PROTEINURIA

ELISE BARNEY, DO

NEPHROLOGIST

ASSOCIATE PROFESSOR, UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE

BUMC INTERNAL MEDICINE ACADEMIC HALF-DAY

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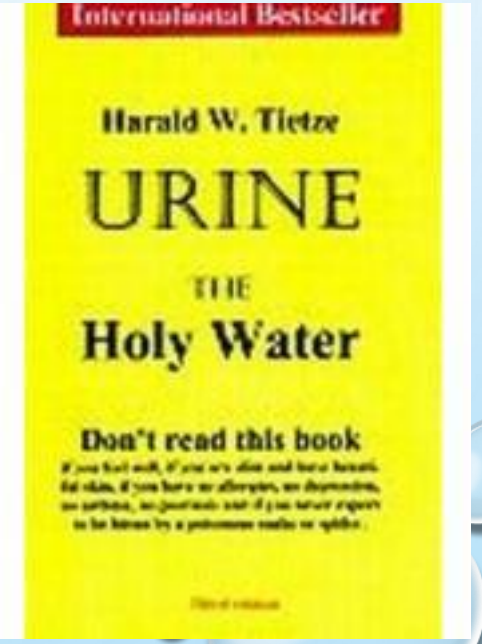
LEARNING OBJECTIVES

- DESCRIBE THE NORMAL MAKEUP OF URINARY PROTEIN.
- PERFORM A PROPER URINALYSIS AND IDENTIFY ITS LIMITATIONS.
- DEFINE PROTEINURIA AND BE ABLE TO CALCULATE OR QUANTIFY IT.
- DEFINE GLOMERULAR HEMATURIA AND THE PATHOGNOMONIC FINDINGS.
- DESCRIBE AND IDENTIFY NEPHROTIC SYNDROME AND CHARACTERISTIC URINE MICROSCOPY FINDINGS.
- DESCRIBE BENIGN AND NON-GLOMERULAR CAUSES OF PROTEINURIA.

URINALYSIS

- 2ND URINE OF THE MORNING, MID-STREAM
- CLEANSE WITH WATER (DISINFECTANTS CAN FAVOR CELL LYSIS)
- SHOULD BE CONCENTRATED AND ACIDIC
- AVOID STRENUOUS EXERCISE 24 HOURS PRIOR
- WOMEN SHOULD NOT BE MENSTRUATING

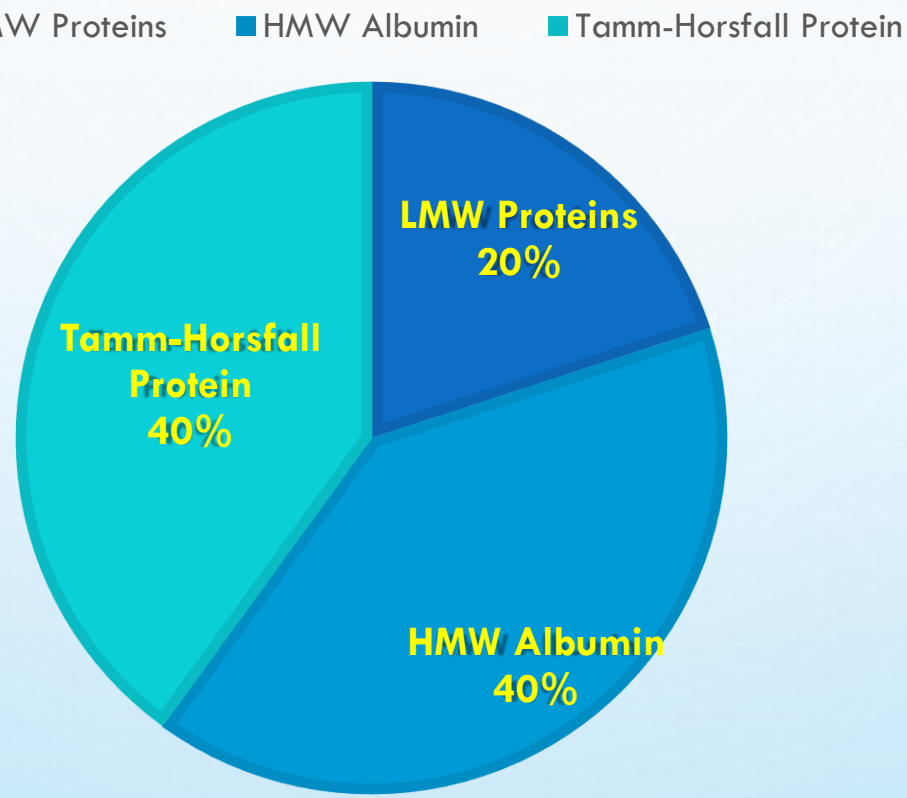


IDENTIFICATION

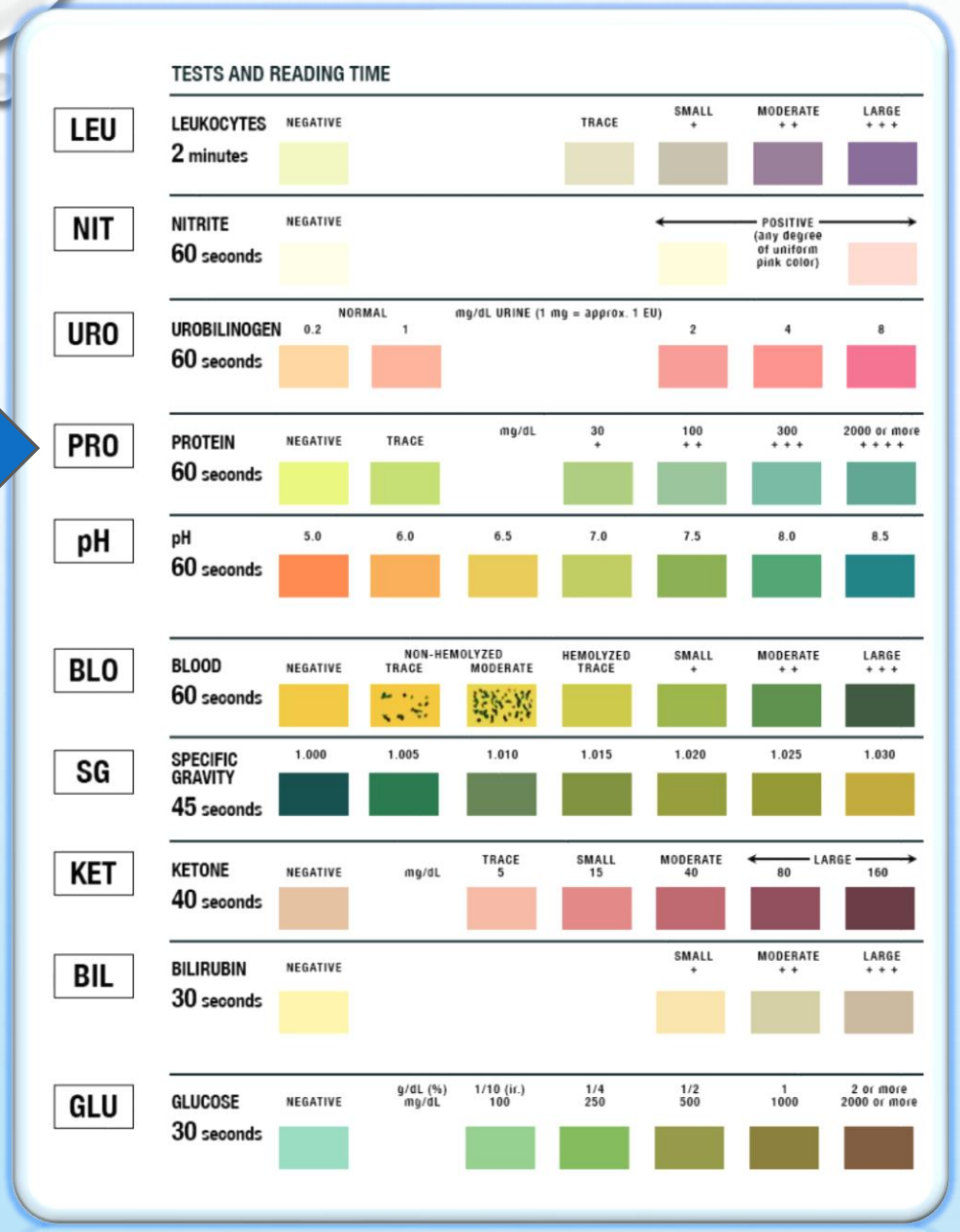
ACTUAL PATIENT QUOTES

- "MY URINE IS FOAMY"
- "THERE ARE LOTS OF BUBBLES IN MY PEE"
- "DOC, I DON'T LOOK AT MY URINE!"
- "DID THIS HAPPEN TO MY URINE FROM DRINKING TOO MUCH CHOCOLATE MILK?"
- "I DON'T EVEN DRINK BEER! HOW DID BEER GET INTO MY URINE?"

WHAT MAKES UP "NORMAL" URINARY PROTEIN?



URINE DIP



Dip detects protein with Bromphenol blue indicator dye - sensitive to albumin and less sensitive to Bence-Jones protein and globulins

Proteinuria threshold detection (+) trace
> 150 mg/24h

PROTEIN URINALYSIS: LIMITATIONS

Factor	False Positive + protein	False Negative - protein
Fluid status	Very concentrated urine	Very dilute urine
Acid/base	Alkaline urine (pH > 7.5)	Acidic urine
Hematuria	Increases	
Infection	+Proteins from organism/bacteria + cellular reactions to infection	
Exercise	Normal increase in urinary albumin excretion	
High fever	Normal increase in urinary albumin excretion	
Vaginal mucus, semen	Non-urinary proteins contaminate specimen	
Non-albumin Urine proteins (BJ proteins/globulins)		Not detected on dip
Drugs	Bleach, acetazolamide, cephalosporins, NaHCO3, PCN, sulfonamides	

URINE DIP & UA PROTEIN QUANTIFICATION

Urine Dipstick Protein Reading	Urinalysis Protein Excretion mg/dL	Protein Excretion mg/ 24 Hours
Negative	< 10	< 100 mg
Trace	15	100 - 300
+1	30	200 – 500
+2	100	500 - 1500
+3	300	2000 - 5000
+4	> 1000	> 5000

PROTEINURIA QUANTIFICATION METHODS

- FOR SPOT URINE, NEED 2 OR MORE SAMPLES 1-2 WEEKS APART TO CONFIRM DX " PERSISTENT PROTEINURIA"
- UACR: SPOT URINE ALBUMIN / CREATININE RATIO
- UPC OR PCR: SPOT URINE PROTEIN / CREATININE RATIO
- 24 HR URINE COLLECTION
  - ALWAYS GET A URINE CREATININE WHEN YOU ORDER THIS!!!

PROTEINURIA DETECTION METHODS LIMITATIONS

SPOT UACR AND UPC

- LOWER CREATININE IN WOMEN LEADS TO FALSELY HIGHER RATIO
- LOWER CREATININE IN ELDERLY/MALNOURISHED LEADS TO FALSELY HIGHER RATIO
- HIGHER CREATININE IN AA & PTS WITH HIGH MUSCLE MASS --> UNDERESTIMATES RATIO

24 HR URINE COLLECTION

- CUMBERSOME
- ACCURACY
- VARIATION DURING DAY
- VARIATION WITH RECUMBENCY
- ? NOCTURNAL COLLECTION AS AN ALTERNATIVE

DEFINITIONS

Microalbuminuria
UACR
30 – 300 mg/g

Proteinuria (sub-nephrotic)
UPC > 300 mg

Nephrotic Proteinuria
UPC > 3 grams
24hr urine > 3.5 grams

CAUSES OF PROTEINURIA

- TRANSIENT
- ORTHOSTATIC
- GLOMERULAR
- TUBULOINTERSTITIAL
- OVERFLOW

ORTHOSTATIC PROTEINURIA

- PATIENTS < 30 YEARS OLD
- BENIGN CONDITION, 3-5 % OF YOUNG ADULTS
- NORMAL RENAL FUNCTION WITH NO INCREASED RISK CKD
- INACTIVE SEDIMENT ON URINALYSIS
- INCREASED URINARY PROTEIN EXCRETION IN UPRIGHT POSITION **ONLY**
- URINE PROTEIN < 2 GRAMS / 24 HRS
- DX: SPLIT 24 HR URINE
  - DAY 16 HR URINE COLLECTION
  - 8 HOUR NOCTURNAL COLLECTION < 50 MG
  - ALTERNATELY CHECK 1ST AM UPC

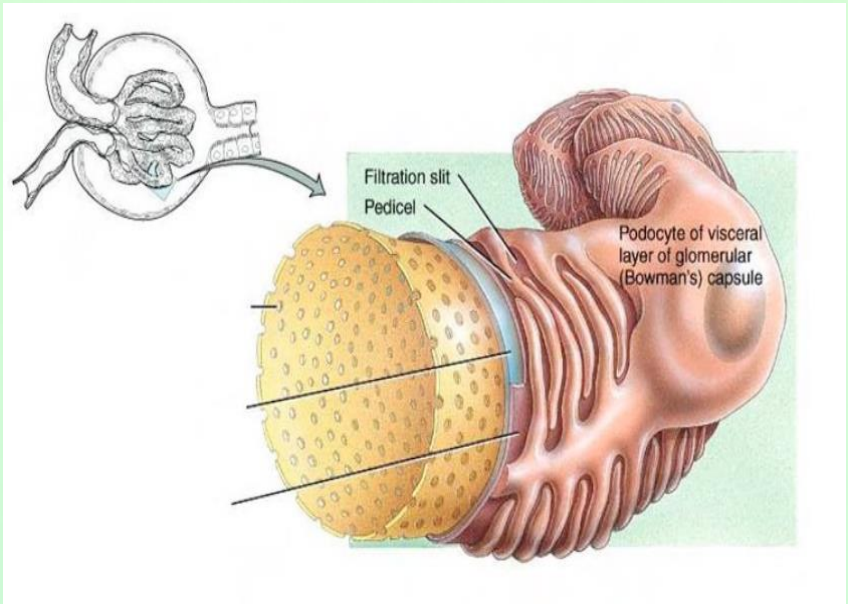
GLOMERULAR

- MOST COMMON & IMPORTANT CAUSE
- SUSPECT IF ACTIVE URINARY SEDIMENT
  - RBCS, CELLULAR CASTS
- SUSPECT IF > 1000 MG PROTEINURIA
- SEROLOGICAL WORKUP
- RENAL BIOPSY FOR DIAGNOSIS

- PATHOPHYSIOLOGY:
  - INCREASED GLOMERULAR CAPILLARY PERMEABILITY TO PROTEIN
  - IMPAIRED PROTEIN REABSORPTION BY EPITHELIAL CELLS OF PROXIMAL TUBULES

GLOMERULAR BARRIERS

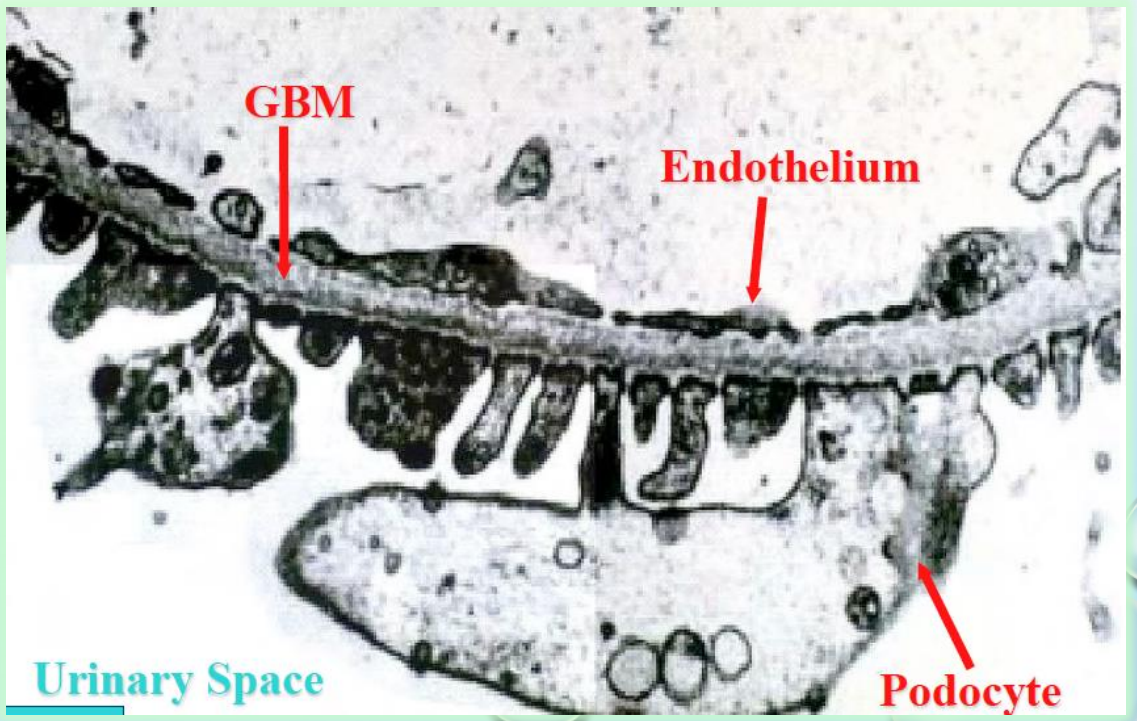
GBM Normal Barriers



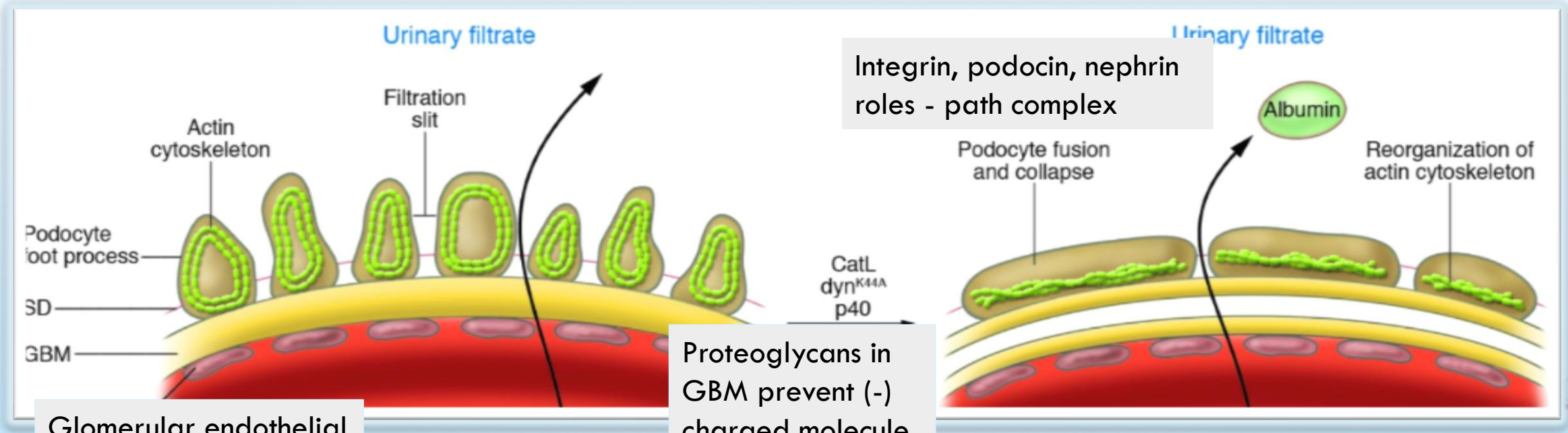
The Podocyte: a key cell in the selective filtering action of the glomerular capillary wall

Normally the GBM restricts passage into Bowmans space by:

- Molecular size
- Electrical charge
- Sterical configuration



PROTEINURIA MECHANISMS

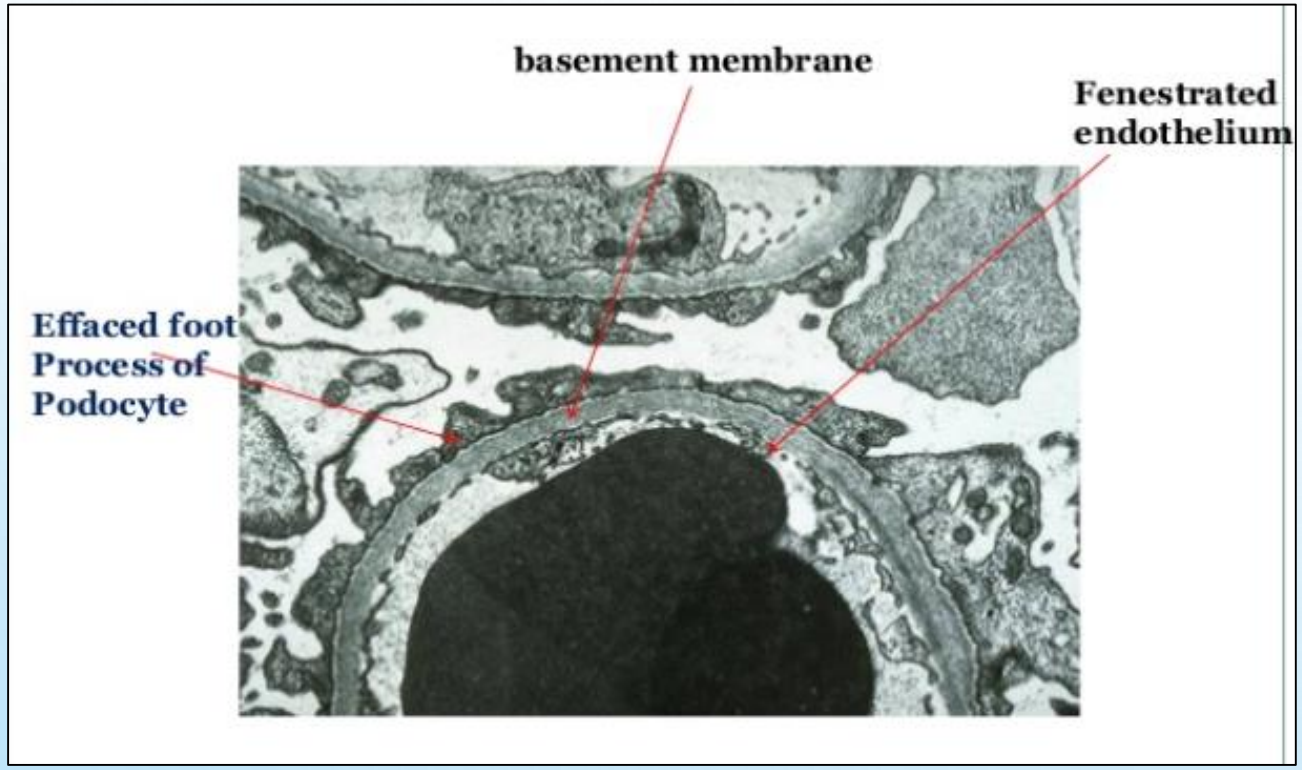


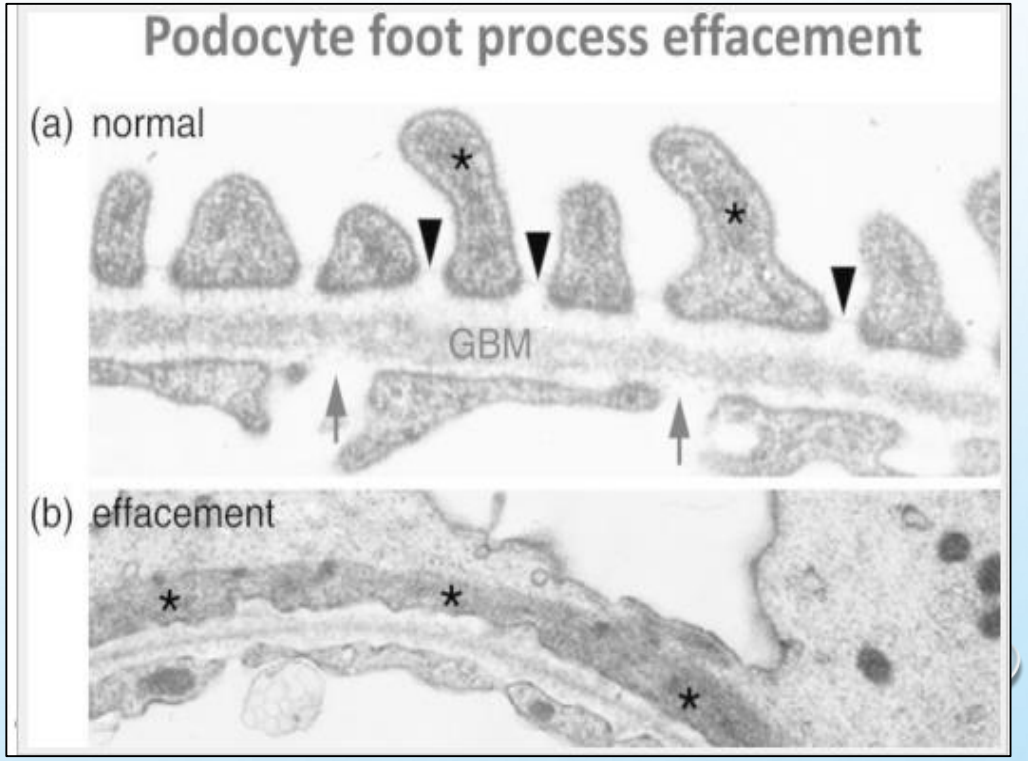
Integrin, podocin, nephrin roles - path complex

Glomerular endothelial cell: glycocalyx albumin barrier; also requires VEGF to fxn

Proteoglycans in GBM prevent (-) charged molecule passage

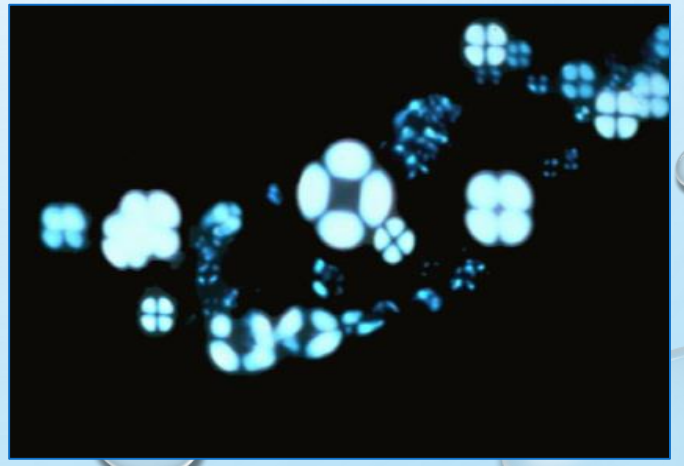
PODOCYTOPATHY





NEPHROTIC SYNDROME

- NEPHROTIC-RANGE PROTEINURIA
  - > 3.5 GM / 24 HR URINE
  - > 3 GM ON UPC
- LIPIDURIA – FATTY CASTS, OVAL FAT BODIES
- HYPOALBUMINEMIA
- EDEMA
- HYPERLIPIDEMIA
- HYPERCOAGUABLE STATE DUE TO ATIII LOSS IN URINE
- INCREASED RISK OF INFECTION (LOSS OF IG IN URINE)

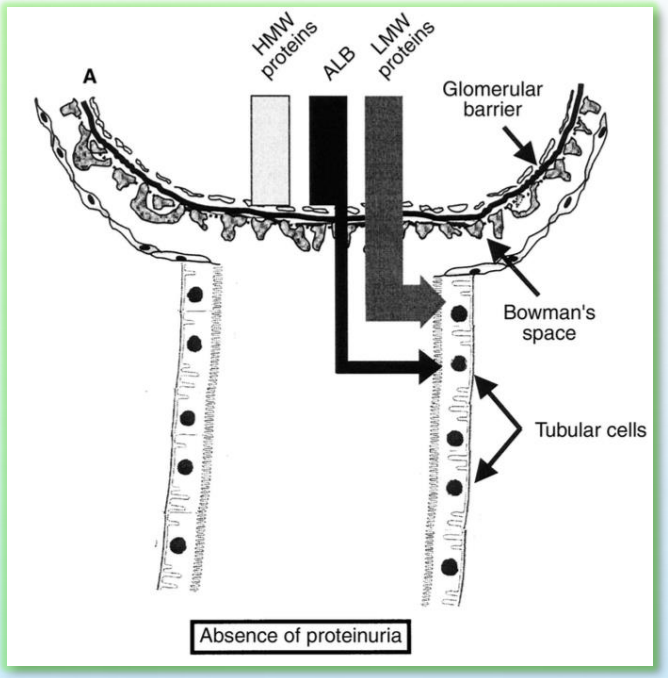


PATHOGENESIS OF LIPID ABNORMALITIES IN NEPHROTIC SYNDROME

- REDUCED PLASMA ONCOTIC PRESSURE
  - STIMULATES HEPATIC APOLIPOPROTEIN B GENE TRANSCRIPTION
  - ENHANCED HEPATIC SYNTHESIS OF LIPOPROTEINS CONTAINING APOLIPOPROTEIN B AND CHOLESTEROL
- DIMINISHED LIPID CATABOLISM
- INCREASED PCSK9

TUBULOINTERSTITIAL

- HYPERTENSIVE ARTERIONEPHROSCLEROSIS
- CHRONIC INTERSTITIAL NEPHRITIS
- FANCONI SYNDROME



- PATHOGENESIS:

  DECREASED PROXIMAL TUBULE REABSORPTION OF LOW-MOLECULAR-WEIGHT PROTEINS (PART OF NORMAL GLOMERULAR ULTRAFILTRATE)

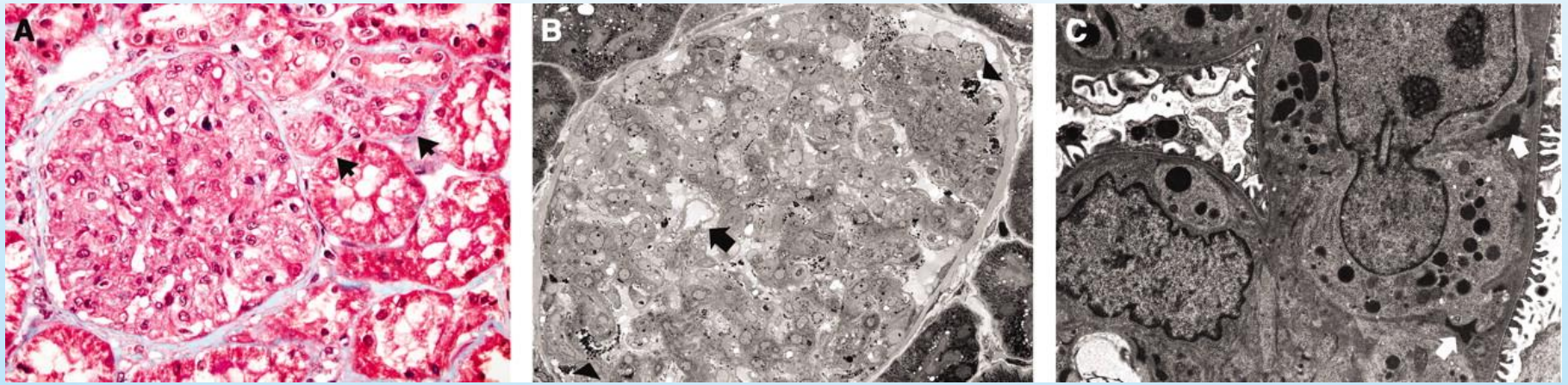
OVERFLOW

- LOW-MOLECULAR-WEIGHT PROTEINS OVERWHELM THE ABILITY OF THE PROXIMAL TUBULES TO REABSORB FILTERED PROTEINS

- HEMOGLOBINURIA
- MYOGLOBINURIA
- MYELOMA
- AMYLOID
- LYMPHOMA

PREECLAMPSIA

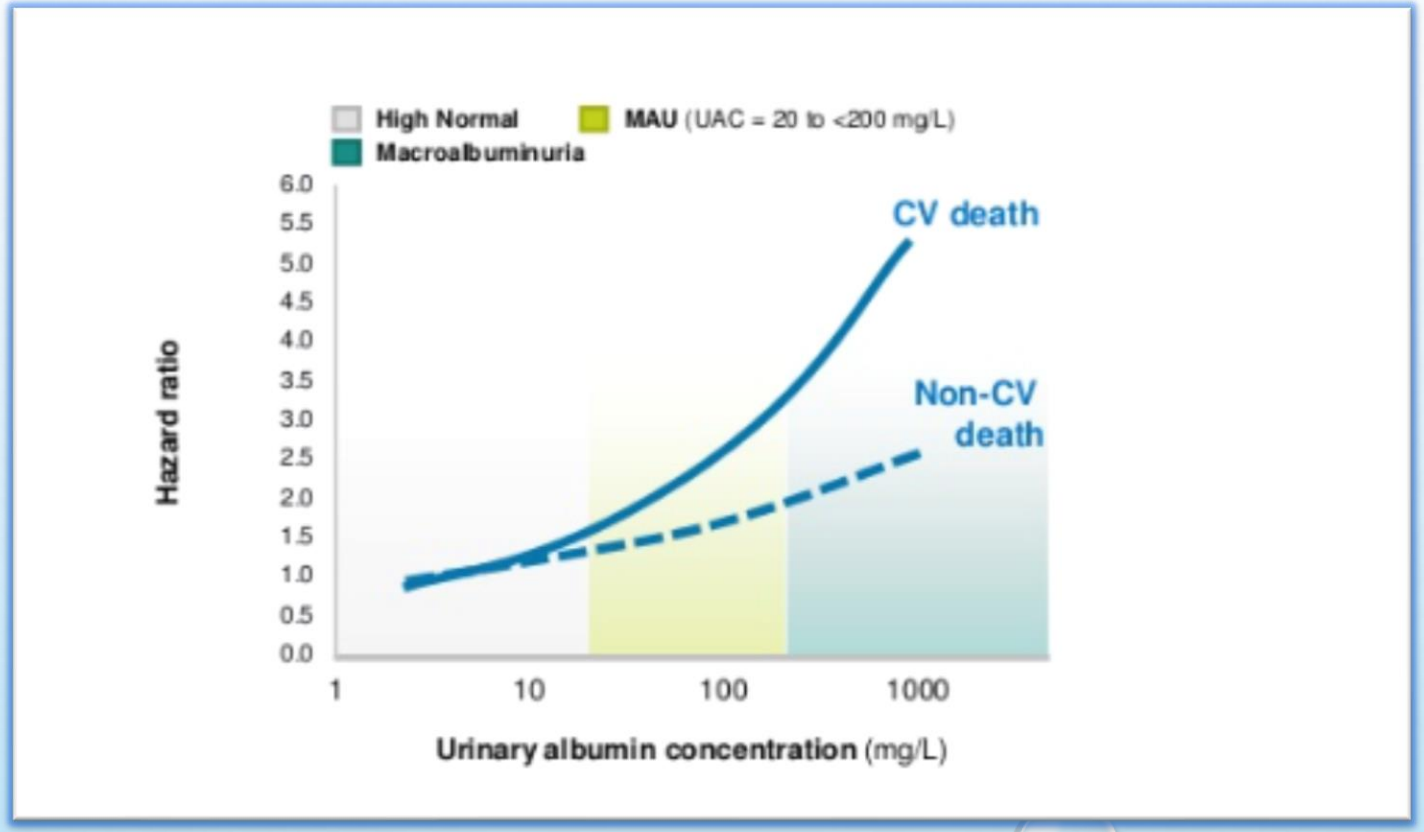
- NEW ONSET HYPERTENSION AND PROTEINURIA > 20 WEEKS GESTATION
- RENAL PATH: GLOMERULAR ENDOTHELIOSIS (SWELLING OF ENDOCAPILLARY CELLS & CAPILLARY OCCLUSION) AND THROMBOTIC MICROANGIOPATHY (TMA)



ALBUMINURIA: CLINICAL SIGNIFICANCE

- INDEPENDENT PREDICTOR OF PROGRESSIVE LOSS OF RENAL FUNCTION
- INDEPENDENT CV RISK FACTOR
    - INCREASED MORBIDITY AND MORTALITY

URINE ALBUMIN IS A PREDICTOR OF ALL-CAUSE MORTALITY IN GENERAL POPULATION: PREVEND STUDY

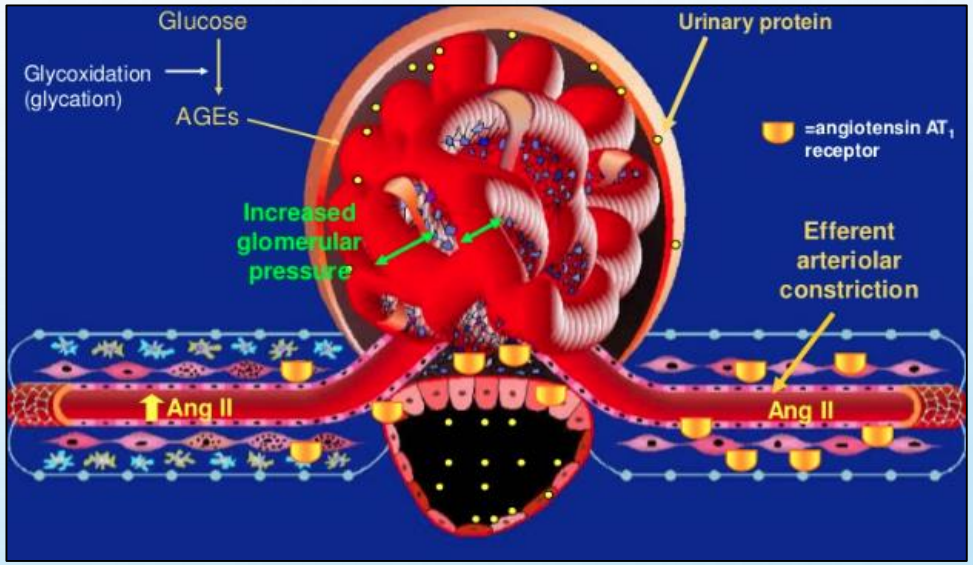


PROTEINURIA SCREENING

- NOT COST-EFFECTIVE OR RECOMMENDED IN GENERAL POPULATION
- SHOULD BE DONE ANNUALLY IN ALL DIABETICS AND CONSIDER IN HIGH-RISK PATIENTS (HTN, SMOKING, OBESITY, OLDER AGE)
- URINE ALBUMIN/CREATININE IS THE SCREENING TEST OF CHOICE

PROTEINURIA TREATMENT

- TREAT THE UNDERLYING PATHOLOGY
- SALT RESTRICTION
- DIURETICS (ESP ALDACTONE R ANTAGONIST)
- RAAS INHIBITORS
- STATINS



IM BOARD QUESTION

A 28 YEAR-OLD WOMAN IS EVALUATED DURING A FOLLOW-UP VISIT. A RECENT LIFE INSURANCE EXAMINATION REVEALED PROTEINURIA ON DIPSTICK URINALYSIS. SHE IS OTHERWISE HEALTHY AND HAS NO PERTINENT PERSONAL OR FAMILY MEDICAL HISTORY.

ON PHYSICAL EXAMINATION, TEMPERATURE IS 36.1C, BLOOD PRESSURE IS 110/64, PULSE IS 72 AND RESPIRATION RATE IS 12. BMI IS 23. THE REMAINDER OF THE EXAM IS NORMAL.

LABORATORY STUDIES:

SERUM CREATININE:	0.8 MG/DL
ESTIMATED GFR:	> 60 ML/MIN/1.73M^2
URINALYSIS:	1+ PROTEIN, 0-2 ERYTHROCYTES/HPF, 0 LEUKOCYTES/HPF
24 HR URINE COLLECTION:	200 MG PROTEIN / 24 HOURS

BOARD QUESTION CONTINUED

WHICH OF THE FOLLOWING IS THE MOST APPROPRIATE NEXT STEP IN MANAGEMENT?

A. KIDNEY BIOPSY
B. REPEAT 24 HOUR URINE COLLECTION FOR PROTEIN
C. SPLIT URINE COLLECTION
D. SPOT URINE PROTEIN / CREATININE RATIO
E. REASSURANCE

QUESTIONS?

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