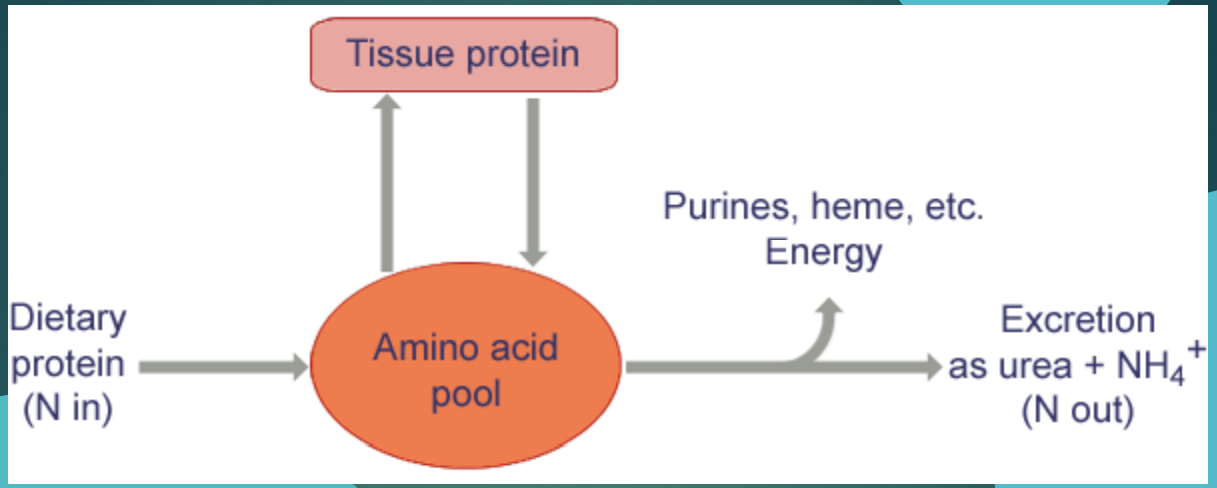

IN THE NAME OF GOD

UREA , CREATININ METABOLISM AND CLINICAL SIGNIFICANCE

PASHA, F. MD
Assistant professor of nephrology
Tehran Islamic Azad University

N balance

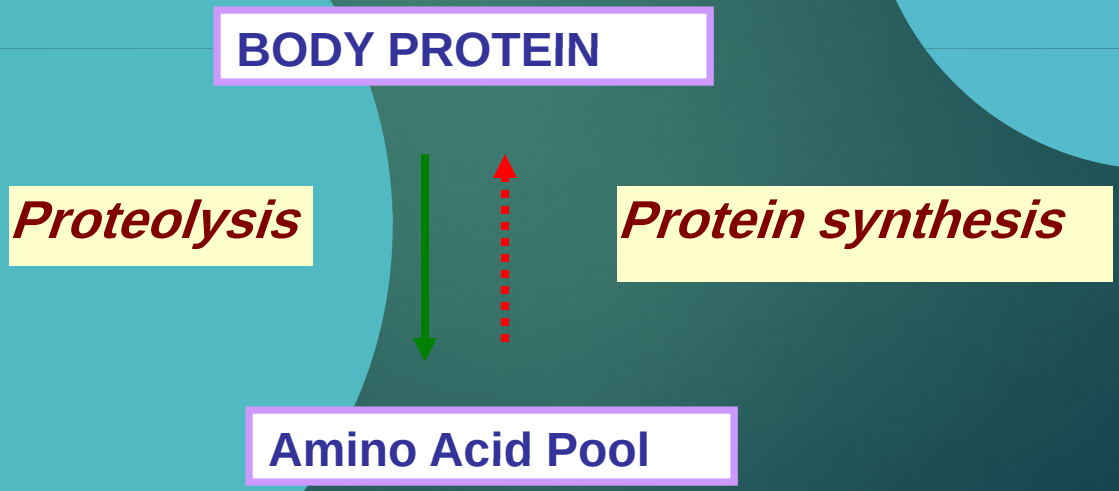


1. Major dietary source of N is Protein (>95%), since the diet has very few free amino acids
2. AA are used for Protein Synthesis & N containing compounds
3. AA in excess are degraded (used for energy)

   N is disposed of in urea (80%), ammonia, uric acid or creatinine in urine with small amounts in fecal matter

PROTEIN BALANCE

- Positive: synthesis > degradation (e.g., growth, body building)
- Negative: synthesis < degradation (e.g., starvation, trauma, cancer cachexia)

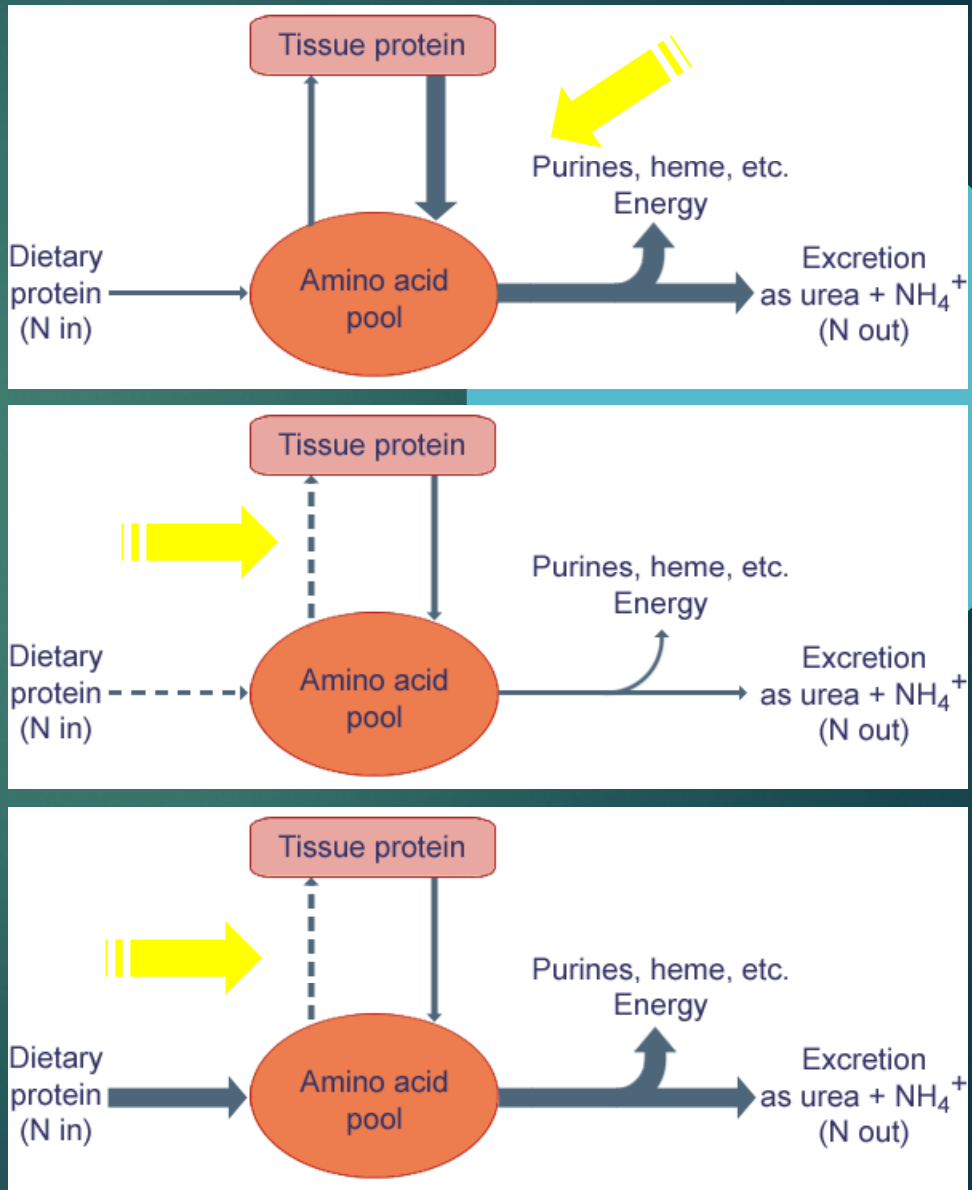


Negative Nitrogen Balance

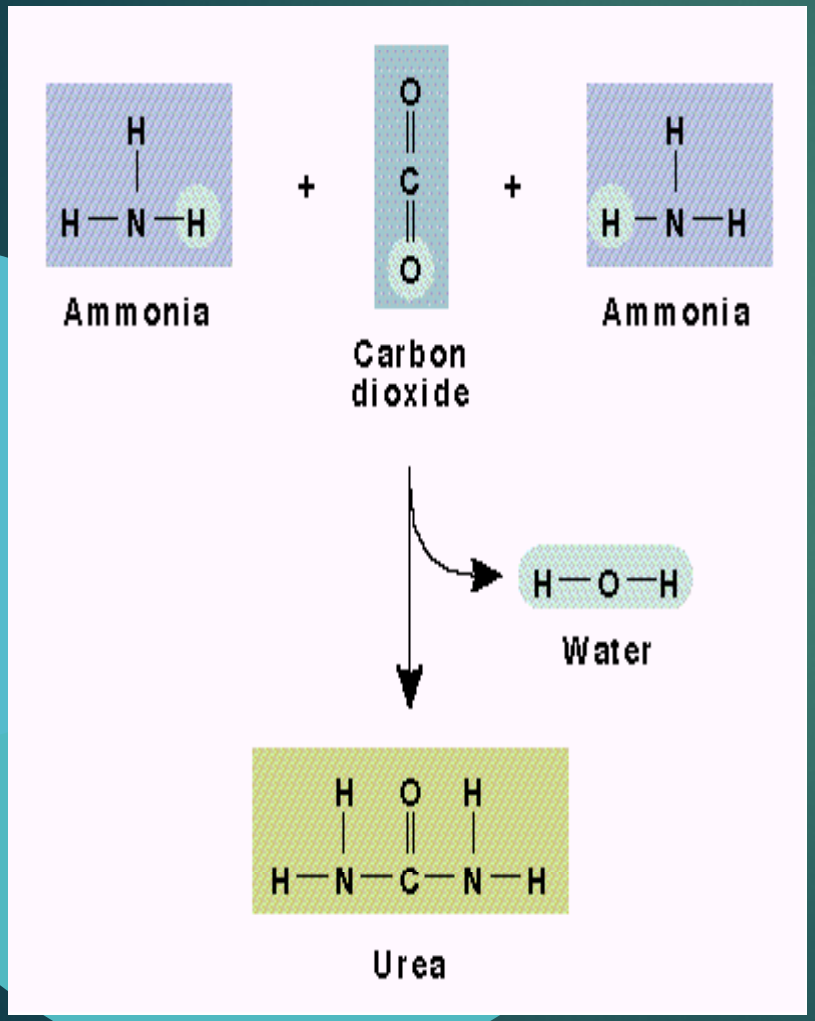
1. Stress

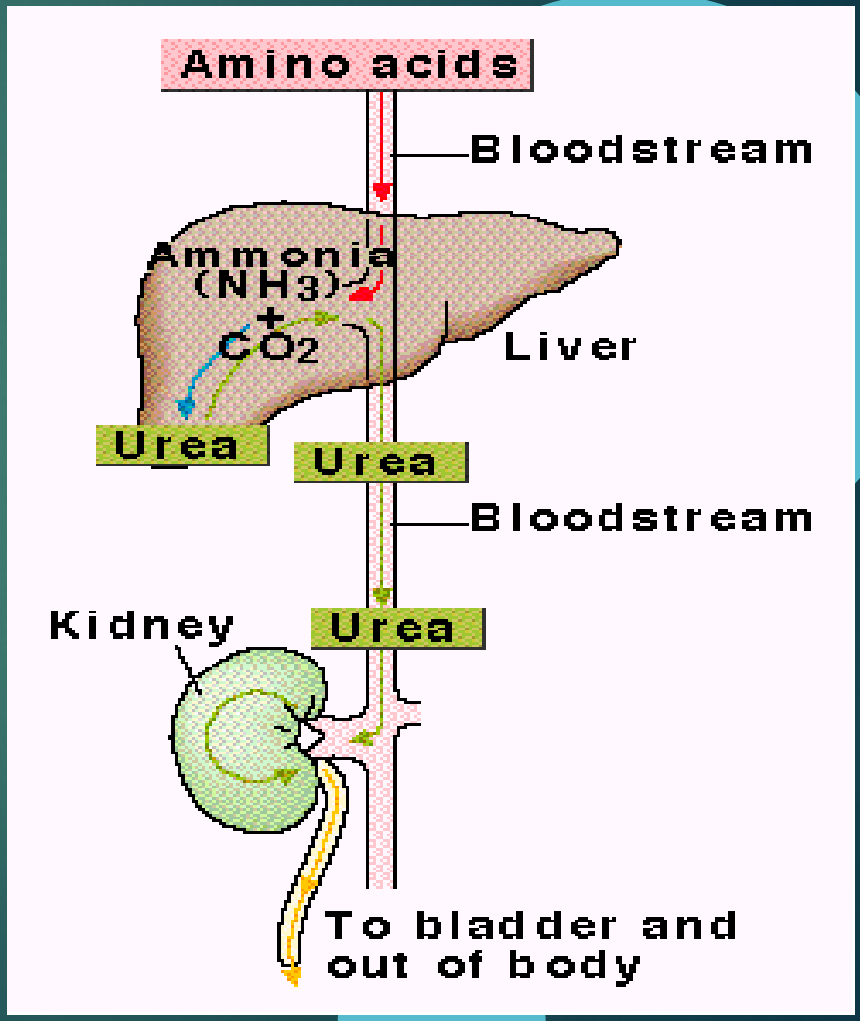
2. Decreased Intake

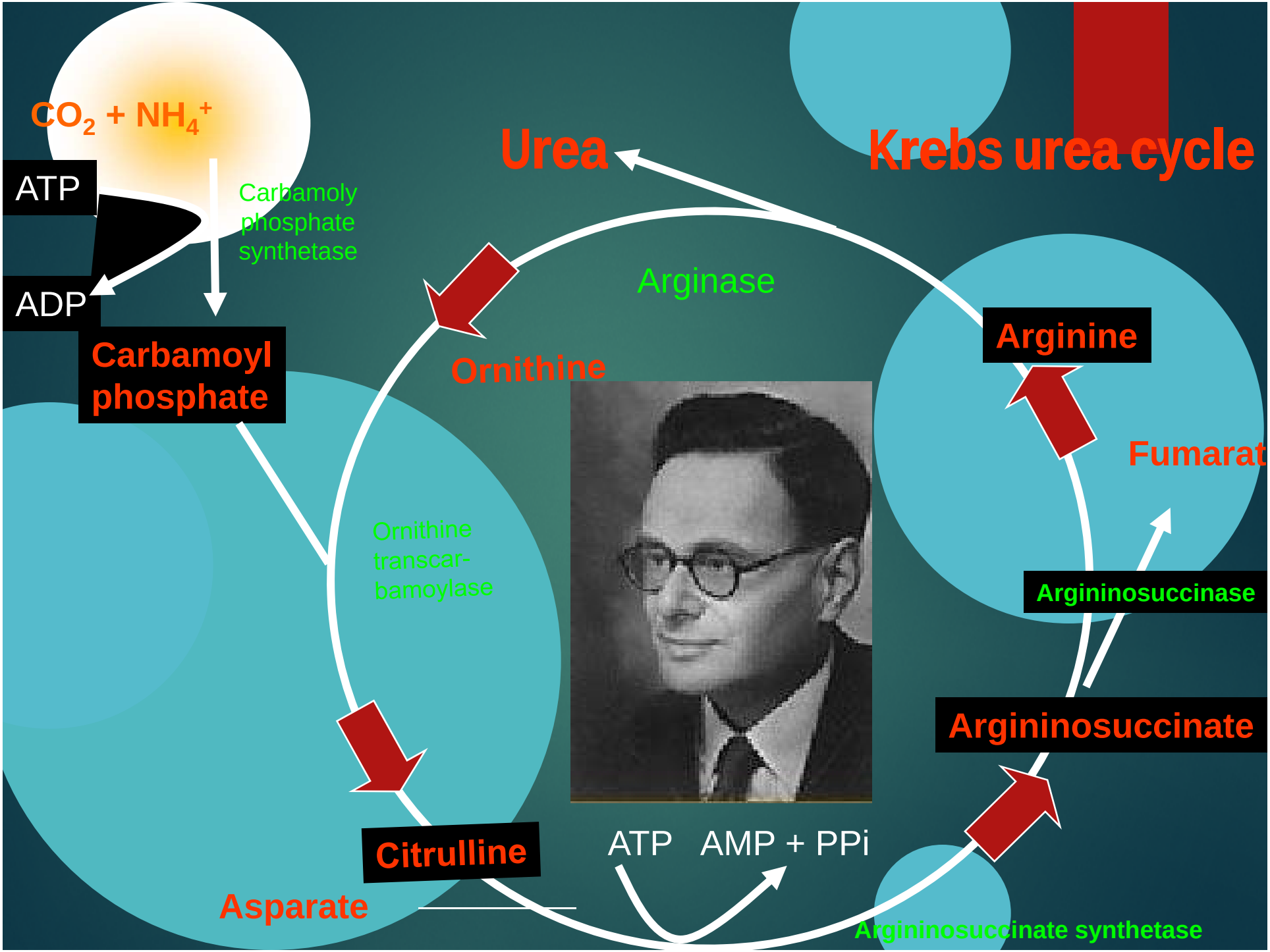
3. Lack of an essential AA



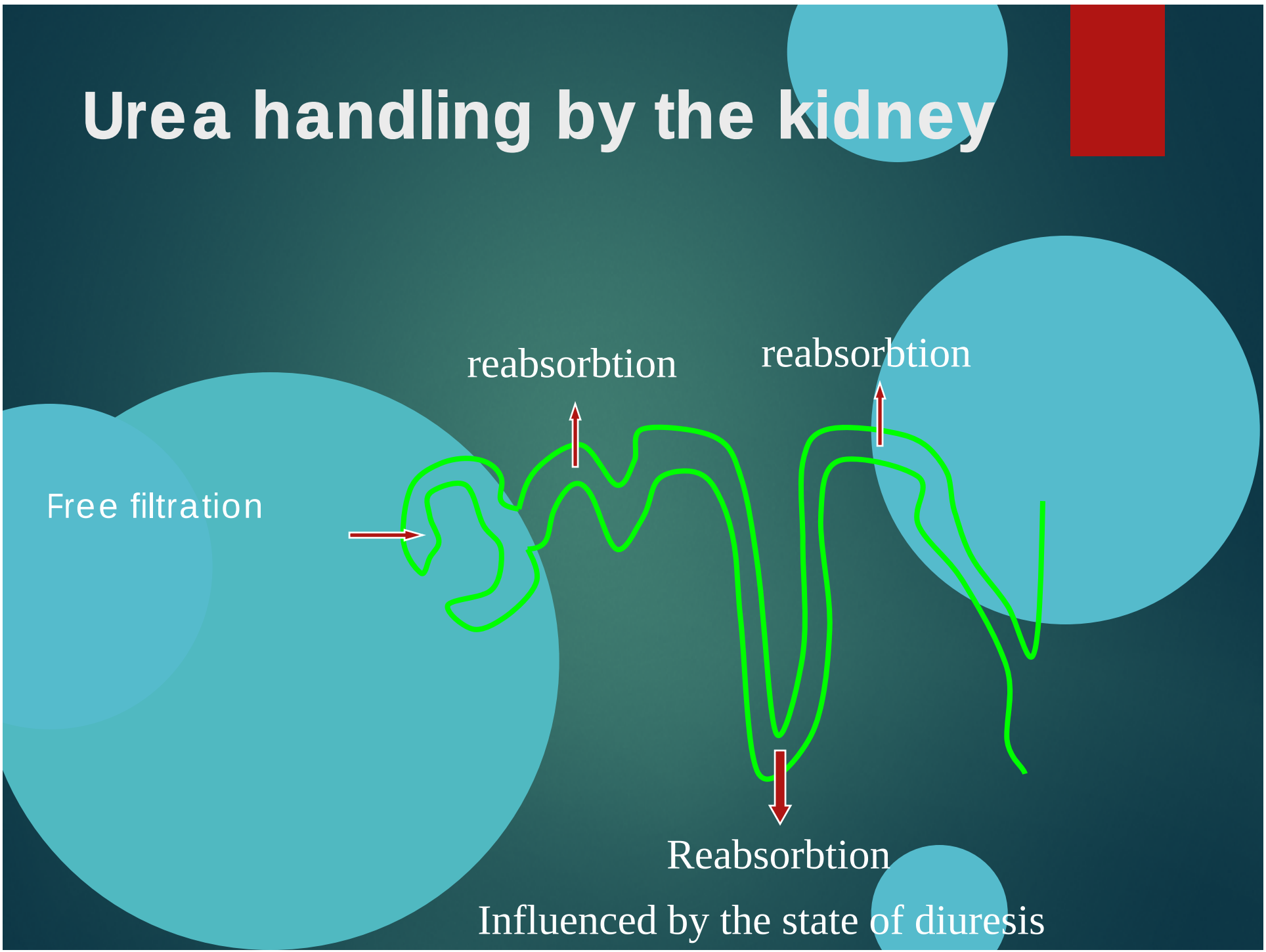
Urea Synthesis and Excretion






$CO_2 + NH_4^+$
ATP
ADP
Carbamoly phosphate synthetase
Carbamoyl phosphate
Urea
Krebs urea cycle
Arginase
Ornithine
Arginine
Fumarat
Ornithine transcar-bamoylase
Argininosuccinase
Argininosuccinate
Citrulline
ATP AMP + PPi
Asparate
Argininosuccinate synthetase

Urea handling by the kidney



Influenced by the state of diuresis

DEFINITION of AZOTEMIA

- nitrogen retention noted as incr. BUN

PATHOPHYSIOLOGY:

Decreased glomerular filtration rate (GFR)

Failure of waste excretion

Elevated concentration of wastes in the blood stream

- **incr. creatinine (Cr)**
- **incr. urea (blood urea nitrogen, BUN)**

BUN

- **Incr. BUN**

  renal insufficiency — urea retention

  incr renal reabsorb — urea retention

  GI bleed — incr. substrate

  high protein intake — incr. substrat

- **Decr. BUN**

  liver failure — decr. urea pdt

  malnutrition — decr. Substrate

  pregnancy — incr. excretion

BUN

- Almost all urea is filtered out of blood by glomerular function. Some urea reabsorbed with water but most is removed in urine.
- Many non-renal conditions can increase BUN, i.e. hypovolemia, shock, burns, dehydration, congestive heart failure, excess protein catabolism.
- Thus, BUN needs to be compared to creatinine to determine true renal dysfunction

RENAL INSUFFICIENCY: classification

	BUN/Cr ratio	Explanation
normal	varies between	10 : 1 --> - - - 20 :1
decr. renal perf. prerenal azotemia	> ~ 20 : 1	Cr: secretion continues Urea: decr. peritubular blood flow: incr. urea reabsorption
intrinsic renal dis. renal azotemia	<~10:1	mimics usual ratio (no incr. urea reabsorption)

NOTE: calculate ratio when *either* Cr or BUN are abn.

Elevation of the BUN compared to creatinine

The low tubular flow rate and increased recycling of urea :

- prerenal azotemia
- upper gastrointestinal bleeding
- hyperalimentation
- increased tissue catabolism
- glucocorticoid use

CREATINE: synthesized in: muscle, pancreas, kidney

Transported to tissues (muscle, brain) via blood

Creatine + ATP <--Creatine kinase (CK)--> ADP + creatine phosphate*

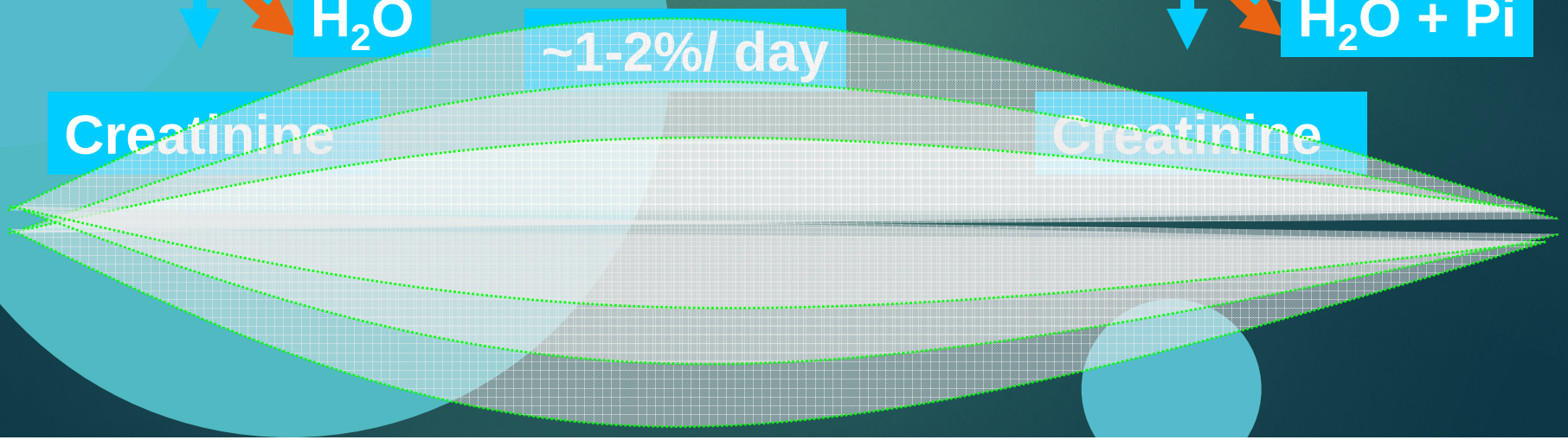
H_2O

~1-2%/ day

Creatinine

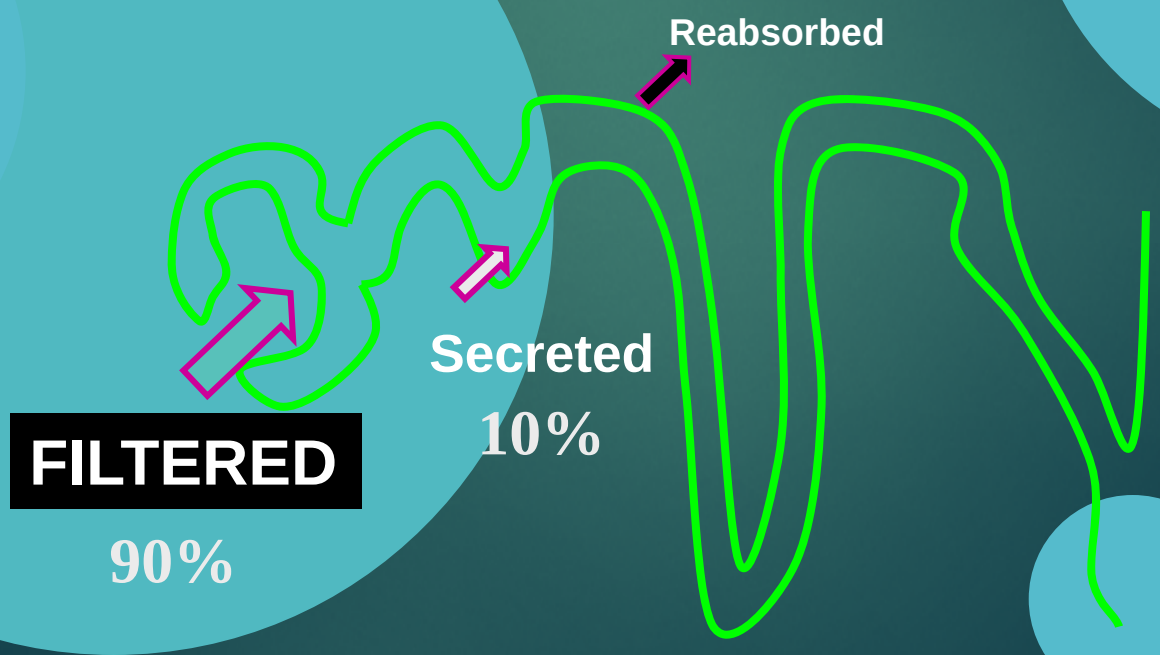
H_2O + Pi

Creatinine



CrEATININE: renal excretion

- - Cr: freely filtered through GBM
- - Cr: secreted via tubules
- - Cr: negligible amount: reabsorbed

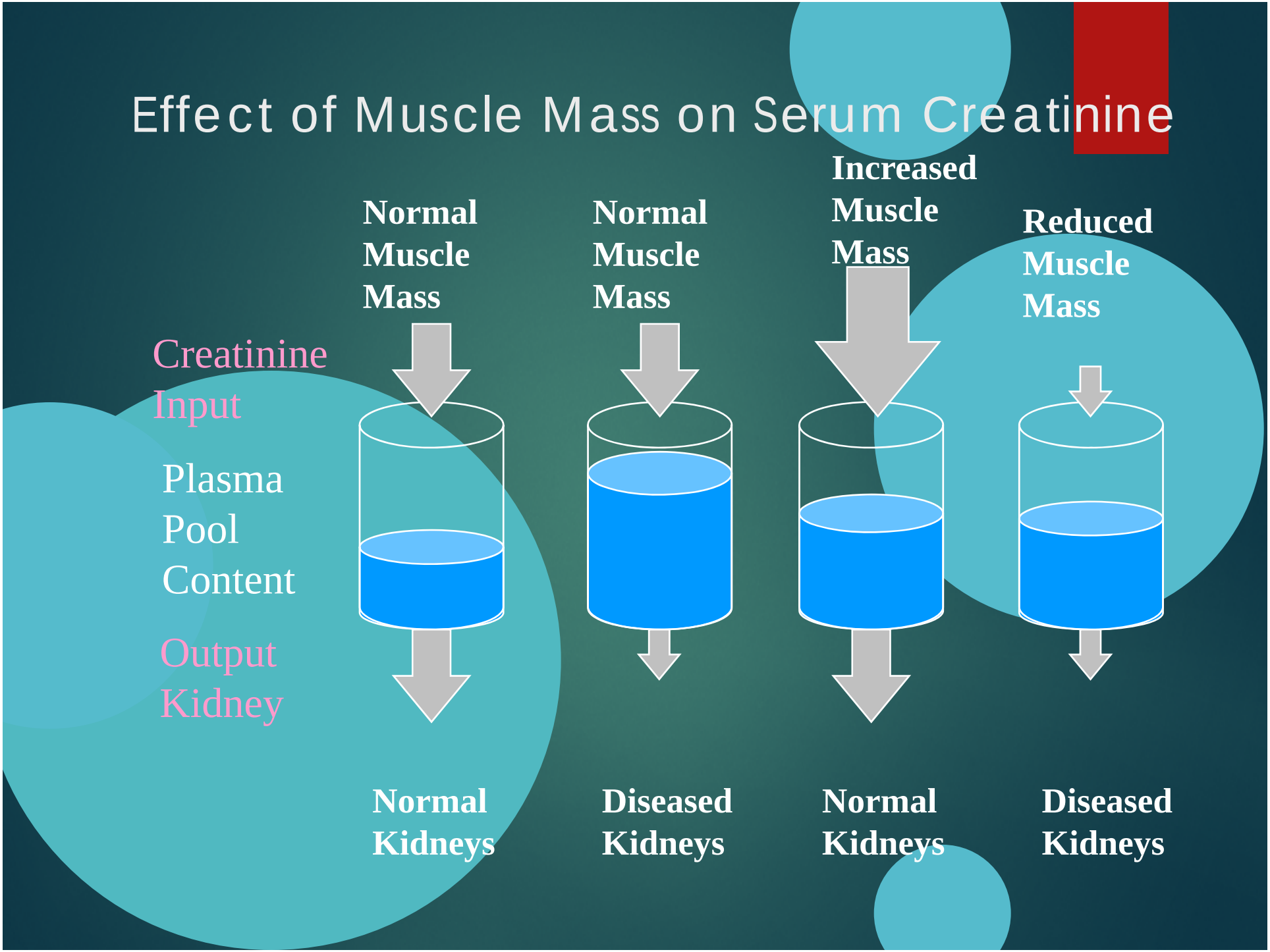


CREATININE: breakdown product of: creatine

- concentration in blood is related to:
  - muscle mass
  - creatine intake (body builders)
  - excretion by the kidney

- concentration in blood is *inversely* proportional to:
  - clearance via the kidney (GFR)

Effect of Muscle Mass on Serum Creatinine



Measurement of Glomerular Filtration Rate (GFR)

- GFR is essential to renal function
- Most frequently performed test of renal function.
- Measurement is based on concept of clearance: -

"The determination of the volume of plasma from which a substance is removed by glomerular filtration during it's passage through the kidney"

RENAL INSUFFICIENCY

- Etiologies:

- - decr. renal perfusion — prerenal azotemia

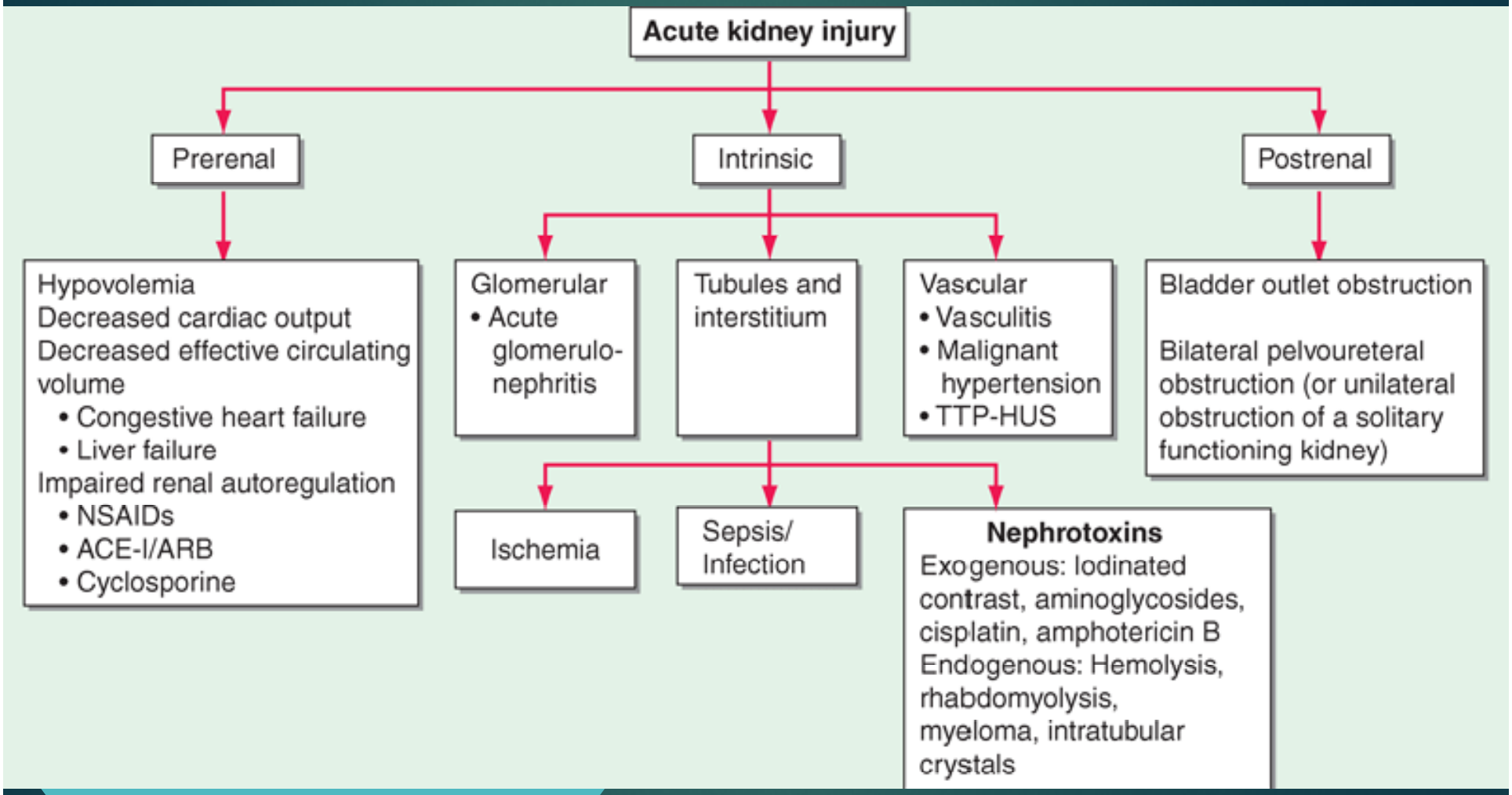
  hypovolemia, decr. cardiac output, vasodilation

- - intrinsic renal disease — renal azotemia

  ATN , GN , Intrestitial nephritis , vasculitis

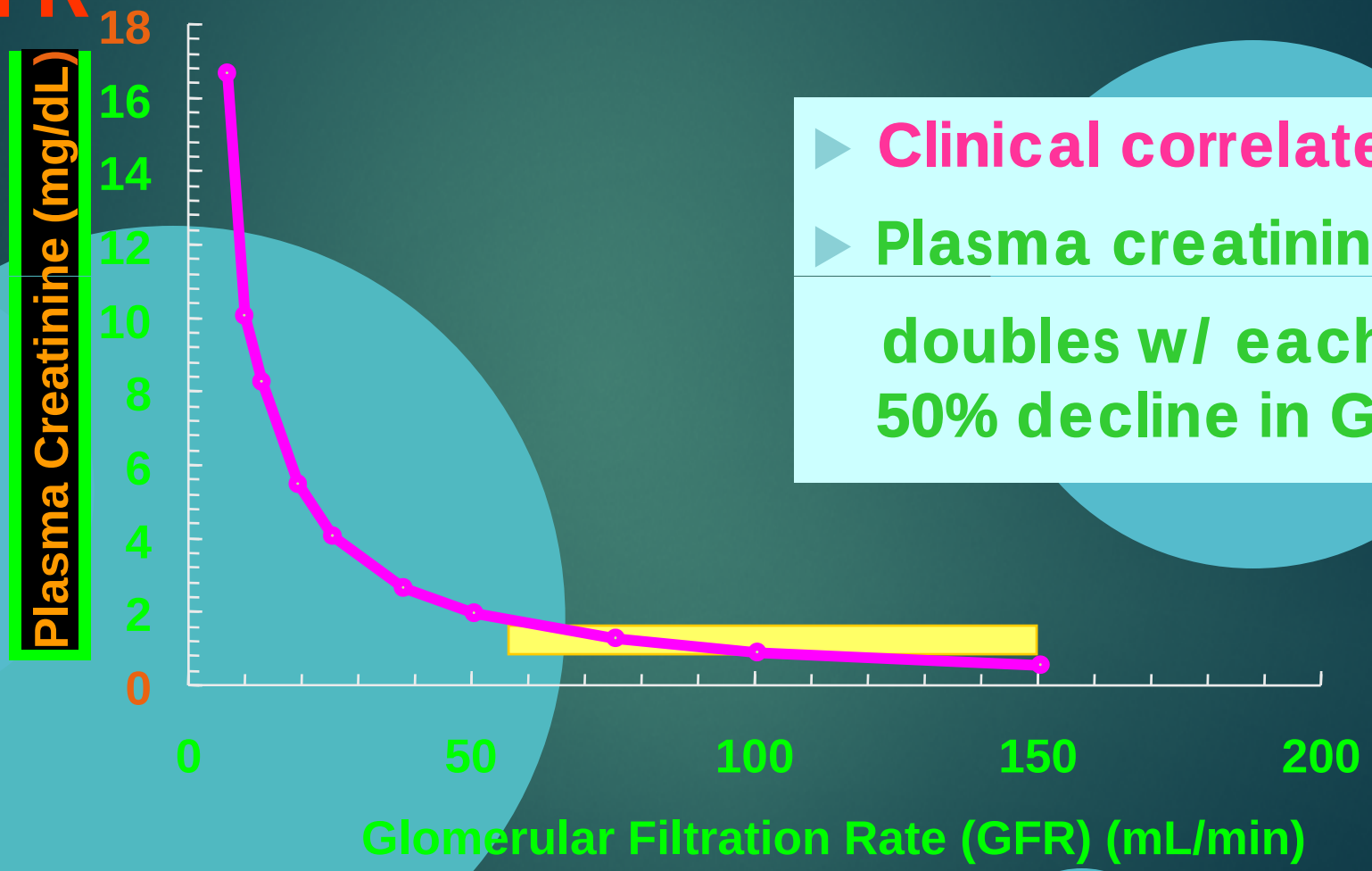
- - obstructive uropathy — postrenal azotemia

  tumor, stone, inflammation, prostate enlargement


Acute kidney injury
Prerenal
Intrinsic
Postrenal
Hypovolemia
Decreased cardiac output
Decreased effective circulating volume
• Congestive heart failure
• Liver failure
Impaired renal autoregulation
• NSAIDs
• ACE-I/ARB
• Cyclosporine
Glomerular
• Acute glomerulo-nephritis
Tubules and interstitium
Vascular
• Vasculitis
• Malignant hypertension
• TTP-HUS
Bladder outlet obstruction
Bilateral pelvoureteral obstruction (or unilateral obstruction of a solitary functioning kidney)
Ischemia
Sepsis/ Infection
Nephrotoxins
Exogenous: Iodinated contrast, aminoglycosides, cisplatin, amphotericin B
Endogenous: Hemolysis, rhabdomyolysis, myeloma, intratubular crystals

Property	Urea	Creatinine	Inulin	^{99m}TcDTPA
Not Protein Bound	*Yes*	*Yes*	*Yes*	*Yes*
Freely Filtered	*Yes*	*Yes*	*Yes*	*Yes*
No secretion or absorbtion	*Flow related reabsorption*	*Some secretion*	*Yes*	*Yes*
Constant endogenous production rate	*No*	*Yes*	*No*	*No*
Easily Assayed	*Yes*	*Yes*	*No*	*No*

Relationship between Cr and GFR



- Clinical correlate:
- Plasma creatinine

doubles w/ each 50% decline in GFR

characteristic patterns in the rise and fall of SCr

- Contrast nephropathy :rise in SCr within 24–48 h, peak within 3–5 days, and resolution within 5–7 days.
- atheroembolic disease usually manifests with more subacute rises in SCr, although severe AKI with rapid increases in SCr can occur in this setting.
- aminoglycoside antibiotics and cisplatin, the rise in SCr is characteristically delayed for 4–5 days to 2 weeks after initial exposure

Other biomarkers

- **Cystatin C**
- 1. Important extracellular inhibitor of cysteineproteases
- 2. Filtered by the glomerulus and reabsorbed by proximal tubule cells
- 3. Elevated urinary levels reflect tubular dysfunction; high levels may predict poorer outcome

Other biomarkers

- ***Neutrophil gelatinase associated lipocalin (NGAL)***
- was first discovered as a protein in granules of human neutrophils. NGAL can bind to iron siderophore complexes and may have tissue-protective effects in the proximal tubule. NGAL is highly upregulated after inflammation and kidney injury and can be detected in the plasma and urine within 2 hours of cardiopulmonary bypass–associated AKI

Other biomarkers

- ***Kidney injury molecule-1 (KIM-1)*** is a type 1 transmembrane protein that is abundantly expressed in proximal tubular cells injured by ischemia or nephrotoxins such as cisplatin. KIM-1's functional role may be to confer phagocytic properties to tubular cells, enabling them to clear debris from the tubular lumen after kidney injury. KIM-1 can be detected shortly after ischemic or nephrotoxic injury in the urine and, therefore, may be an easily tested biomarker in the clinical setting.

symptoms	Findings
Chronic renal failure	Azotemia for >3 months Prolonged symptoms or signs of uremia Symptoms or signs of renal osteodystrophy Kidneys reduced in size bilaterally Broad casts in urinary sediment
Acute nephritis	Hematuria, RBC casts ,proteinuria Azotemia, oliguria Edema, hypertension
Urinary tract obstruction	Azotemia, oliguria, anuria Polyuria, nocturia, urinary retention Slowing of urinary stream Large prostate, large kidneys Flank tenderness, full bladder after voiding
Nephrotic syndrome	Proteinuria >3.5 g per 1.73 m2 per 24 h Hypoalbuminemia Edema Hyperlipidemia

Index	prerenal	ATN
BUN/P_{Cr} ratio	>20:1	10-15:1
Urine sodium (U_{Na}), meq/L	<20	>40
Urine osmolality, mosmol/L H_2O	>500	<350
Fractional excretion of sodium	<1%	>2%
Urine/plasma creatinine (U_{Cr}/P_{Cr})	>40	<20

summary

- Bun and Cr are the most accessible and accurate yet.
- The clinical correlation and clinical Dx are greatly recommended.
- Significance of laboratories in performing accurate Cr test is very important


Thanks for your attention