Clinical Nephrotic and Nephritic Syndromes

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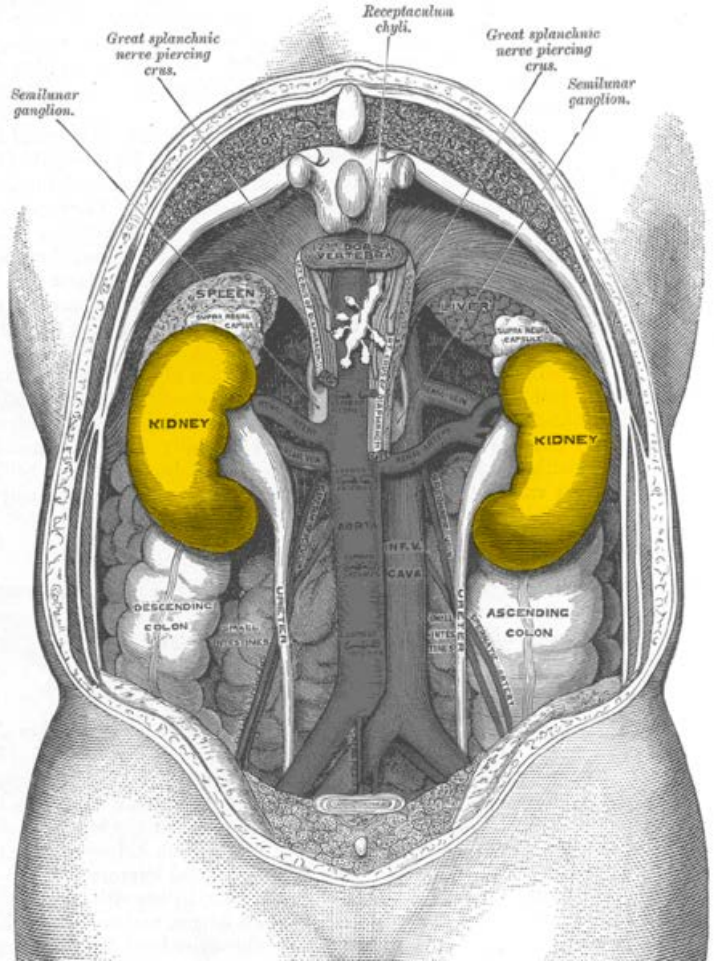
Anatomy of the Renal Block

Physiology	Pathophysiology	Urology
~~Body Fluids -1~~	Glomerular Diseases – 3	Histology Lab
~~GFR, Clearance -1~~	Acute Kidney Injury – 1	Malignancy – 1
Sodium / Diuretics – ~~2~~ 1	Chronic Kidney Disease – 3	
~~Potassium – 2~~	Renal Lab -2	
~~Acid – 2~~	Transplant Pathology-1	
Water – 2	Vascular Diseases – 1/2	
~~Steady State - 1~~	Plumbing- 1/2	



Learning Objectives (3)

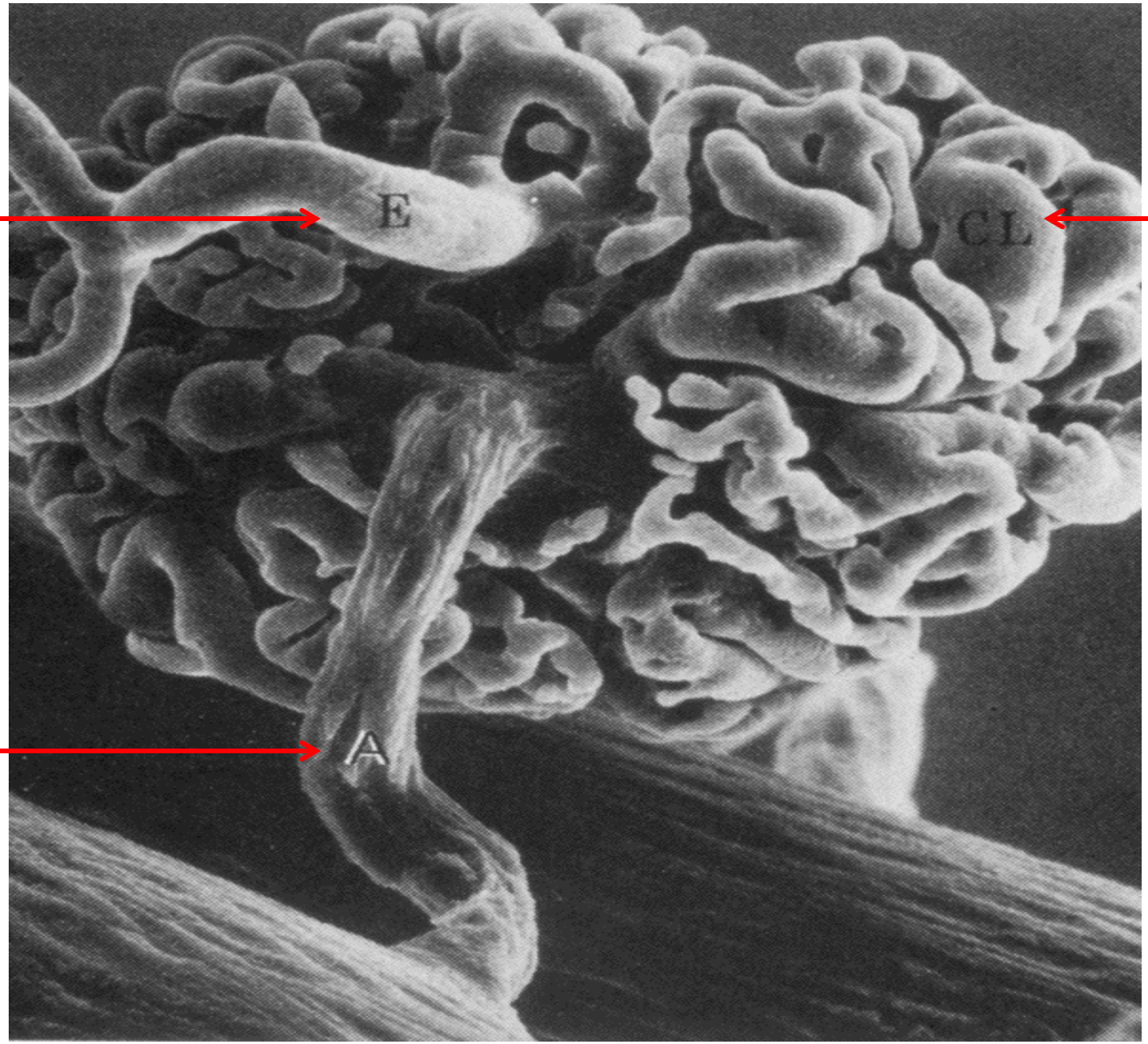
- Review the basic structure and function of the normal glomerulus
- Understand the pathophysiology and clinical presentation of patients with nephrotic and nephritic syndromes
- Formulate a differential diagnosis of a patient with glomerular disease

Outline

- Normal Glomerulus
- Nephrotic Syndrome
- Nephritic Syndrome(s)

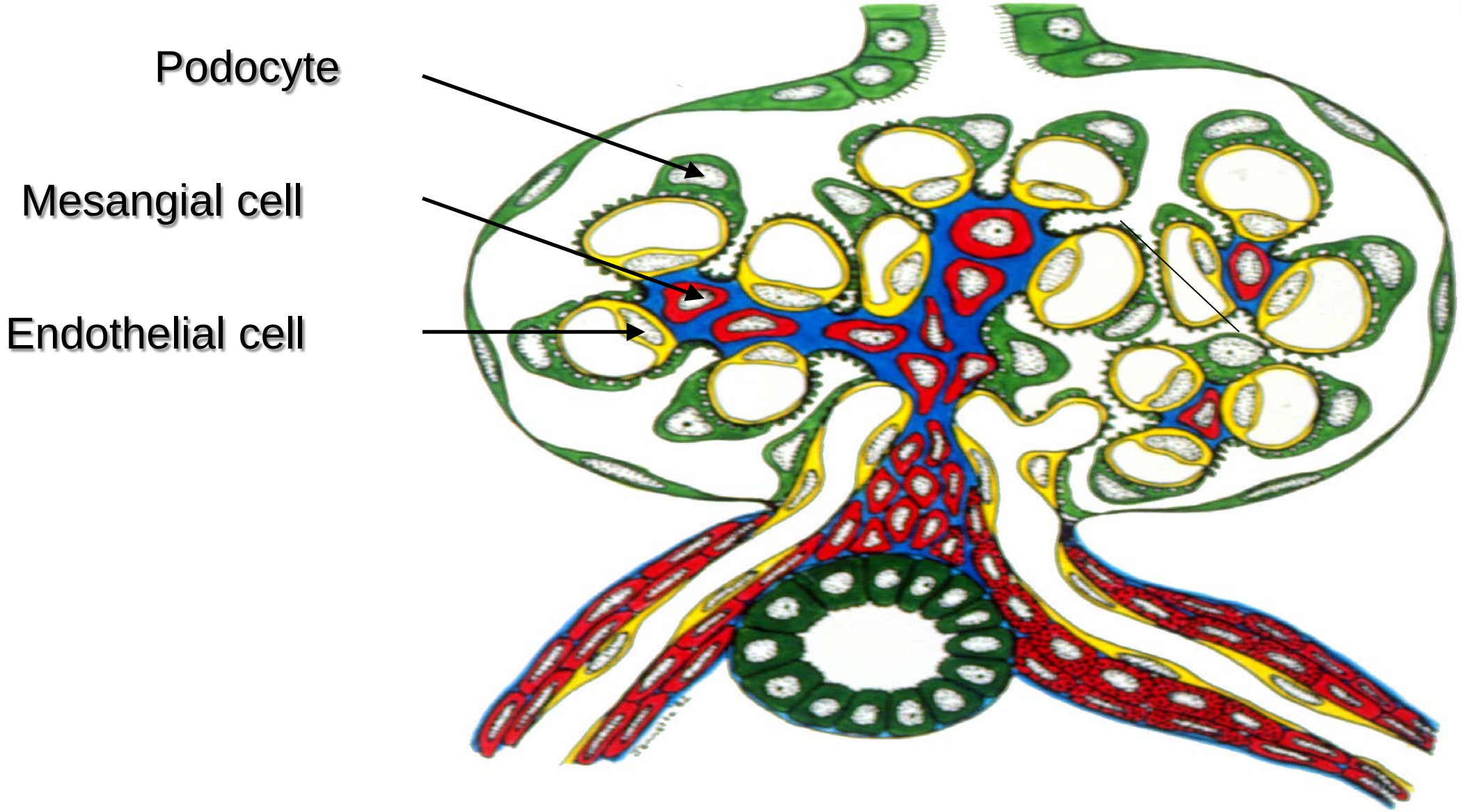
Efferent Arteriole

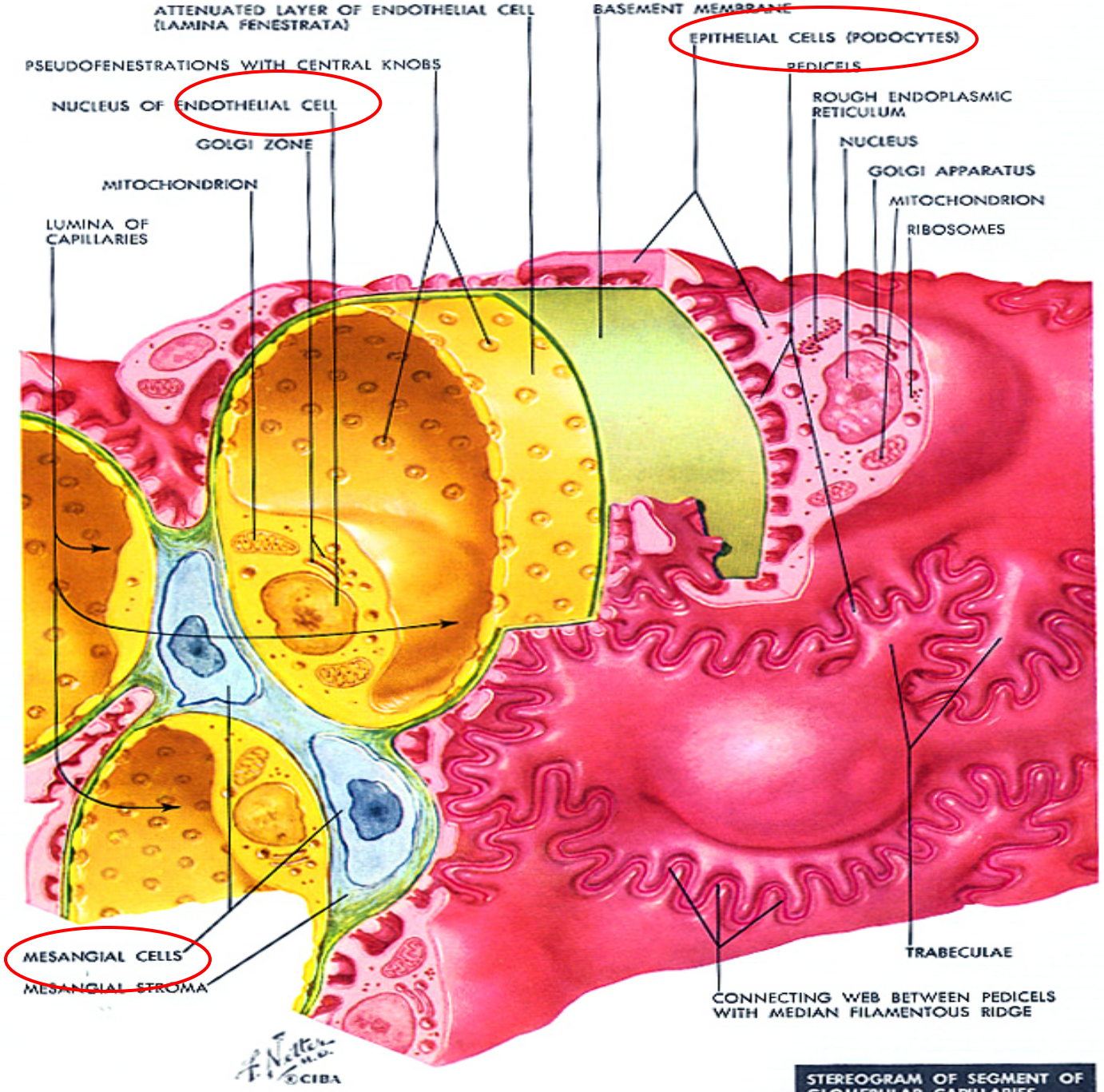
Afferent Arteriole



Capillary Loop

Three Glomerular Cell Types





STEREOGRAM OF SEGMENT OF GLOMERULAR CAPILLARIES

Three Glomerular Cell Types

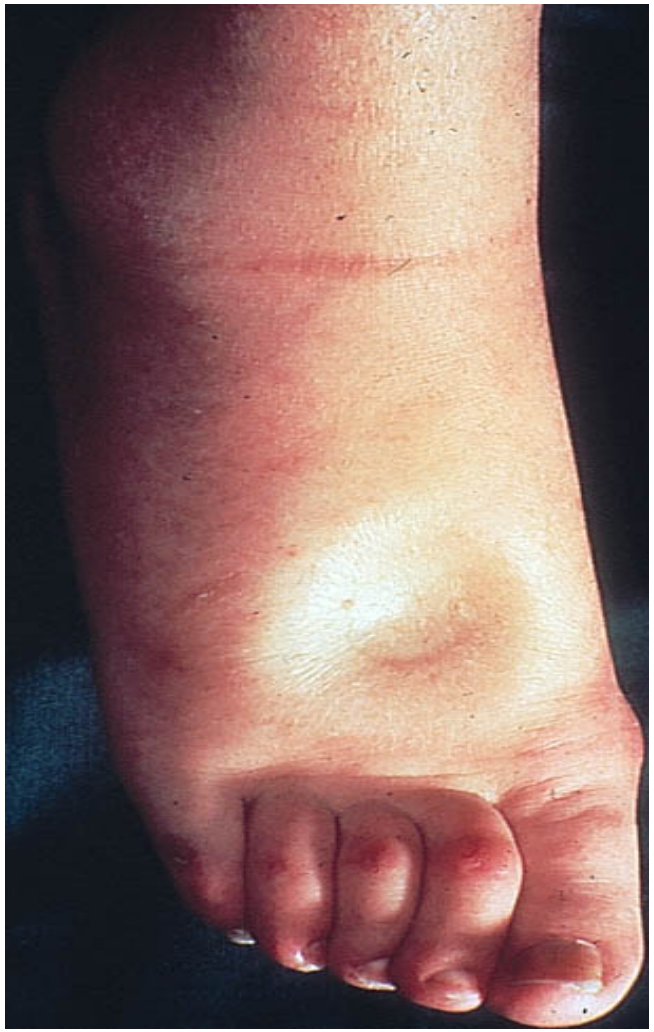
- Endothelial cells
  - Restrict filtration of cells and macromolecules through fenestrae
  - Make inflammatory mediators in response to injury
- Mesangial cells
  - Regulate vascular tone
  - Make mesangial matrix
  - Response to injury as effector cells
- Podocytes
  - Maintain impermeability to protein filtration (prevent proteinuria)

Outline

- Normal Glomerulus
- Nephrotic Syndrome
- Nephritic Syndrome(s)

Case 1

- 30 yo M presents with periorbital and lower extremity edema, 10 kg weight gain and foamy urine
- Physical exam: BP 120/80, pitting edema
- Laboratory:
  - Cr 0.9 mg/dL
  - Urinalysis: 3+ protein, no RBC, no WBC
  - Urine protein/Cr = 4 (normal < 0.15)



The Nephrotic Syndrome

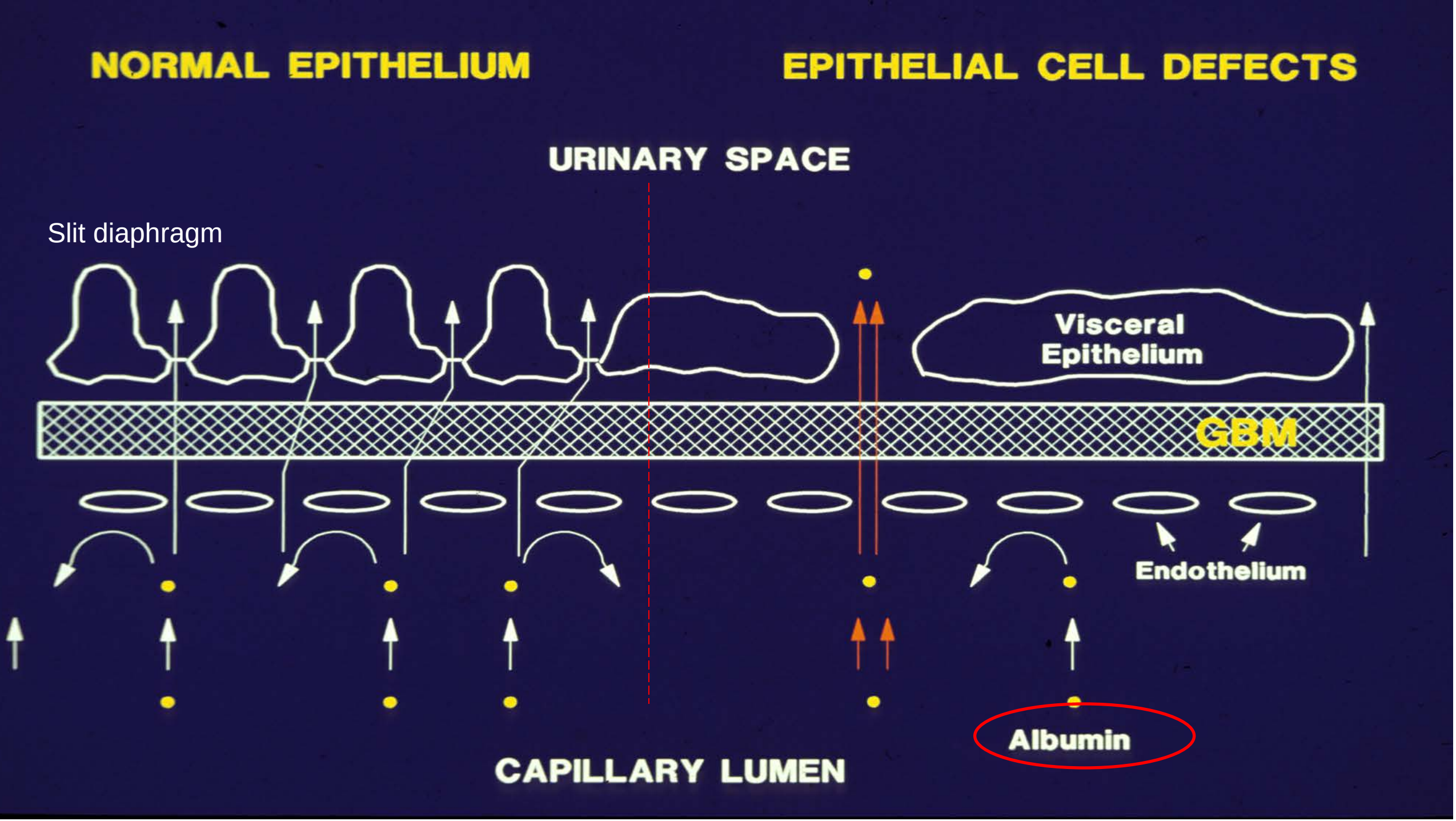
Proteinuria (>3.5g/day)

Hypoalbuminemia

Hyperlipidemia

Lipiduria

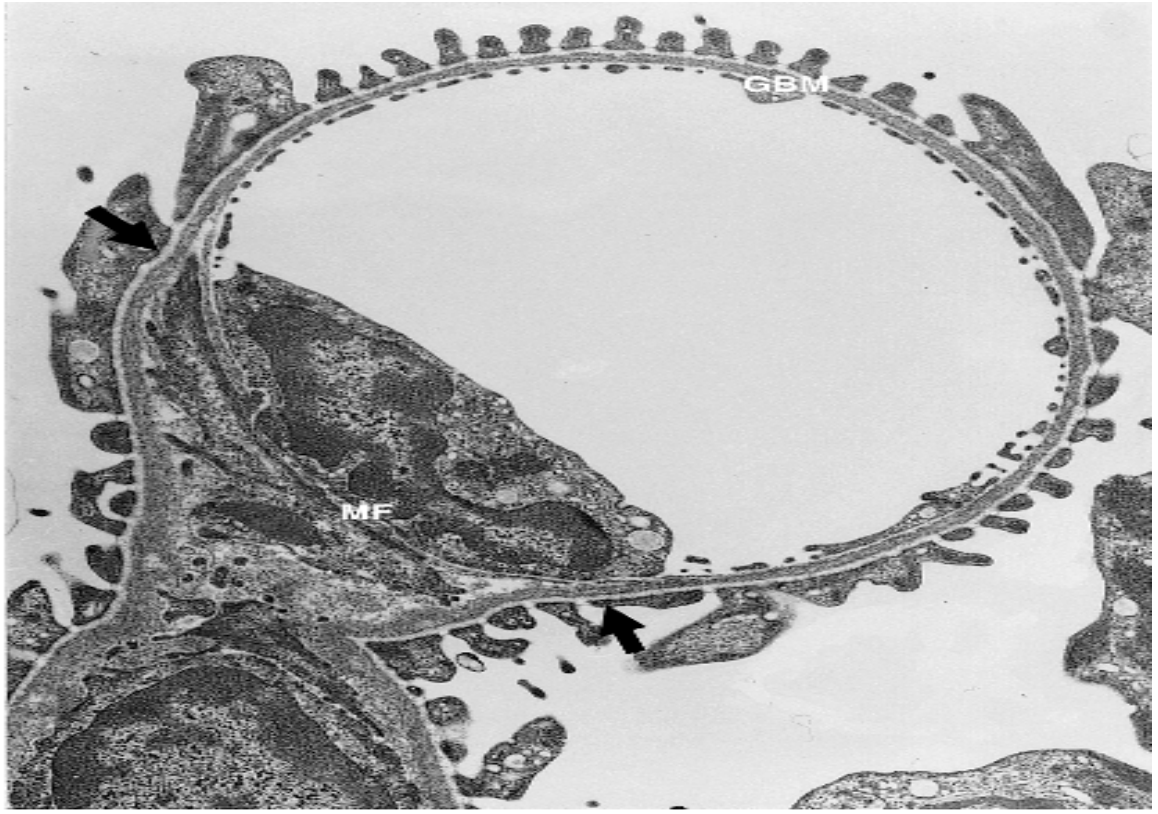
Edema


NORMAL EPITHELIUM
EPITHELIAL CELL DEFECTS
URINARY SPACE
Slit diaphragm
Visceral Epithelium
GBM
Endothelium
Albumin
CAPILLARY LUMEN

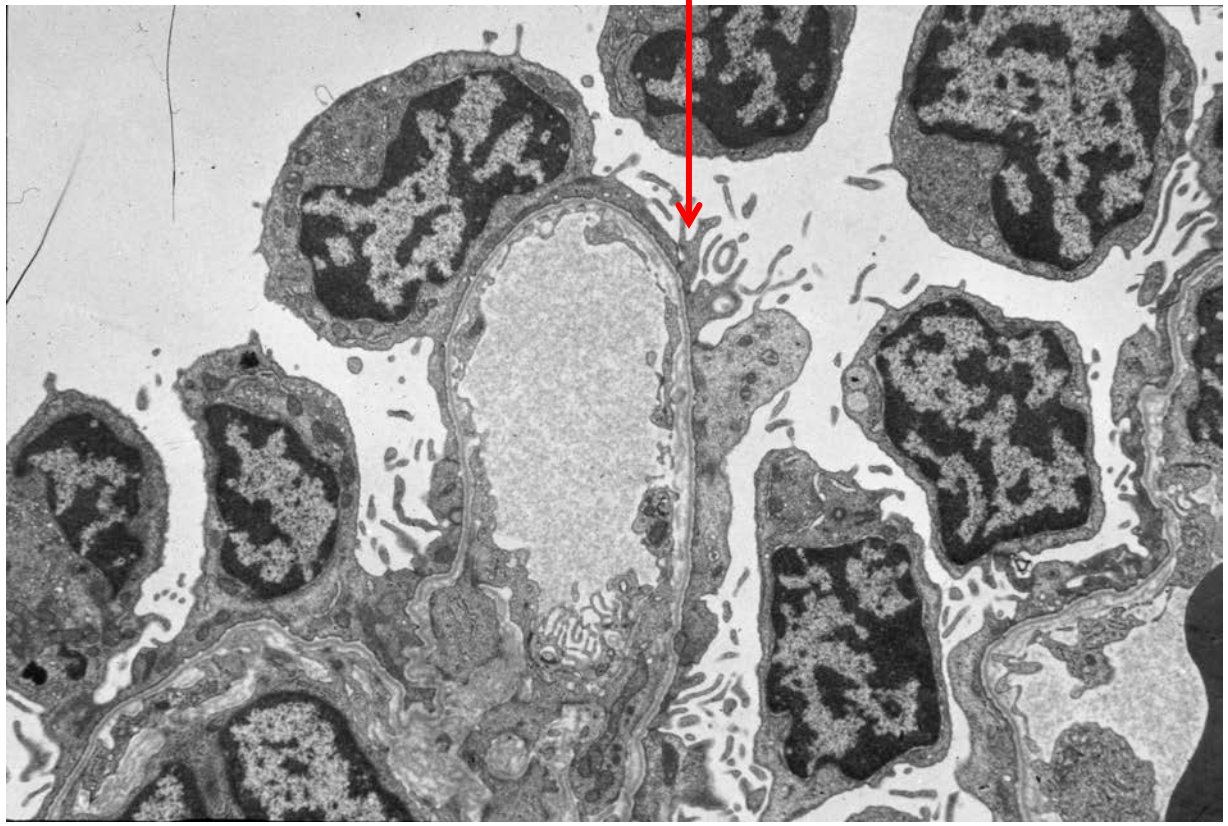
The Nephrotic Syndrome

Structural abnormality common to all nephrotic syndromes is diffuse “fusion” of the foot processes of the podocytes

Normal Podocyte

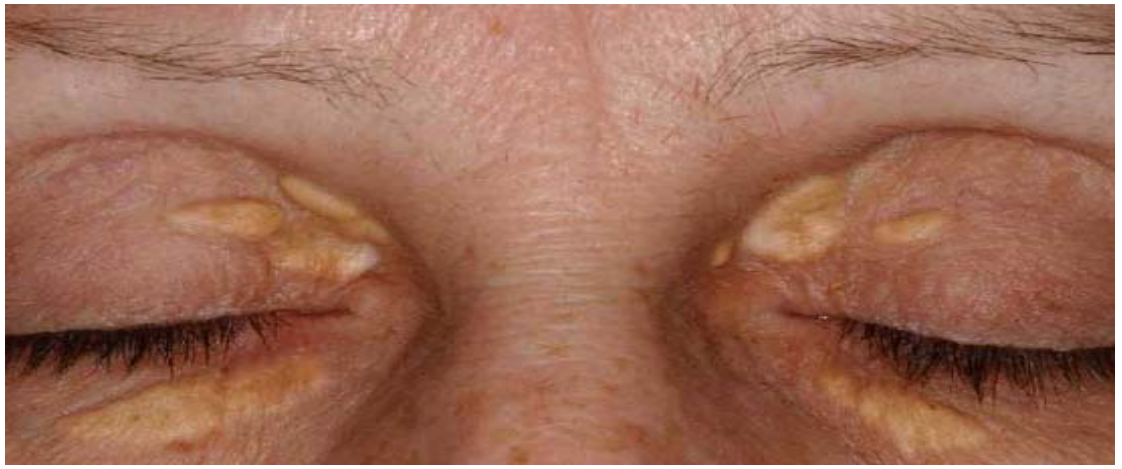


Fused Podocyte

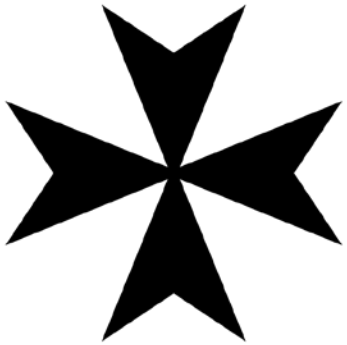


Hyperlipidemia

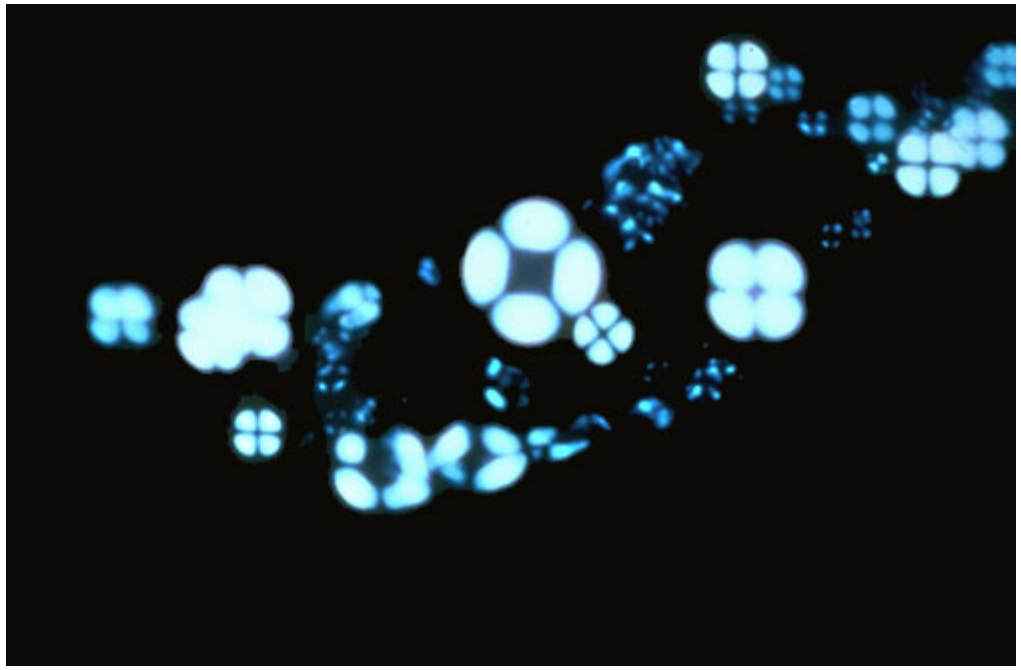
- Poorly understood but clinically relevant
- Hypercholesterolemia
  - Decreased oncotic pressure stimulates hepatic lipoprotein synthesis
- Hypertriglyceridemia
  - Impaired metabolism



Lipiduria



Maltese Cross



Mechanisms of Edema

- “Underfill”
  - Low oncotic pressure (hypoalbuminemia) leads to plasma volume depletion (water moves from plasma to interstitial compartment)

- “Overfill”
  - Sodium retention
  - Poorly understood

Hypercoagulable State

- Urinary losses of antithrombin III, Protein C & S, increased platelet activation, hyperfibrinogenemia

- 10-40% develop arterial or venous thromboembolism

The Nephrotic Syndrome

Proteinuria (>3.5g/day)

Hypoalbuminemia

Hyperlipidemia

Lipiduria

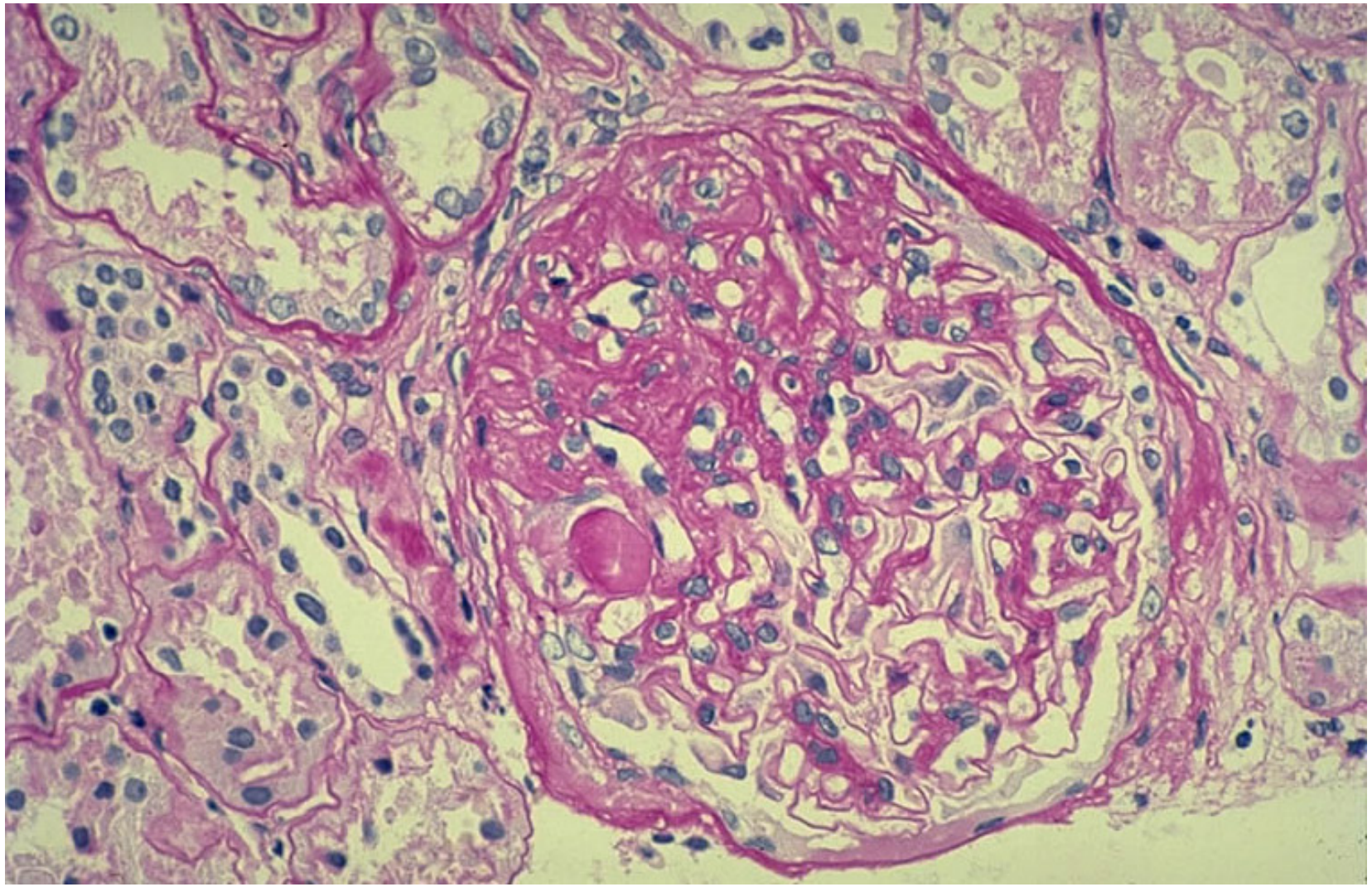
Edema

The Nephrotic Syndrome

- Primary renal disease
  - Focal segmental glomerulosclerosis
  - Membranous nephropathy
  - Minimal Change Disease
- Systemic disease
  - Diabetes mellitus
  - Amyloidosis
  - Systemic lupus erythematosus (SLE)

Focal Segmental Glomerulosclerosis (FSGS)

Focal Segmental Glomerulosclerosis (named for the histology)



T·H·E
NEPHCURE
FOUNDATION

Epidemiology

- Most common cause of nephrotic syndrome in adults in the United States
- Patients less than 40
- African-Americans

Major Causes of FSGS

- Idiopathic/Primary
- Familial

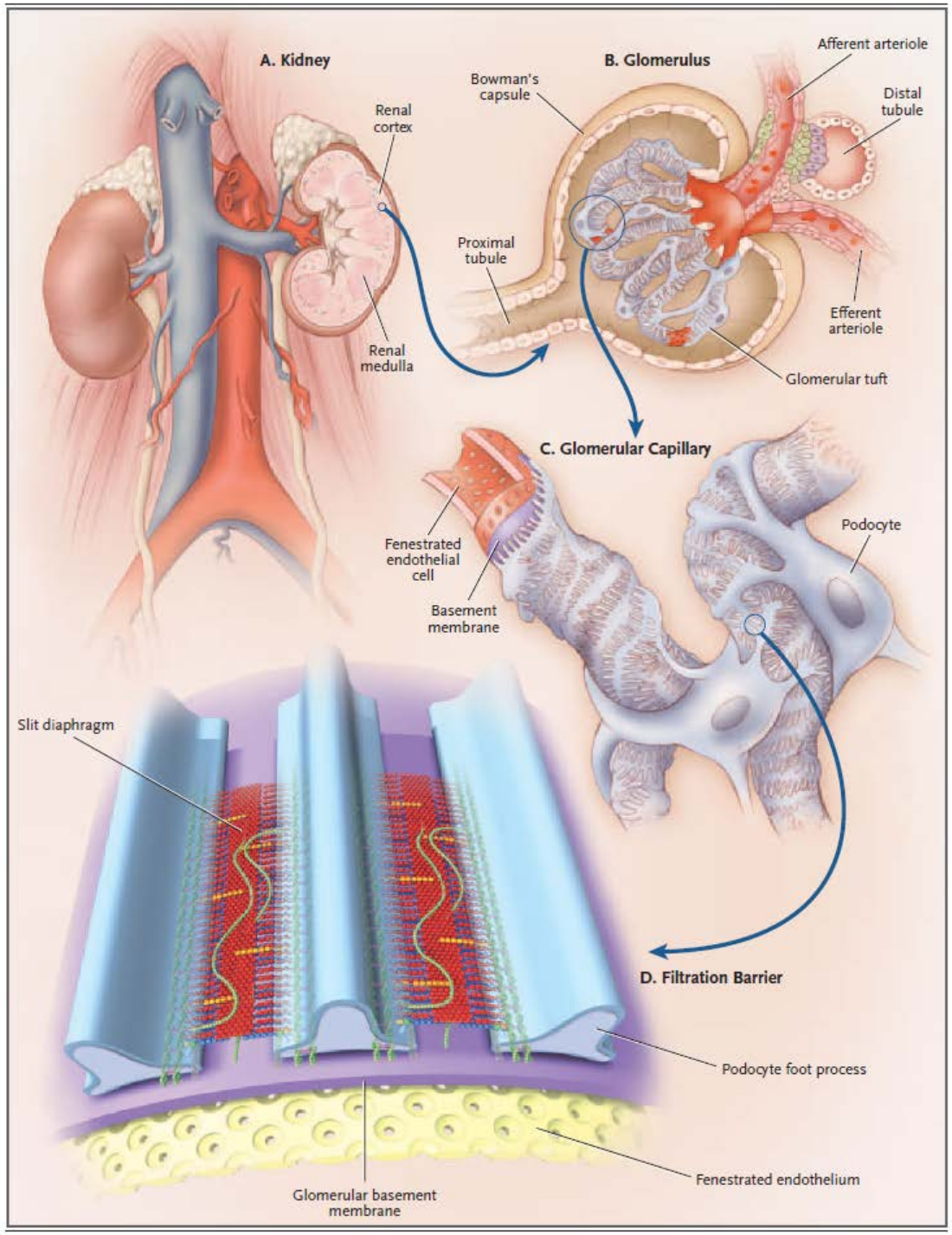
- Secondary
  - Infection (e.g. HIV)
  - Drugs (e.g. heroin)
  - Obesity (hyperfiltration)
  - Reduced nephron number (hyperfiltration)
    - Reflux nephropathy, unilateral renal agenesis, sickle cell disease, advanced renal disease

Pathogenesis

- Not completely understood
- Possible circulating glomerular permeability factor in primary FSGS that targets the podocyte
- Disease of the podocyte
  - Familial forms localized to podocyte-specific genes, including APOL1 (in African Americans)

FSGS

Disease of
the podocyte



Membranous Nephropathy

Epidemiology

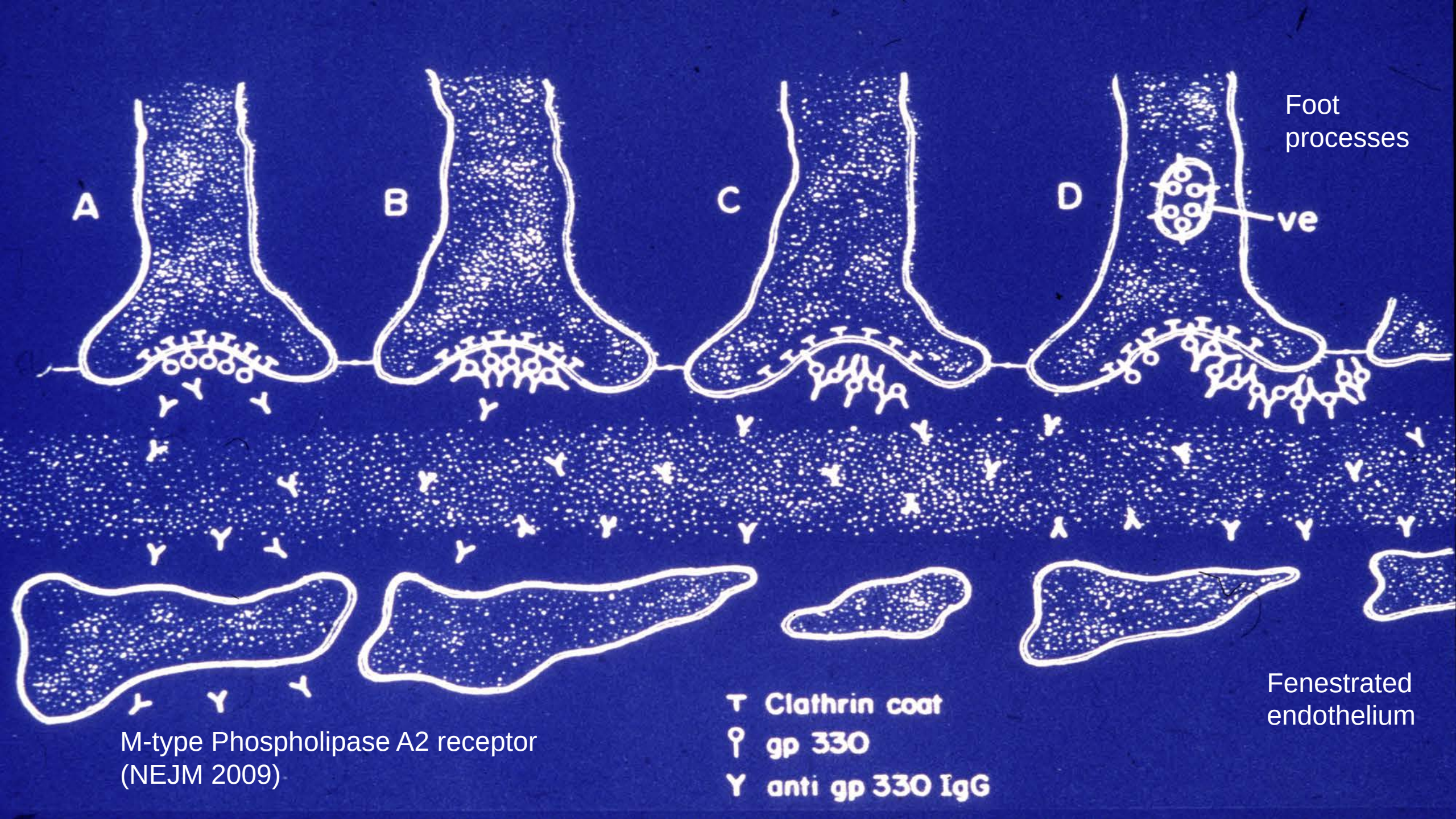
- Most common cause of nephrotic syndrome in Caucasian adults and > 60 yrs
- Incidence increases with age
- Men > women

Major Causes Membranous Nephropathy

- Idiopathic/Primary 80%
  - Antibodies to Phospholipase A_2 receptor (PLA2R)
- Secondary 20%
  - Solid tumors
    - Bowel, breast, lung
  - SLE
  - Infections
    - Hepatitis B/C, malaria, syphilis
  - Rheumatoid arthritis
    - Drugs
      - Penicillamine
      - Gold

Pathogenesis

- Autoantibody to glomerular antigens causing in situ immune complex formation
  - Phospholipase A2 receptor



M-type Phospholipase A2 receptor
(NEJM 2009)

Minimal Change Disease

Epidemiology

- Most common cause of nephrotic syndrome in children

Major Causes
Minimal Change Disease

- Idiopathic/Primary

- Secondary
  - NSAID (fenoprofen)
  - Malignancy
    - Hodgkin's disease
    - Leukemia

Diabetic Nephropathy

Epidemiology

- Most common cause of end-stage renal disease (ESRD)

- 30-40% of type 1 and 15-20% of patients with type 2 diabetes mellitus develop diabetic nephropathy after 10 –20 years

Amyloidosis

Amyloidosis

- Older patients
- Variety of proteins form ß-pleated sheets
  - Immunoglobulin light chains in primary (AL)
  - Amyloid AA secondary to chronic inflammation (e.g. rheumatoid arthritis)
- Poor prognosis
- Deposition in the heart, liver, GI tract

The Nephrotic Syndrome

- Primary renal disease
  - Focal segmental glomerulosclerosis (adults)
  - Membranous nephropathy (older)
  - Minimal Change Disease (younger)

- Systemic disease
  - Diabetes mellitus (common disease with renal involvement)
  - Amyloidosis (rare disease with renal involvement)
  - Systemic lupus erythematosus (SLE)

Case 1 – Nephrotic Syndrome

- 30 yo M presents with periorbital and lower extremity edema, 10 kg weight gain and foamy urine
- Physical exam: BP 120/80, pitting edema
- Laboratory:
  - Cr 0.9 mg/dL
  - Urinalysis: 3+ protein, no RBC, no WBC
  - Urine protein/Cr = 4 (normal < 0.15)

The Nephrotic Syndrome

Proteinuria (>3.5g/day)

Hypoalbuminemia

Hyperlipidemia

Lipiduria

Edema

History and Physical Clues

- NSAID use (gold, penicillamine)
- History of malignancy
- History of diabetes, HIV
- Age
  - Children: Minimal change disease
  - Adults: FSGS and Membranous
- EDEMA
- Foamy urine

The Nephrotic Syndrome Laboratories

- Focal segmental glomerulosclerosis
  - HIV antibody
- Membranous nephropathy
  - Hepatitis B surface antigen, Hepatitis C antibody, RPR (for syphillis)
- Minimal Change Disease
- Diabetes mellitus
- Amyloidosis
  - SPEP, UPEP (serum and urine protein electrophoresis)
- Systemic lupus erythematosus (SLE)
  - ANA, anti-DNA, serum complements (C3, C4)

Diagnosis: Nephrotic Syndrome

- Kidney biopsy is required in most cases to establish the diagnosis

Outline

- Normal Glomerulus
- Nephrotic Syndrome
- Nephritic Syndrome(s)

The Nephritic Syndrome

Proteinuria < 3.5 grams/day

Edema

Hematuria (red cell casts, dysmorphic RBCs)

Hypertension

Renal Failure

Nephritic Syndrome(s)

- Focal Nephritic
  - Mild, benign
- Diffuse Nephritic
  - Moderate level of disease
  - Rapidly progressive glomerulonephritis (RPGN)

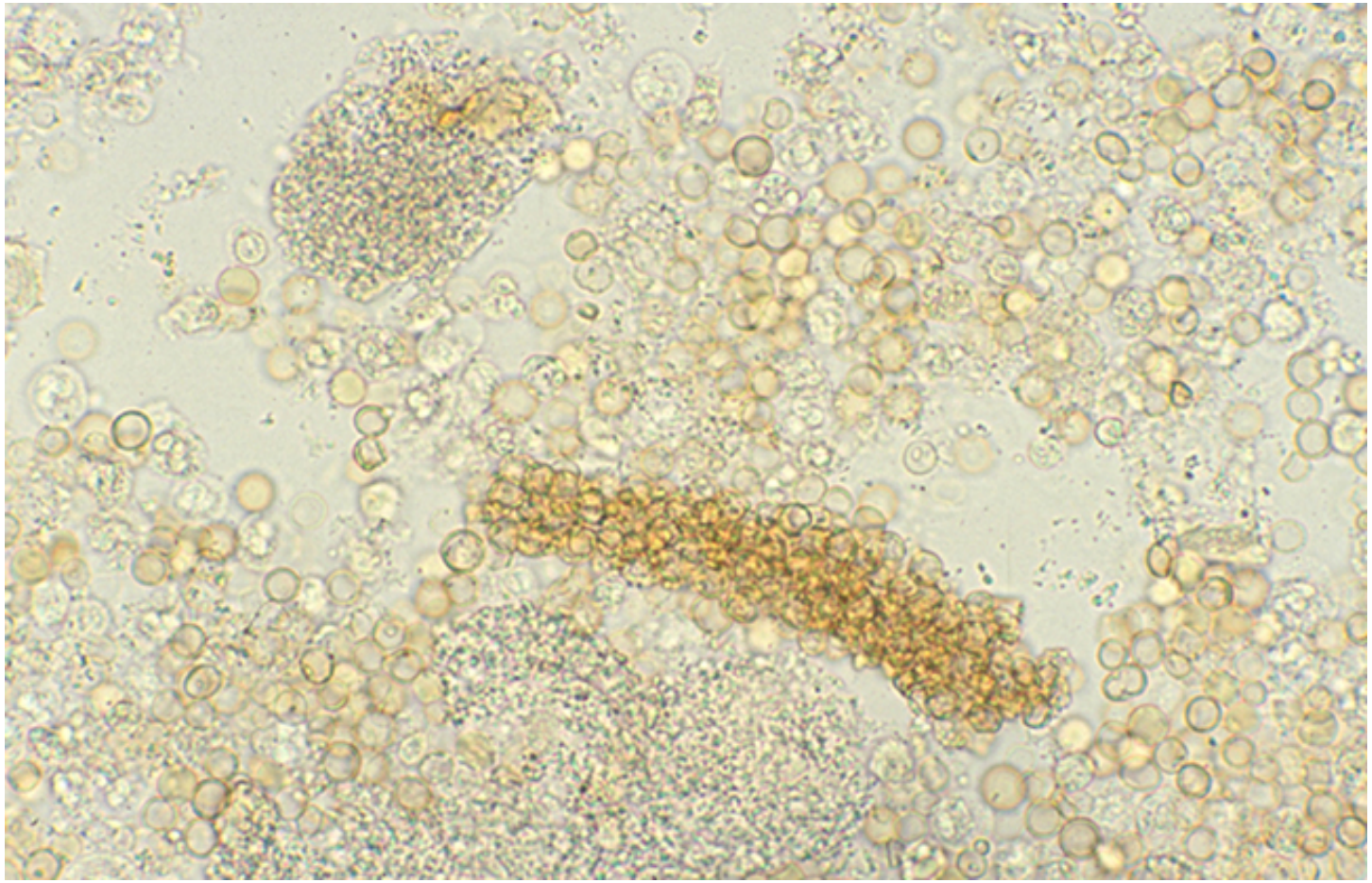
Case 2

- 30 yo M presents with
  - Ankle edema in the evenings
  - Intermittent “coca-cola” colored urine 3 days after upper respiratory infection (over 10 years)
- Physical exam: BP 110/70, trace ankle edema
- Laboratory
  - Cr 0.9 mg/dL
  - Urinalysis: 1+ protein, 10-20 RBC, no WBC
  - Urine protein/Cr = 0.5

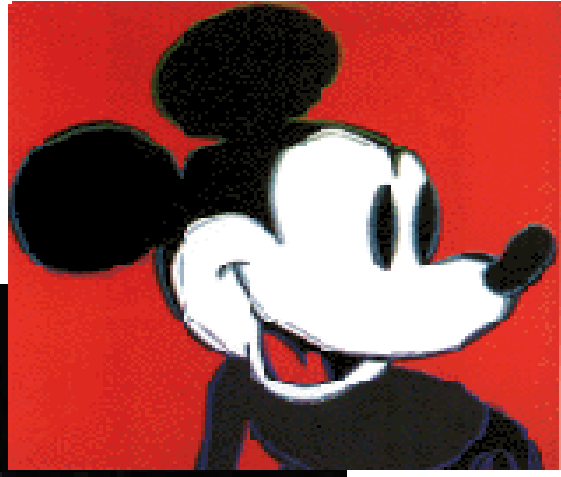
Macroscopic Hematuria

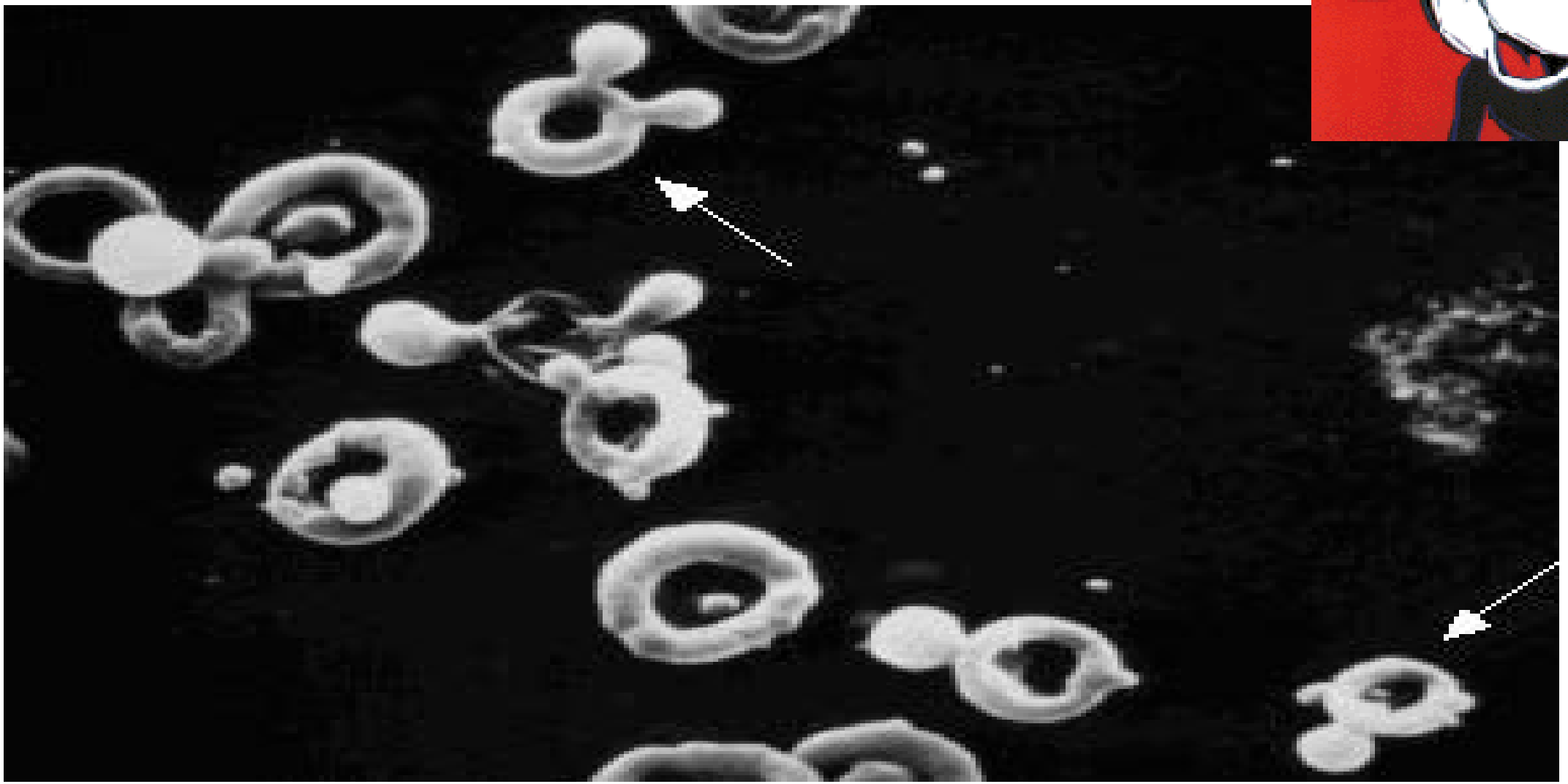
Coca-cola urine

Red Blood Cell cast in the urine



Dysmorphic RBCs





Focal Nephritic Syndrome

- Pathology
  - Inflammatory lesions < 50% of glomeruli
- Clinical
  - RBCs, RBC casts, mild proteinuria (< 1.5 g/day)
  - Mild or no edema, hypertension, renal failure

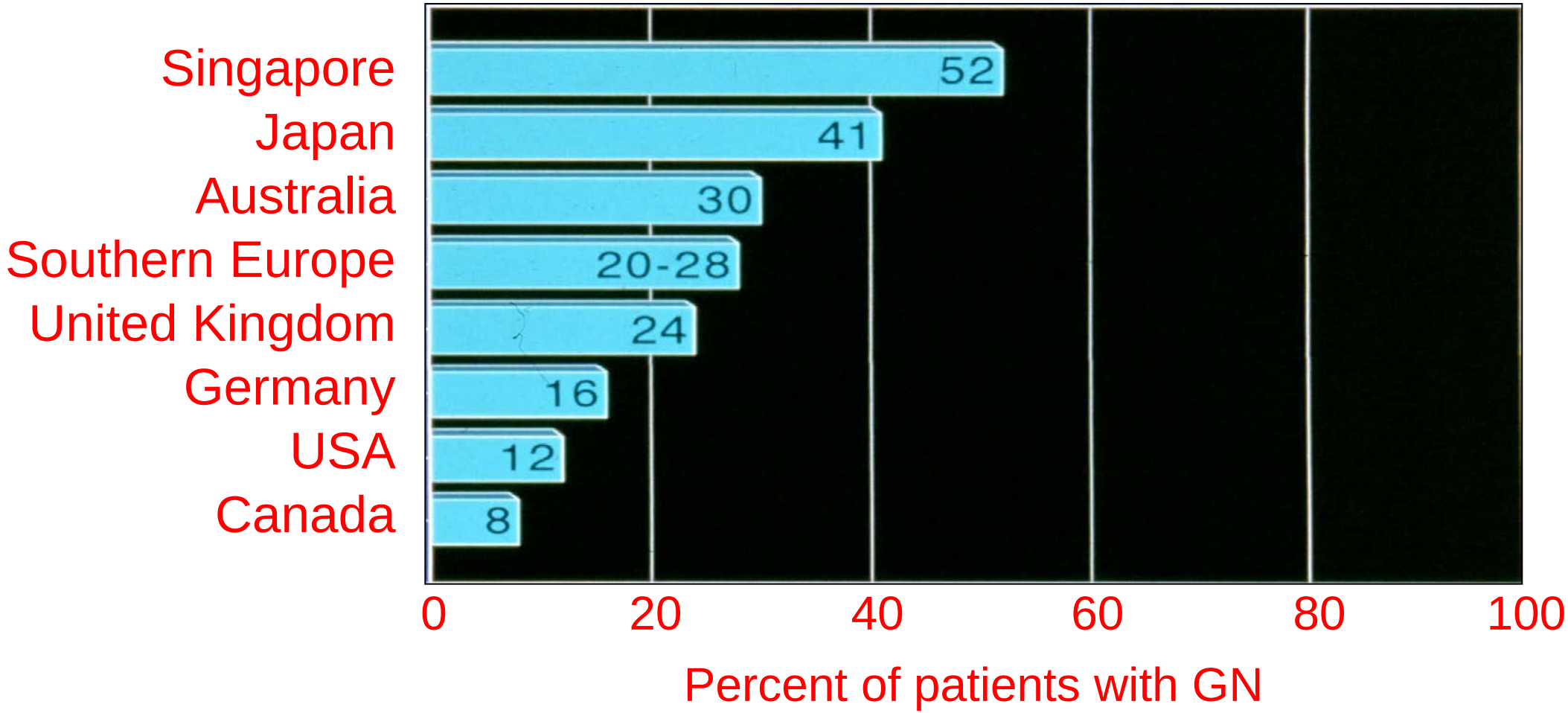
Focal Nephritic Syndrome

- Primary renal disease
  - IgA Nephropathy
  - Alport's Syndrome
  - Thin Basement Disease

- Systemic disease
  - SLE (focal /mesangial)
  - Henoch Schonlein Purpura (HSP)

IgA Nephropathy

Epidemiology

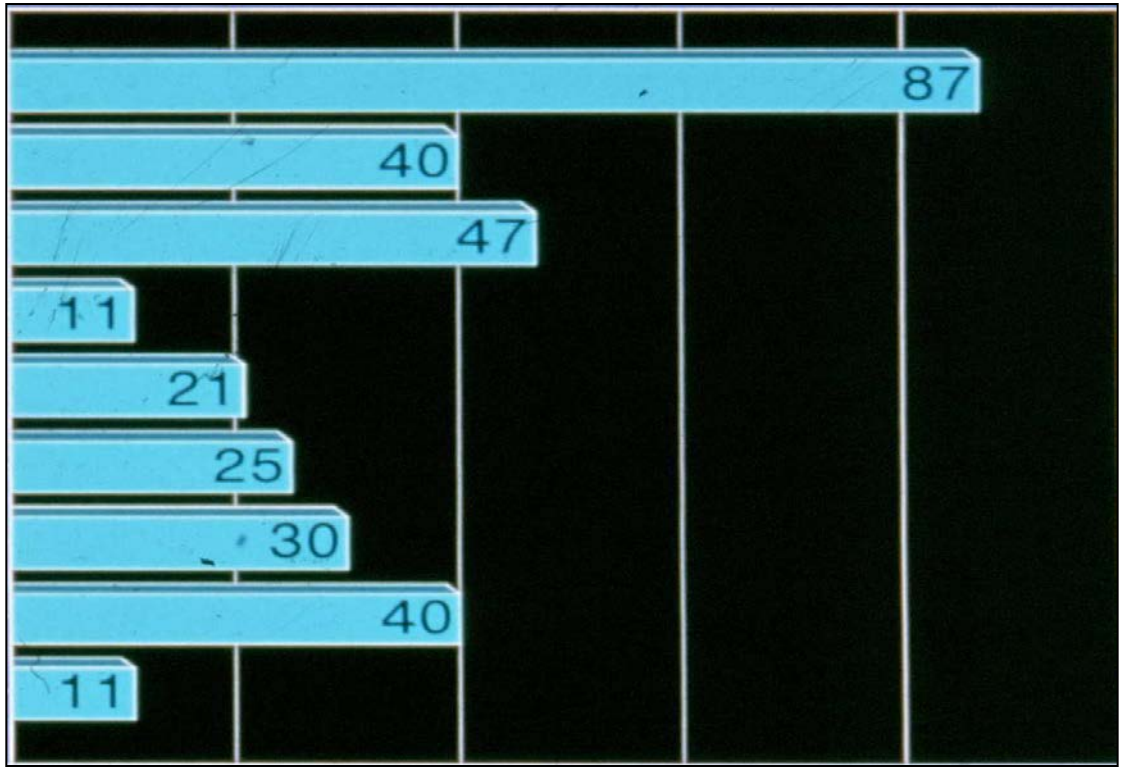


IgA Nephropathy

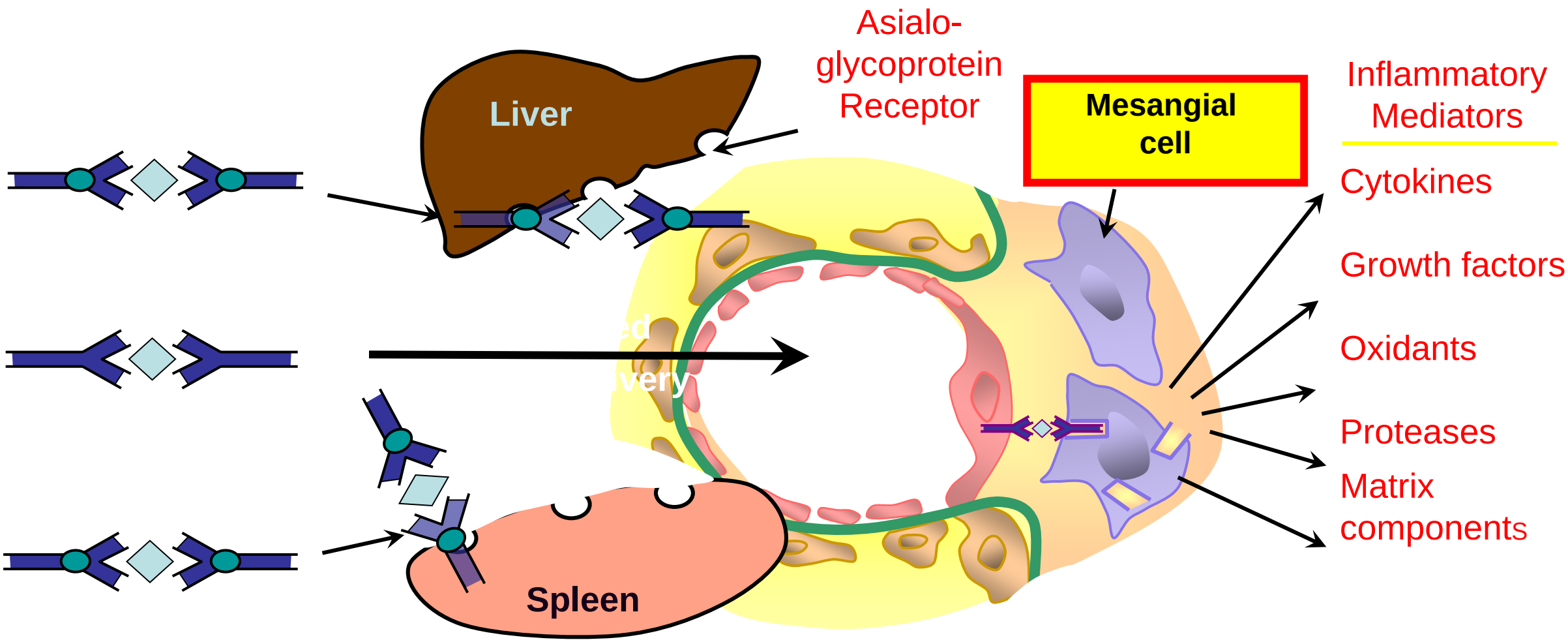
Clinical and laboratory features at presentation

Male/female 2:1; age usually 20-40 years

Microscopic hematuria
Macroscopic hematuria
Proteinuria > 1 g/d
Proteinuria > 3 g/d
Elevated creatinine
Elevated BP
Loin pain
Infection-related exacerbations
Familial history



Pathogenesis



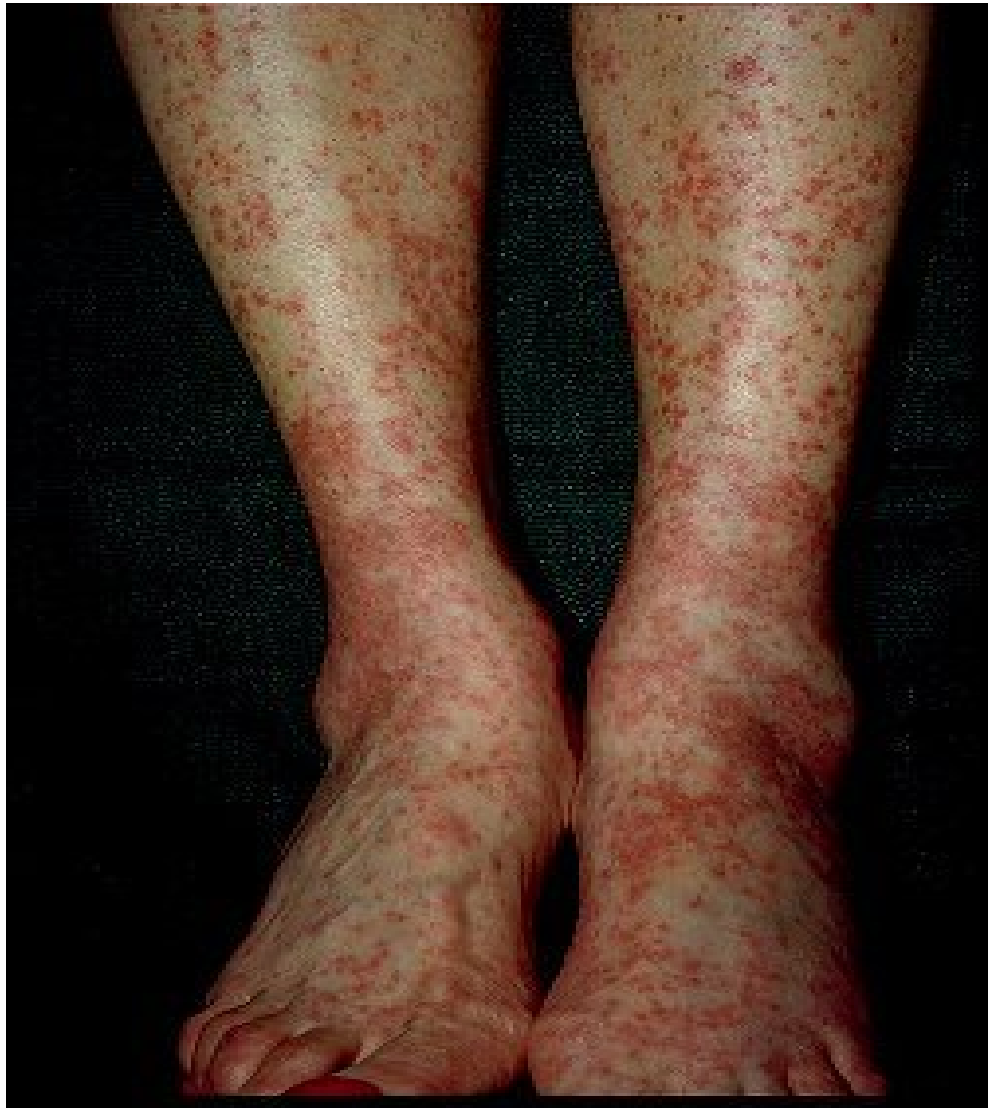
Differential Diagnosis – Focal, Nephritic

Disease	Gross Hematuria	Frequency	Family History
IgA	Yes	Variable	No
Alport's	Yes	1:50,000 live births	Males X-linked 15% - none
TBMD	<10%	5-9% of population	No

Case 3

- 30 yo M presents
  - 2-3 weeks periorbital and pitting edema to mid-calf
  - Dark urine
- Physical exam: BP 195/110
  - Purpura on thighs, pitting edema to knees
- Laboratory
  - Creatinine 2.3 mg/dL (from 0.9 last year)
  - Urinalysis: 3+ protein, 50-100 RBC, 10-20 WBC
  - Urine protein/Cr = 3

Purpuric skin lesions



Nephrotic vs. Nephritic Syndrome

Clinical Feature	*Nephritic*	*Nephrotic Syndrome*
Onset	Abrupt	Insidious
Urine sediment	RBCs, RBC casts	Lipid, fatty casts, Oval fat bodies
Protein excretion	< 3.5 g/day	> 3.5 g/ day
BP	Increased	Normal
GFR	Decreased	Normal

Diffuse Nephritic Syndrome

- Hypocomplementemic (low C3, C4) disorders
  - Postinfectious glomerulonephritis
  - Membranoproliferative glomerulonephritis
    - Cryoglobulinemia (HCV)
    - Systemic lupus erythematosus (SLE)

- Normal complement (normal C3, C4) disorders
  - Anti-GBM disease or Goodpasture syndrome
  - Vasculitis (ANCA-related)
  - IgA nephropathy

Postinfectious Glomerulonephritis

Post infectious Glomerulonephritis

Post streptococcal

Bacterial endocarditis

Shunt (ventriculo-peritoneal shunt) nephritis

Nephritis with visceral abscesses

Poststreptococcal Glomerulonephritis

- Children > adults
- Streptococcus, group A beta-hemolytic (types 1, 4, and 12)
- Dark urine (hematuria)
- Sore throat - 10 to 14 days earlier
- No long-term sequelae in most patients

Membranoproliferative Glomerulonephritis

Membranoproliferative GN

- Types I, II and III
- Children and young adults
- Nephrotic and nephritic

- Secondary forms - older adults
  - Most commonly associated with hepatitis C, cryoglobulinemia, SLE

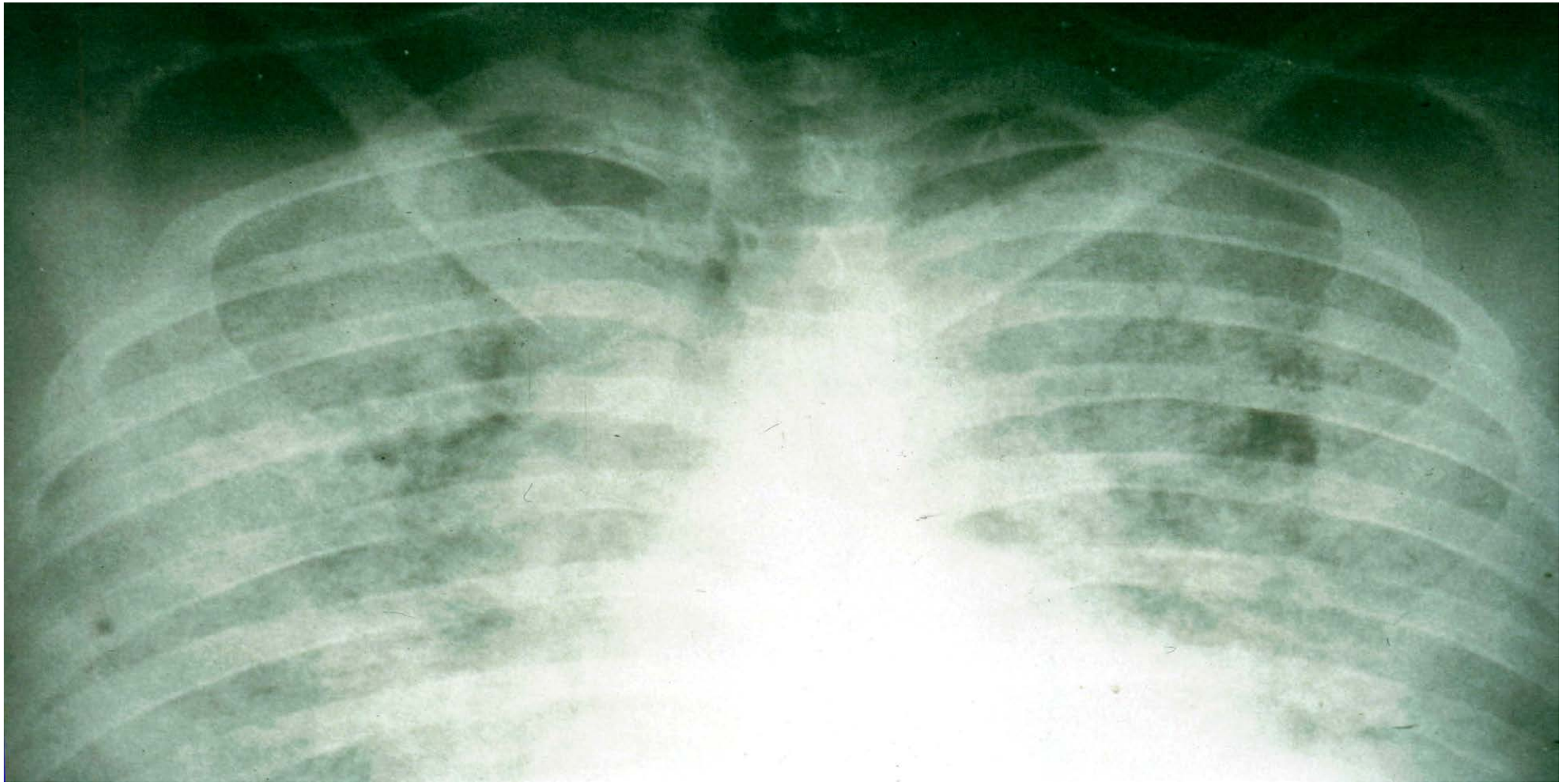
Rapidly Progressive Glomerulonephritis

Rapidly progressive decline in renal function

Active urine sediment characterized by an inflammatory process

Formation of cellular crescents within Bowman’s space

Anti-glomerular Basement Membrane (anti-GBM) Disease



Anti-GBM Disease and Goodpasture's Syndrome

Pulmonary hemorrhage, iron deficiency anemia, RPGN

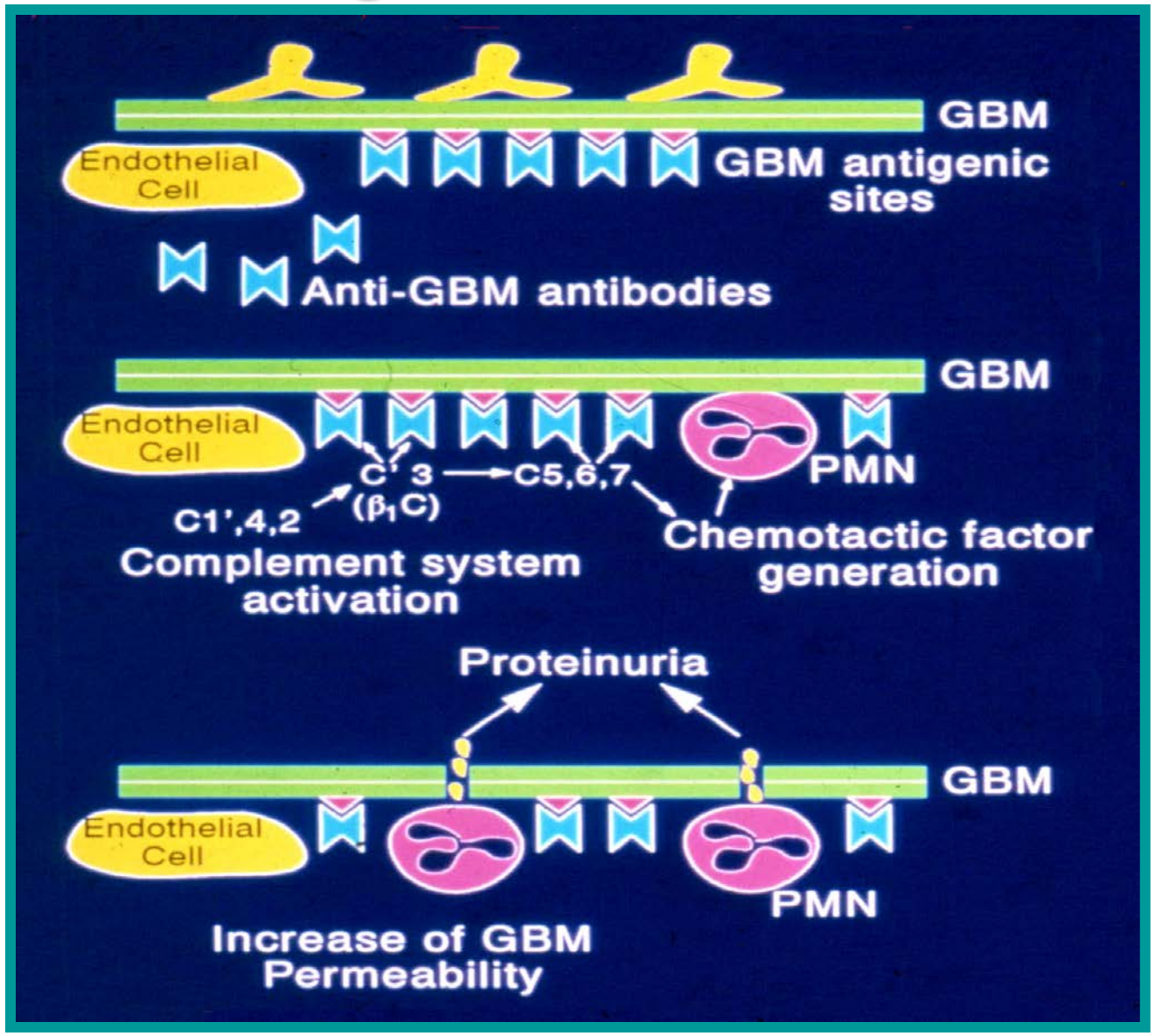
Age 15-30 yrs or 60-70 yrs, 6:1 male

Pulmonary toxins: cigarettes, hydrocarbons, influenza

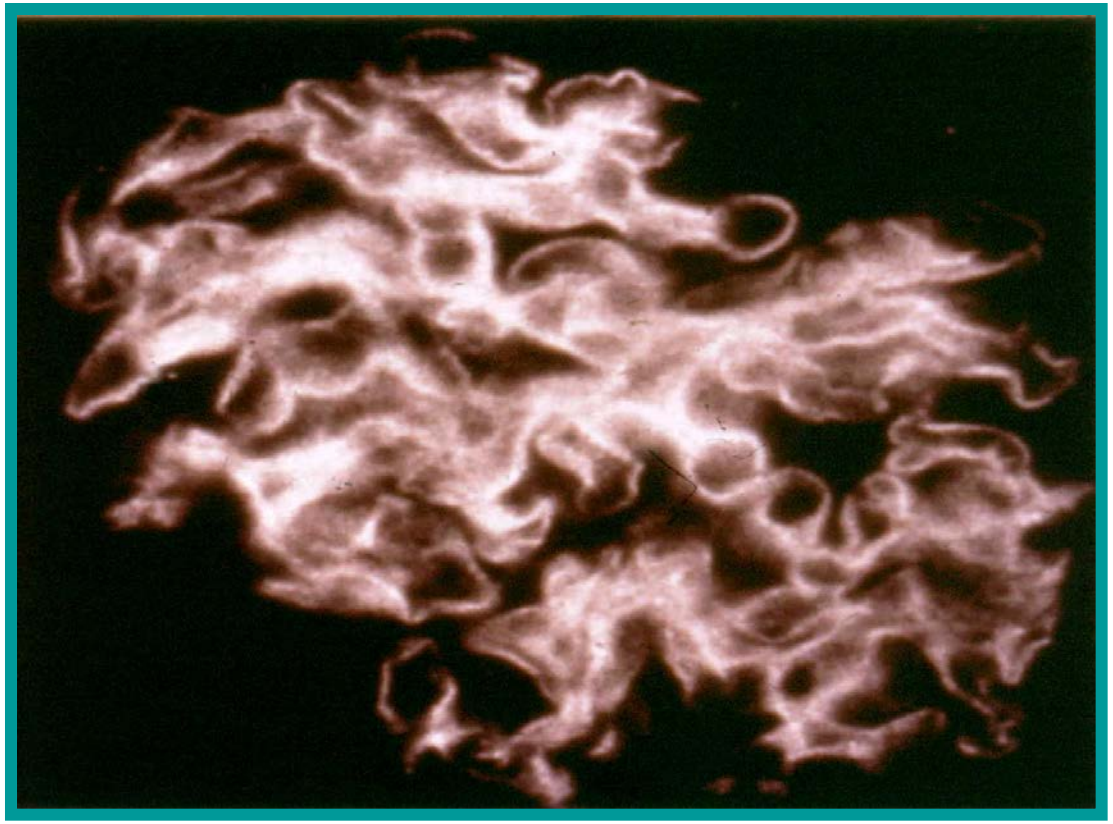
Lab: Positive anti-GBM antibody

Biopsy: Crescents; linear IgG, C3

Pathogenesis OF Anti-GBM Nephritis



Antibody to Type IV Collagen, Alpha-3 chain, NC1 domain



The Nephritic Syndrome

Proteinuria < 3.5 grams/day

Edema

Hematuria (red cell casts, dysmorphic RBCs)

Hypertension

Renal Failure

History and Physical Clues

- Sore throat
- Rash
- Liver disease
- Pulmonary symptoms
- Hypertension
- Dark urine
- Edema

Nephritic Syndrome

- Hypocomplementemic Disorders (low C3, low C4)
  - Postinfectious glomerulonephritis
    - ASO titer
  - Systemic lupus erythematosus (SLE)
    - ANA, anti-DNA
  - Membranoproliferative glomerulonephritis
    - Hepatitis C
  - Cryoglobulinemia (HCV)
    - Cryoglobulins

- Normal complement disorders
  - Anti-GBM disease or Goodpasture syndrome
    - Anti-GBM antibodies
  - Vasculitis (ANCA-related)
    - ANCA (Anti-Neutrophil Cytoplasmic Antibody)
  - IgA nephropathy

Diagnosis of Nephritic Syndrome

- Kidney biopsy is usually needed

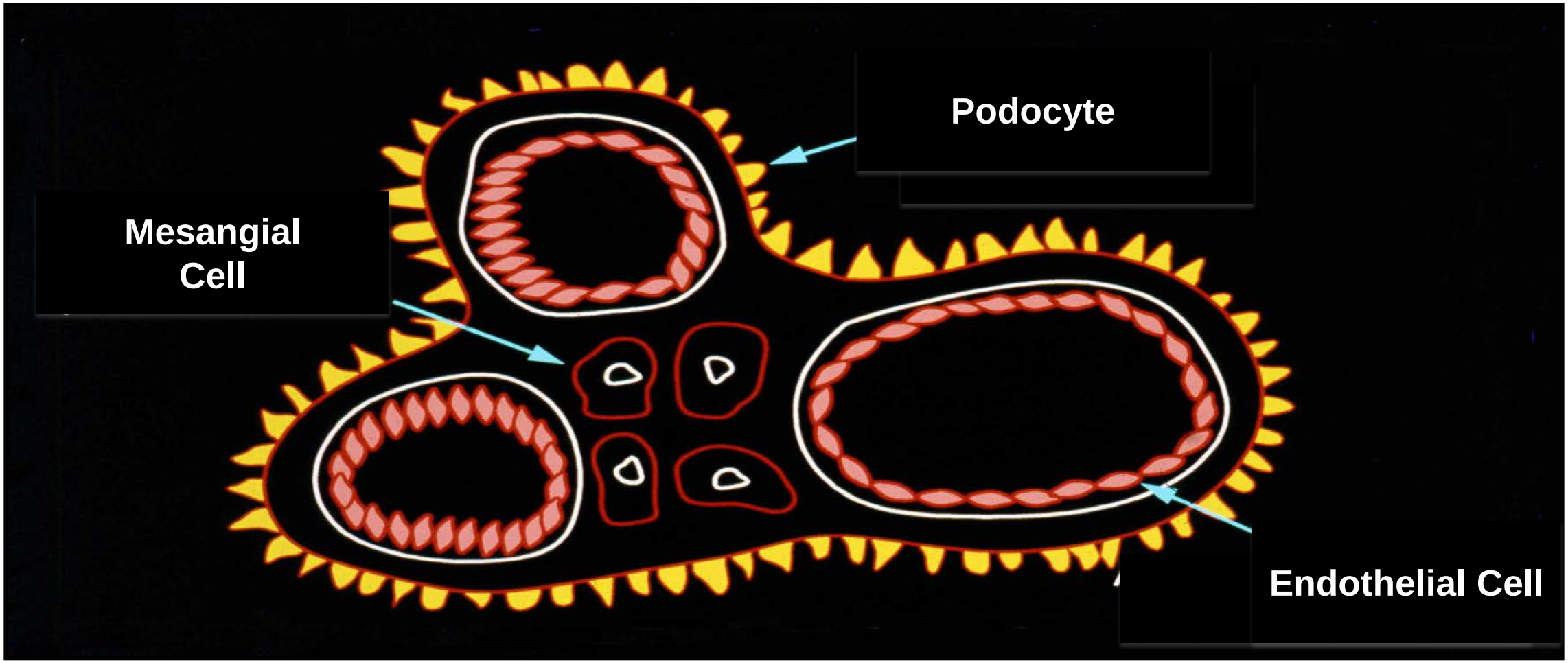
A word or two about Systemic Lupus Erythematosus (SLE)…

Systemic Lupus Erythematosus (SLE)

- SLE Can Present as All Forms of Glomerular Disease
  - Nephrotic syndrome
  - Nephritic syndrome
    - Diffuse or more severe, RPGN

- SLE Affects All Three Glomerular Cell Types

SLE Affects All Three Glomerular Cell Types

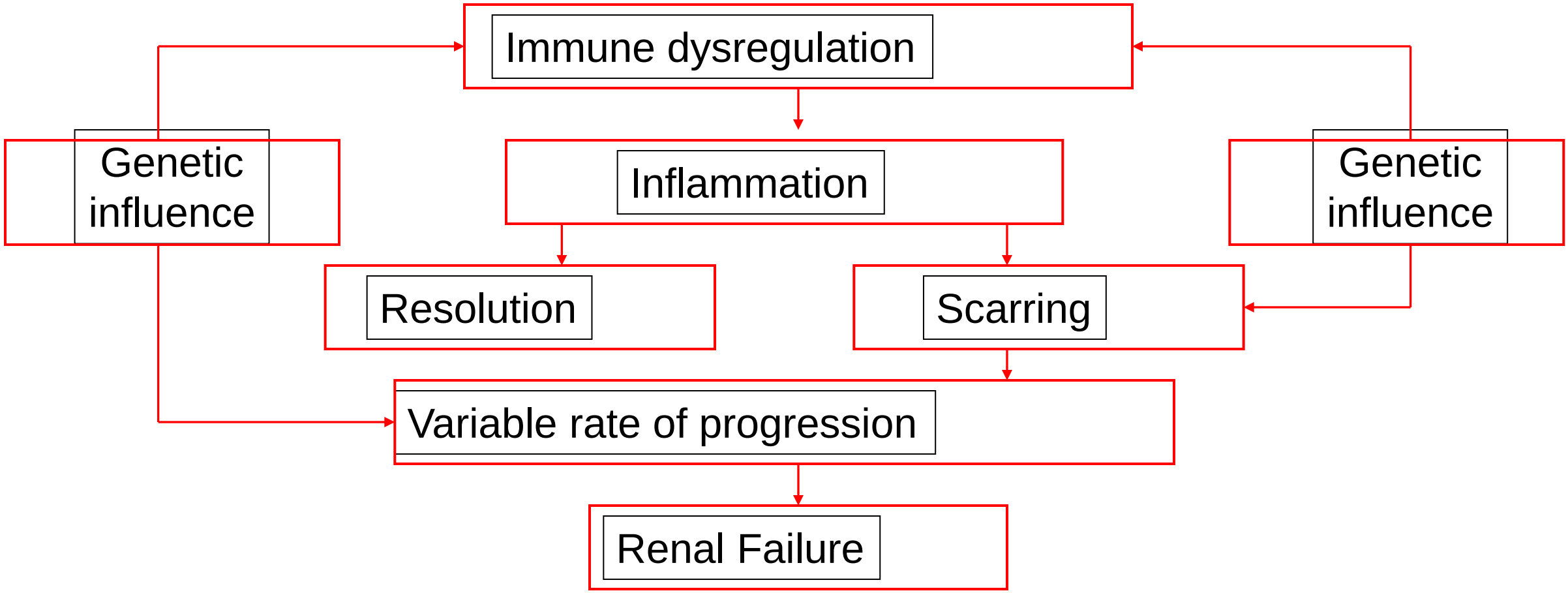


Systemic Lupus Erythematosis

- Immune complex GN
  - Anti-DNA

- Classification
  - Type I Normal Kidney
  - Type II Mesangial
  - Type III Focal proliferative
  - Type IV Diffuse proliferative
  - Type V Membranous

Pathogenesis of Glomerular Injury



Three Glomerular Cell Types

- Endothelial cells
  - Restrict filtration of cells and macromolecules through fenestrae
  - Make inflammatory mediators in response to injury
- Mesangial cells
  - Regulate vascular tone
  - Make mesangial matrix
  - Response to injury as effector cells
- Podocytes
  - Maintain impermeability to protein filtration (prevent proteinuria)

Summary

Glomerular Diseases

	Nephritic Syndrome	Nephrotic syndrome
Primary renal disease	Post infectious IgA nephropathy MPGN Anti-GBM	Minimal change Focal sclerosis Glomerulosclerosis (FSGS) Membranous nephropathy (MPGN)
Systemic disease	Vasculitis - SLE - HSP - Microscopic polyangiitis -Cryoglobulinemia - Wegener's granulomatosis	Diabetes Amyloid SLE

Differential Diagnose by Age

	< 15 years old	15-40 years old	> 40 years old
Nephrotic syndrome	MCD FSGS	MCD FSGS Membranous Diabetes SLE	(MCD) (FSGS) Membranous Diabetes Amyloid (>60)
Focal nephritic	Postinfectious IgA Alport's Thin BMD	IgA Alport's Thin BMD SLE	IgA
Diffuse nephritic	Postinfectious MPGN	Postinfectious MPGN Anti-GBM SLE	Postinfectious Anti-GBM ANCA Vasculitis

Learning Objectives (3)

- Review the basic structure and function of the normal glomerulus
- Understand the pathophysiology and clinical presentation of patients with nephrotic and nephritic syndromes
- Formulate a differential diagnosis of a patient with glomerular disease