Renal Physiology

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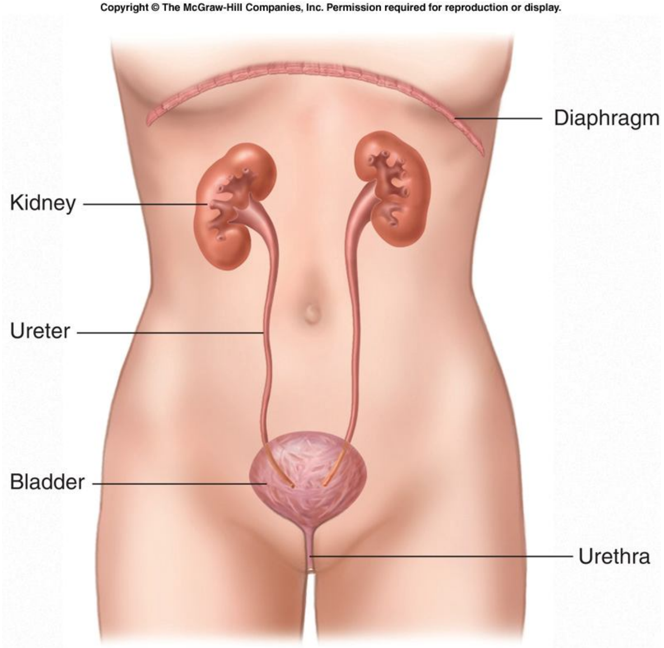
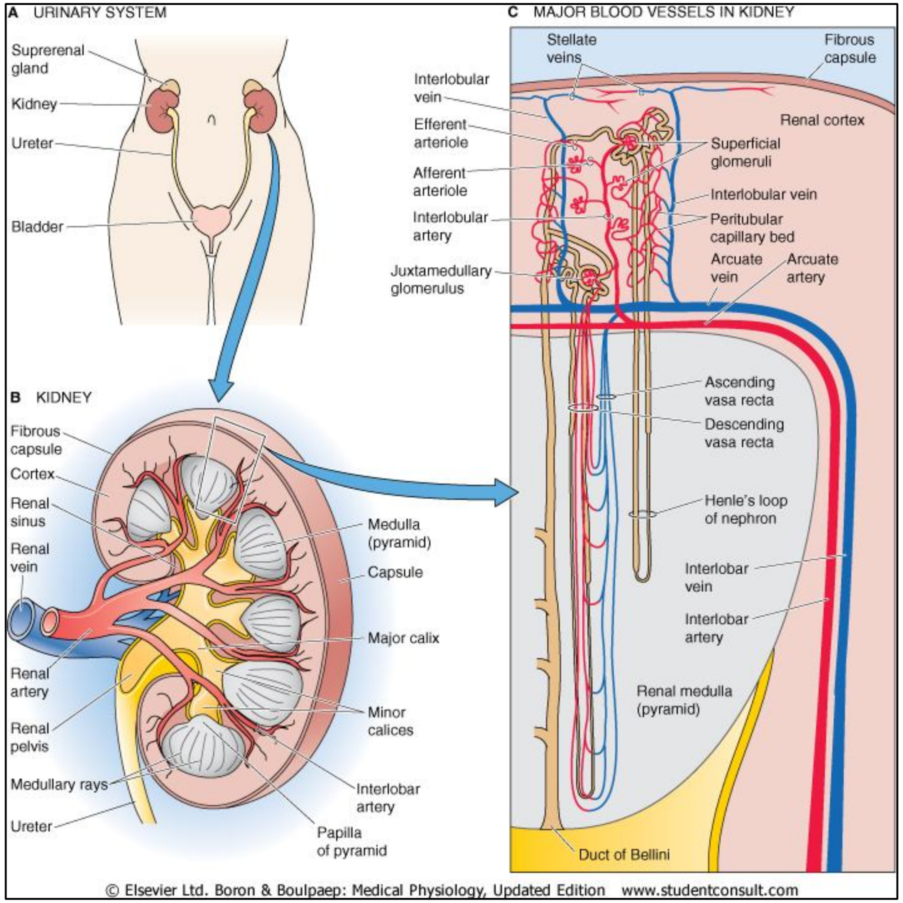


Renal Function



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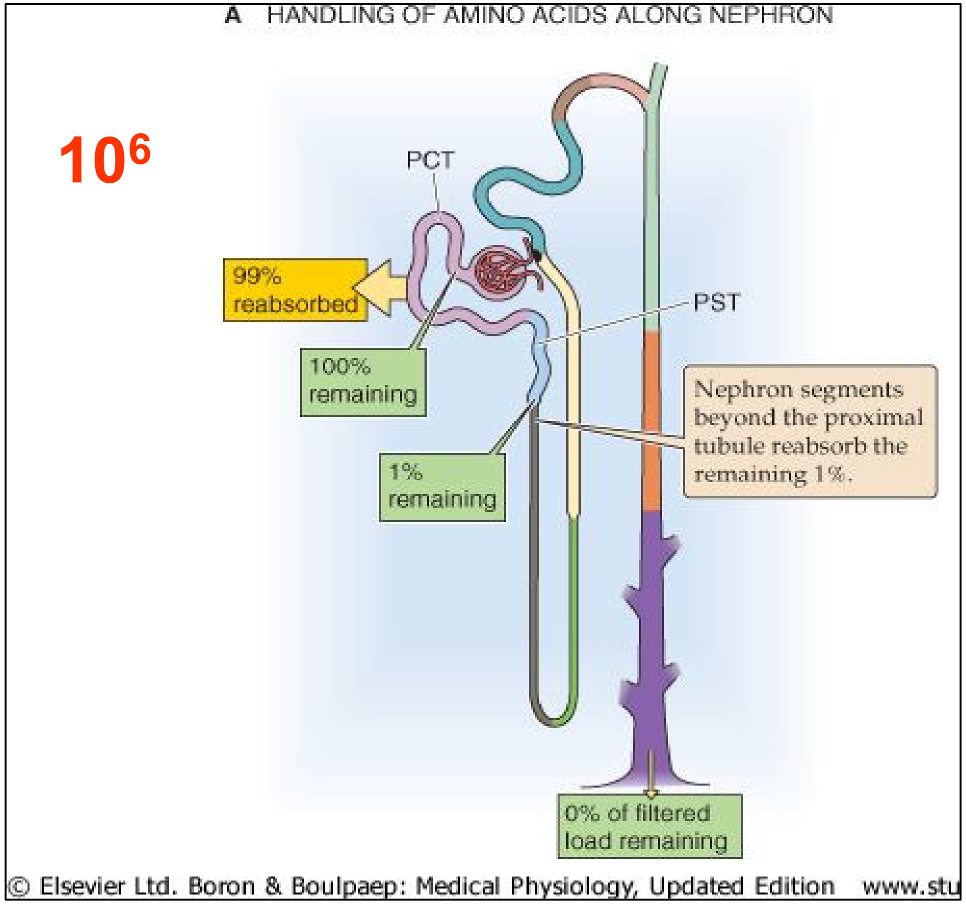


Functions of the kidneys

- Regulation of body fluid osmolality & volume: Excretion of water and NaCl is regulated in conjunction with cardiovascular, endocrine, & central nervous systems
- Regulation of electrolyte balance:
  - Daily intake of inorganic ions (Na^+, K^+, Cl^-, HCO^{3-}, H^+, Ca^{2+}, Mg^+ & PO_4^{3-})
  - Should be matched by daily excretion through kidneys.
- Regulation of acid-base balance: Kidneys work in concert with lungs to regulate the pH in a narrow limits of buffers within body fluids.

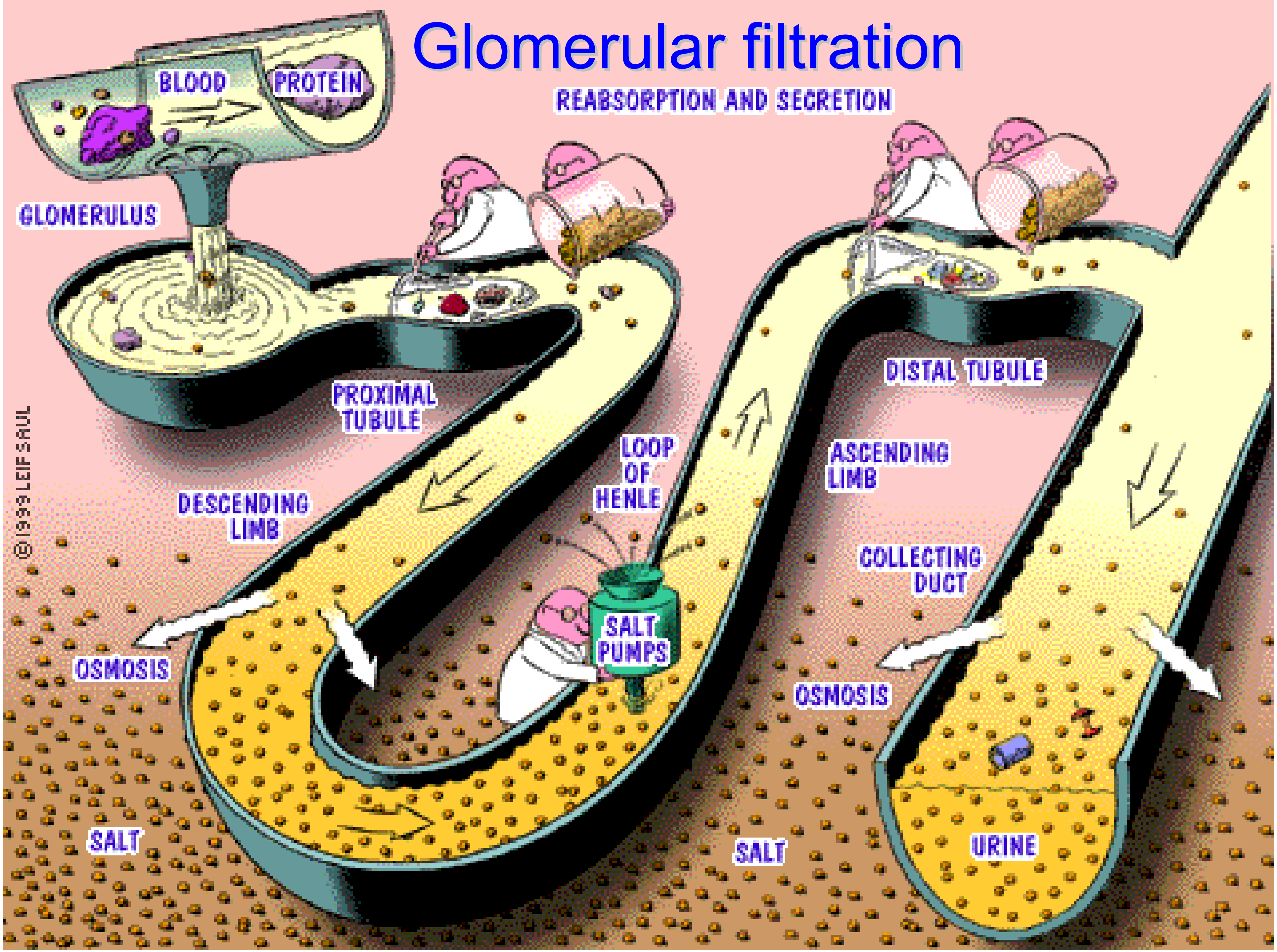
Functions of the kidneys

- Excretion of metabolic products & foreign substances:
  - **Urea** from amino acid metabolism
  - **Uric acid** from nucleic acids
  - **Creatinine** from muscles
  - **End products** of hemoglobin metabolism
  - **Hormone metabolites**
  - **Foreign substances** (e.g., Drugs, pesticides, & other chemicals ingested in the food)

Functions of the kidneys

- Production and secretion of hormones:
  - **Renin** -activates the renin-angiotensin-aldosterone system, thus regulating blood pressure & Na+, K+ balance
  - **Prostaglandins/kinins** - bradykinin = vasoactive, leading to modulation of renal blood flow & along with angiotensin II affect the systemic blood flow
  - **Erythropoietin** -stimulates red blood cell formation by bone marrow

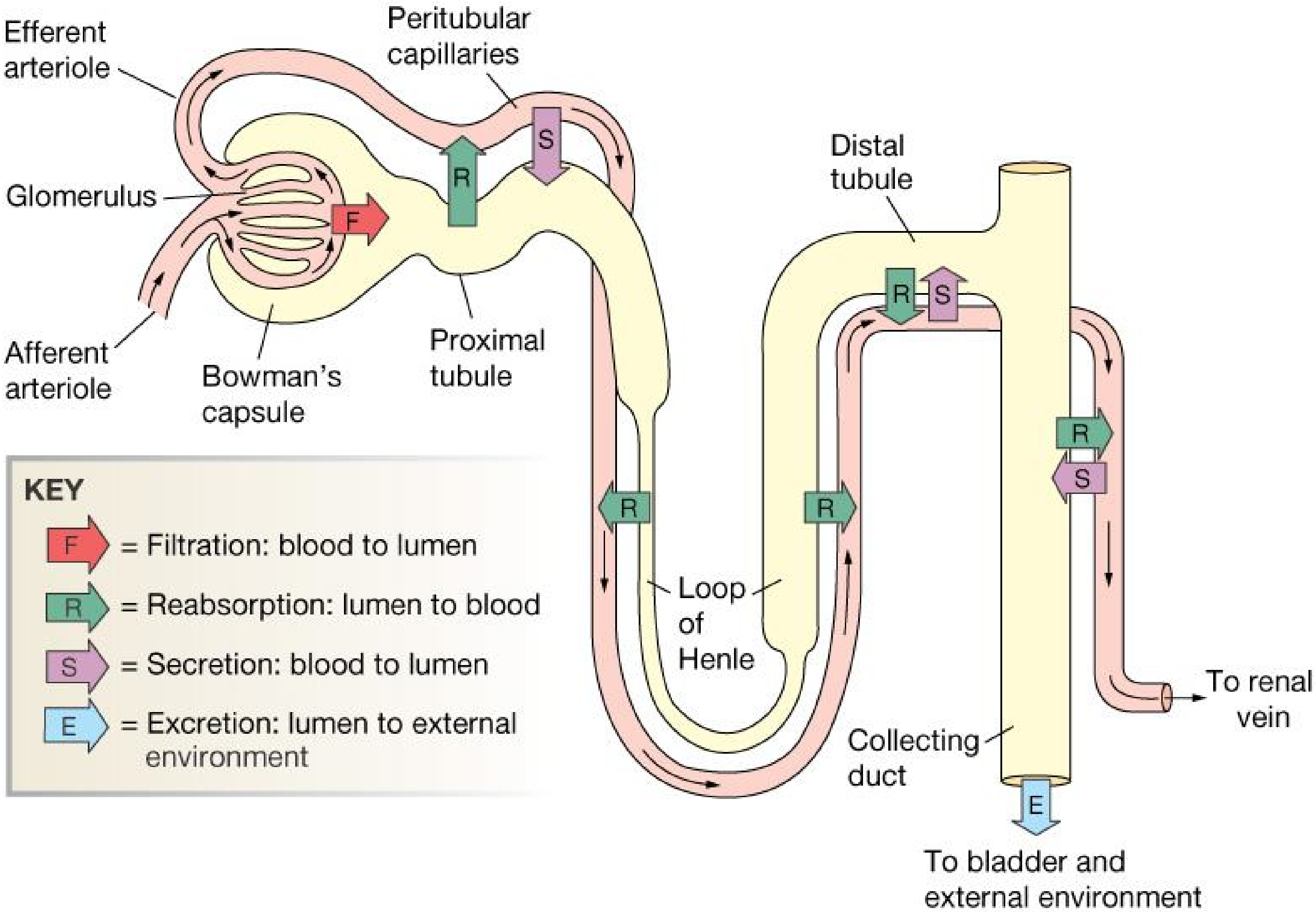
Glomerular filtration



Glomerular filtration

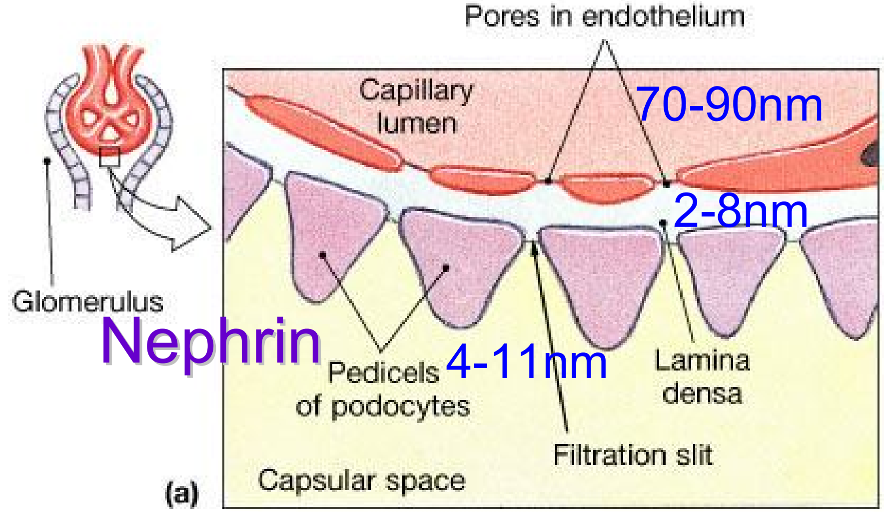
Glomerular filtration ; Tubular reabsorption

Tubular secretion

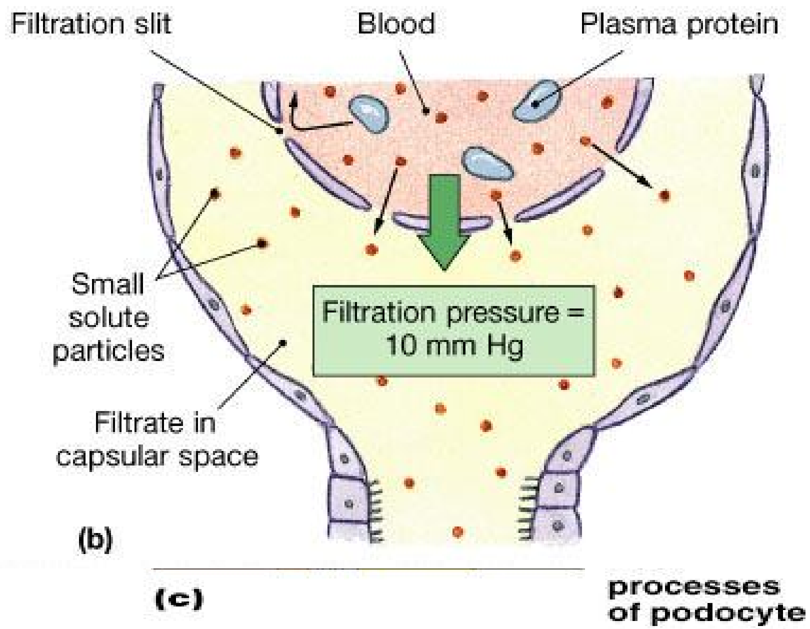


Glomerular filtration

- Glomerular filtrate is produced from blood plasma
- Must pass through:
  - Pores between endothelial cells of the glomerular capillary
  - Basement membrane acellular gelatinous membrane made of collagen and glycoprotein
  - Filtration slits formed by podocytes-Nephrin



Negative charge glycoprotein



Glomerular filtration

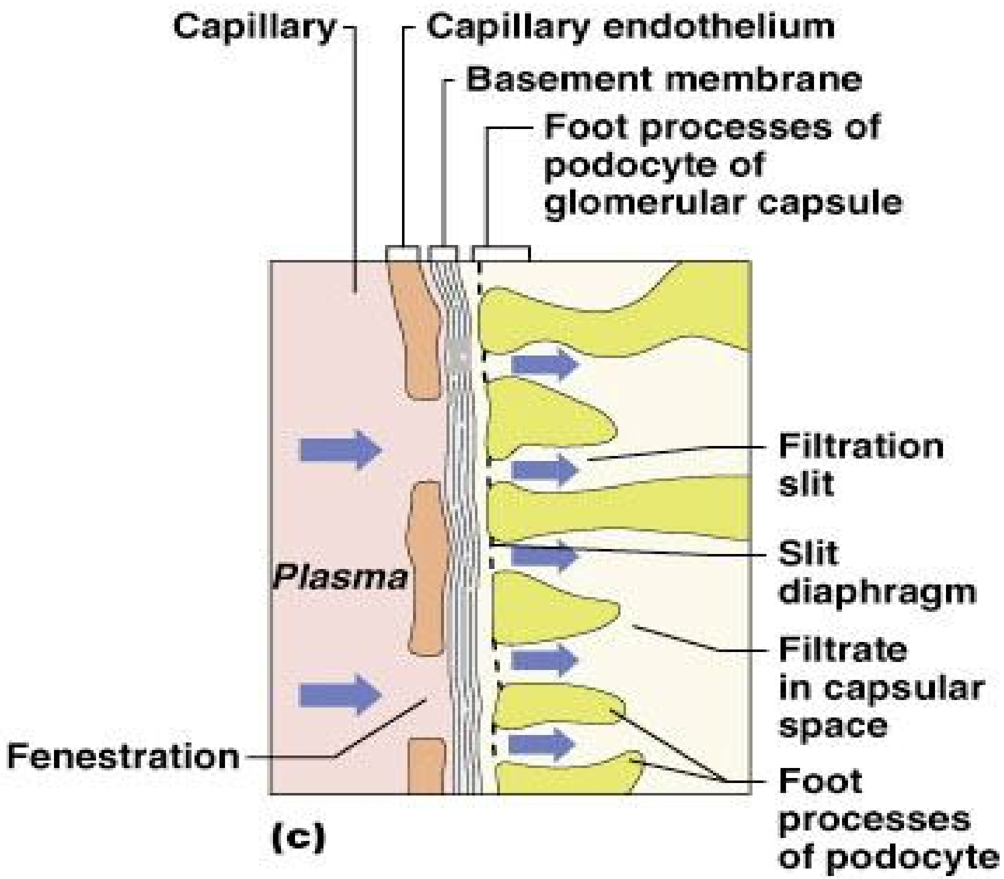
- Glomerular filtration barrier:

  restricts the filtration of molecules on the basis of size and electrical charge

- Neutral solutes:
  - Solutes smaller than 2 nanometers in radius are freely filtered
  - Solutes greater than 4.2 nanometers do not filter
  - Solutes between 2 and 4.2 nm are filtered to various degrees

Filtrate Composition

Filtrate is similar to plasma in terms of concentrations of salts and of organic molecules (e.g., glucose, amino acids) except it is essentially protein-free



Filtrate Composition

- Serum albumin is anionic and has a 3.6 nm radius, only ~7 g is filtered per day.

- In a number of glomerular diseases, the negative charge on various barriers for filtration is lost due to immunologic damage and inflammation, resulting in proteinuria (i.e.increased filtration of serum proteins that are mostly negatively charged).

Glomerular filtration

- Principles of fluid dynamics that account for tissue fluid in the capillary beds apply to the glomerulus as well

- Filtration is driven by Starling forces across the glomerular capillaries, and changes in these forces and in renal plasma flow alter the glomerular filtration rate (GFR)

Glomerular filtration

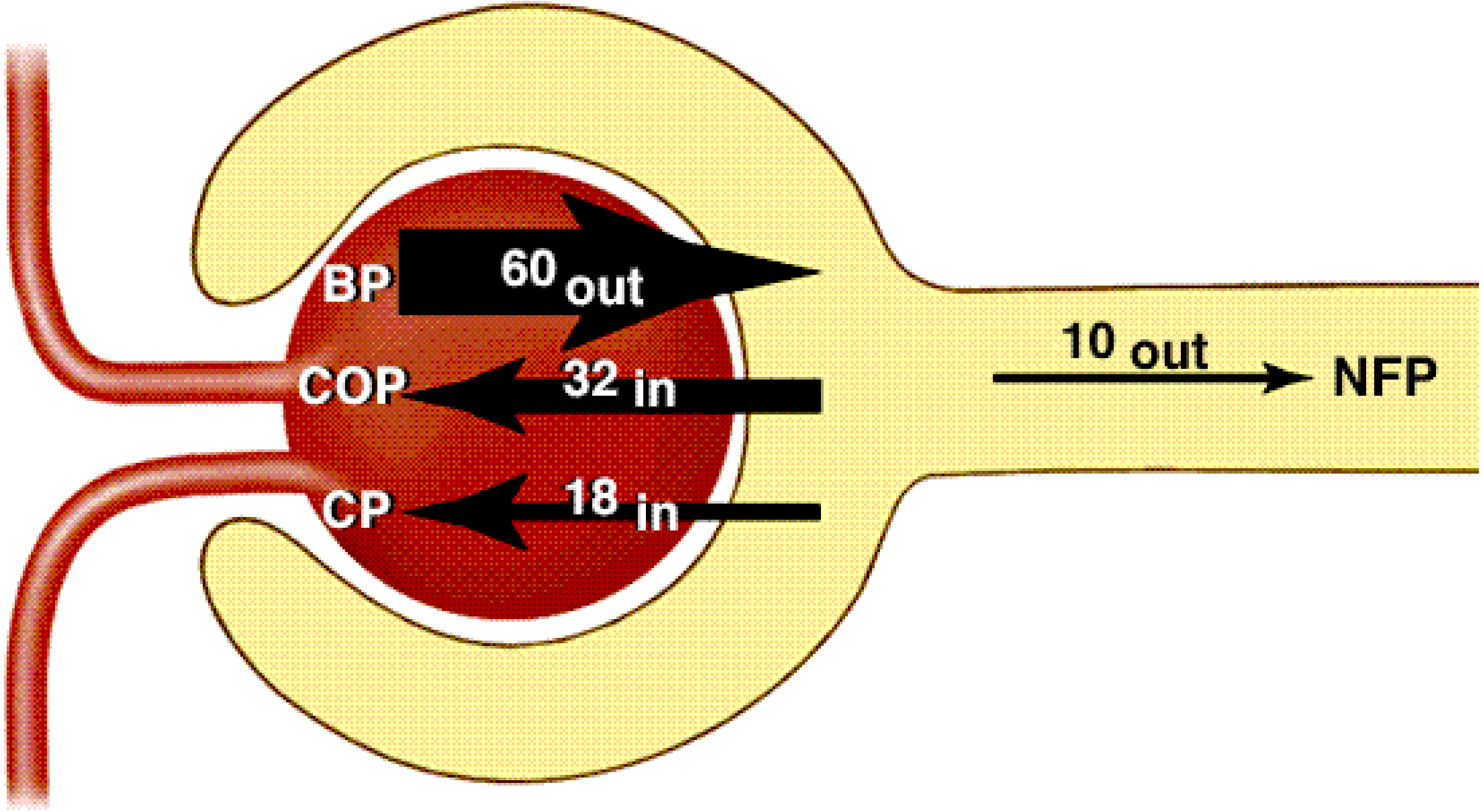
- The glomerulus is more efficient than other capillary beds because:
  - Its filtration membrane is significantly more permeable
  - Glomerular blood pressure is higher
  - It has a higher net filtration pressure
- Plasma proteins are not filtered and are used to maintain oncotic (colloid osmotic) pressure of the blood

Forces Involved in Glomerular Filtration

- Mechanism: Bulk flow-filtration
- Direction of movement : From glomerular capillaries to capsule space
- Driving force: Pressure gradient (net or efficient filtration pressure, NFP or EFP)
- Types of pressure:

  Favoring Force: Capillary Blood Pressure (BP),
  Opposing Force: Blood colloid osmotic pressure(COP) and Capsule Pressure (CP)

Glomerular Filtration Forces



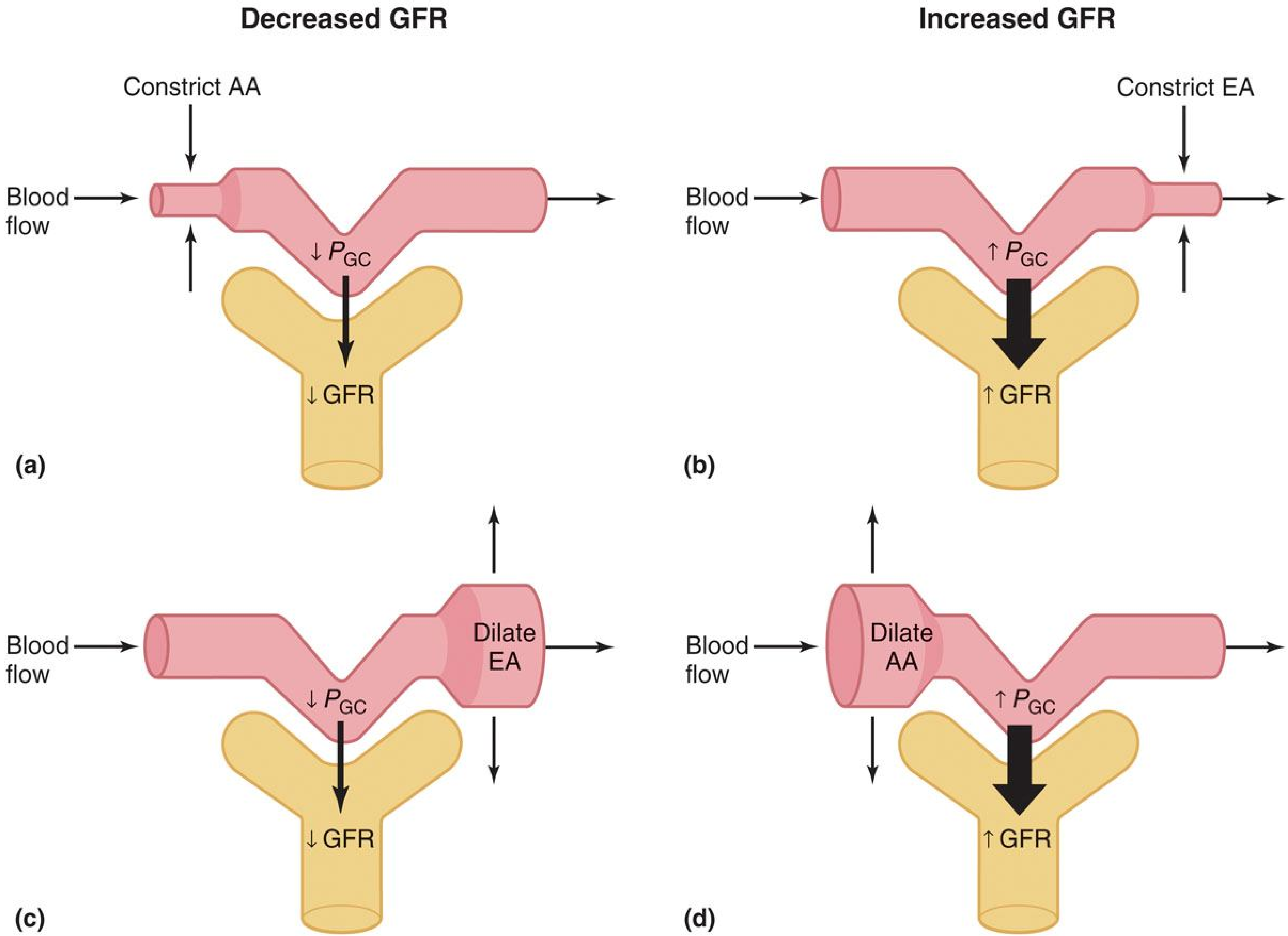
Capillary blood pressure (BP)	60 mmHg out
Colloid osmotic pressure (COP)	− 32 mmHg in
Capsular pressure (CP)	− 18 mmHg in
Net filtration pressure (NFP)	10 mmHg out

Glomerular Filtration Rate (GFR)

- The total amount of filtrate formed per minute by the kidneys
- Filtration rate factors:
  - Total surface area available for filtration and membrane permeability (filtration coefficient = Kf)
  - Net filtration pressure (NFP) EFP
  - GFR = Kf x NFP
- GFR is directly proportional to the NFP
- Changes in GFR normally result from changes in glomerular capillary blood pressure

Factors affecting GFR

- Changes in renal blood flow
- Changes in glomerular capillary hydrostatic P
    - changes in systemic BP
    - afferent or efferent arteriolar constriction
- Changes in hydrostatic P in Bowman's capsule
    - ureteral obstruction, renal edema
- Changes in plasma protein concentration
- Reduction in effective filtration surface area
- Changes in glomerular capillary permeability



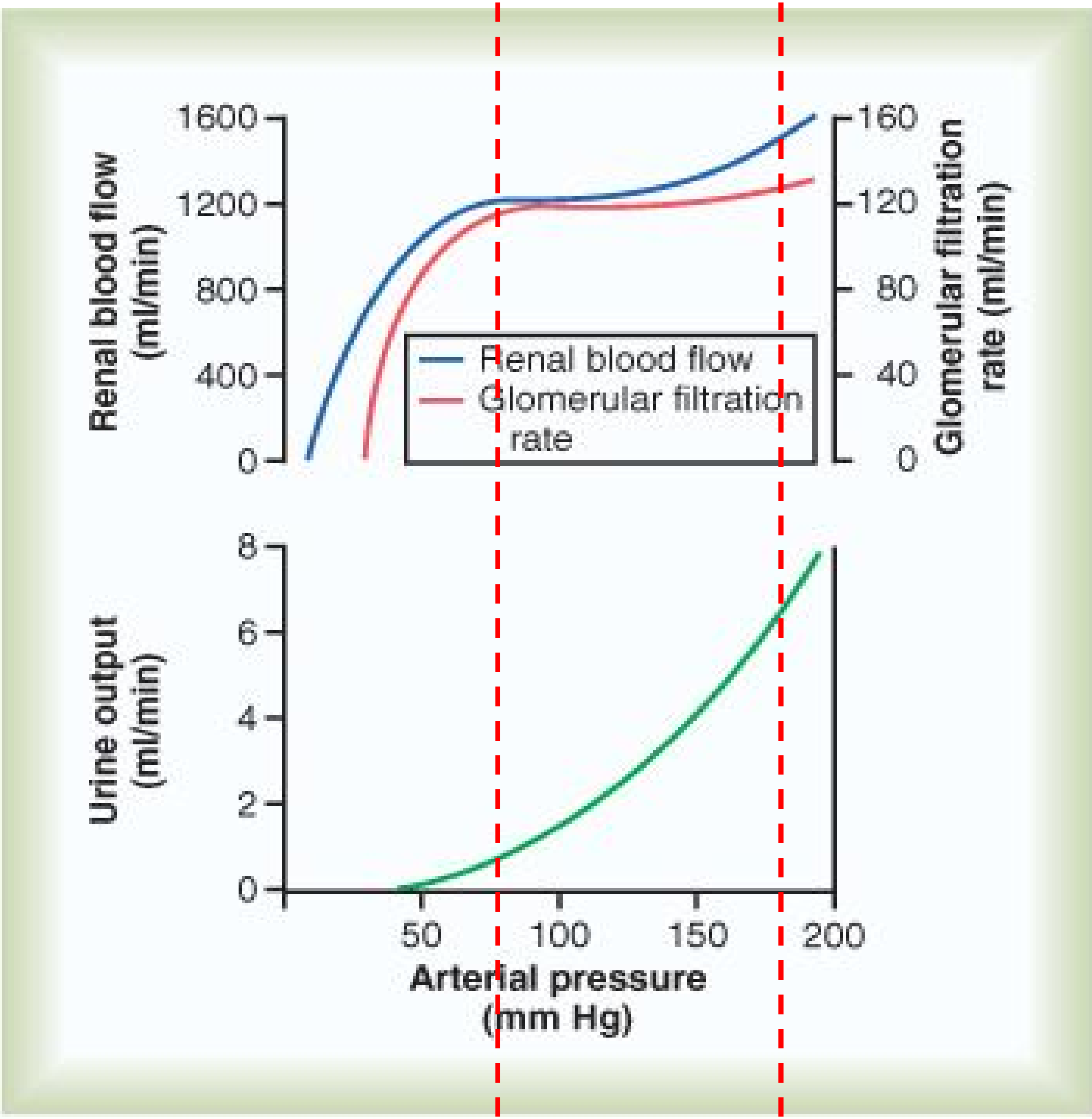
Decreased GFR
Increased GFR
Constrict AA
Blood flow
↓ P_{GC}
↓ GFR
(a)
Constrict EA
Blood flow
↑ P_{GC}
↑ GFR
(b)
Blood flow
Dilate EA
↓ P_{GC}
↓ GFR
(c)
Blood flow
Dilate AA
↑ P_{GC}
↑ GFR
(d)

Regulation of Glomerular Filtration

- If the GFR is too high, needed substances cannot be reabsorbed quickly enough and are lost in the urine
- If the GFR is too low - everything is reabsorbed, including wastes that are normally disposed of
- Control of GFR normally result from adjusting glomerular capillary blood pressure
- Three mechanisms control the GFR
  - Renal autoregulation (intrinsic system)
  - Neural controls
  - Hormonal mechanism (the renin-angiotensin system)

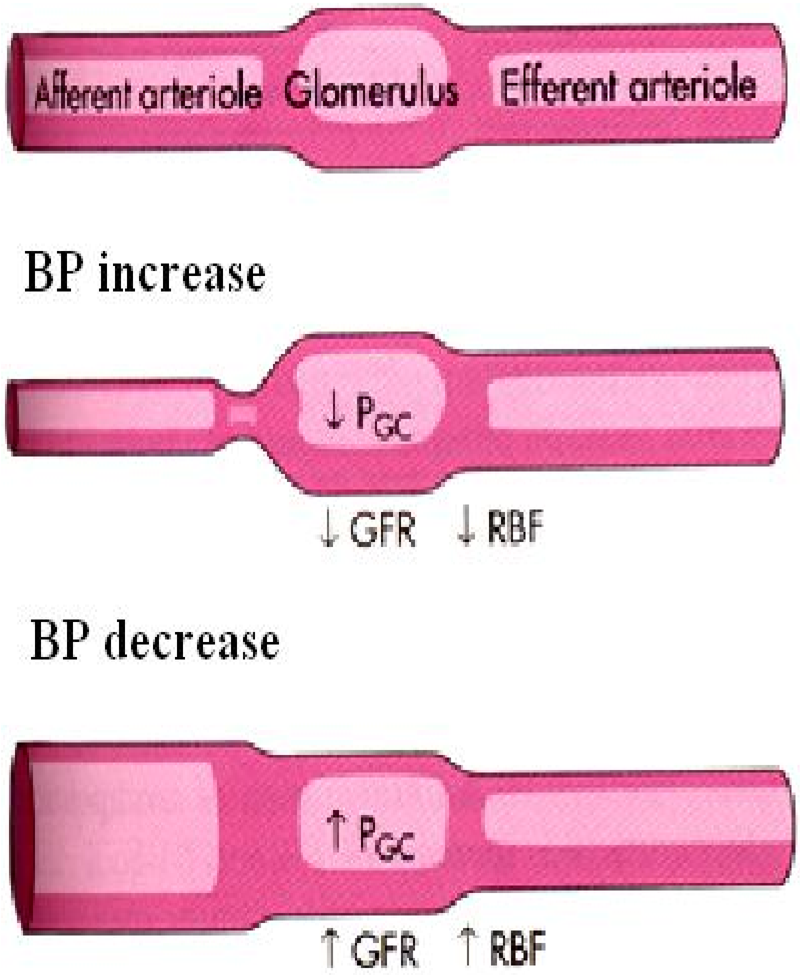
Autoregulation of GFR

- Under normal conditions (MAP =80-180mmHg) renal autoregulation maintains a nearly constant glomerular filtration rate
- Two mechanisms are in operation for autoregulation:
  - Myogenic mechanism
  - Tubuloglomerular feedback
- Myogenic mechanism:
  - Arterial pressure rises, afferent arteriole stretches
  - Vascular smooth muscles contract
  - Arteriole resistance offsets pressure increase; RBF (& hence GFR) remain constant.



Renal blood flow (ml/min)
1600
1200
800
400
0
160
120
80
40
0
Glomerular filtration rate (ml/min)
Renal blood flow
Glomerular filtration rate
Urine output (ml/min)
8
6
4
2
0
50
100
150
200
Arterial pressure (mm Hg)

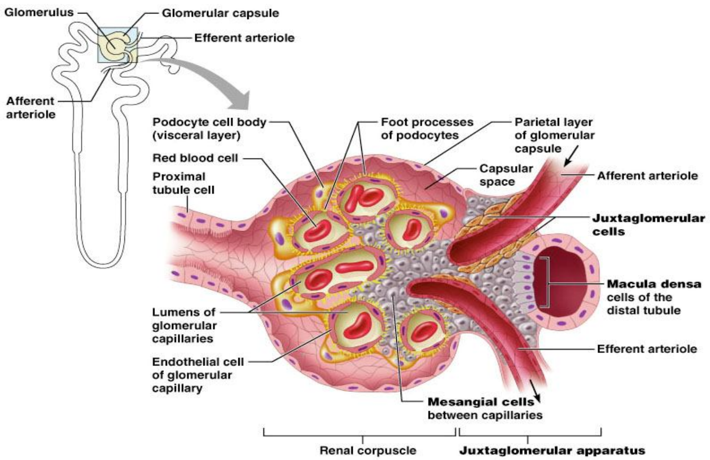
Blood Flow =
Capillary Pressure /
Flow resistance

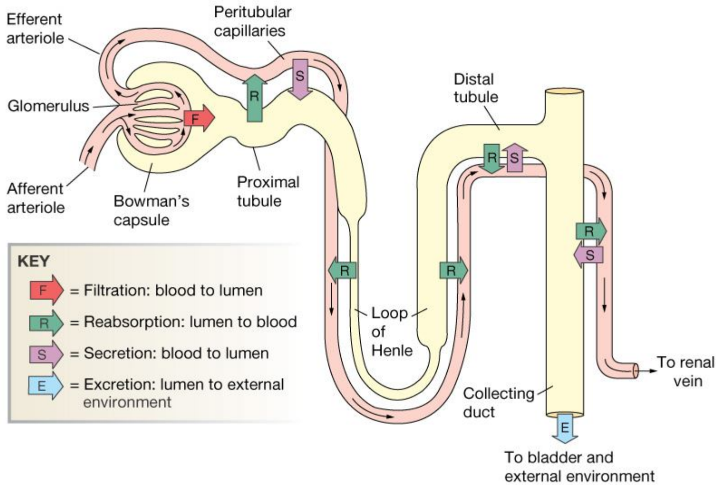


Tubuloglomerular feed back

Tubuloglomerular feed back mechanism:

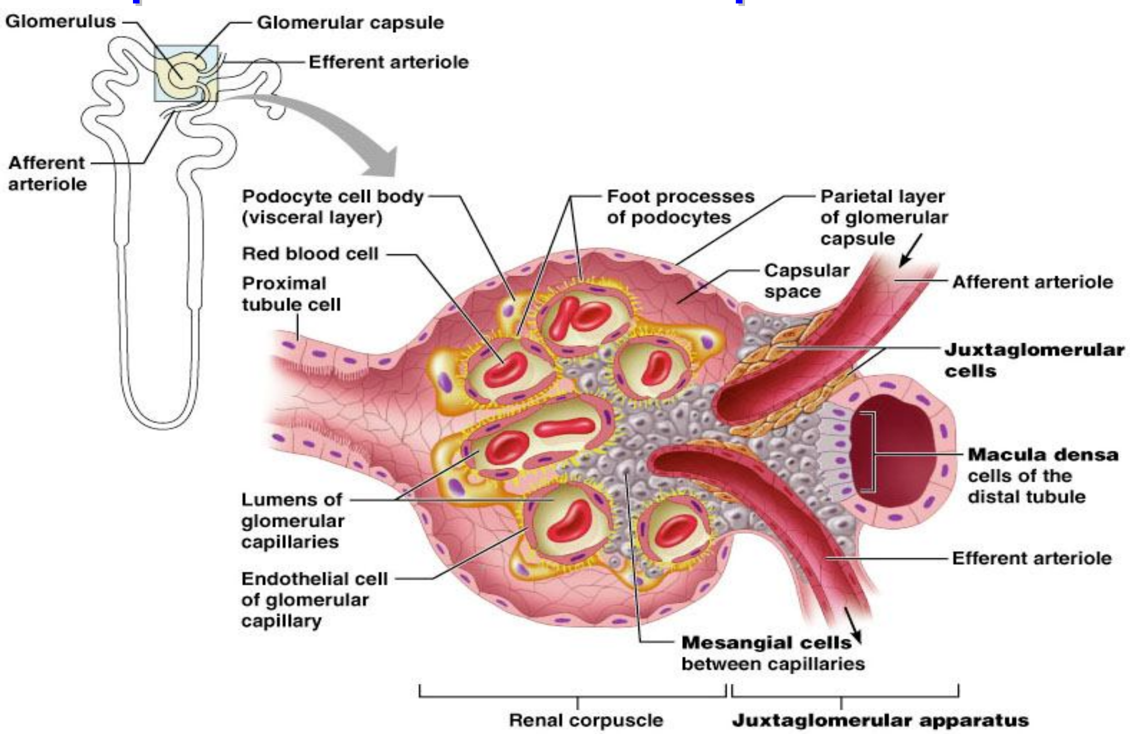
- -Feedback loop consists of a flow rate (increased NaCl) sensing mechanism in macula densa of juxtaglomerular apparatus (JGA)
- -Increased GFR (& RBF) triggers release of vasoactive signals
- -Constricts afferent arteriole leading to a decreased GFR (& RBF)





Juxtaglomerular Apparatus

- Arteriole walls have juxtaglomerular (JG) cells - enlarged, smooth muscle cells, have secretory granules containing renin, act as mechanoreceptors
- Macula densa - tall, closely packed distal tubule cells, lie adjacent to JG cells function as chemoreceptors or osmoreceptors



↑ GFR

↓

↑ Rate of fluid flow through tubules

↓

Stimulation of macula-densa cells to release vasoactive chemicals

↓

Chemicals released that induce afferent arteriolar vasoconstriction

↓

↓ Blood flow into glomerulus

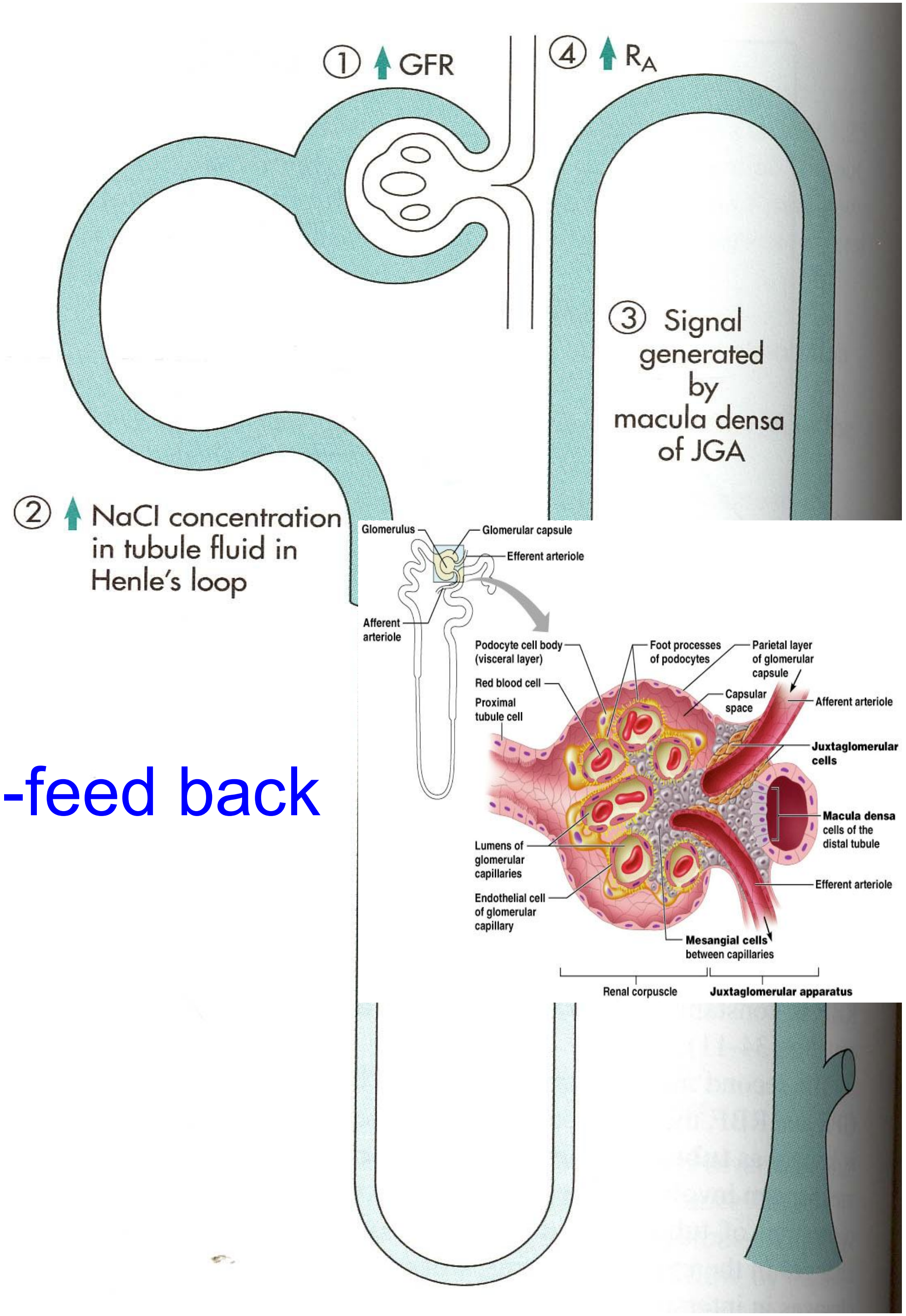
↓

↓ Glomerular capillary pressure to normal

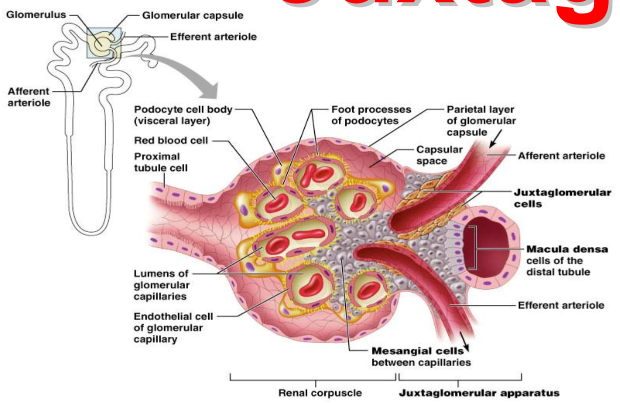
↓

↓ GFR to normal

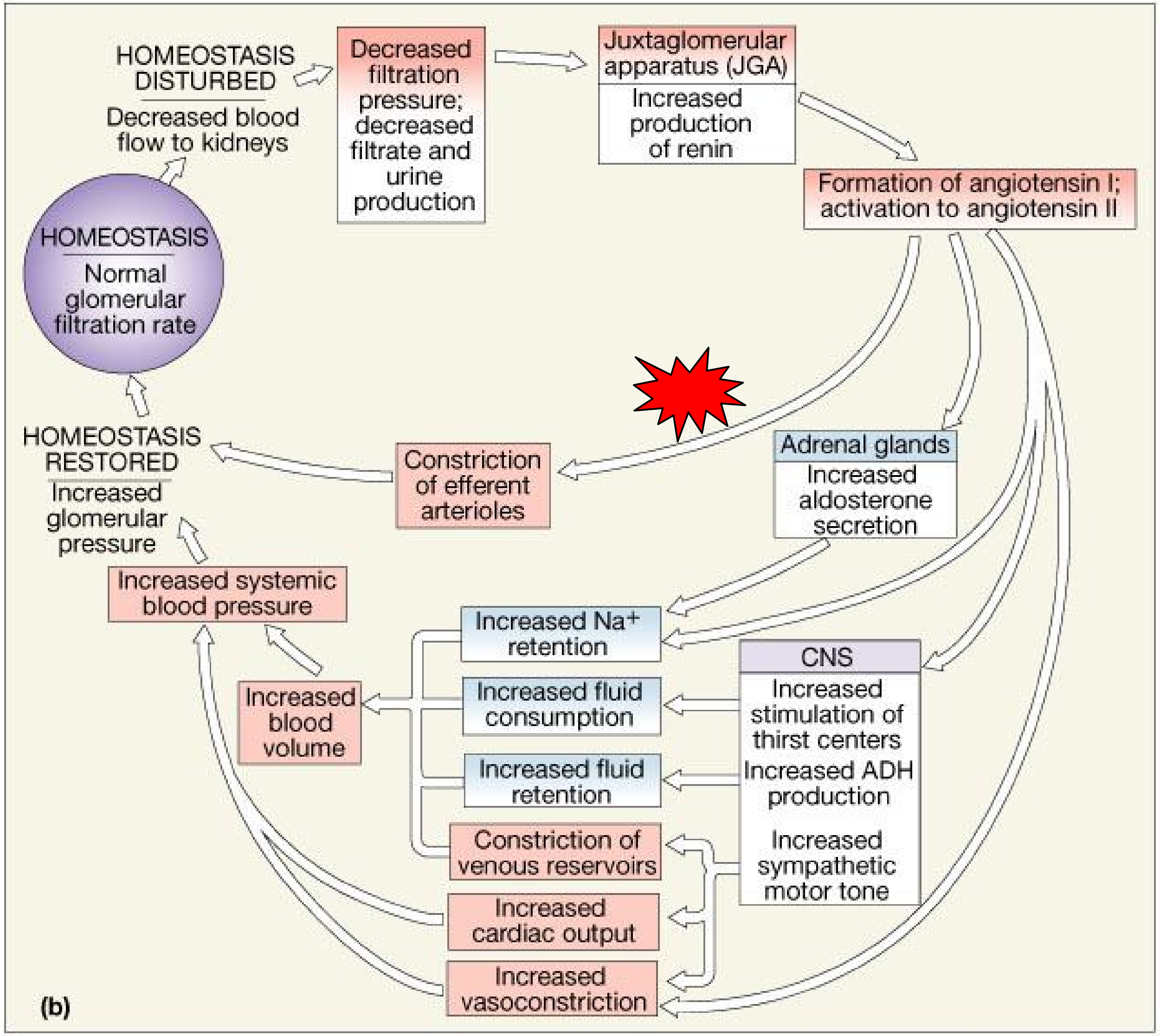
TG-feed back



Juxtaglomerular Apparatus



JG cells-Renin

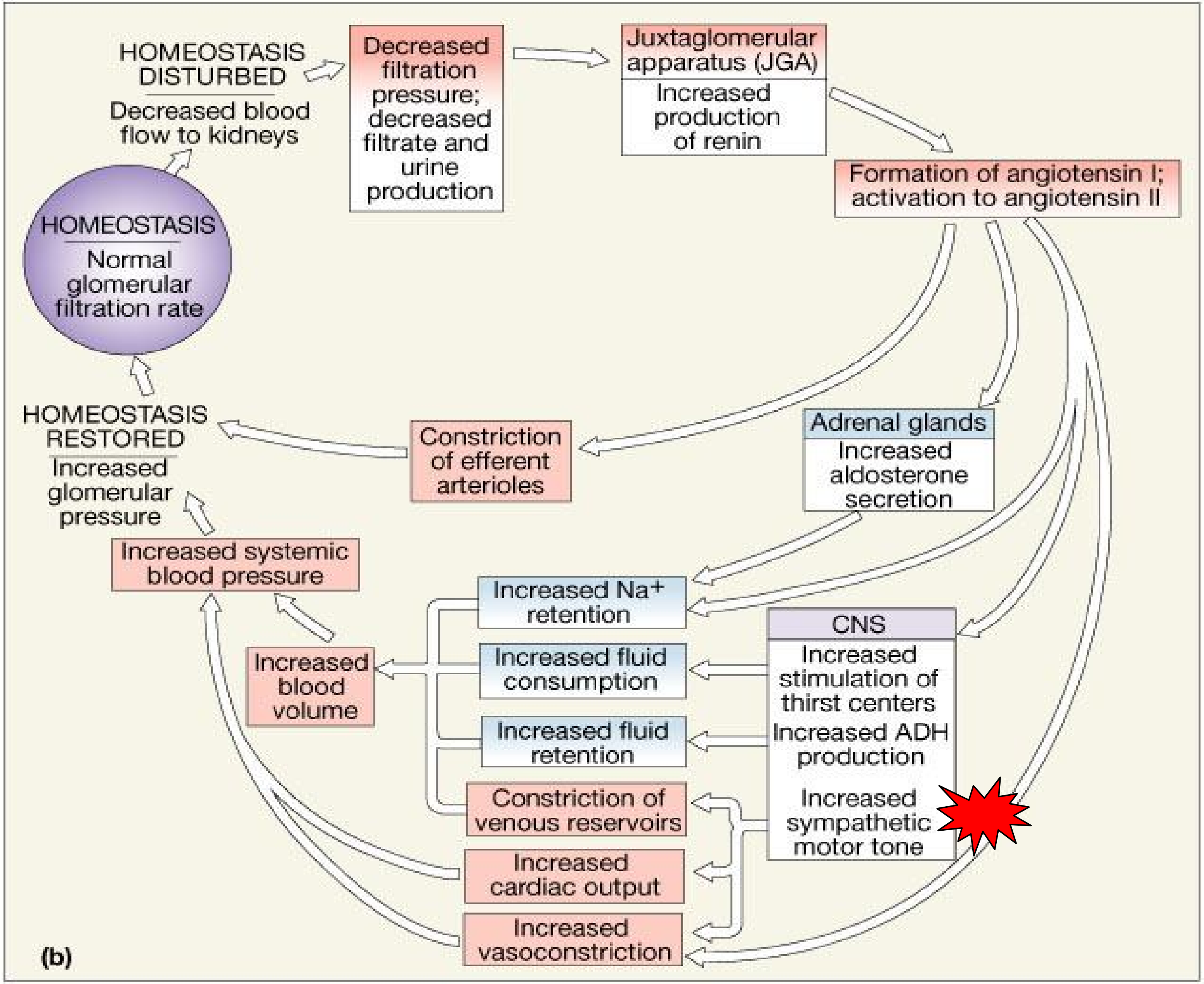


TG-feed back

Neural regulation of GFR

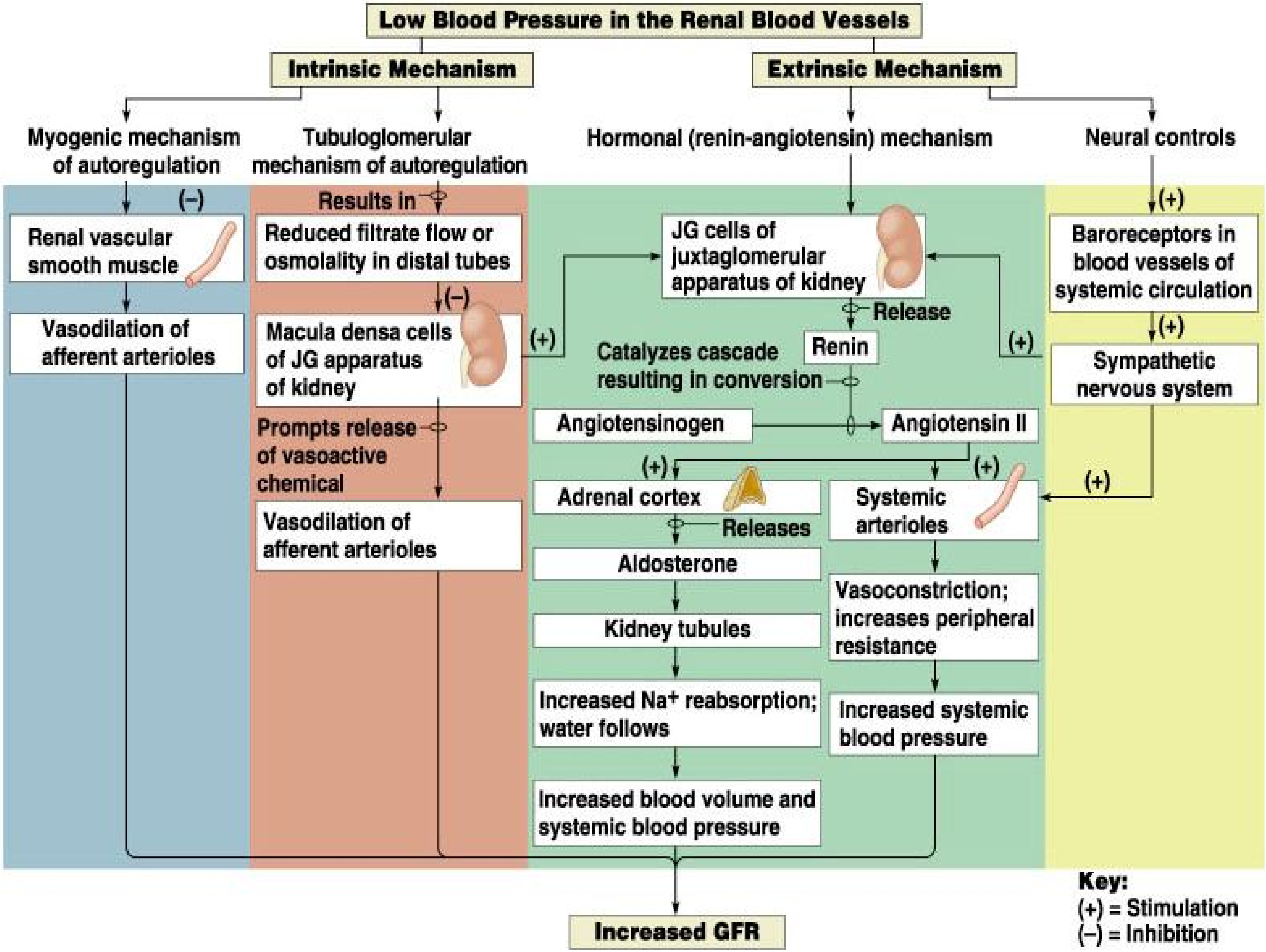
- When the sympathetic nervous system is at rest:
  - Renal blood vessels are maximally dilated
  - Autoregulation mechanisms prevail
- Under stress:
  - Norepinephrine is released by the sympathetic nervous system
  - Epinephrine is released by the adrenal medulla
  - Afferent arterioles constrict and filtration is inhibited
- The sympathetic nervous system also stimulates the renin-angiotensin mechanism
- A drop in filtration pressure stimulates the Juxtaglomerular apparatus (JGA) to release renin and erythropoietin

Response to a Reduction in the GFR



Renin-Angiotensin Mechanism

- Renin release is triggered by:
  - Reduced stretch of the granular JG cells
  - Stimulation of the JG cells by activated macula densa cells
  - Direct stimulation of the JG cells via $\beta 1$-adrenergic receptors by renal nerves
- Renin acts on angiotensinogen to release angiotensin I which is converted to angiotensin II
- Angiotensin II:
  - Causes mean arterial pressure to rise
  - Stimulates the adrenal cortex to release aldosterone
- As a result, both systemic and glomerular hydrostatic pressure rise



Low Blood Pressure in the Renal Blood Vessels
Intrinsic Mechanism
Extrinsic Mechanism
Myogenic mechanism of autoregulation
Tubuloglomerular mechanism of autoregulation
Hormonal (renin-angiotensin) mechanism
Neural controls
(–)
Results in
Renal vascular smooth muscle
Reduced filtrate flow or osmolality in distal tubes
JG cells of juxtaglomerular apparatus of kidney
(+)
Baroreceptors in blood vessels of systemic circulation
Release
(+)
Vasodilation of afferent arterioles
(–)
Macula densa cells of JG apparatus of kidney
(+)
Renin
Catalyzes cascade resulting in conversion
(+)
Sympathetic nervous system
Angiotensinogen
Angiotensin II
Prompts release of vasoactive chemical
(+)
(+)
(+)
Adrenal cortex
Systemic arterioles
Releases
Vasodilation of afferent arterioles
Aldosterone
Vasoconstriction; increases peripheral resistance
Kidney tubules
Increased Na+ reabsorption; water follows
Increased systemic blood pressure
Increased blood volume and systemic blood pressure
Increased GFR
Key:
(+) = Stimulation
(–) = Inhibition

Other Factors Affecting Glomerular Filtration

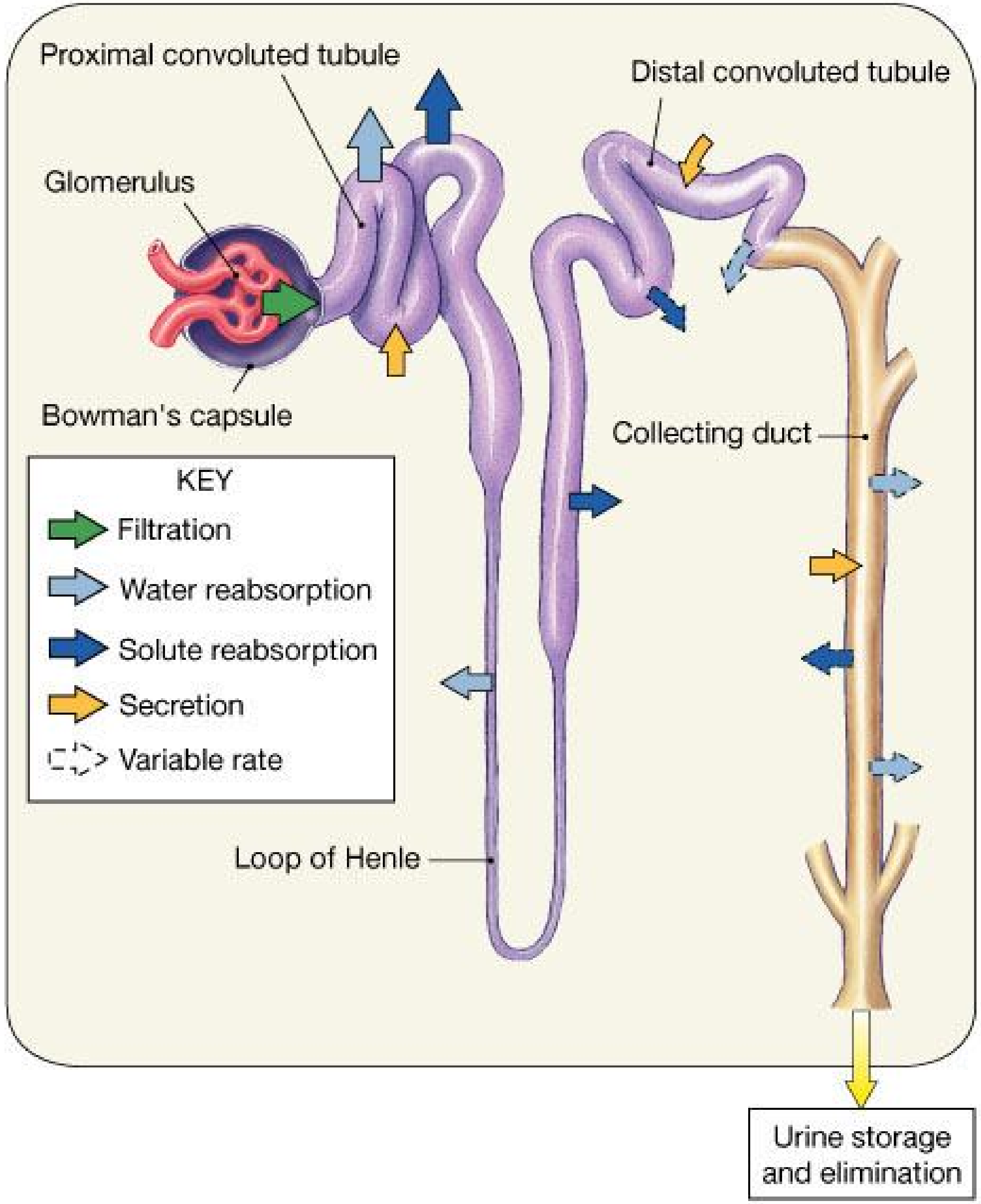
- Prostaglandins (PGE_2 and PGI_2)
  - Vasodilators produced in response to sympathetic stimulation and angiotensin II
  - Are thought to prevent renal damage when peripheral resistance is increased
- Nitric oxide – vasodilator produced by the vascular endothelium
- Adenosine – vasoconstrictor of renal vasculature
- Endothelin – a powerful vasoconstrictor secreted by tubule cells

Process of Urine Formation

Glomerular filtration

Tubular reabsorption of the substance from the tubular fluid into blood

Tubular secretion of the substance from the blood into the tubular fluid



Renal tubular reabsorption

- Transcellular: movement of solutes and water through cells
- Paracellular: movement of solutes and water between cells
- Epithelial cell junctions can be “leaky” (proximal tubule) or “tight” (distal convoluted tubule, collecting duct). Therefore paracellular movement is affected.

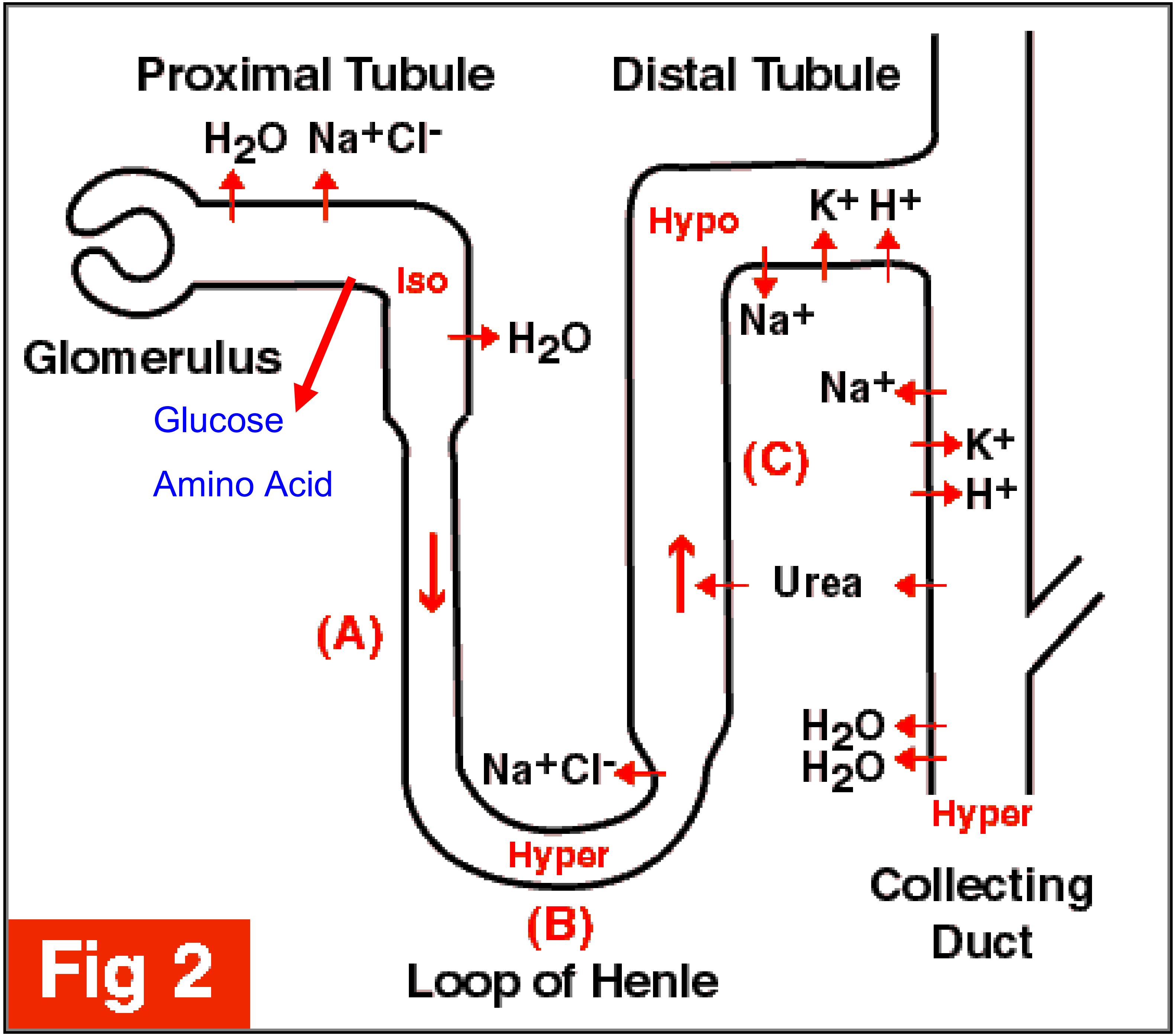
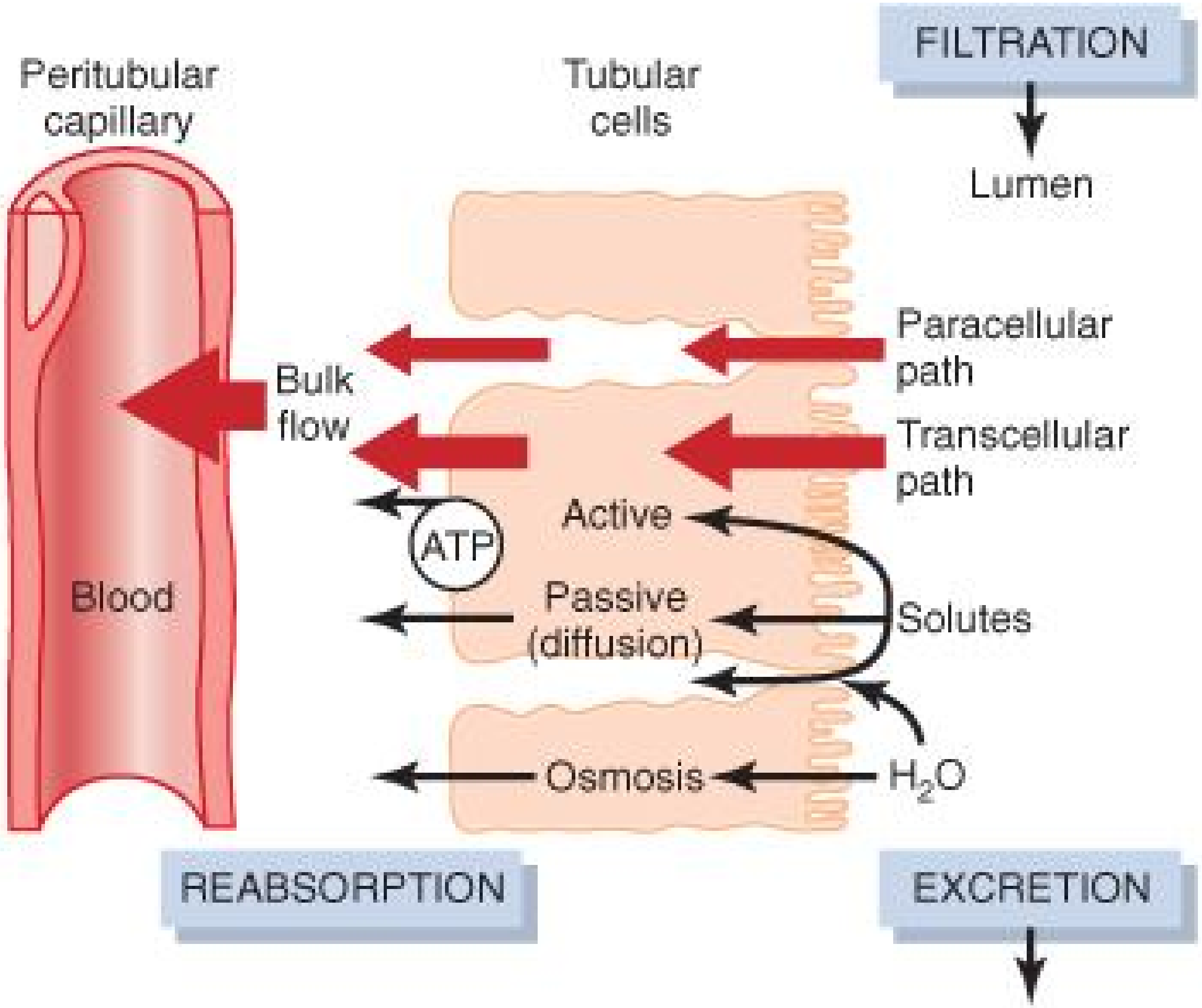

Proximal Tubule
Distal Tubule
H_2O Na^+Cl^-
Glomerulus
Iso
H_2O
Glucose
Amino Acid
Hypo
K^+ H^+
Na^+
Na^+
K^+
H^+
(C)
Urea
(A)
Na^+Cl^-
H_2O
H_2O
Hyper
Hyper
(B)
Loop of Henle
Collecting Duct

Fig 2

Renal tubular endothelium

- The luminal or apical cell membranes
  - Face the tubular lumen
  - (“urine” side)
- The basolateral cell membranes
  - in contact with the lateral intercellular spaces and peritubular interstitium
  - (“blood” side)


FILTRATION
Peritubular capillary
Tubular cells
Lumen
Paracellular path
Bulk flow
Transcellular path
Active
ATP
Blood
Passive (diffusion)
Solutes
Osmosis
H_2O
REABSORPTION
EXCRETION

Routes of transport across proximal tubular epithelium

- Paracellular
  - 1% of surface area
  - 5-10% of water transfer
  - Passive diffusion or solvent drag only
  - Requires favourable electro-chemical gradient
  - Passive diffusion of ions and large non-polar solutes
- Transcellular
  - 99% of surface area
  - 90-95% of water transfer
  - Passive or active transport
  - All active transport occurs by this route

Types of transport processes

- Passive transport (simple diffusion)
- Facilitated diffusion
- Primary active transport
- Secondary active transport
- Pinocytosis
- Solvent drag

Renal tubular activity

Net result

- **Excretion:** removal of solutes and water from the body in urine
- **Retention**: solutes and water remain in the body

Direction of movement

- **Reabsorption:** movement from tubular fluid to peritubular blood
- **Secretion:** movement from peritubular blood to tubular fluid

Table 14–2 Average Values for Several Components that Undergo Filtration and Reabsorption

Substance	Amount Filtered Per Day	Amount Excreted Per Day	Percent Reabsorbed
Water, L	180	1.8	99
Sodium, g	630	3.2	99.5
Glucose, g	180	0	100
Urea, g	54	30	44

Table 14–3 Average Daily Water Gain and Loss in Adults

Intake	
In liquids	1200 ml
In food	1000 ml
Metabolically produced	350 ml
Total	**2550 ml**
Output	
Insensible loss (skin and lungs)	900 ml
Sweat	50 ml
In feces	100 ml
Urine	1500 ml
Total	**2550 ml**

Table 14–5 Summary of "Division of Labor" in the Renal Tubules

Tubular Segment	Major Functions	Controlling Factors
Glomerulus/Bowman's capsule	Forms ultrafiltrate of plasma	Starling forces (P_{GC}, P_{BS}, π_{GC})
Proximal tubule	Bulk reabsorption of solutes and water Secretion of solutes (except potassium) and organic acids and bases	Active transport of solutes with passive water reabsorption Parathyroid hormone inhibits phosphate reabsorption
Loop of Henle	Establishes medullary osmotic gradient (juxtamedullary nephrons) Secretion of urea	
Descending limb	Bulk reabsorption of water	Passive water reabsorption
Ascending limb	Reabsorption of NaCl	Active transport
Distal tubule and cortical collecting duct	Fine-tuning of the reabsorption/ secretion of small quantity of solute remaining	Aldosterone stimulates sodium reabsorption and potassium excretion Parathyroid hormone stimulates calcium reabsorption
Cortical and medullary collecting duct	Fine-tuning of water reabsorption Reabsorption of urea	Vasopressin increases passive reabsorption of water

Proximal tubule

- Solute reabsorption in the proximal tubule is isosmotic (water follows solute osmotically and tubular fluid osmolality remains similar to that of plasma)
- 60-70% of water and solute reabsorption occurs in the proximal tubule
  - 90% of bicarbonate
  - 100% of glucose & amino acids
- Proximal tubules: coarse adjustment

  (Distal tubules and CTs: fine adjustment)

Functions of Proximal Convoluted Tubules

Reabsorption

- Na^+, K^+, Ca^{2+}, Mg^{2+}, HCO_3^-, PO_4^-, H_2O
- Amino acids, Proteins, Glucose, Uric Acid, Urea
- Lactate, Citrate, Water soluble Vitamins

Secretion

- H^+, Organic acids and bases, uric acid &drugs

Regulation of pH

- Excretion of H^+ and HCO_3^-
- Na+-K+ Exchange
- Excretion of NH_3^+

Table 38–6. Transport proteins involved in the movement of Na^+ and Cl^- across the apical membranes of renal tubular cells.[1]

Site	Apical Transporter	Function
Proximal tubule	Na^+/glucose CT	Na^+ uptake, glucose uptake
	Na^+/Pi CT	Na^+ uptake, Pi uptake
	Na^+ amino acid CT	Na^+ uptake, amino acid uptake
	Na^+/lactate CT	Na^+ uptake, lactate uptake
	Na^+/H^+ exchanger	Na^+ uptake, H extrusion
	Cl^-/base exchanger	Cl^- uptake

Proximal tubule