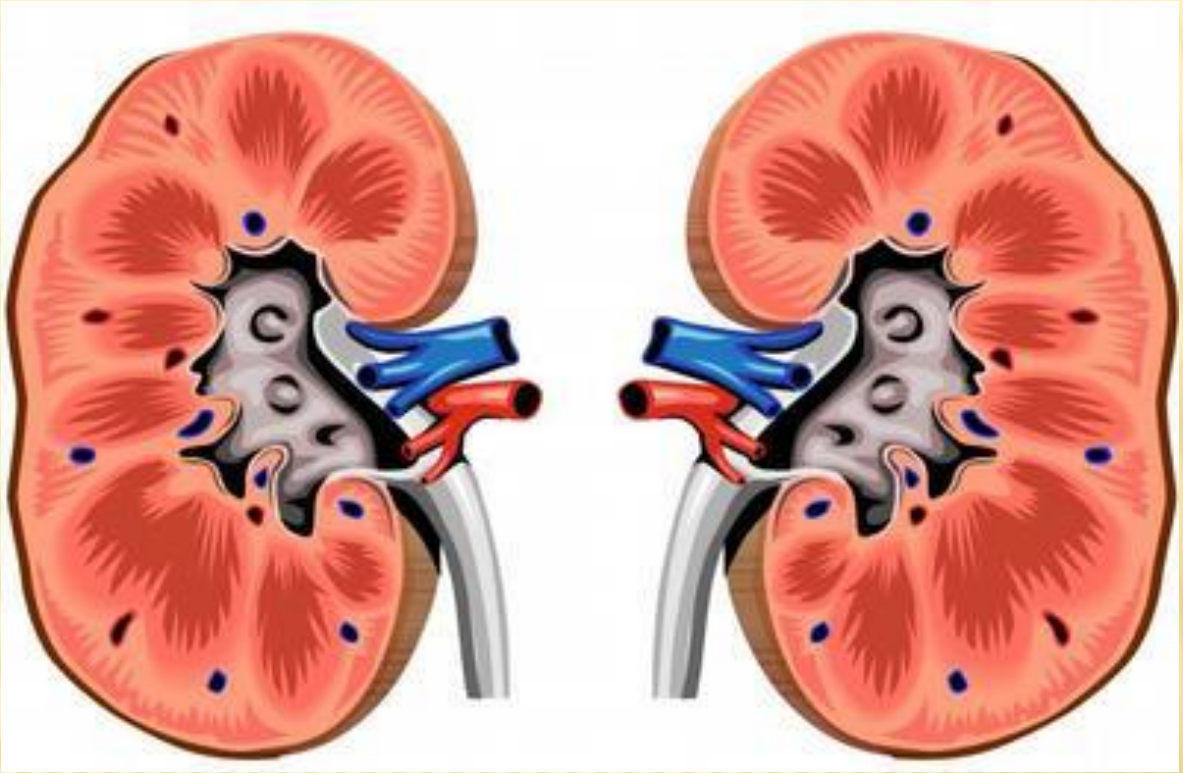


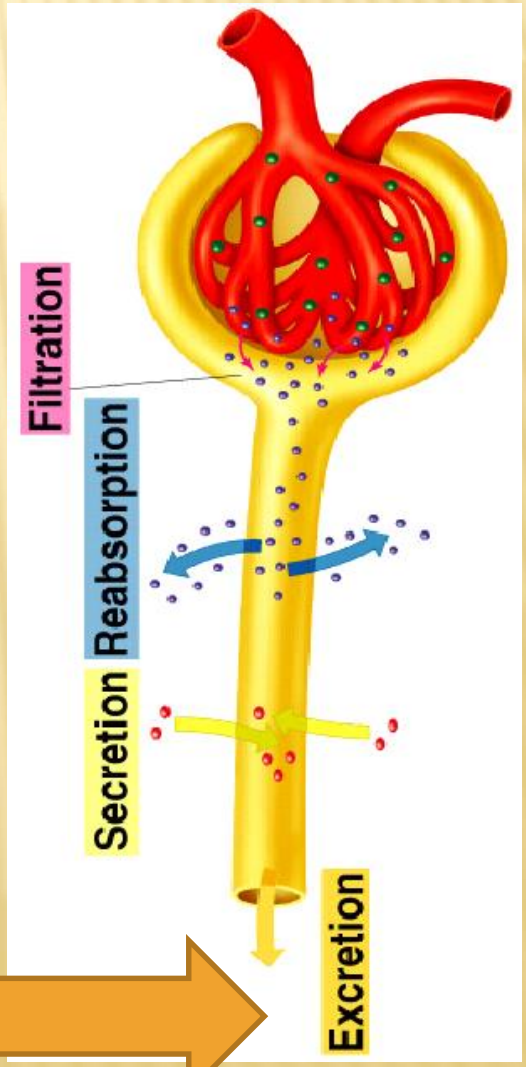
VLA, November 20, 2018

PATHOPHYSIOLOGICAL ASPECTS OF RENAL FUNCTIONS. KIDNEY DISEASES

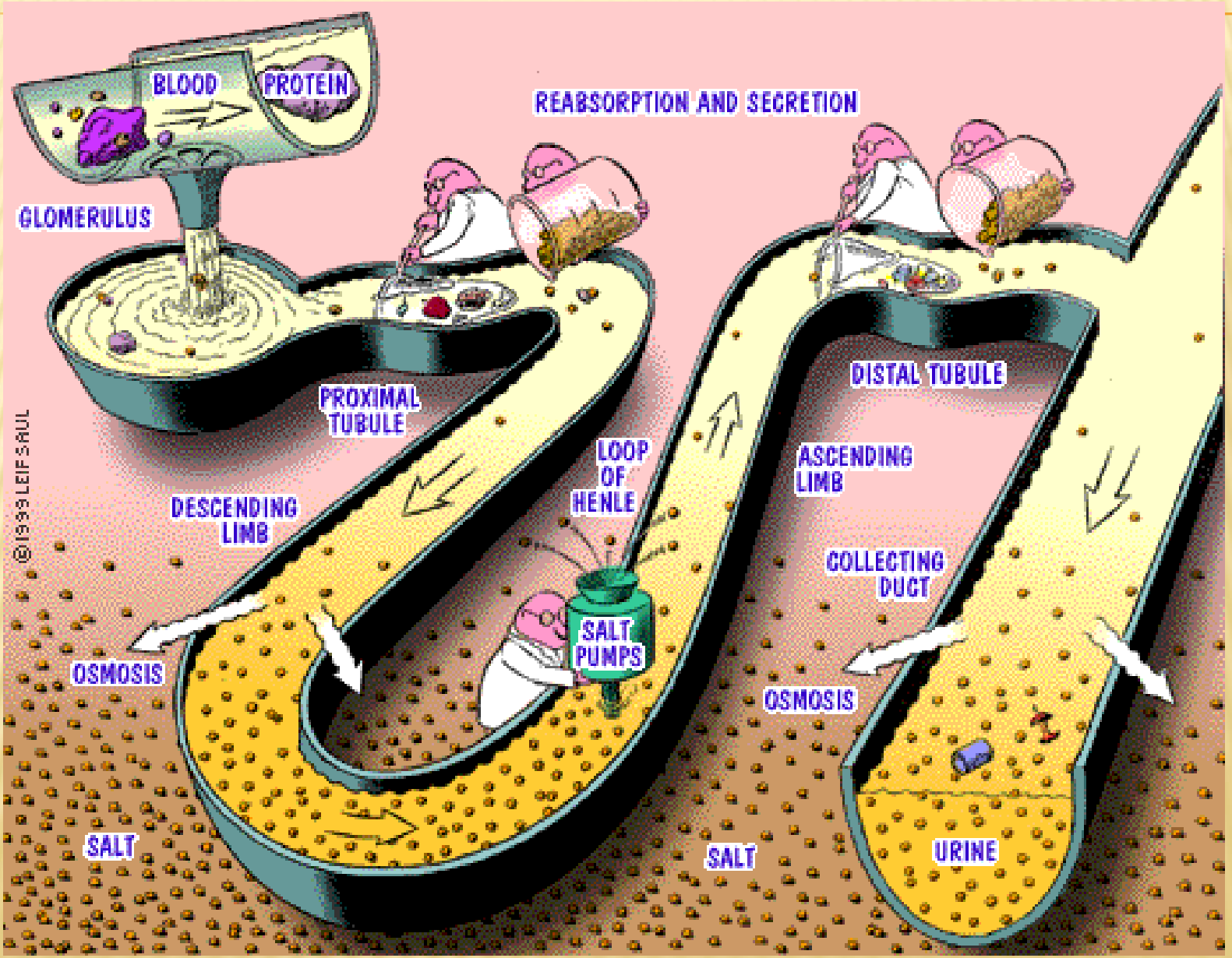
Filtration

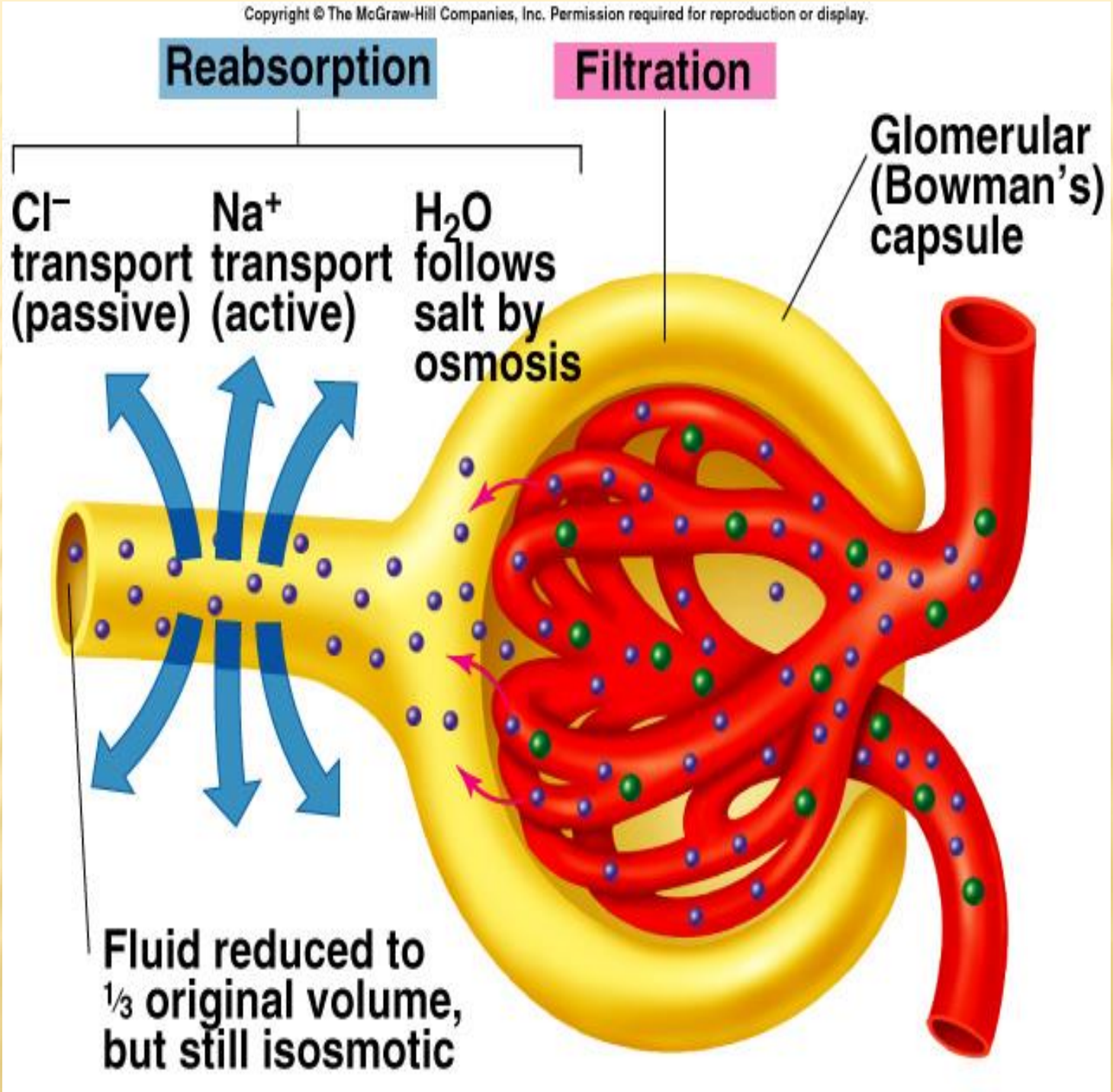
Reabsorbtion

Secretion

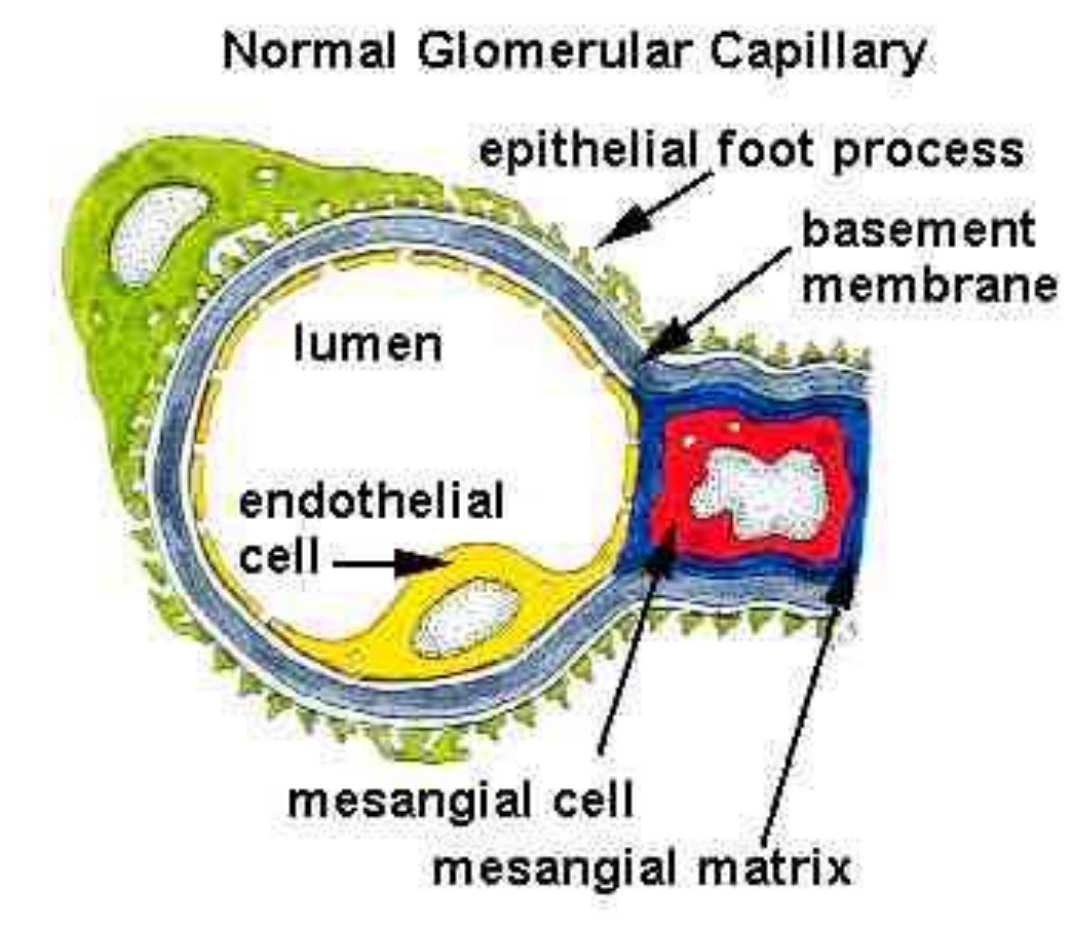


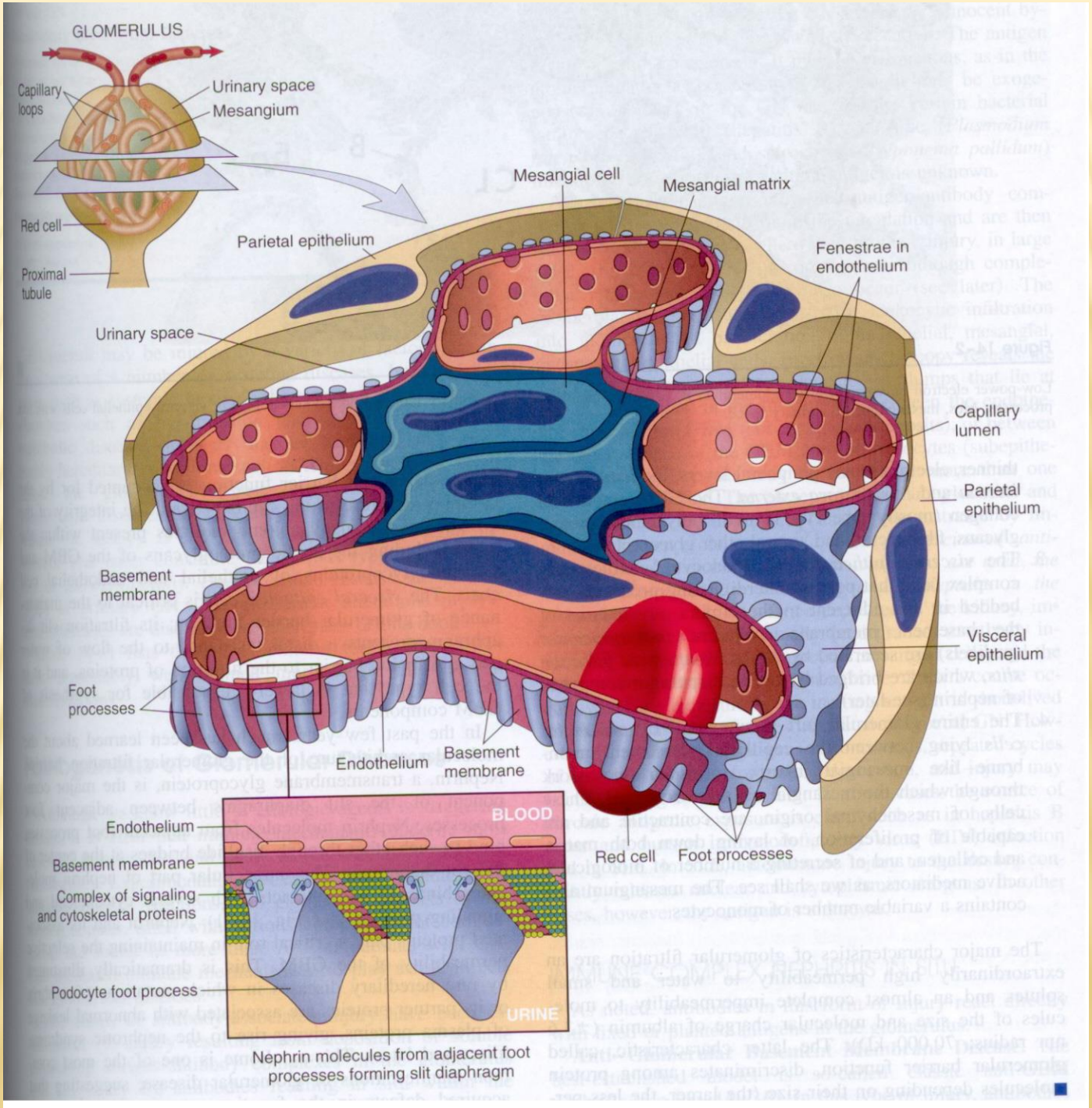
KIDNEY - FUNCTION

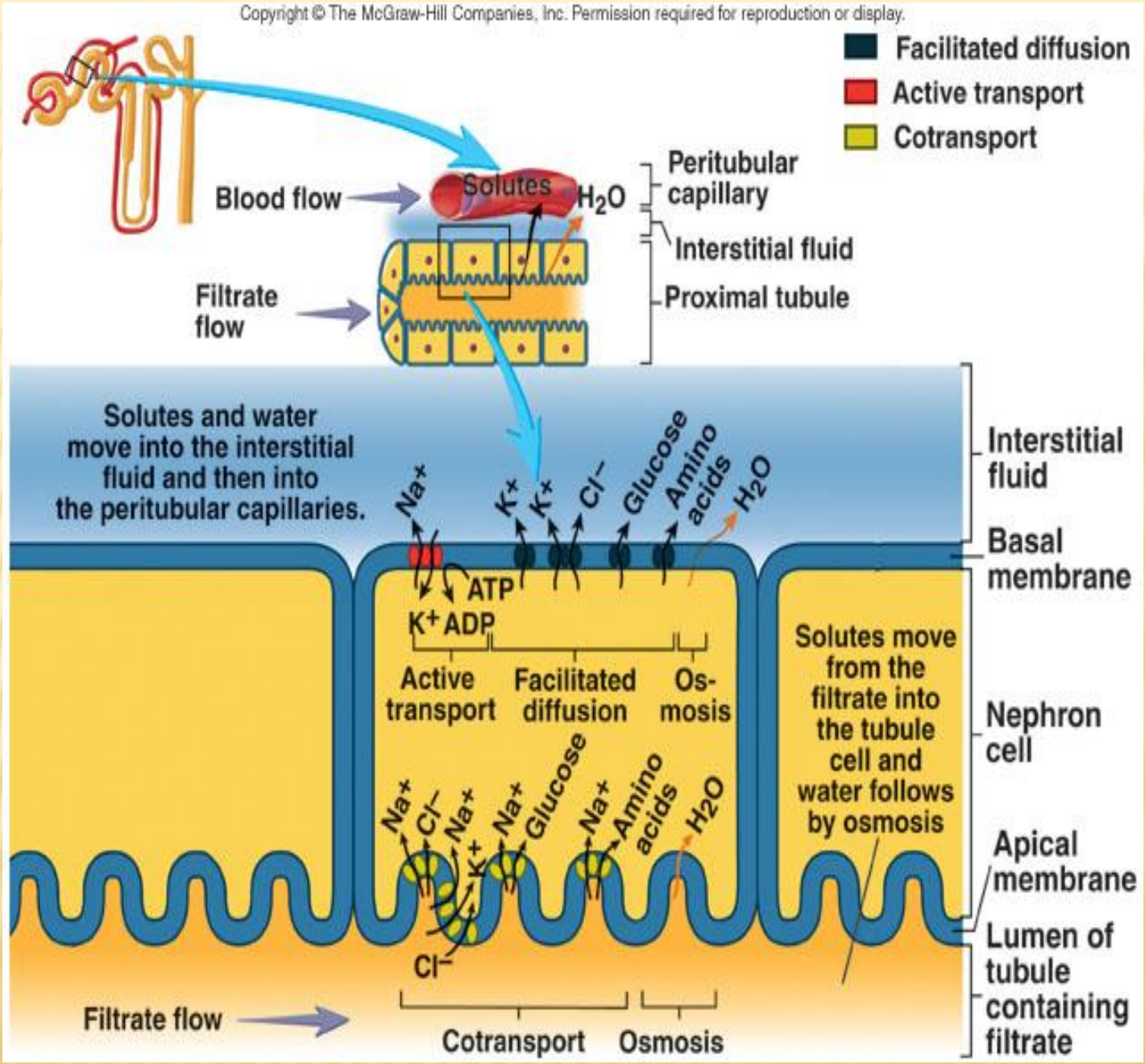




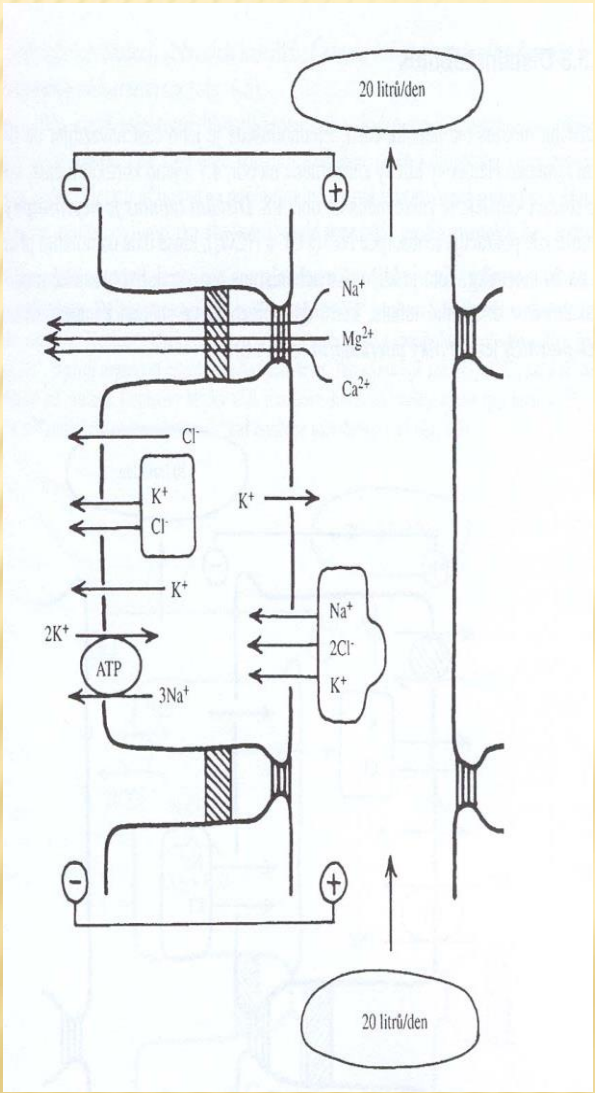
NEPHRON: THE GLOMERULUS

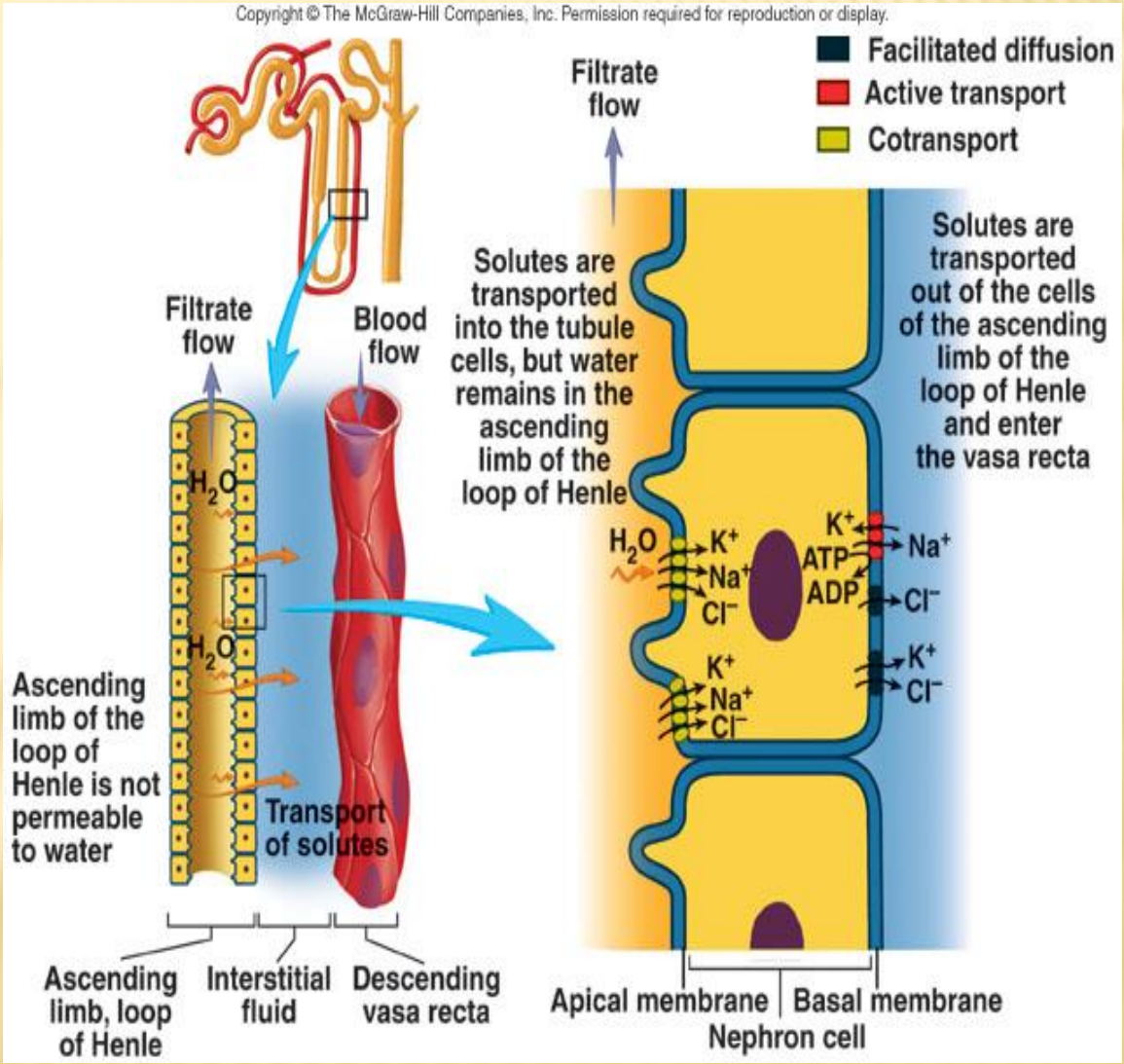


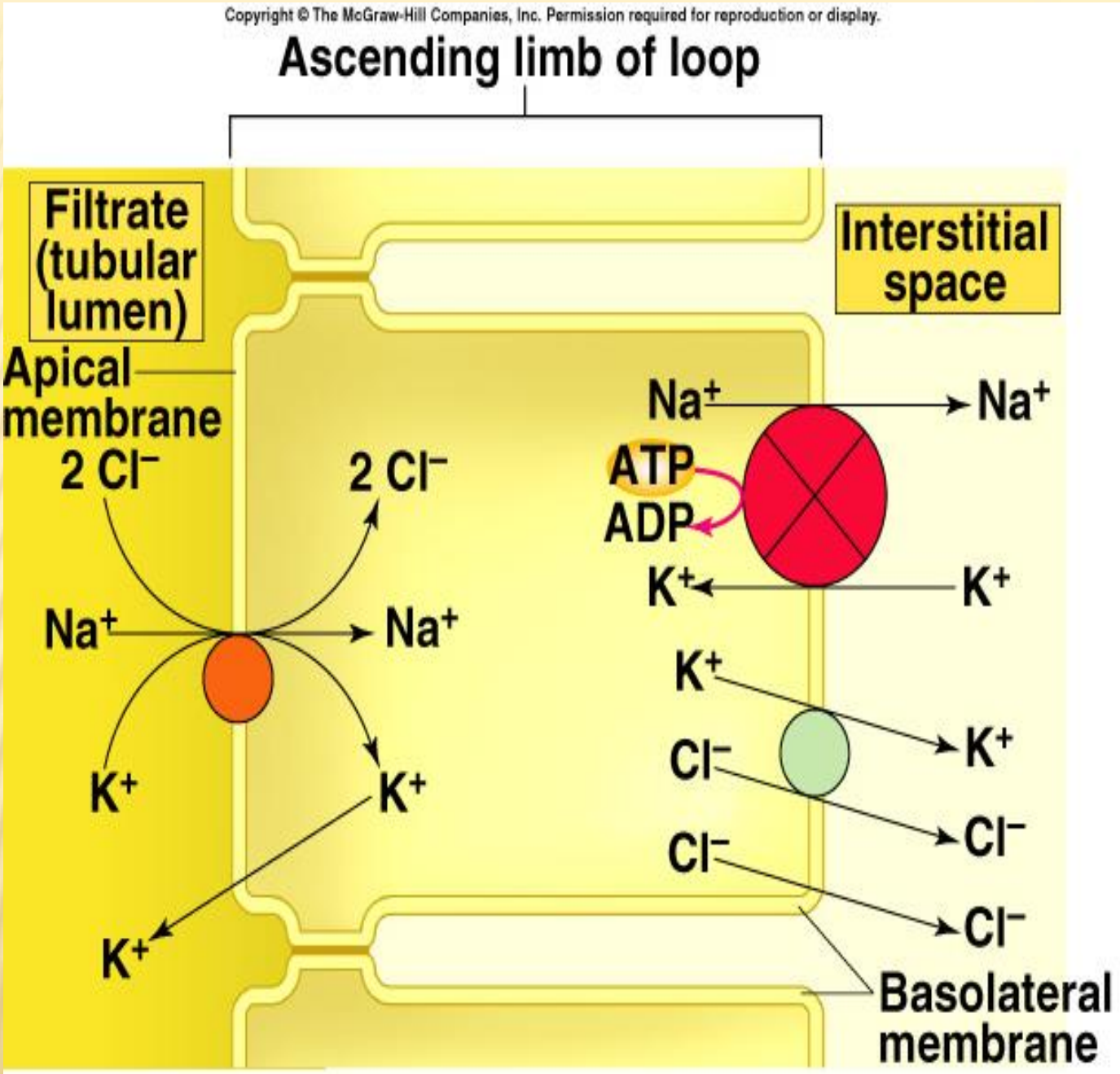

GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Mesangial cell
Mesangial matrix
Parietal epithelium
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium
Foot processes
Endothelium
Basement membrane
Red cell
Foot processes
BLOOD
Endothelium
Basement membrane
Complex of signaling and cytoskeletal proteins
Podocyte foot process
URINE
Nephrin molecules from adjacent foot processes forming slit diaphragm

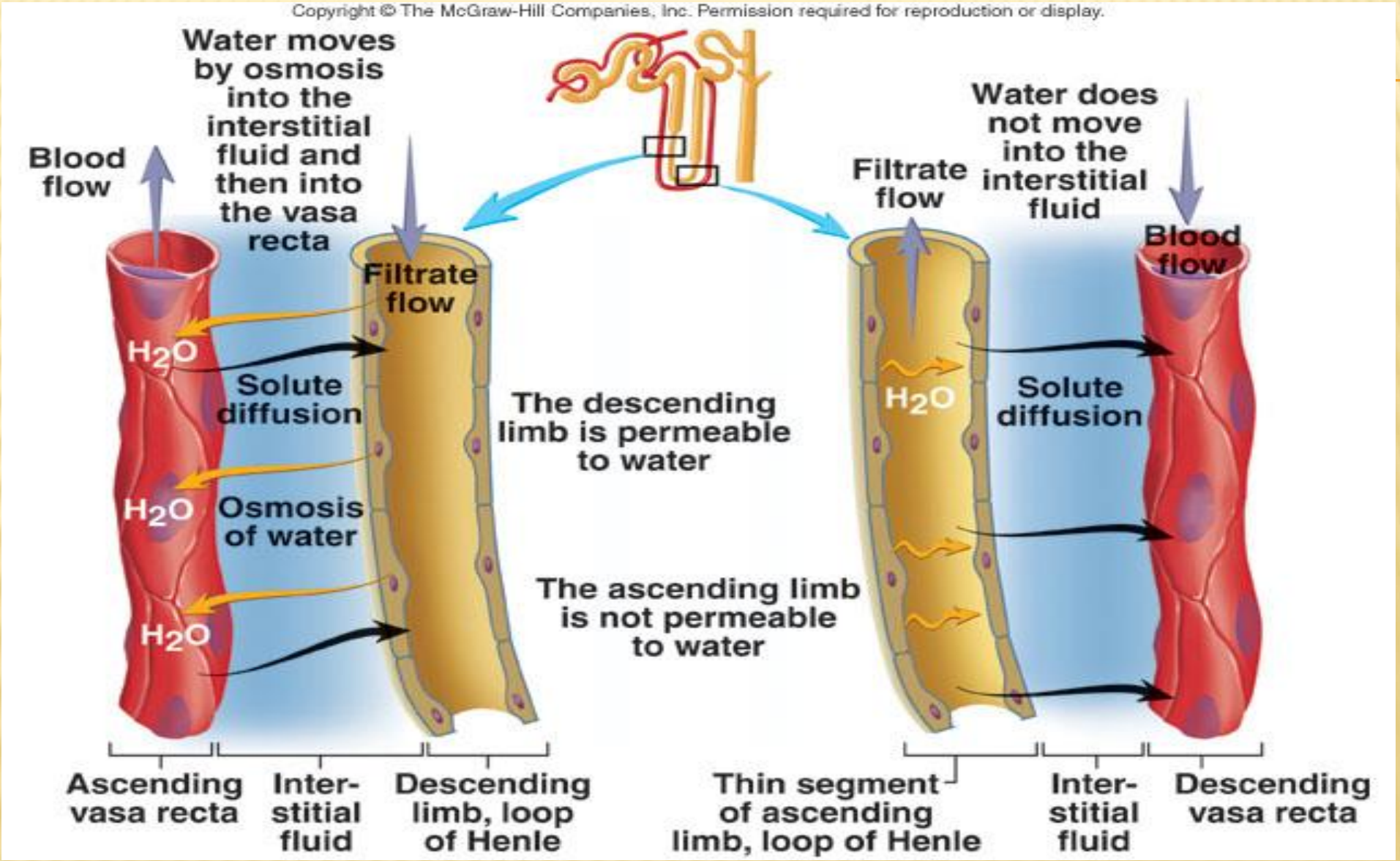


Reabsorbtion in Henle´s loop

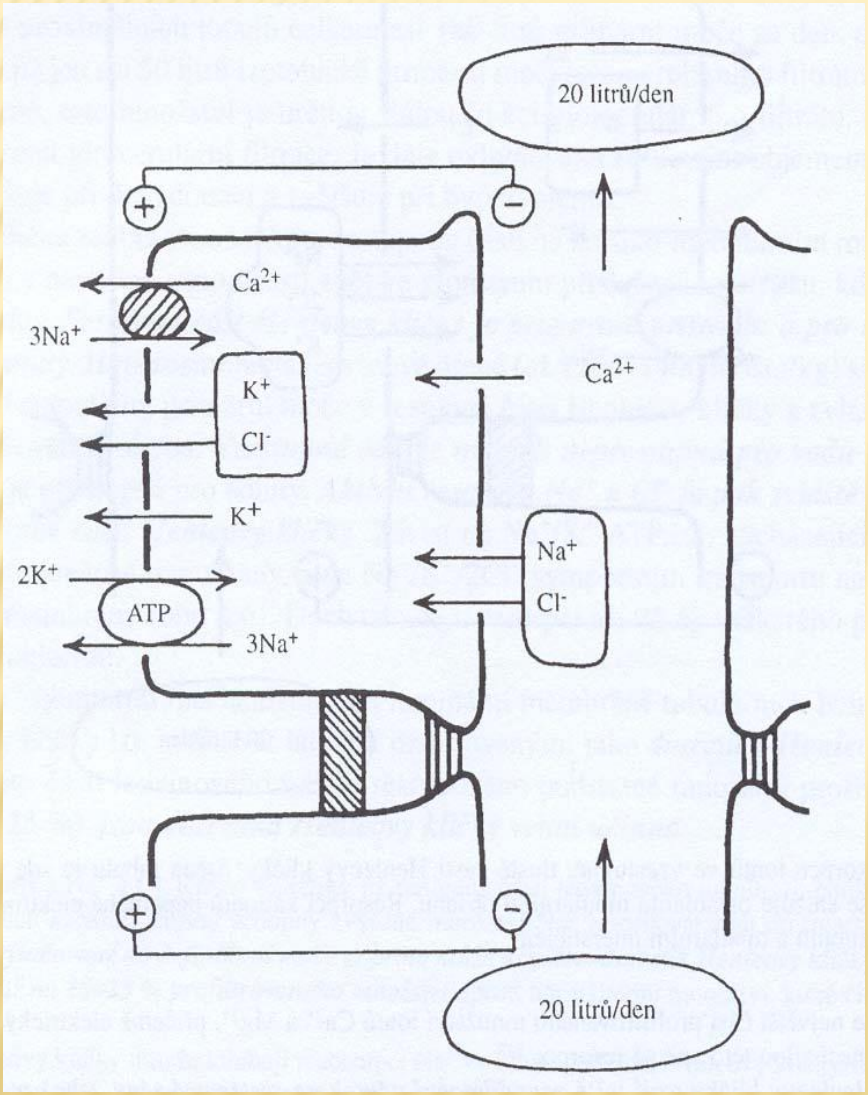


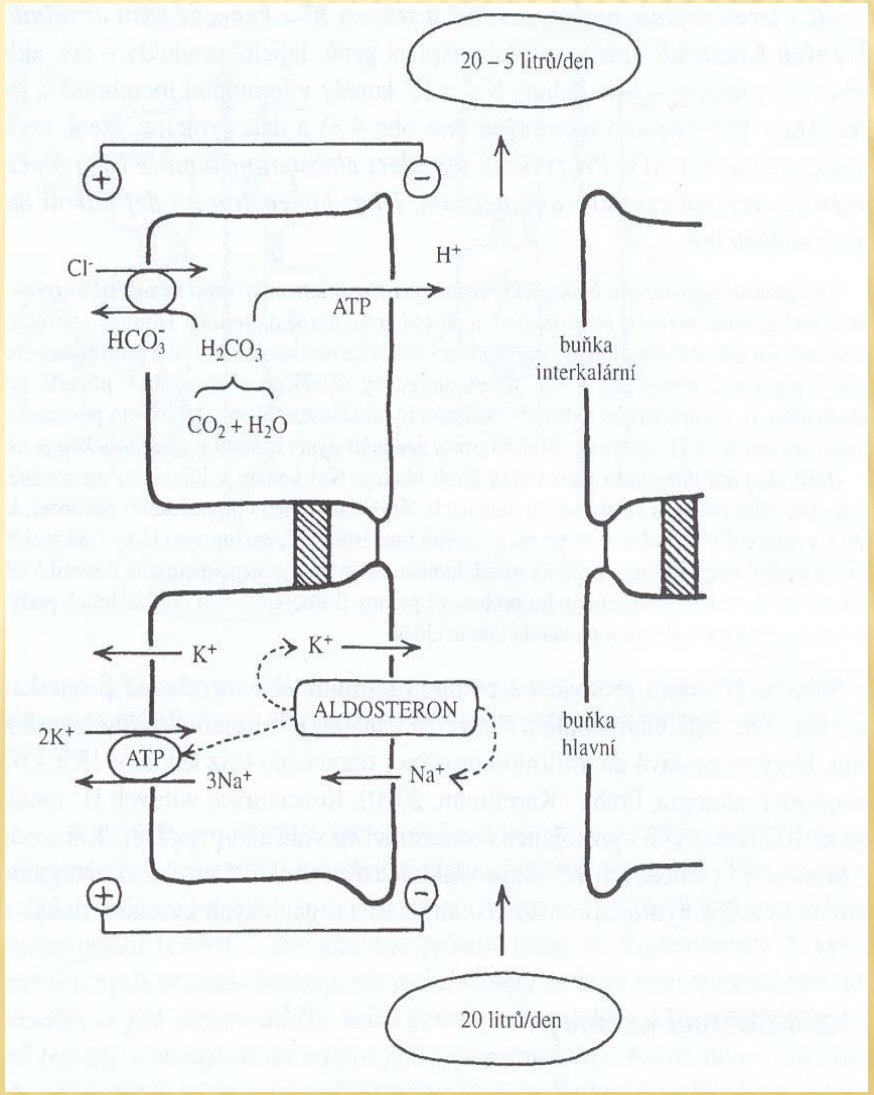






DISTAL TUBULE

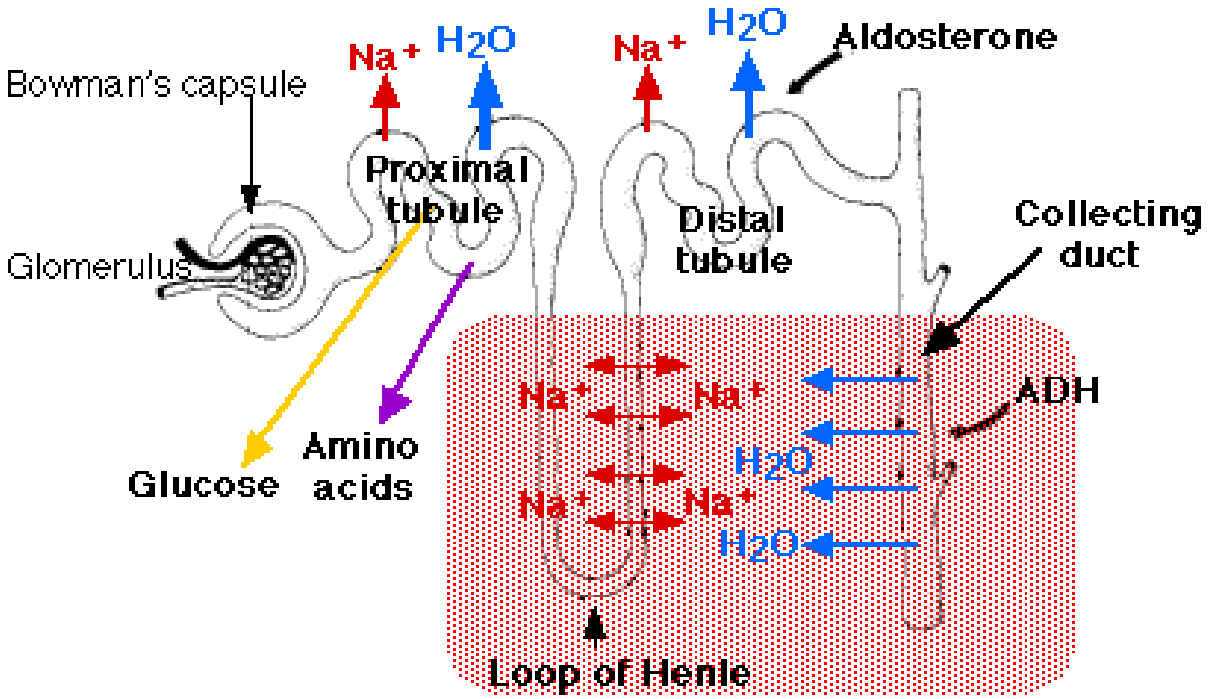




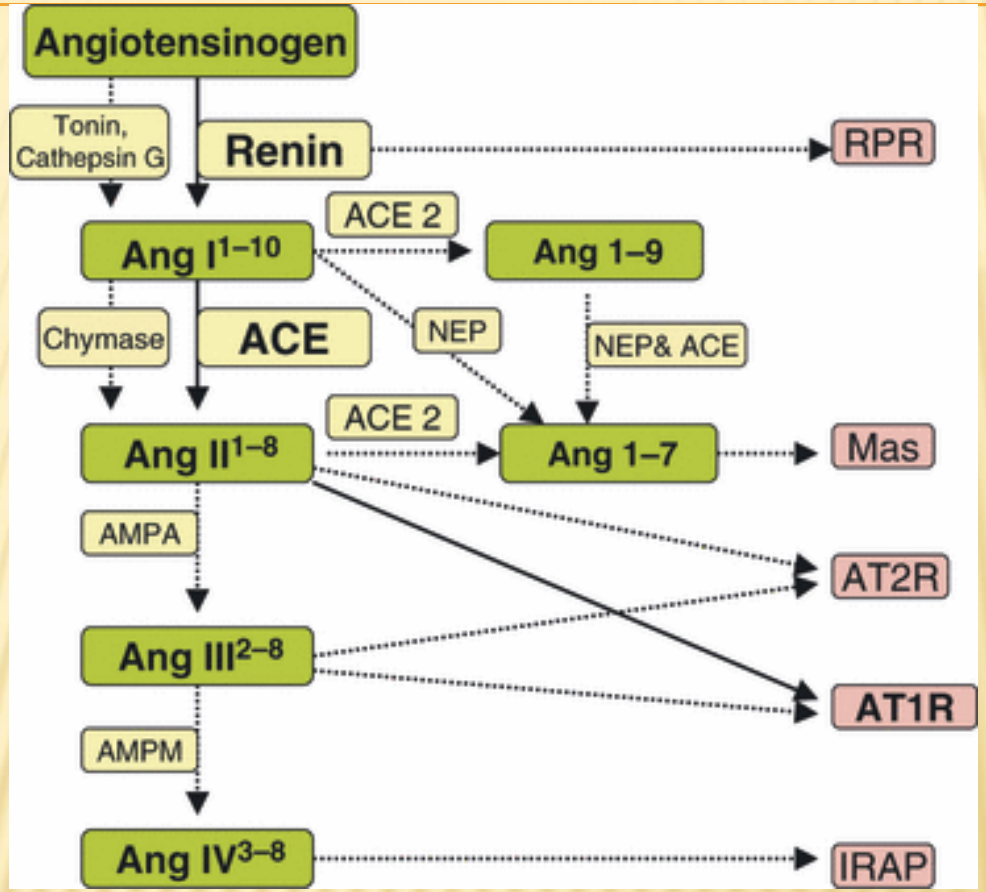
TUBULAR RESORPTION

- Proximal Tubules: GF: 120-125 mL/min
  - Reabsorption of Na (55%), Cl, phosphate, amino acids, glucose and bicarbonate (85%). Secretion of proton (CA)
- Loop of Henle: (30 mL/min)
  - Na/K/2Cl Cotransporter (25% Na reabsorbed)
  - Water impermeable: Hypertonic medullary inst
  - Ca & Mg paracellular diffusion
- Distal Tubules:
  - Na/Cl cotransporter; Ca/Na counter transport
  - Na Channels, K channels, H pump: Aldosterone reg.
- Collecting Tubules: 5-10 mL/min
  - Water channels: Vasopressin regulated
- Ureters: 1-2 mL/min (stored in bladder until voiding)

SUMMARY OF TUBULAR RESORPTIVE PROCESSES

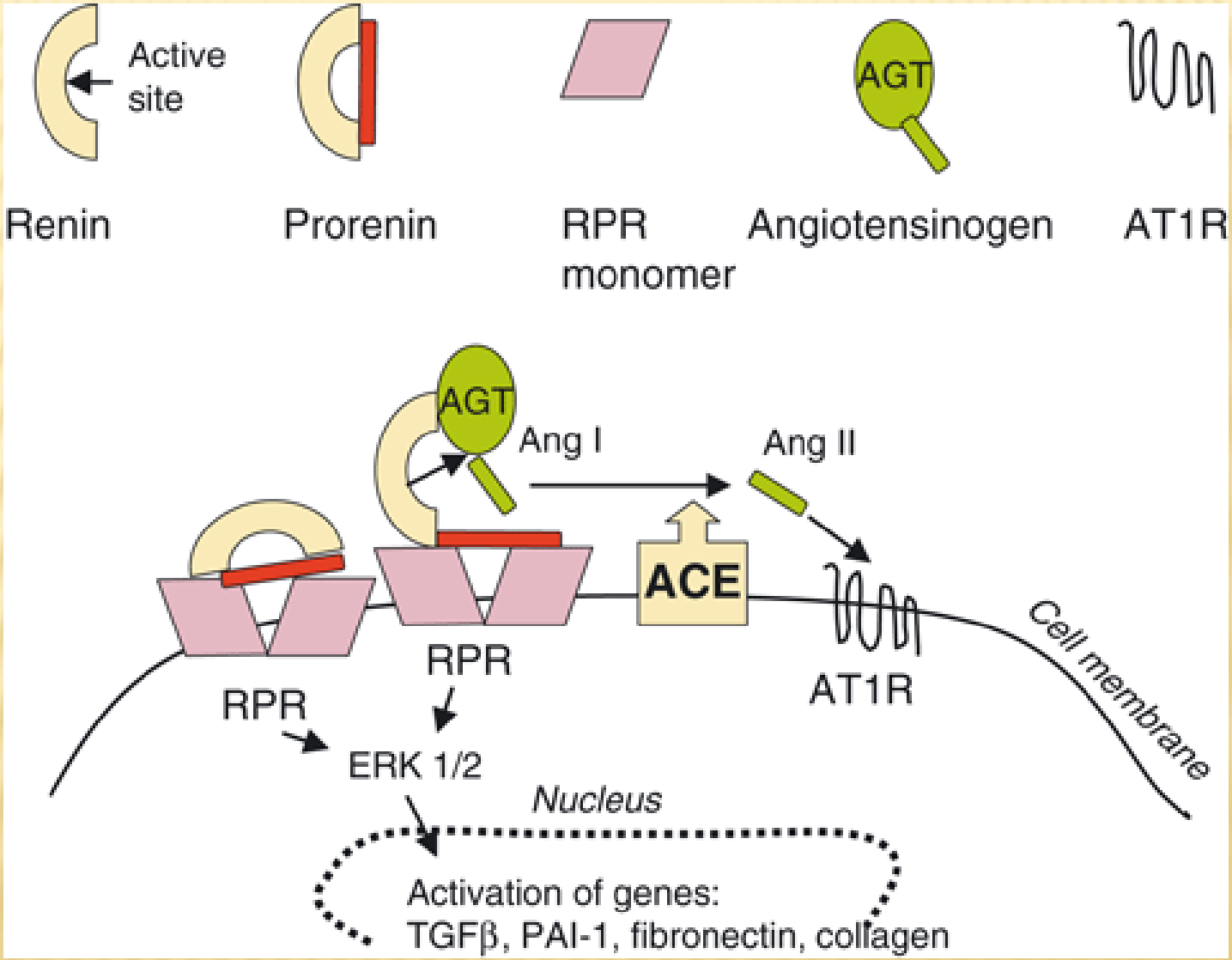


SYSTEM RENIN-ANGIOTENSIN -ALDOSTERON

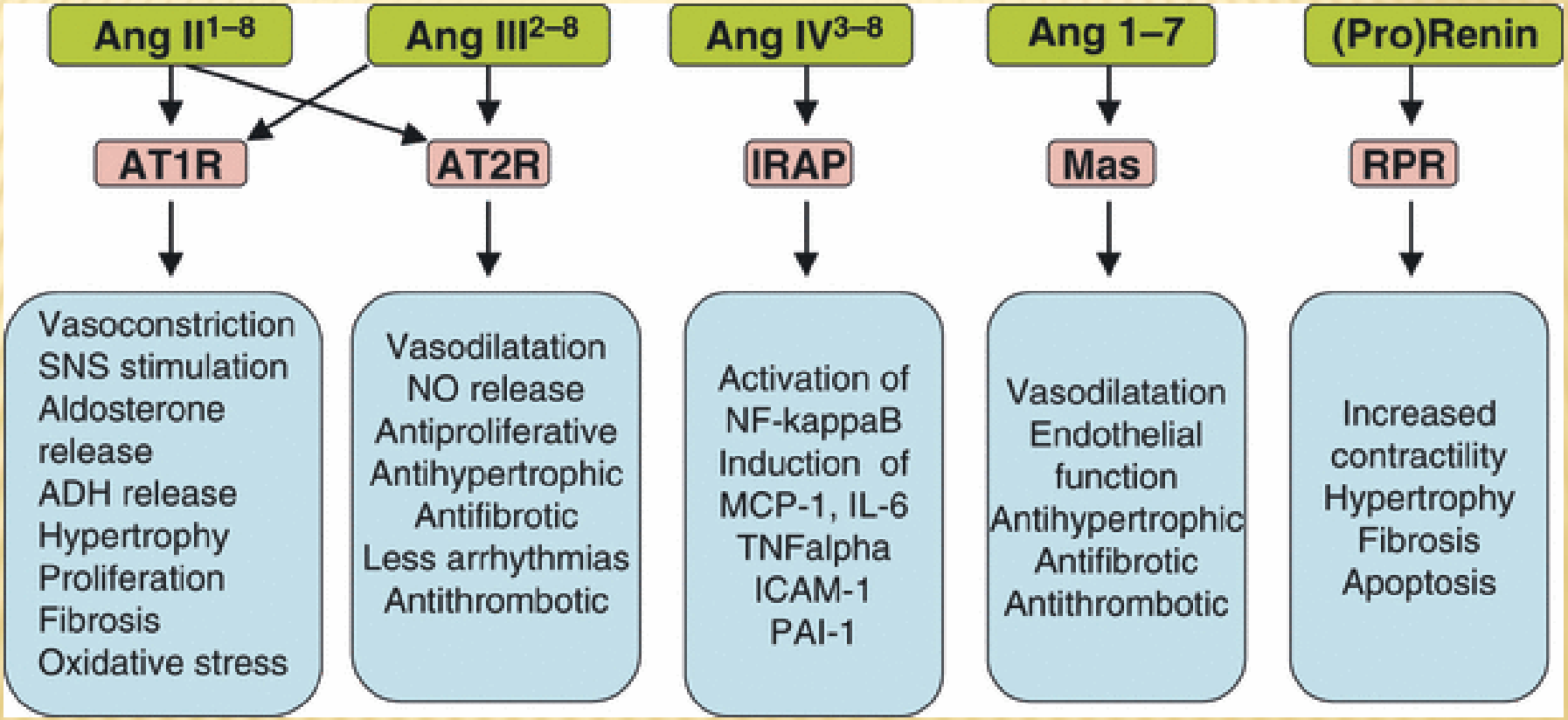


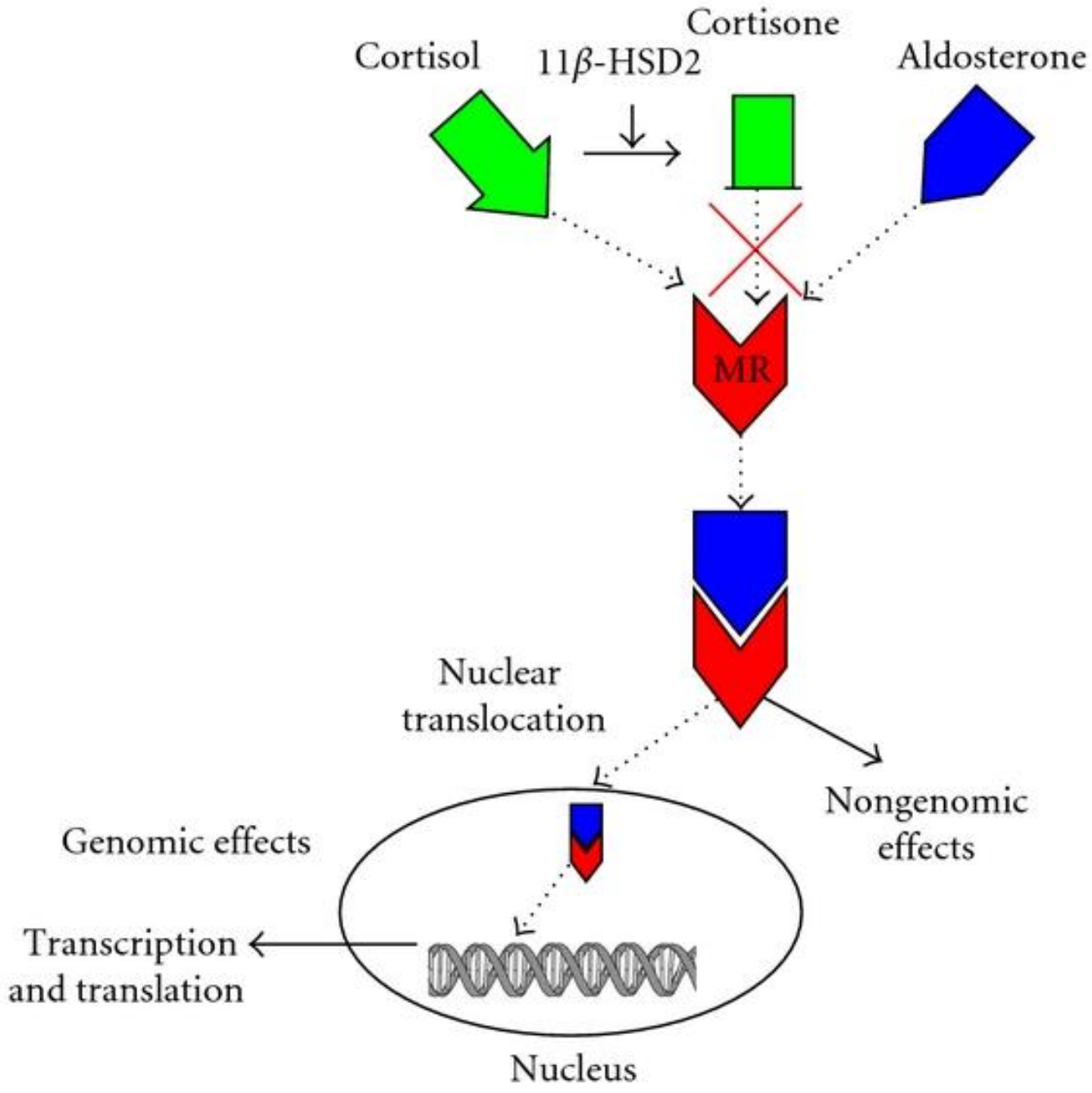
RPR, renin/prorenin receptor; Mas, mas oncogene, receptor for Ang 1–7; AT2R, angiotensin type 2 receptor AT1R, angiotensin type 1 receptor, IRAP, insulin-regulated aminopeptidase; Ang IV receptor AMPA, aminopeptidase A; AMPM, aminopeptidase M; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; NEP, neutral endopeptidase.

PRORENIN INTERACTION WITH RENIN/PRORENIN RECEPTOR (RPR, NGUYEN 2007)



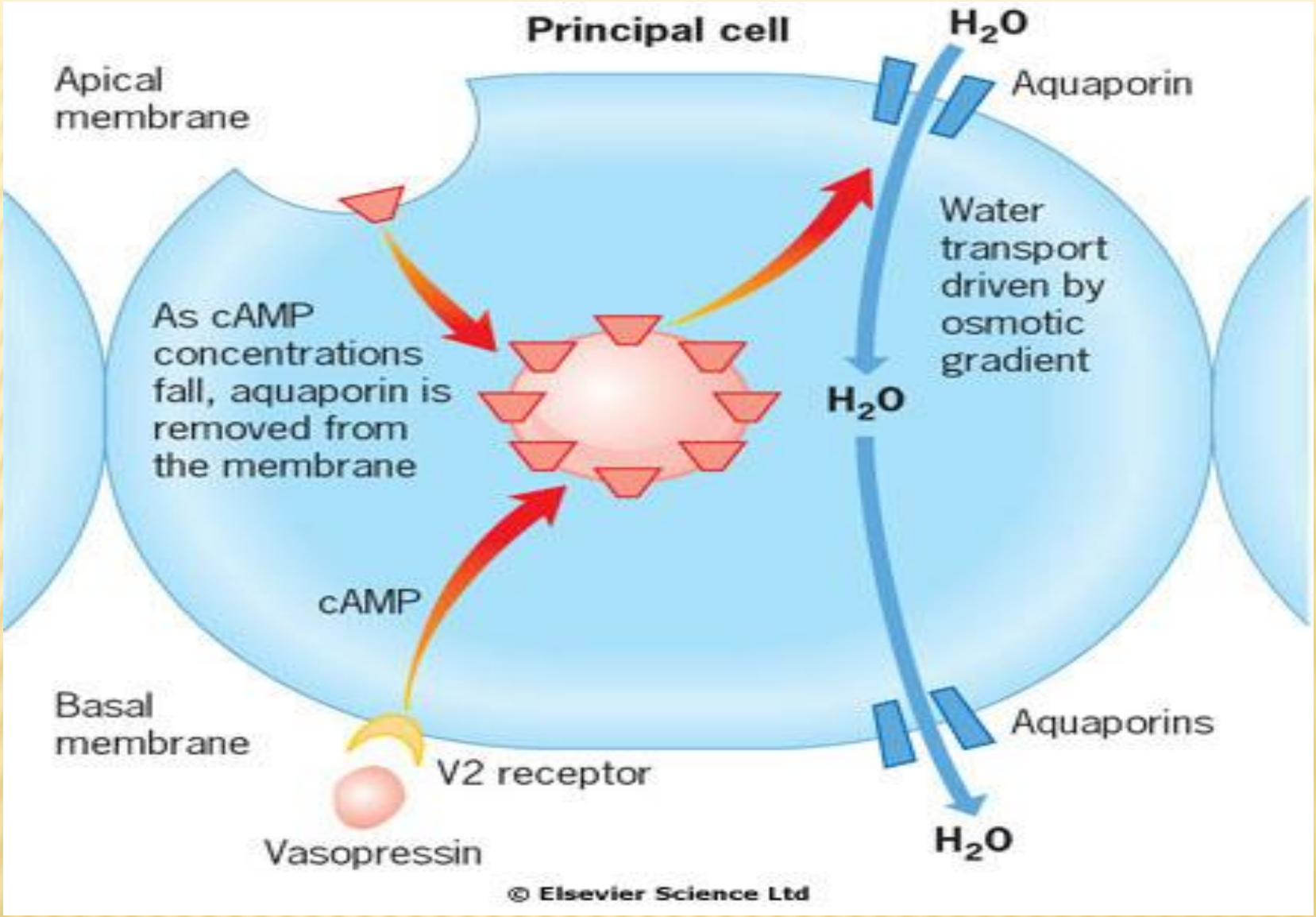
SYSTEM RENIN-ANGIOTENSIN



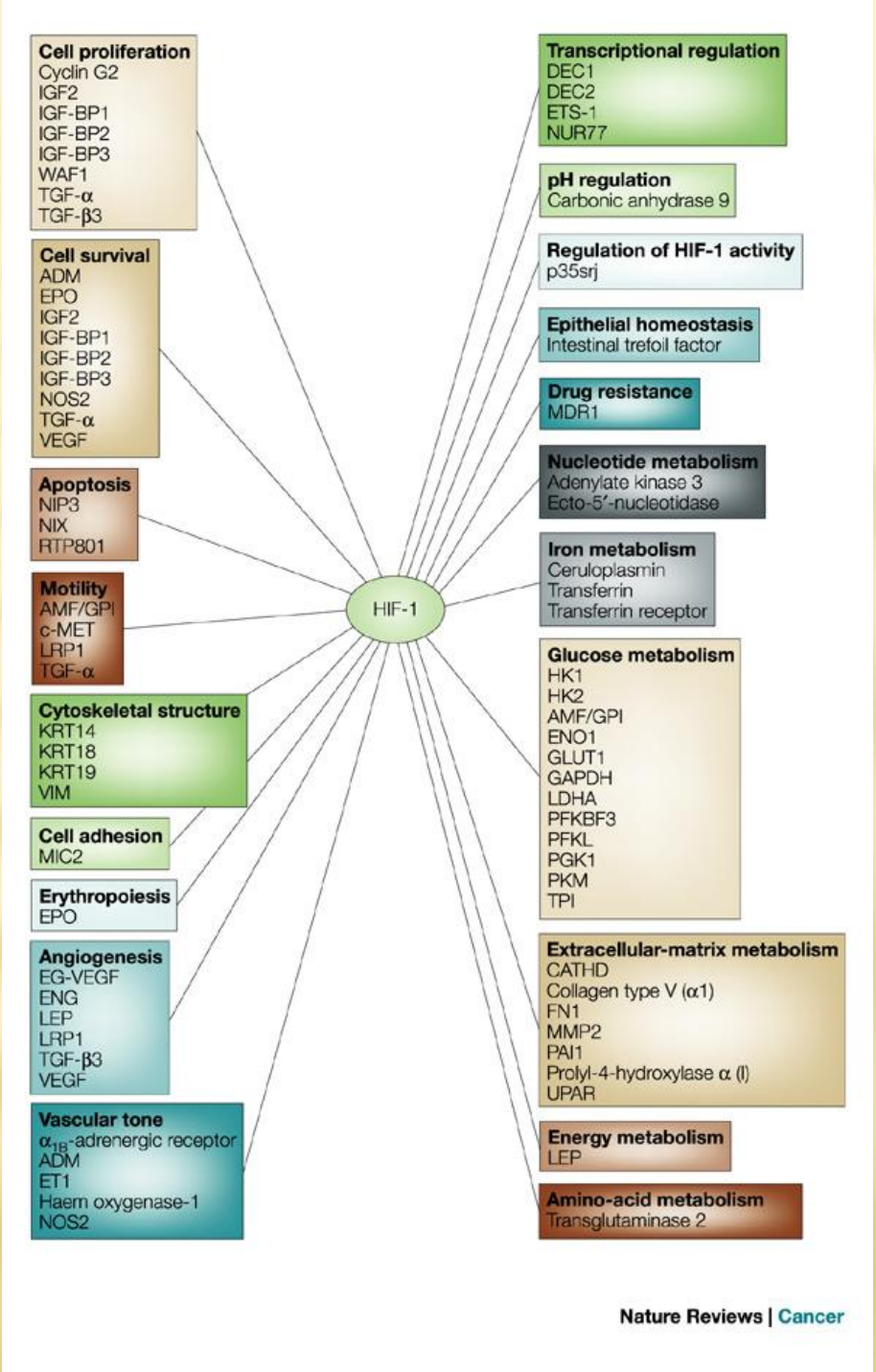


11β-HSD2 =

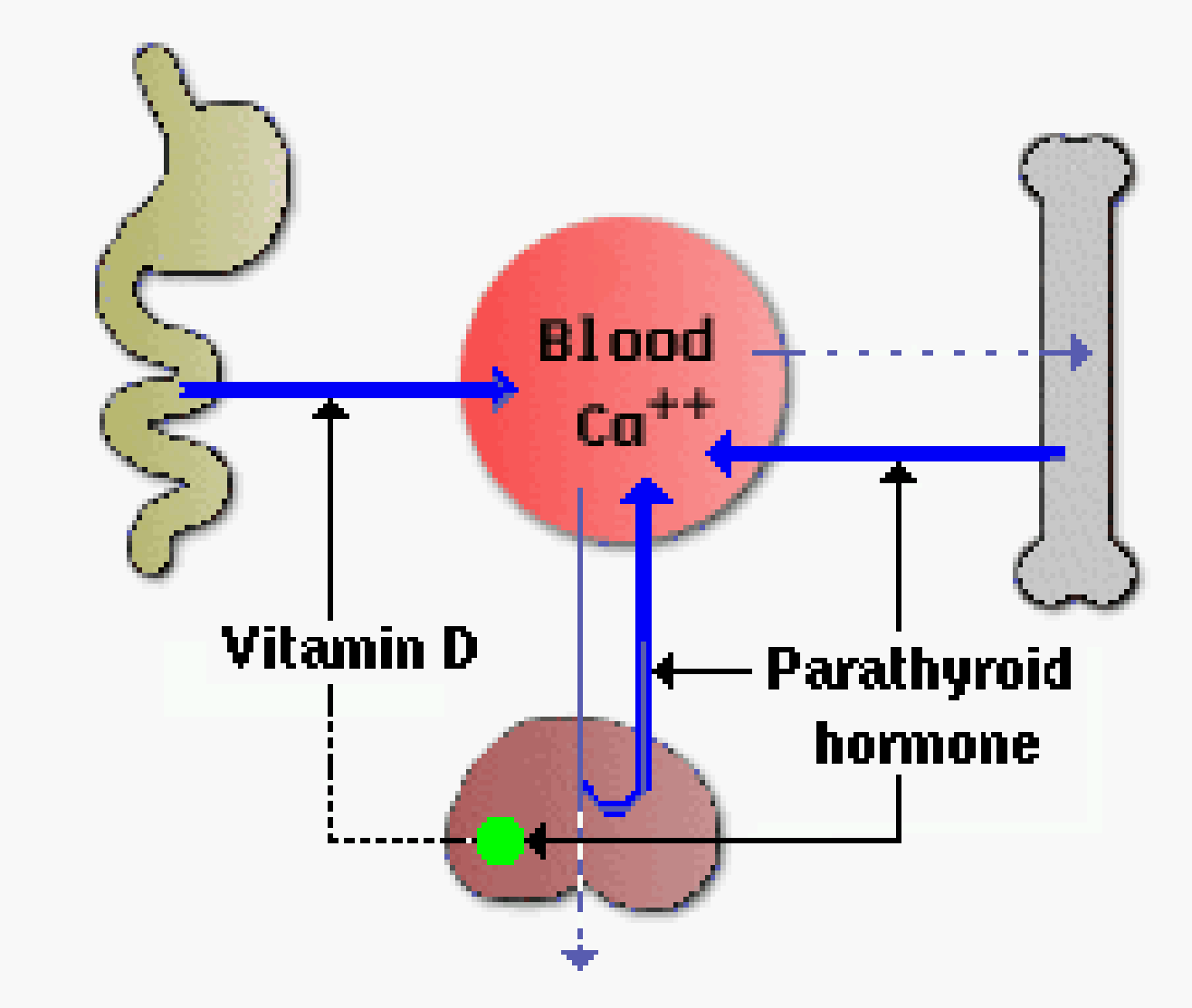
11β-hydroxy steroid dehydrogenase, type 2



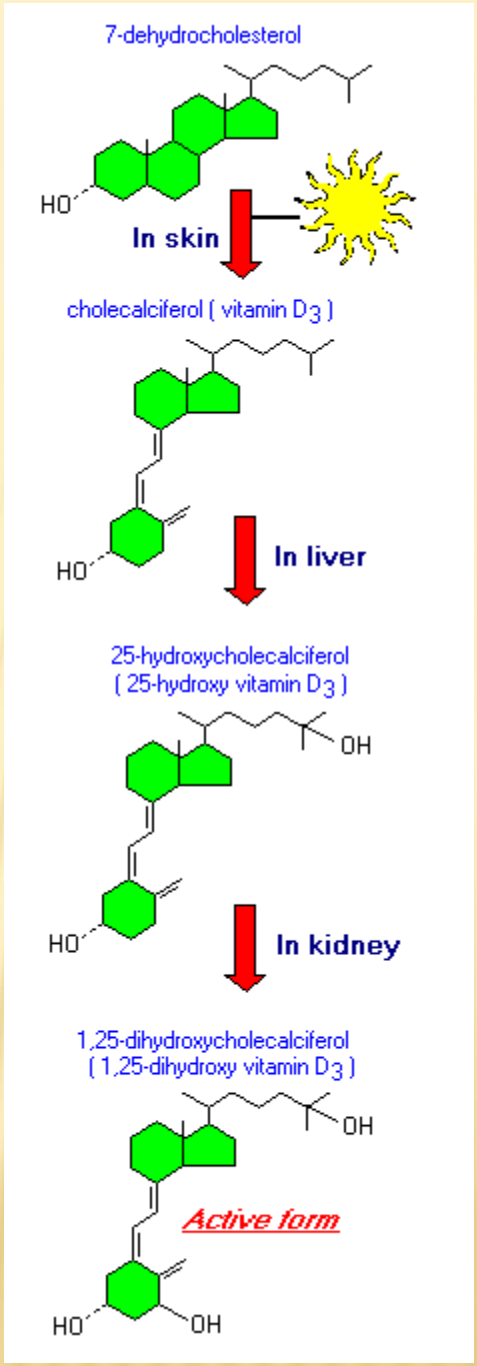
Vasopressin function . Stimulation of V2 receptor for ADH causes aquaporin2 insertion (using cAMP second messenger) to apical membrane which enables water transport along the osmotic gradient.


Cell proliferation
Cyclin G2
IGF2
IGF-BP1
IGF-BP2
IGF-BP3
WAF1
TGF-α
TGF-β3
Cell survival
ADM
EPO
IGF2
IGF-BP1
IGF-BP2
IGF-BP3
NOS2
TGF-α
VEGF
Apoptosis
NIP3
NIX
RTP801
Motility
AMF/GPI
c-MET
LRP1
TGF-α
Cytoskeletal structure
KRT14
KRT18
KRT19
VIM
Cell adhesion
MIC2
Erythropoiesis
EPO
Angiogenesis
EG-VEGF
ENG
LEP
LRP1
TGF-β3
VEGF
Vascular tone
α1B-adrenergic receptor
ADM
ET1
Haem oxygenase-1
NOS2
HIF-1
Transcriptional regulation
DEC1
DEC2
ETS-1
NUR77
pH regulation
Carbonic anhydrase 9
Regulation of HIF-1 activity
p35srj
Epithelial homeostasis
Intestinal trefoil factor
Drug resistance
MDR1
Nucleotide metabolism
Adenylate kinase 3
Ecto-5′-nucleotidase
Iron metabolism
Ceruloplasmin
Transferrin
Transferrin receptor
Glucose metabolism
HK1
HK2
AMF/GPI
ENO1
GLUT1
GAPDH
LDHA
PFKBF3
PFKL
PGK1
PKM
TPI
Extracellular-matrix metabolism
CATHD
Collagen type V (α1)
FN1
MMP2
PAI1
Prolyl-4-hydroxylase α (I)
UPAR
Energy metabolism
LEP
Amino-acid metabolism
Transglutaminase 2
Nature Reviews | Cancer

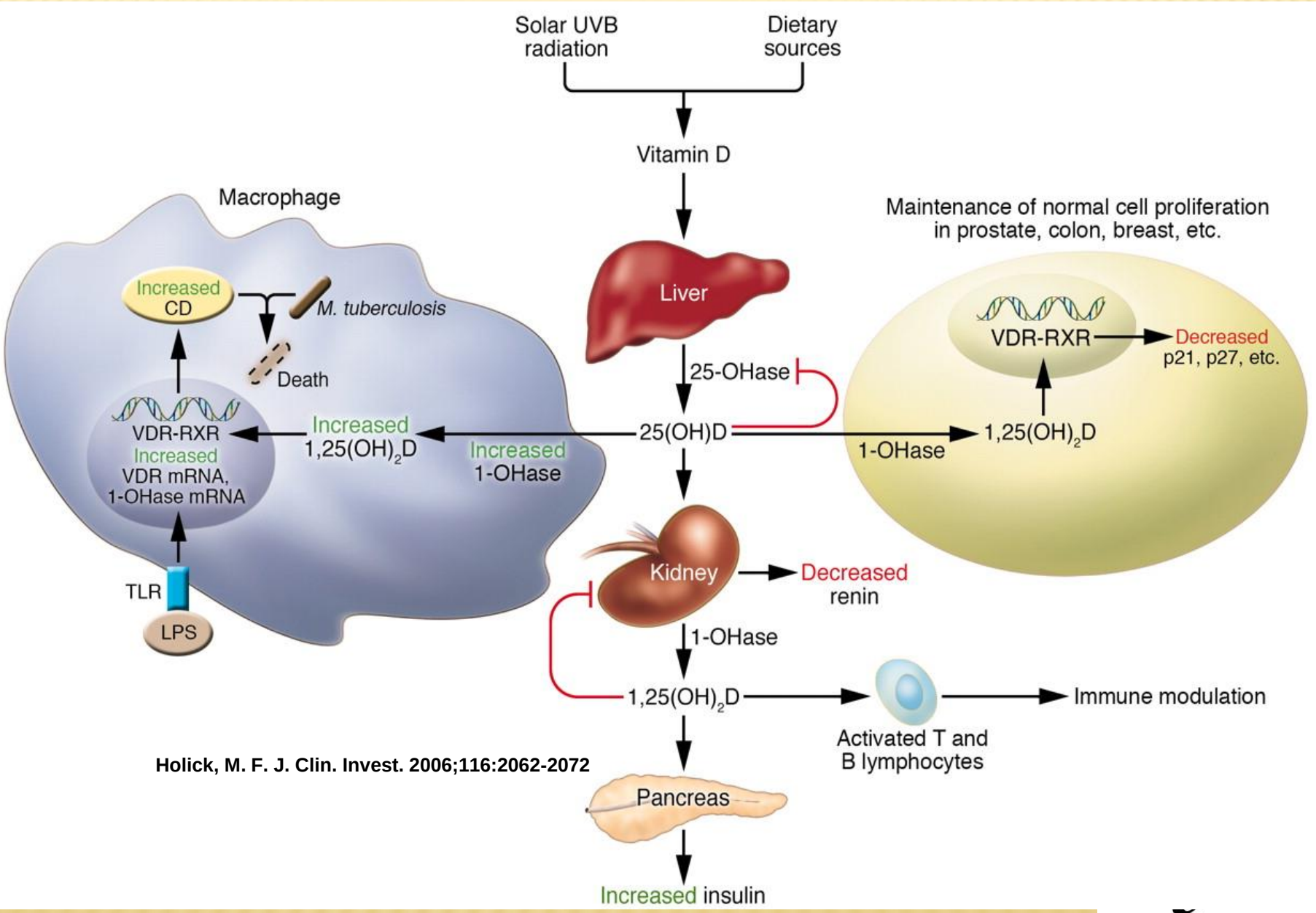
REGULATION OF HYPOCALCEMIA BY KINDNEY



Calcitriol


7-dehydrocholesterol
HO
In skin
cholecalciferol (vitamin D3)
HO
In liver
25-hydroxycholecalciferol
(25-hydroxy vitamin D3)
OH
HO
In kidney
1,25-dihydroxycholecalciferol
(1,25-dihydroxy vitamin D3)
OH
Active form
HO
OH

Calcitriol



Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

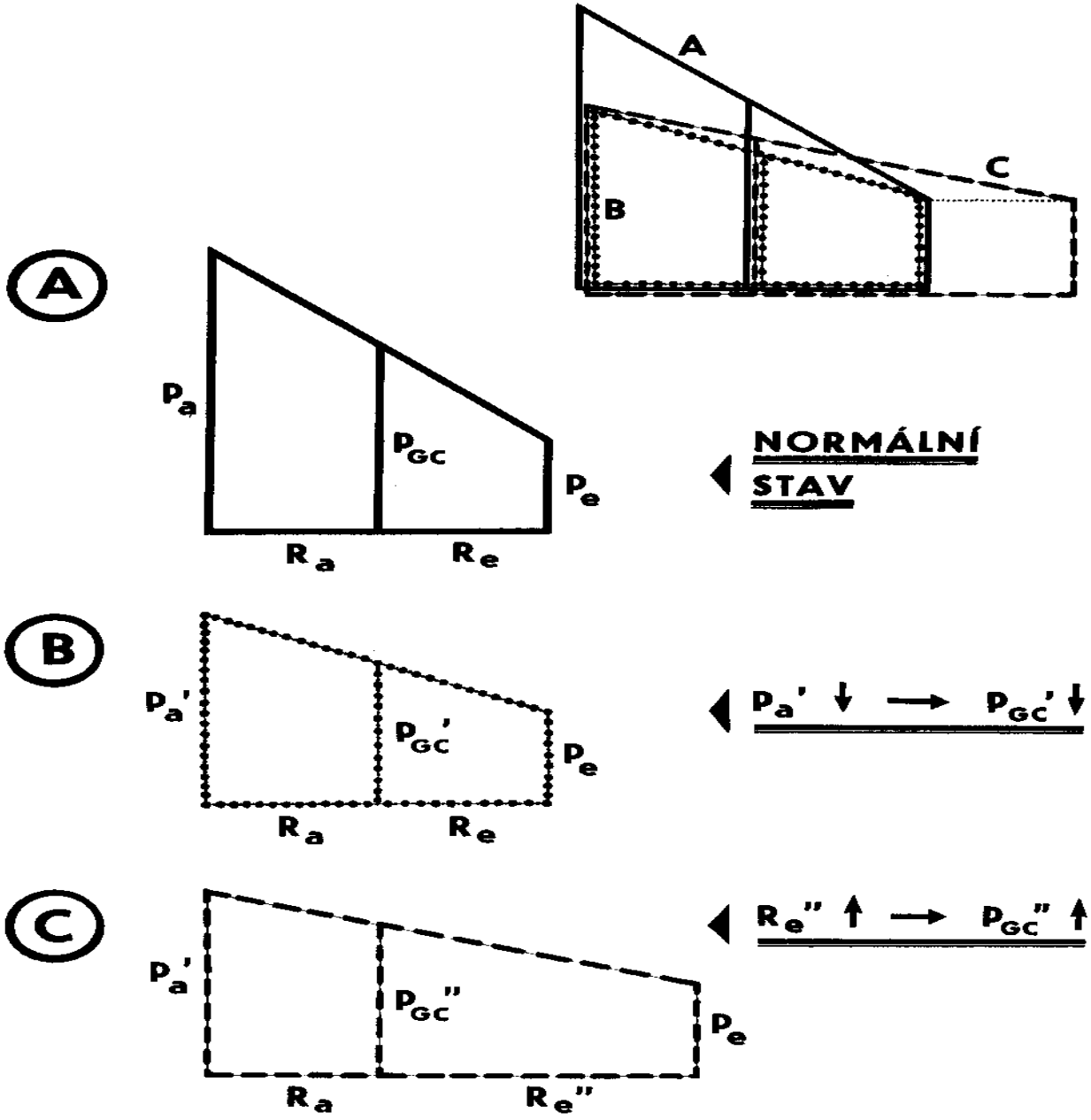
GLOMERULAR FILTRATION

- Rate (GFR): 120 mL/min (normal)
- Substances "Filtered":
  - water, electrolytes (Na, K, etc.), sugars (glucose), nitrogenous waste (urea, creatinine)
- Substances "Excluded":
  - Substances of size > 70 kDa
  - Plasma protein bound substances

FACTORS DETERMINING GFR

EFFECTIVE TRANSGLOMERULAR PRESSURE

$$P_{GC} = \frac{R_e P_a + R_a P_e}{R_a + R_e}$$


A
B
C
A
p_a
p_{GC}
p_e
R_a
R_e
NORMÁLNÍ STAV
B
p_a'
p_{GC}'
p_e
R_a
R_e
p_a' ↓ → p_{GC}' ↓
C
p_a'
p_{GC}''
p_e
R_a
R_e''
R_e'' ↑ → p_{GC}'' ↑

Renal blood flow(RBF) and filtration

Kidneys autoregulation

1st Ohm´s law:

$$RBF = \Delta P / R$$

where $\Delta P = P_a - P_e$ and $R = R_a + R_e$

R must be variable , because renal perfusion as well as GFR vary in large range of systemic blood pressure (90-190 mm Hg of mean arterial pressure.

$$RBF = \frac{\Delta P}{R_a + R_e},$$

KIDNEY SITES SUSCEPTIBLE TO RENAL DISEASE

- General: Renal medulla:
  - Low oxygen environment: Ischemia
- Glomerulus:
  - Structure predisposes it to immune complex deposition and complement fixation
- Tubules:
- ischemia, inflammation

"Post-Renal" Structures (ureters, bladder)

- Malformations, Obstruction, Masses (i.e. cancer)

Diseases of the glomerulus	Glomerulonephritis Focal segmental glomerulosclerosis Membranoproliferative glomerulonephritis Membranous glomerulonephritis Nephritic syndrome Post-streptococcal glomerulonephritis Nephrotic syndrome Minimal change disease IgA nephropathy Lupus nephritis - Diabetic nephropathy Rapidly progressive glomerulonephritis
Tubulointerstitial diseases of the kidney	Interstitial nephritis - Pyelonephritis - Hydronephrosis - Pyonephrosis - Balkan nephropathy - Reflux nephropathy
Renal failure	Acute renal failure Acute tubular necrosis) - Chronic renal failure
Diseases of the renal tubule and other disorders of kidney and ureter	Renal osteodystrophy - Nephrogenic diabetes insipidus - Renal tubular acidosis - Nephroptosis - Ureterocele
Other diseases and disorders of urinary system	Cystitis Interstitial cystitis, Trigonitis) - Neurogenic bladder - Vesicointestinal fistula - Urethritis - Urethral stricture - Urinary tract infection - Kidney stone
Tumors of the kidney	Renal cell carcinoma - Wilms' tumor (children)

See also congenital conditions (Q60-Q64, 753)

RENAL DISEASE: GENERAL CHARACTERISTICS:

- Early Renal Disease: Abnormal urine volume and/or composition (electrolytes, proteins, cells)
- Advanced: Edema, electrolyte abnormalities, anemia, etc.
- Rate of Progression: Disease-dependent
- Disease Course: Transient-fatal: Disease-dependent
- Pain: Variable, depending on nature of disease

- Renal Disease prominent in:
  - Diabetes Mellitus
  - Hypertension
  - Autoimmune disorders (SLE)

CATEGORIZATION

- Generalized site of disease:
  - Prerenal: Inadequate renal blood flow
  - Intrarenal: Nephron damage
  - Postrenal: Obstruction, structural defects
- Site of renal lesion (intrarenal)
  - Glomerulopathy
    - Nephritic:
    - Nephrotic:
  - Tubulointerstitial Disease
- Etiologic Factors: Infection, Diabetes, etc.

CHRONIC KIDNEY DISEASE

- is a progressive loss of renal function over a period of months or years through five stages. Each stage is a progression through an abnormally low and progressively worse glomerular filtration rate, which is usually determined indirectly by the creatinine level in blood serum.
- Stage 1 CKD is mildly diminished renal function, with few overt symptoms.
- Stage 5 CKD is a severe illness and requires some form of renal replacement therapy (dialysis or renal transplant). Stage 5 CKD is also called **end-stage renal disease (ESRD)**.

PROTEINURIA

- In the normal person, urinary protein excretion is less than 150 mg per day (with most subjects being under 100 mg per day) and consists mostly of filtered plasma proteins (60%) and tubular proteins (40%).
- The main plasma protein in the urine is albumin, constituting about 20% of the total normal daily protein excretion.
- In normal subjects the daily amount of albumin is less than 20 mg.

PROTEINURIA

- Proteinuria usually reflects an increase in glomerular permeability for normally non-filtered (?) plasma macromolecules such as albumin.
- A 24-hour urine collection containing more than 150 mg of protein is abnormal.
- Significant proteinuria is suspected when a dipstick test of the urine is persistently positive for protein. In such a situation the daily protein excretion will usually exceed 300-500 mg per day.

MICROALBUMINURIA

- is defined by the presence of >30 and <300 mg of albuminuria daily.
- The albumin to creatinine concentration of >30 mg per gram of creatinine correlates very well with a 24-hour urine albumin measurement. Its detection in Type I diabetes mellitus is the earliest clinical evidence of diabetic nephropathy. Transient increases in urinary albumin excretion may be seen in short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illnesses. There is also diurnal variation in urinary albumin excretion.
- Confirmation of microalbuminuria requires verification on 2 or 3 collections over 3 to 6 months.

Definition of Abnormalities in Albumin Excretion

Category	Time Collection		Spot Collection
	24-h Collection (mg/24 h)	(&microg/ min)	(&microg/g creatinine)
Normal	< 30	< 20	< 30
Microalbuminuria	30-299	20-199	30-299
Clinical proteinuria	> 300	> 200	> 300

GLOMERULAR PROTEINURIA

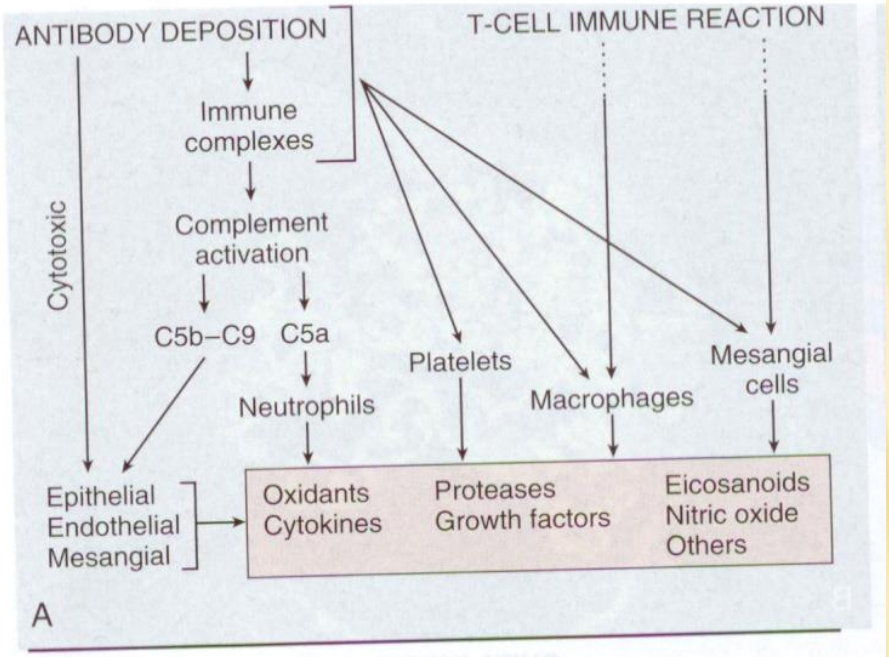
- The glomerular filtration barrier is composed of the endothelial cell, the basement membrane, and the epithelial cell foot processes.
- Proteinuria occurring in glomerular disease is due to increased filtration of albumin and other macromolecules across the glomerular basement membrane. This occurs because of an alteration in both the charge selectivity and size selectivity of the glomerular barrier.

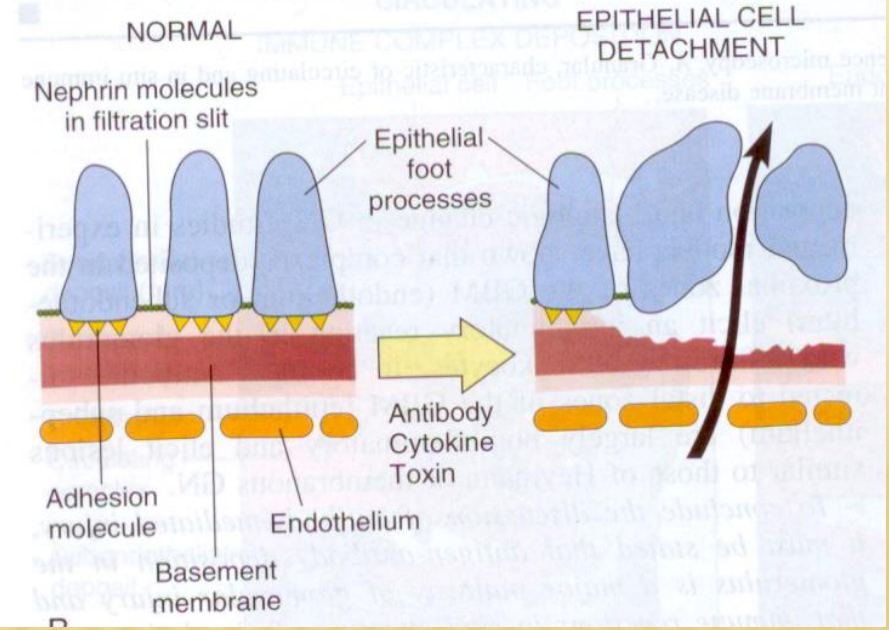
GLOMERULAR PROTEINURIA

- Normally the basement membrane and endothelial cells possess a negative charge. Plasma albumin, which also possesses a negative charge, is repelled by the normal negative charge on the basement membrane and the intact endothelial cells. Circulating IgG has a neutral or positive charge and is not restricted by a negative charge on the basement membrane. Rather, immunoglobulins are restricted by the size selective barrier of the membrane and the epithelial slit diaphragm located across the spaces between the epithelial foot processes.

GLOMERULAR PROTEINURIA

- In glomerular disease, the injury to the glomerular basement membrane causes proteinuria due to a loss in negative charge as well as from an increase in the number of larger non-selective pores.
- Glomerular diseases are also accompanied by disruption and loss of the epithelial foot process covering of the basement membrane.
- It appears that the increased protein leakage occurs especially at the sites of this epithelial alteration.


ANTIBODY DEPOSITION
T-CELL IMMUNE REACTION
Immune complexes
Cytotoxic
Complement activation
C5b–C9
C5a
Platelets
Mesangial cells
Macrophages
Neutrophils
Epithelial
Endothelial
Mesangial
Oxidants
Cytokines
Proteases
Growth factors
Eicosanoids
Nitric oxide
Others
A

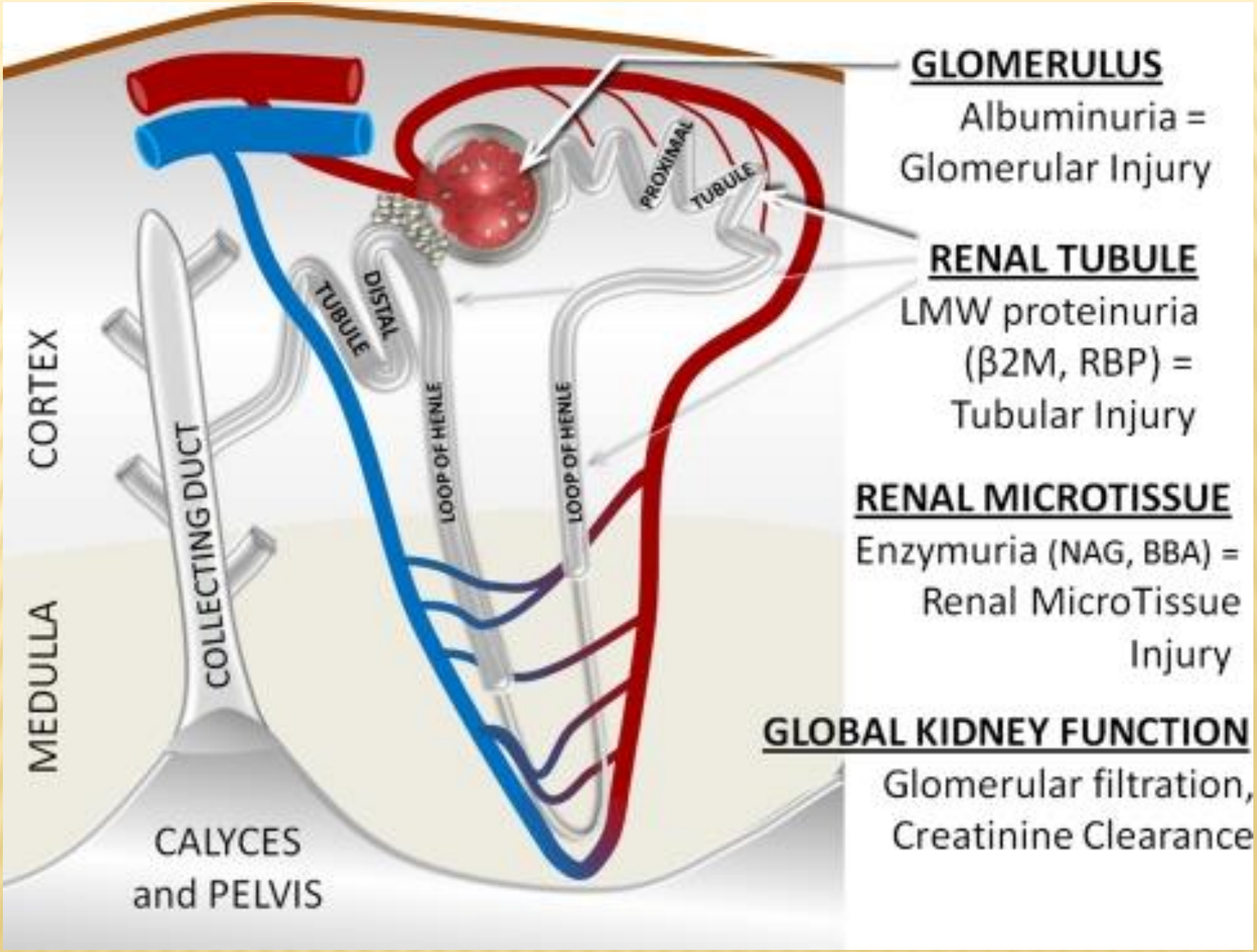

NORMAL
EPITHELIAL CELL DETACHMENT
Nephrin molecules in filtration slit
Epithelial foot processes
Antibody
Cytokine
Toxin
Adhesion molecule
Endothelium
Basement membrane

TUBULAR PROTEINURIA

- Low molecular weight molecules such as $\beta 2$ microglobulin, amino acids, and immunoglobulin light chains have a molecular weight of about 25000 (albumin is 69000). These smaller proteins are easily filtered across the basement membrane and then completely reabsorbed by the proximal tubular cells.
- A variety of diseases that produce tubular and interstitial injury impair the tubular reabsorption of these molecules. Some glomerular diseases are also accompanied by tubular injury and tubular proteinuria. Specific urinary measurements of $\beta 2$ microglobulin are quite sensitive for any tubular injury, but they are not specific for any disease.

OVERFLOW PROTEINURIA

- Increased excretion of low molecular weight proteins might be seen in states where there is significant increased production of these proteins, as in multiple myeloma.
- The proteinuria results from the fact that the amount of these proteins filtered exceeds the reabsorptive capacity of the proximal tubule.



Clin Orthop Relat Res. 2011 Jun; 469(6): 1651–1659.

CLINICAL SIGNS

- Most patients with proteinuria have no signs or symptoms from the proteinuria.
- In states of heavy (nephrotic range) proteinuria exceeding 3 g daily, the patient might report foamy urine and might demonstrate edema.
- The foamy urine is due to increased lipids in the urine, which alters the surface tension of the urine. Lipiduria is caused by the filtration of lipoproteins across the damaged glomerular barrier. On urine microscopy lipiduria might appear as free fat, or as fat droplets in tubular cells or casts where they are referred to as oval fat bodies or fatty casts respectively.

CLINICAL SIGNS

- Edema, which frequently accompanies nephrotic range proteinuria, is caused by reduction of plasma oncotic pressure due to reduced plasma albumin. Hypoalbuminemia is the result of increased glomerular losses and/or defective synthesis of albumin. The loss of albumin stimulates the liver synthetic activity, which also contributes to increased lipoprotein production and hyperlipidemia.

Differential Diagnosis of Kidney Disease by Varying Levels of Proteinuria

Proteinuria Less than 1-2 Grams Daily

- **Nephrosclerosis***
- **Tubulointerstitial disease***
- **Polycystic kidney disease**
- **Orthostatic proteinuria**
- **More benign forms of glomerular disease (eg, IgA nephritis)***

Proteinuria Greater than 3.5 Grams Daily (Nephrotic-Range)

Primary glomerular disease

- Minimal change disease
- Membranous glomerulonephritis*
- Focal and segmental glomerulosclerosis*
- Membranoproliferative glomerulonephritis

Secondary nephrotic syndrome: glomerular disease associated with specific causes

- Systemic disease
  - Diabetic nephropathy*
  - Systemic Lupus Erythematosus
  - Amyloidosis
  - Vasculitic-immunologic diseases (Wegener's, Goodpasture's, Polyarteritis)
- Infectious disease
  - Post-streptococcal glomerulonephritis
  - Hepatitis B and C*
  - Bacterial endocarditis
  - HIV*
- Malignancies
  - Lymphoproliferative disorders, Hodgkin's (minimal change)
  - Solid tumors (membranous)
- Medications:
  - Nonsteroidal anti-inflammatory drugs*
  - Gold, mercury, heavy metals
  - Penicillamine
  - Lithium
  - "Street" heroin
- Hereditary and metabolic disorders
  - Alport's syndrome
  - Fabry's disease
  - Sickle cell anemia
  - Nail-patella syndrome
- Others
  - Accelerated hypertensive nephrosclerosis
  - Massive obesity
  - Transplant rejection nephropathy

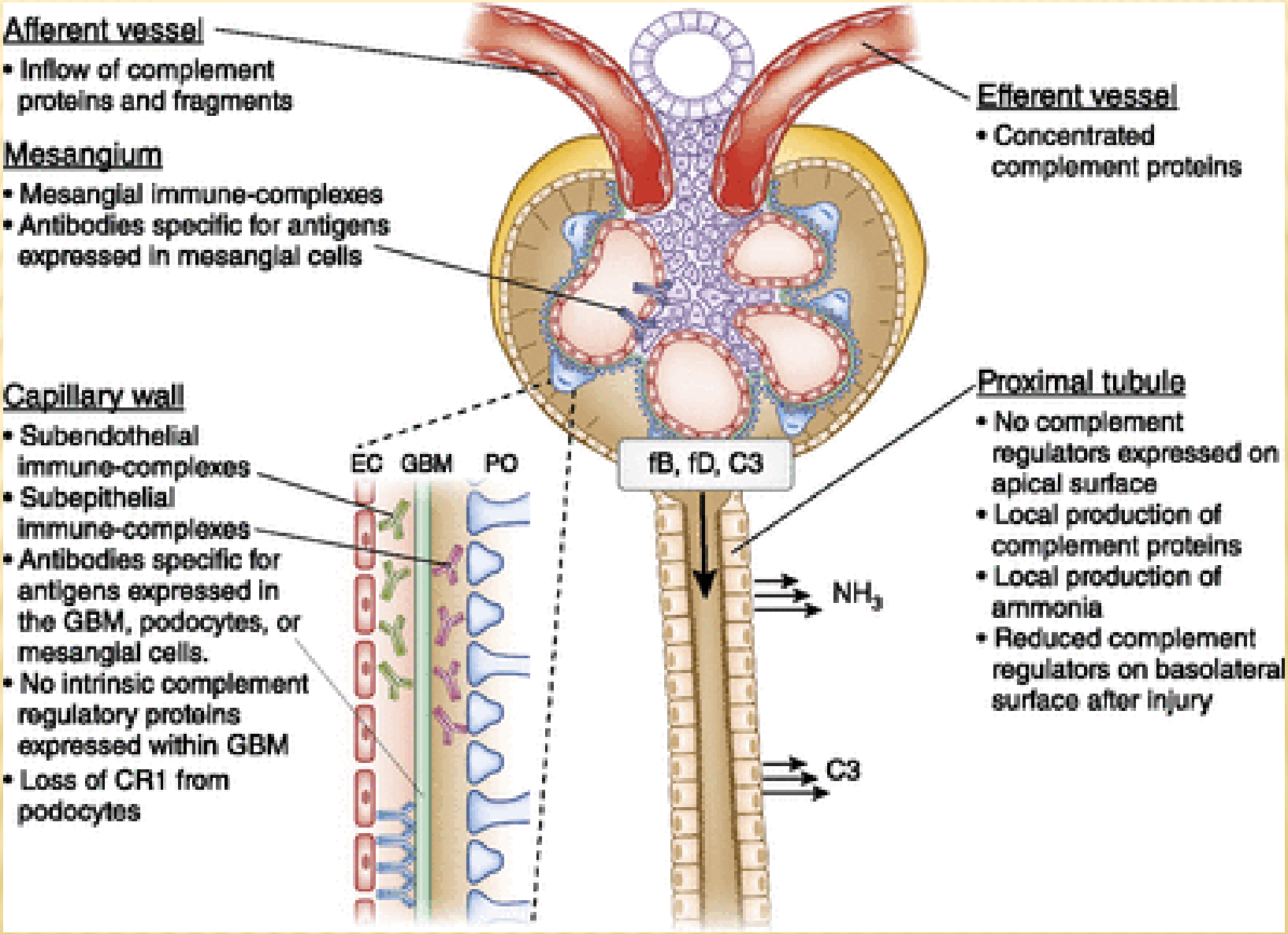
* Most common disorders in adults

GLOMERULONEPHRITIS: CLINICAL MANIFESTATIONS

- Proteinuria and hematuria: damage to capillary wall allows "leakage"
- Decreased GFR:
  - Infiltration of glomerular capillaries with inflammatory cells, OR
  - Expansion of contractile mesangial cells
- Edema and hypertension: Fluid and salt overload from decreased GFR
- Transient decrease in serum complement
- Transient elevations antibody to streptococcal antigen

ACUTE GLOMERULONEPHRITIS:

- Clinical Presentation
  - Abrupt hematuria and proteinuria
  - reduced GFR, salt and water retention
- Pathology & Pathogenesis
  - Infection: Immune response to pathogen (i.e. Streptococci) antigen resulting in deposition of immune complexes and complement in glomerular capillary bed (intrarenal!)
  - Onset:7-10 days after initial infection
  - Full recovery typically occurs within weeks on infection



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Conditions within the kidney that are conducive to complement (C) activation.

- The C cascade is activated by distinct mechanisms at various ultrastructural locations within the kidney.
- Immune-complexes can deposit in the mesangium and at different locations within the glomerular capillary wall.
- In some diseases, autoantibodies bind to specific renal antigens.
- Other conditions in the kidney that favor C activation are increased concentrations of C proteins in the efferent vessels, low pH, increased local concentrations of C proteins due to production by tubular epithelial cells, and high concentrations of ammonia which can activate the alternative pathway.
- The glomerular basement membrane does not express C regulatory proteins, although factor H controls alternative pathway activation on the glomerular basement membrane. The apical surface of tubular epithelial cells also does not express C regulatory proteins, and alternative pathway proteins may be activated at this location in proteinuric conditions.

EC, endothelial cell; PO, podocyte; fB, factor B; fD, factor D.

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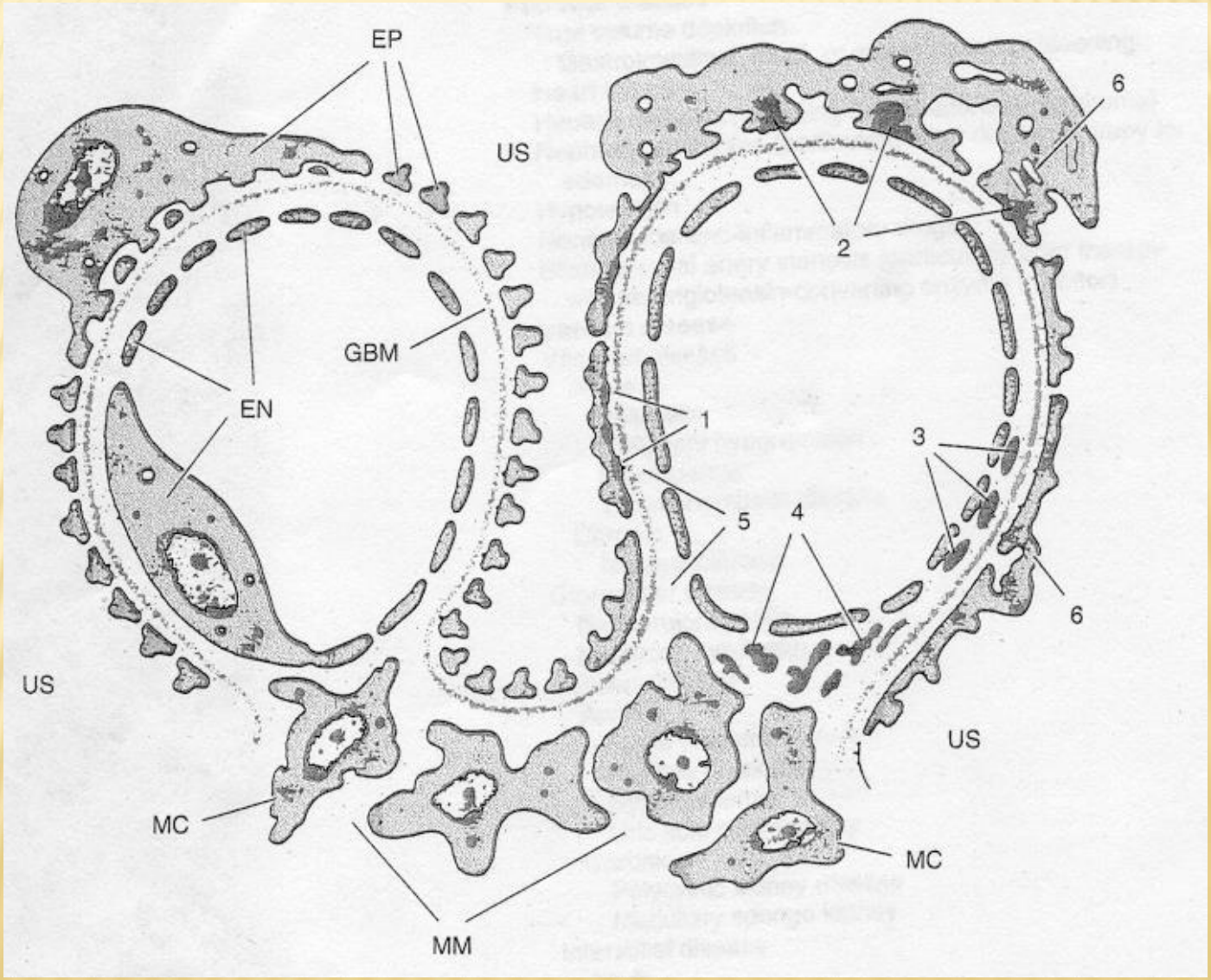
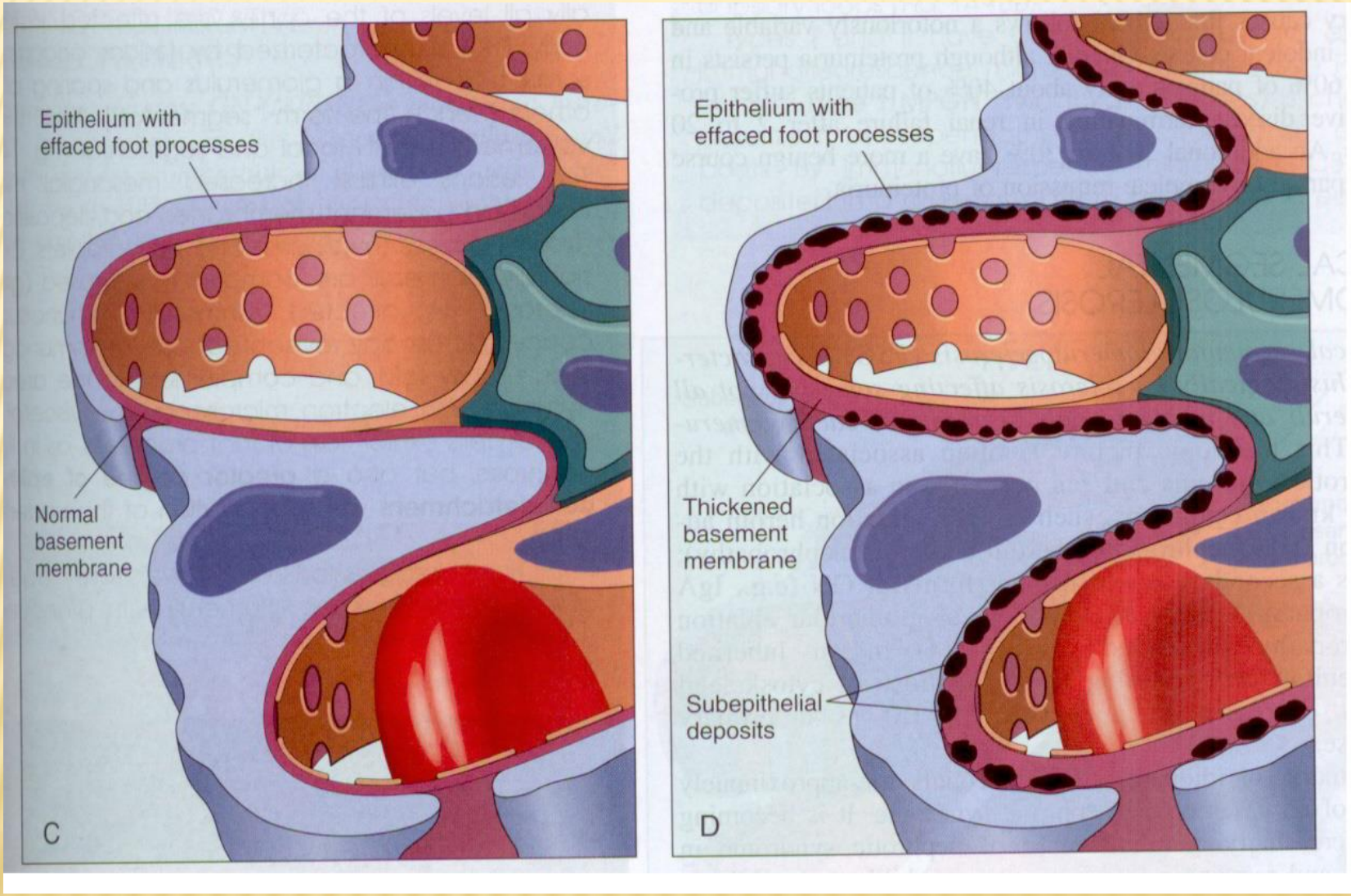
GLOMERULAR CAPILLARY: NORMAL VERSUS PATHOLOGY



GLOMERULAR CAPILLARY PATHOLOGY

1. Membranous nephropathy: Subepithelial deposits
2. Post-infectious glomerulonephritis: Subepithelial
3. Lupus glomerulonephritis: Subendothelial deposits
4. IgA Nephropathy: Mesangial deposits
5. Goodpasture's Syndrome: Antibody binding to GBM
6. Glomerular injury with proteinuria: Podocyte effacement


Epithelium with
effaced foot processes
Normal
basement
membrane
C
Epithelium with
effaced foot processes
Thickened
basement
membrane
Subepithelial
deposits
D

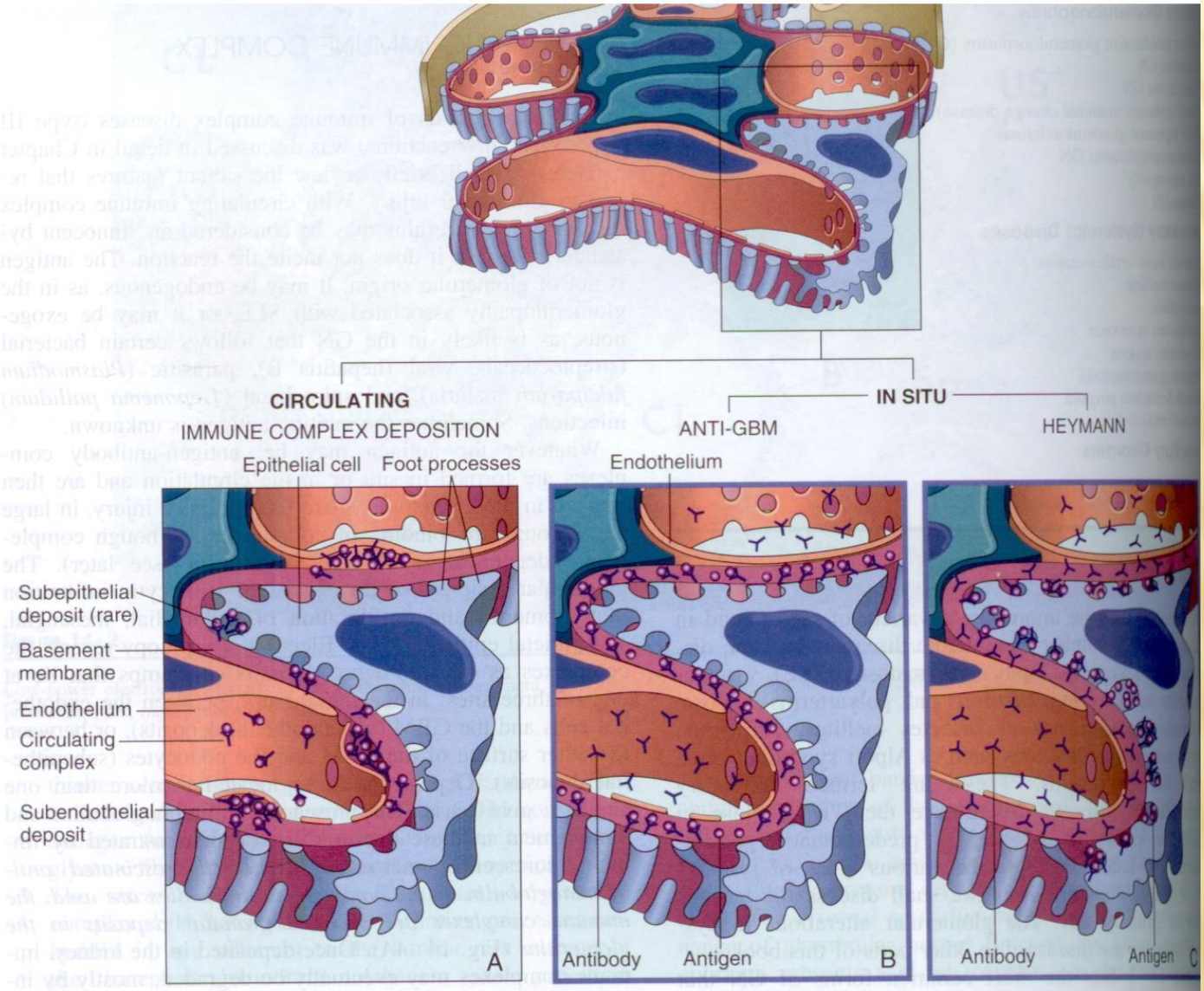
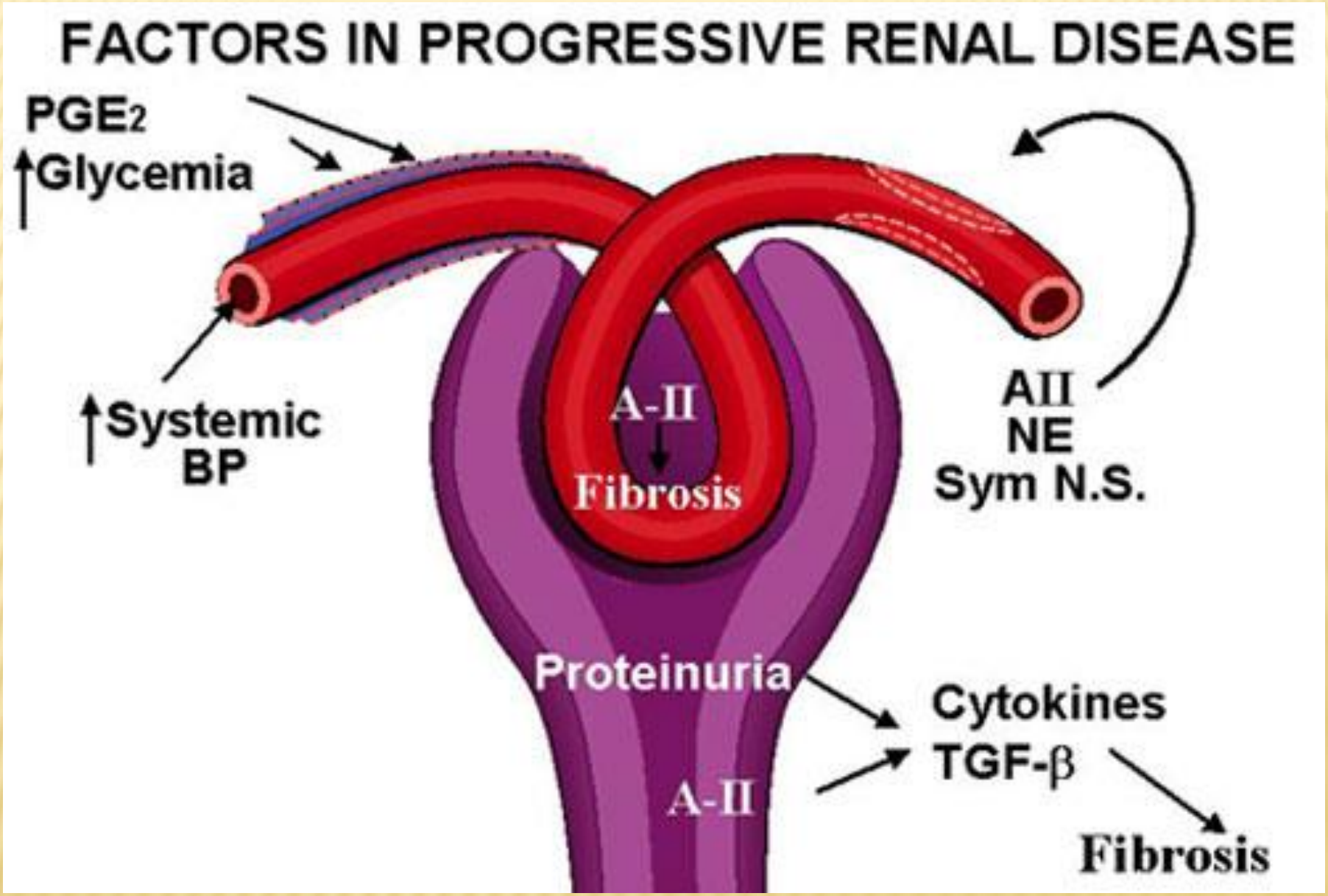


Figure 14–3

Antibody-mediated glomerular injury can result either from the deposition of circulating immune complexes *(A)* or from formation in situ of comple *(B* and *C)*. Anti–glomerular basement membrane (GBM) disease *(B)* is characterized by linear immunofluorescence patterns, whereas lesions caused immune complexes reveal granular patterns.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

- Clinical Presentation: "Intermediate" stage
  - Failure to recover from Acute Glomerulonephritis: Origin unknown
  - Worsening renal function with irreversible and complete renal failure as the outcome
- Pathology & Pathogenesis
  - Intermediate stage between "Acute" and "Chronic"
  - Extracapillary cellular proliferation: 70% of glomeruli
  - Basement membrane gap/discontinuities
  - Deposition of anti-GBM antibodies or granular immunoglobulins


FACTORS IN PROGRESSIVE RENAL DISEASE
PGE2
Glycemia
Systemic
BP
A-II
Fibrosis
AII
NE
Sym N.S.
Proteinuria
A-II
Cytokines
TGF-β
Fibrosis

CHRONIC GLOMERULONEPHRITIS

- Clinical Presentation
  - Slow progression from acute disease to chronic renal failure (5-20 years)
- Pathology & Pathogenesis
  - Capillary or mesangial cellular proliferation
  - Structural obliteration of glomeruli: sclerosing
  - Subepithelial proteinaceous deposits: Membranous glomerulonephritis

NEPHROTIC SYNDROME

- Clinical Presentation
  - Marked proteinuria (albuminuria) >3.5 g/24hr with hypoalbuminemia
  - Edema
  - Hyperlipidemia
  - Fat bodies in the urine
- Pathology & Pathogenesis
  - Minimal cellular infiltration of glomeruli
  - Deposition of antigen-antibody complexes in the subepithelium space

NEPHROTIC SYNDROME: CLINICAL MANIFESTATIONS

- Decreased oncotic pressure: loss of serum protein:
  - Intravascular volume depletion with syncope, shock and acute renal failure
  - Activation of renin-angiotensin-aldosterone system
  - Activation of sympathetic nervous system
  - Increased secretion of vasopressin
  - Hyperlipidemia: Increases hepatic VLDL production
- Loss of other plasma proteins:
  - Increased susceptibility to infection
  - Hypercoagulability
  - Vitamin D deficiency: loss of Vit D binding protein
  - Altered thyroxine binding protein/thyroid tests

NEFROTIC VS. NEFRITIC SYNDROME

- Nephrotic diseases:
  - Severe proteinuria
  - Immune complex deposits in subepithelium space
  - No cell inflammation reaction
  - Increased TAG (as a response to severe chronic proteinuria)
- Nephritic diseases
  - Variable proteinuria
  - Immune complex deposits in subendothelial space and/ or in basal membrane
  - Cell inflammatory reaction

THANK YOU FOR YOUR ATTENTION