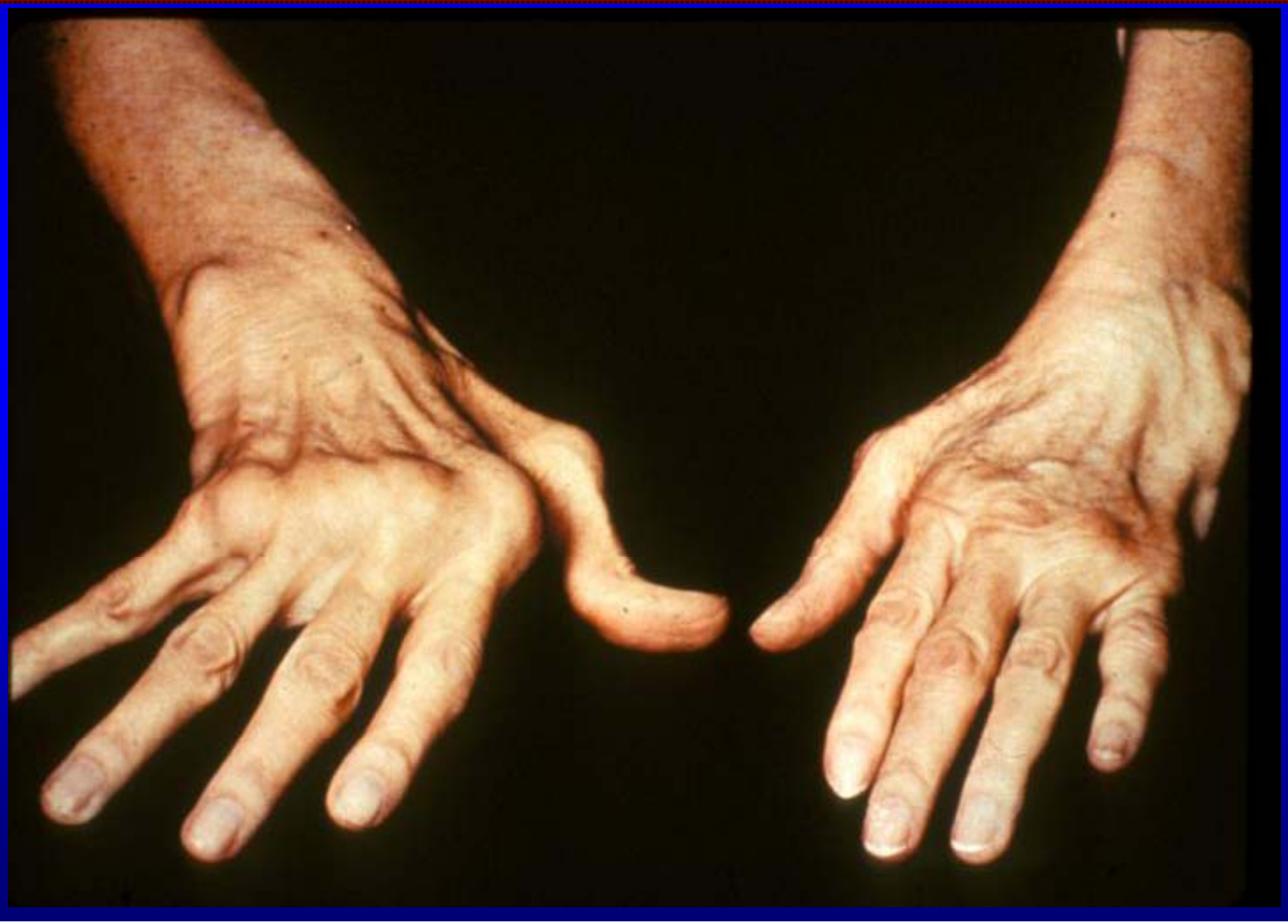
- Symptomatic
  - Furosemide 80mg + Metolazone 5mg
  - Pravastatin 40mg
- Reduction of Proteinuria
  - Ramipril 10mg+ Candesartan 16mg/day

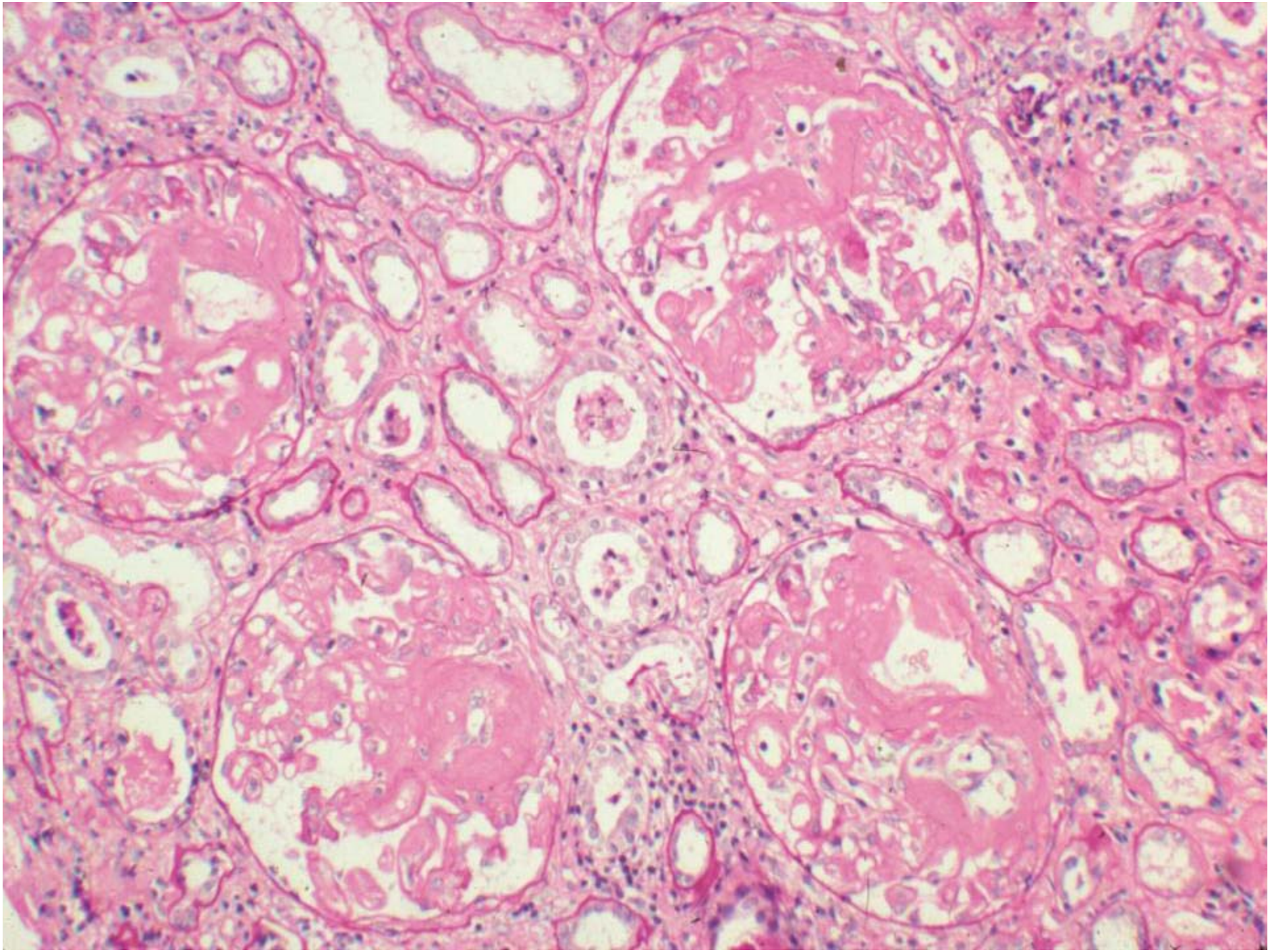
- Edema improved and proteinuria decreased to 200mg/day
- Her GFR however gradually deteriorated over 6 years and she is on hemodialysis awaiting a kidney transplant.

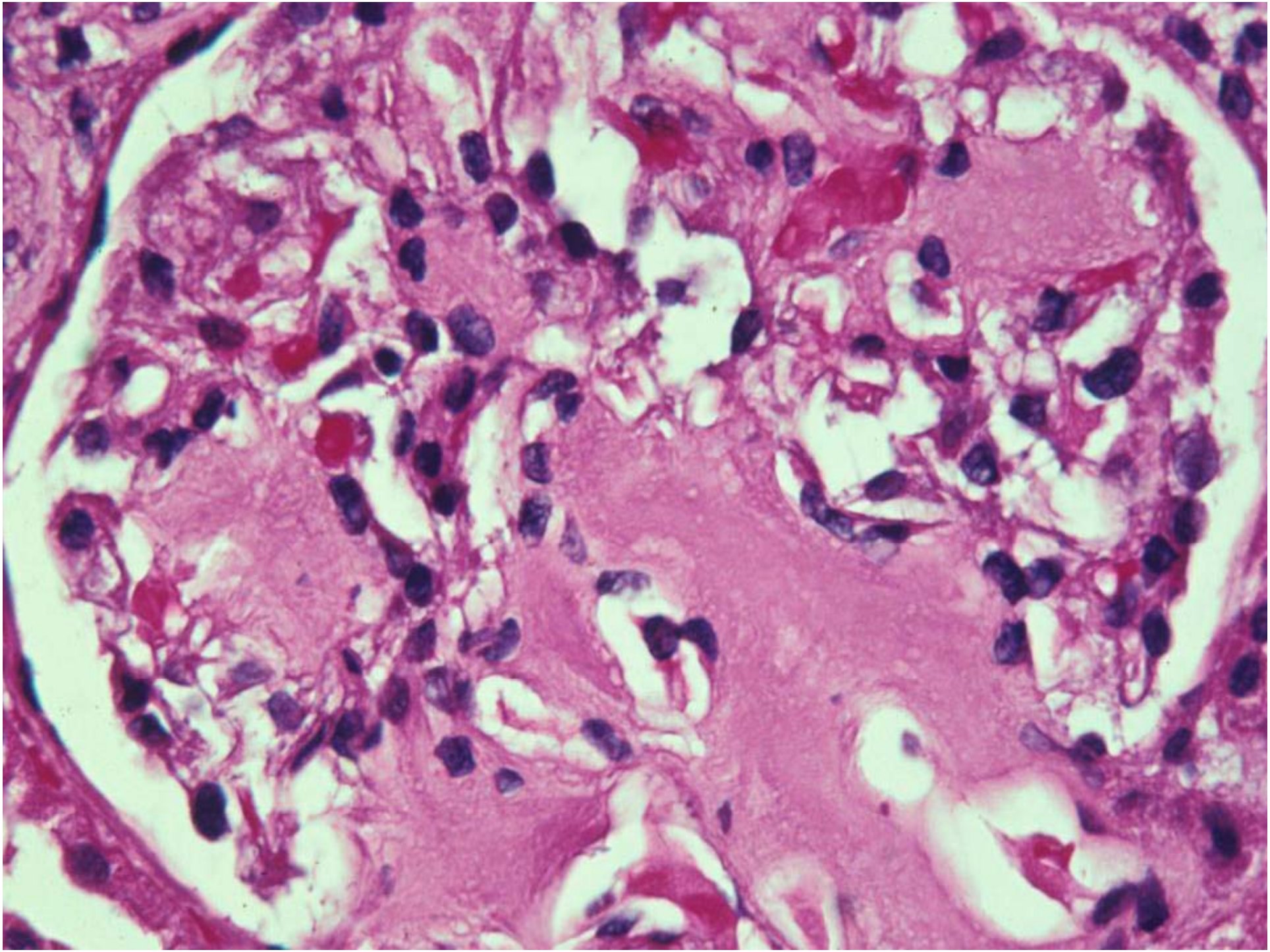
Case 5

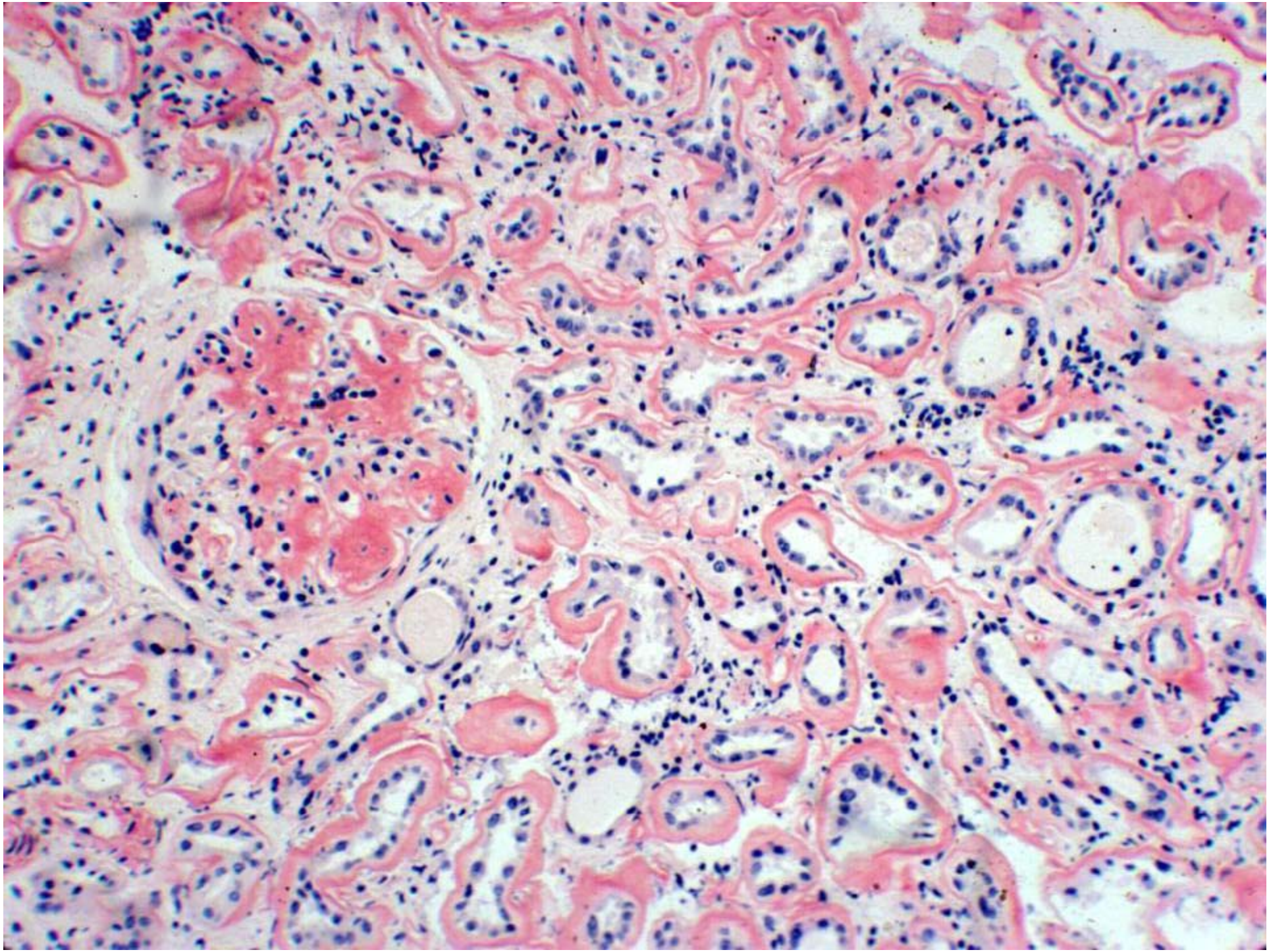
- A 66 y o housewife with severe rheumatoid arthritis for 22 years develops edema. She is currently taking no medications.
- Labs:
  - 9 g proteinuria/day
  - Serum creatinine 1.2mg/day
  - Serologic tests are negative
  - Creatinine clearance of 100 cc/min

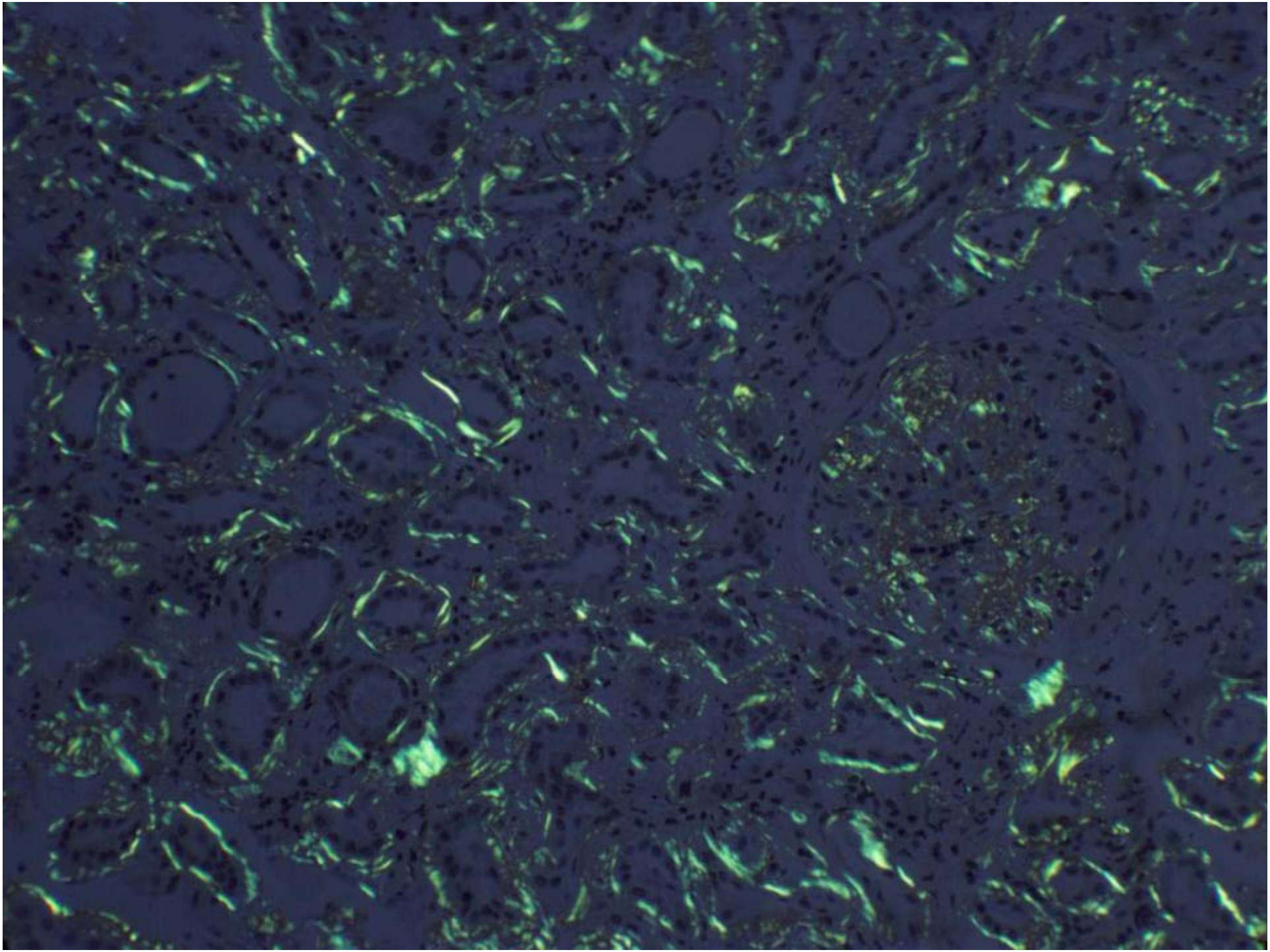
Rheumatoid Hands

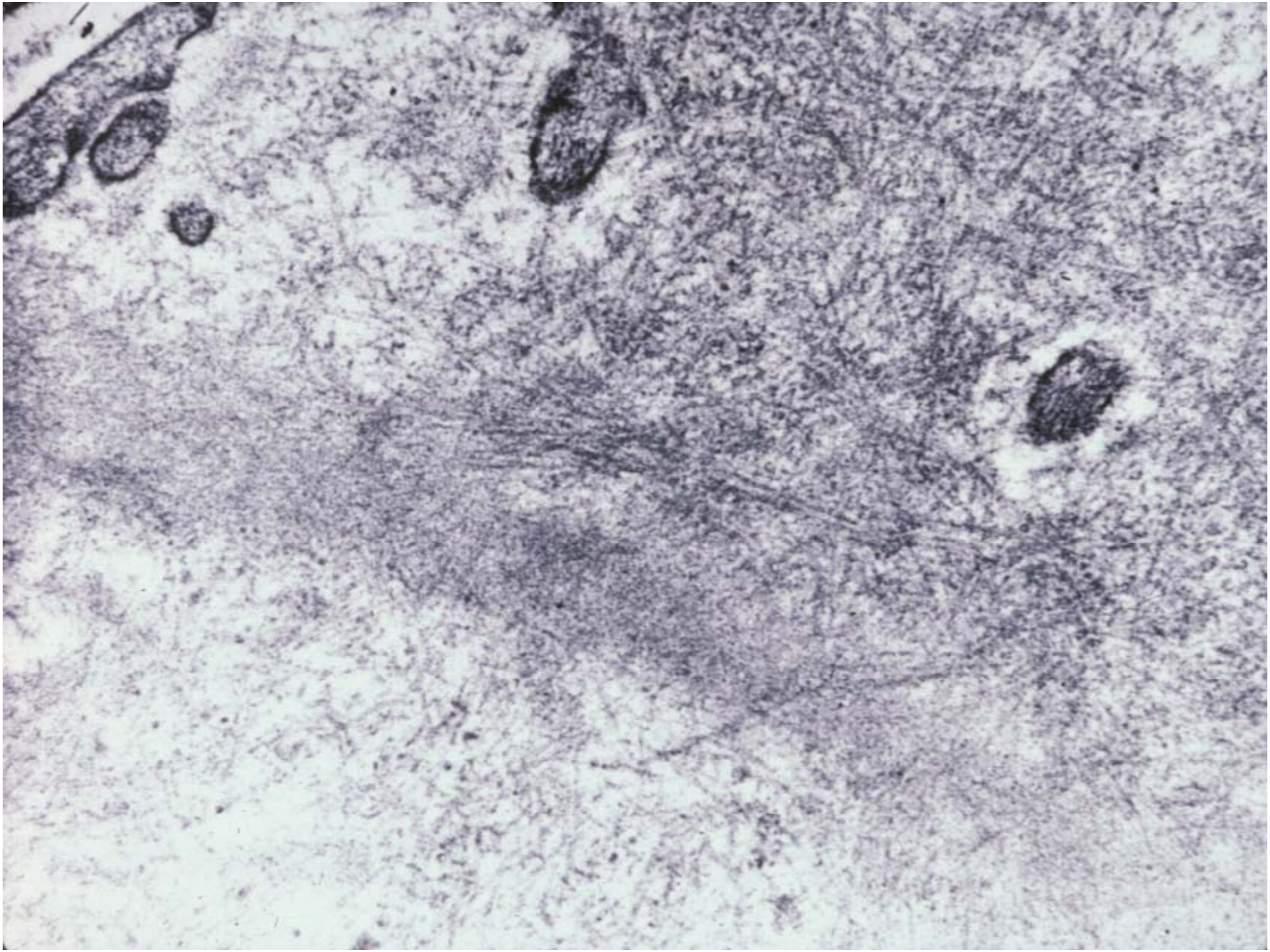


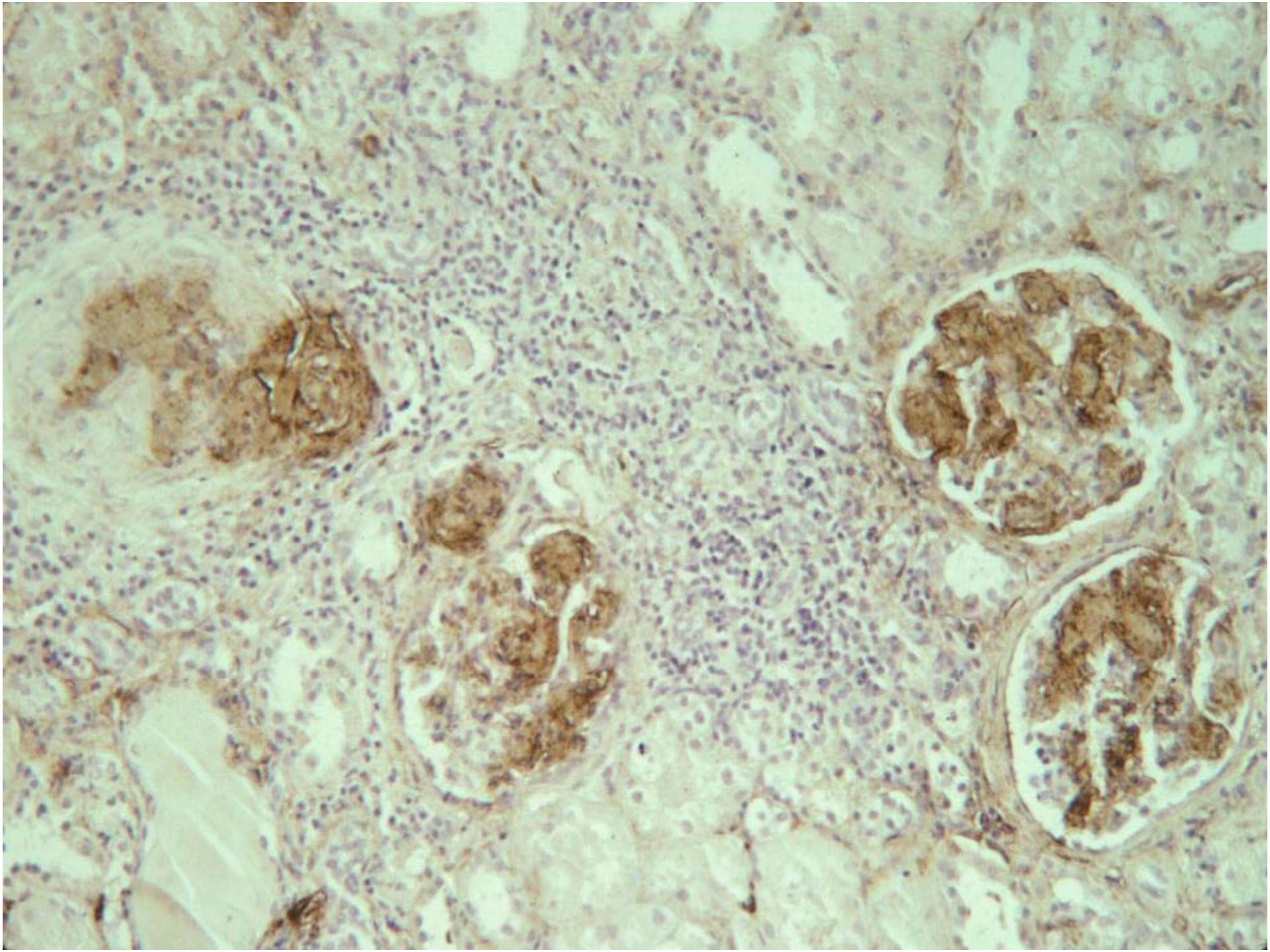












Amyloid

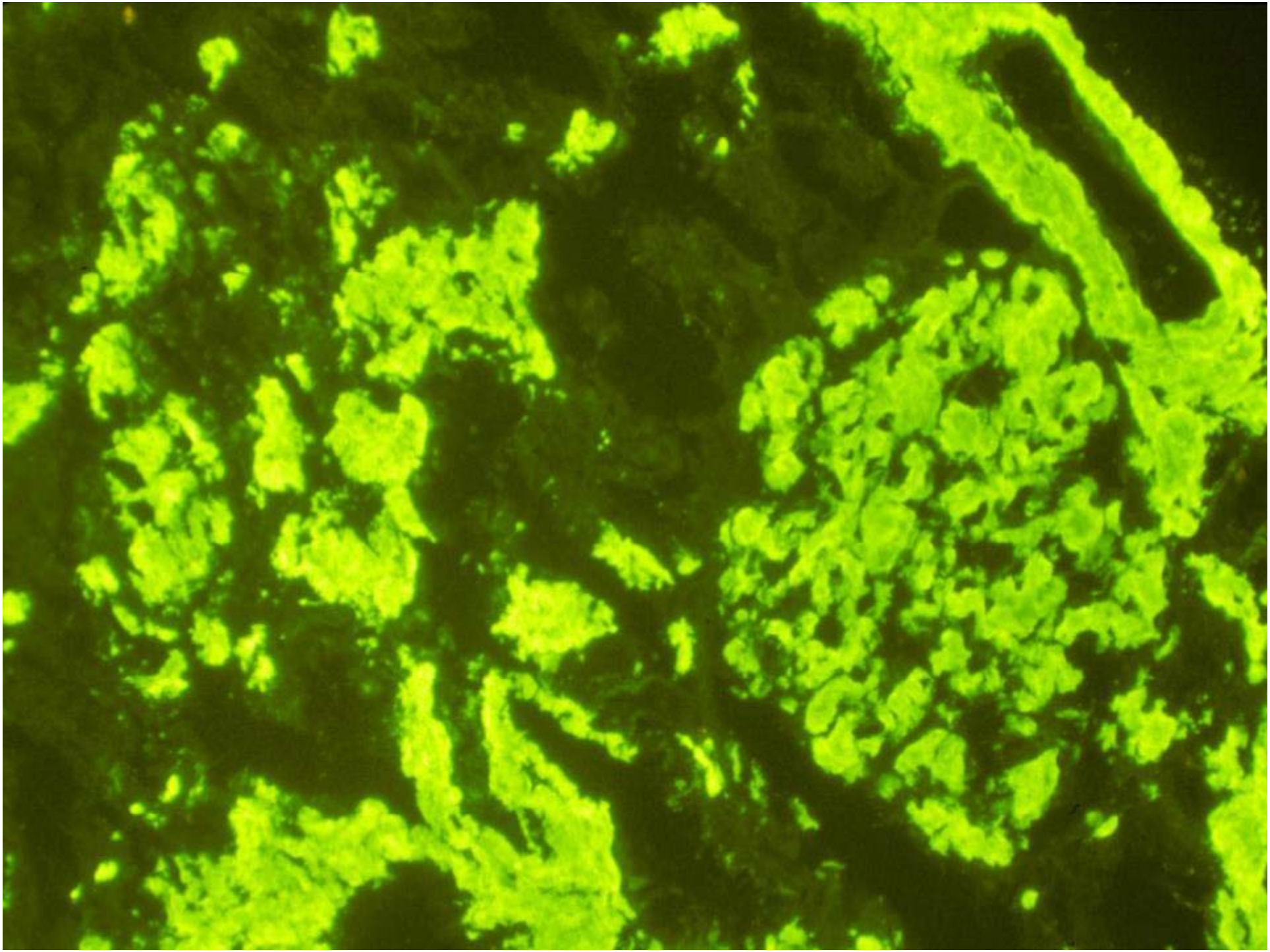
- LM: A homogenous, hyaline eosinophilic proteinaceous substance.
  - Special Stains:
    - Congo Red
    - Methyl Violet
    - Thioflavin t
- EM:
  - Fibrillar Constituent
    - Random arrays of non-branching fibrils, 80-100Å in width, beading with 55Å periodicity
  - Non-Fibrillar Constituents
    - Pentameric discs (AP protein)
- X-ray Diffraction: beta pleated sheet conformation

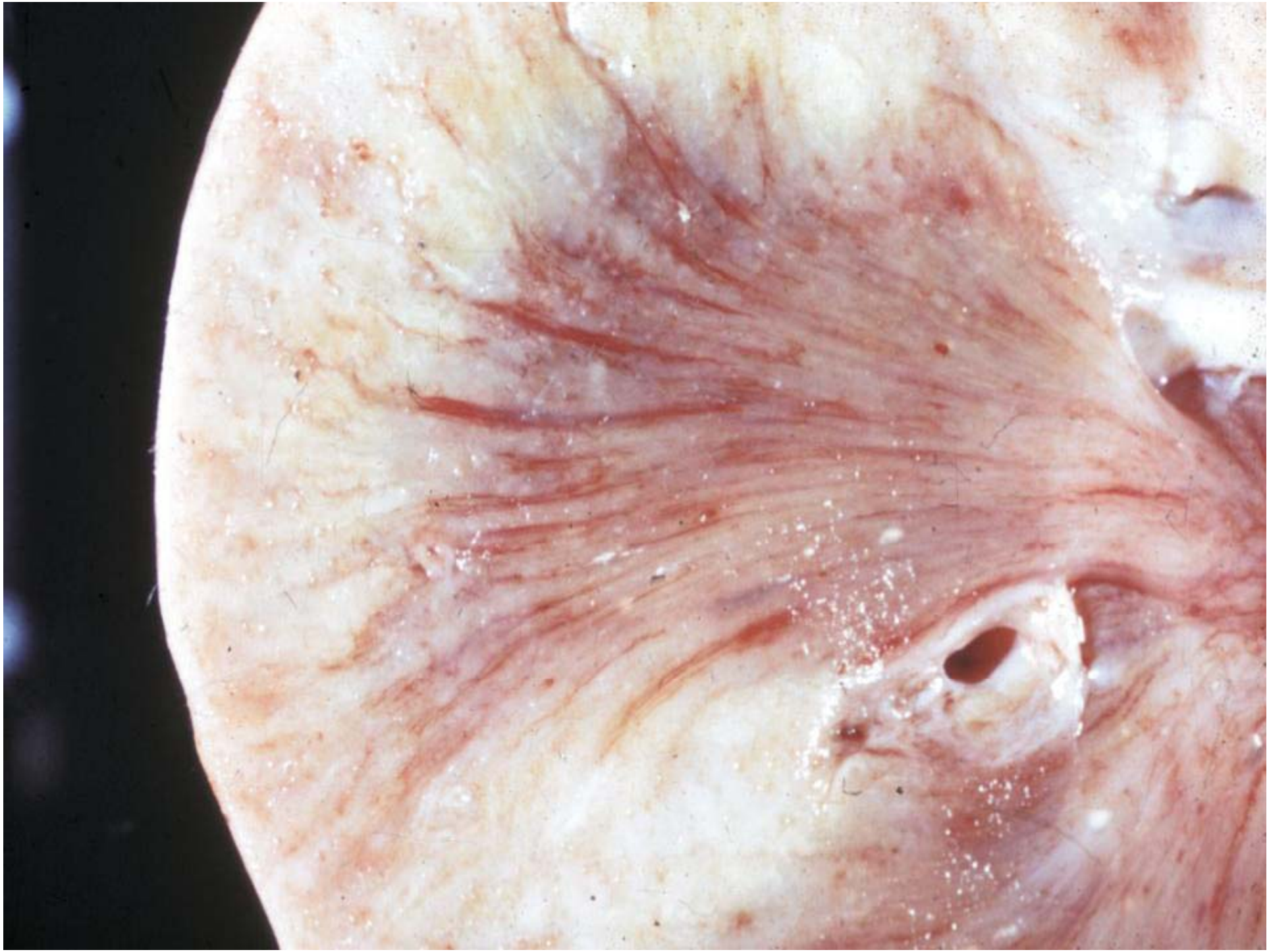
Amyloidosis

Cause	Type	Precursor Protein
1. Dysproteinemias	Primary "AL"	Light chains
2. Longstanding inflammatory or infectious states	Secondary "AA"	SAA-protein (acute phase reactant)

Chronic Diseases Associated with “AA” Amyloidosis

- Tuberculosis
- Leprosy
- Chronic Osteomyelitis
- Paraplegia
- Chronic bronchiectasis
- Cystic Fibrosis
- Chronic Heroin Addiction
- Rheumatoid Arthritis
- Psoriasis
- Familial Mediterranean Fever



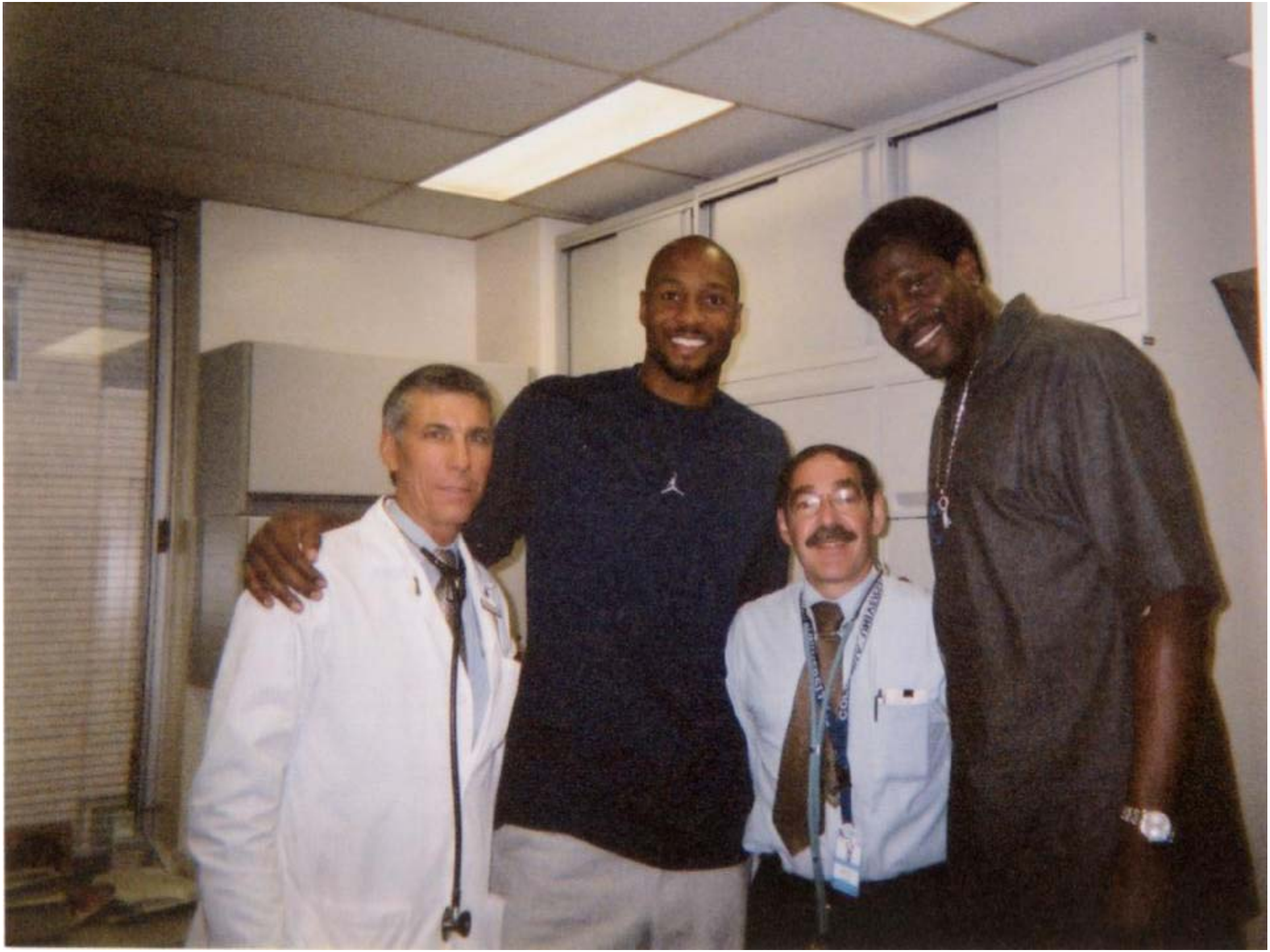


Case 5: follow up

- Symptomatic treatment
  - HCTZ 25mg qd
- Reduction of proteinuria
  - Lisinopril 10mg/day
- Rheumatoid Arthritis
  - Anti TNF therapy

Conclusions

- Glomerular disease due to theNephrotic Syndrome (nephrosis) is a common cause of renal disease.
- A renal biopsy and good nephropathologist are essential in diagnosis
- Treatment includes BP control, use of ACE-inhibitors in addition to specific and symptomatic therapy.



The End
(Et Cetera!)