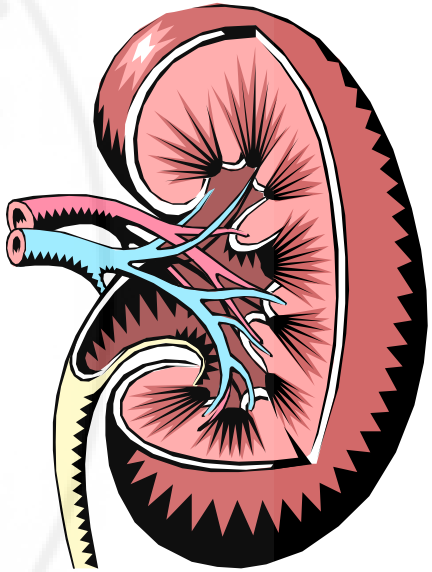
Renal Failure and Treatment



Pr. Dr. Sahar Chamma

Clinical Chemistry

Damascus University

Objectives

- Anatomy
- Function
- Diagnostic Tools for Assessing Renal failure
- Analytical procedures
- Pathophysiology
- Glomerular Diseases:
- Tubular diseases
- Acute Renal Failure (ARF)
- Chronic Renal Failure (CRF)
- Manifestations of CRF
- Dialysis

REVIEW

- What are nephrons?
- What are the functions of the kidneys?
- Hormonal Mechanisms
- Diagnostic tools
- Normal creatinine & BUN?
- Nonprotein Nitrogen compounds
- Urine Electrophoresis
- Urinanalysis

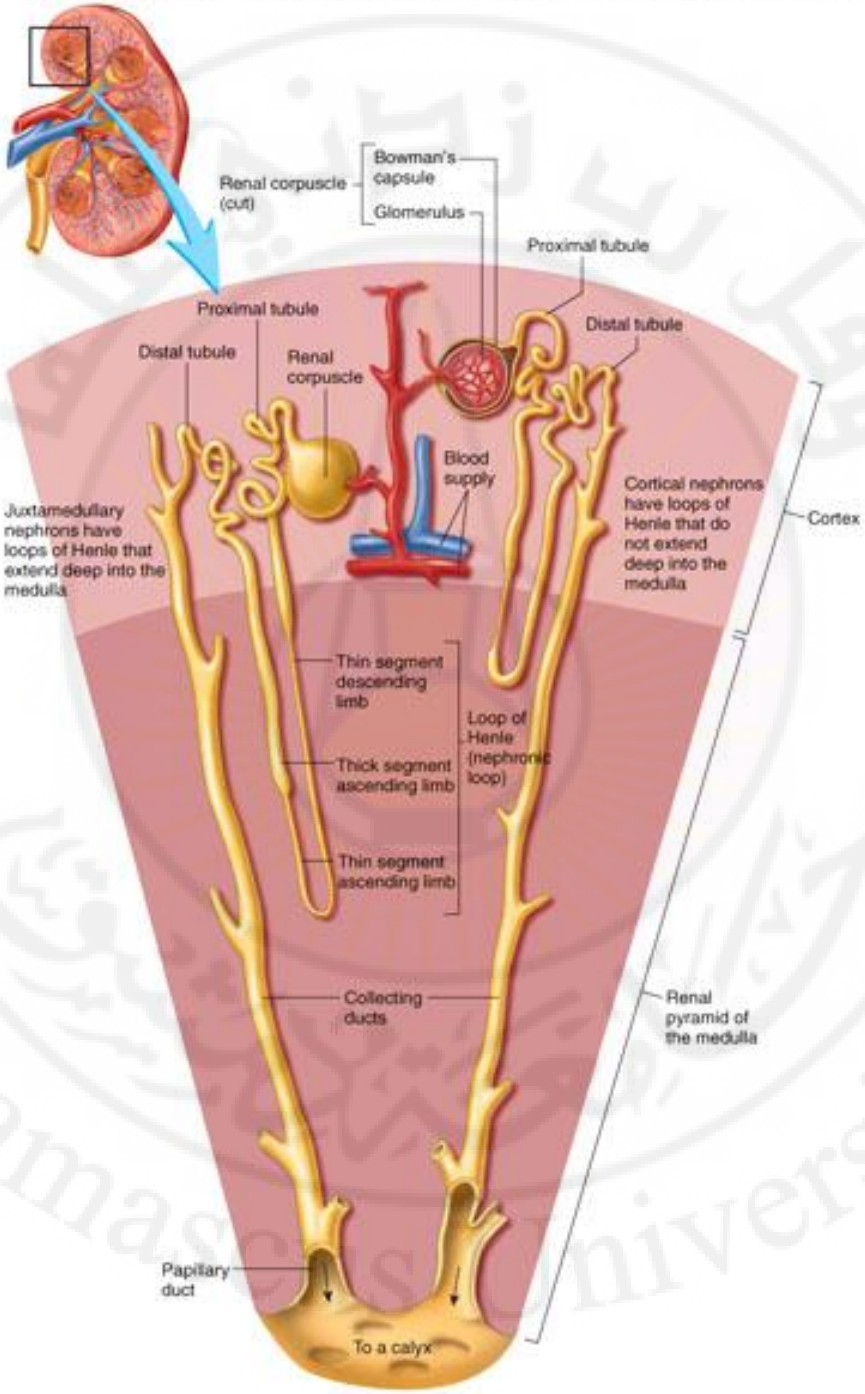
Nephron

- **What is it?**
  - functional unit of kidneys
  - over 1 million/kidney

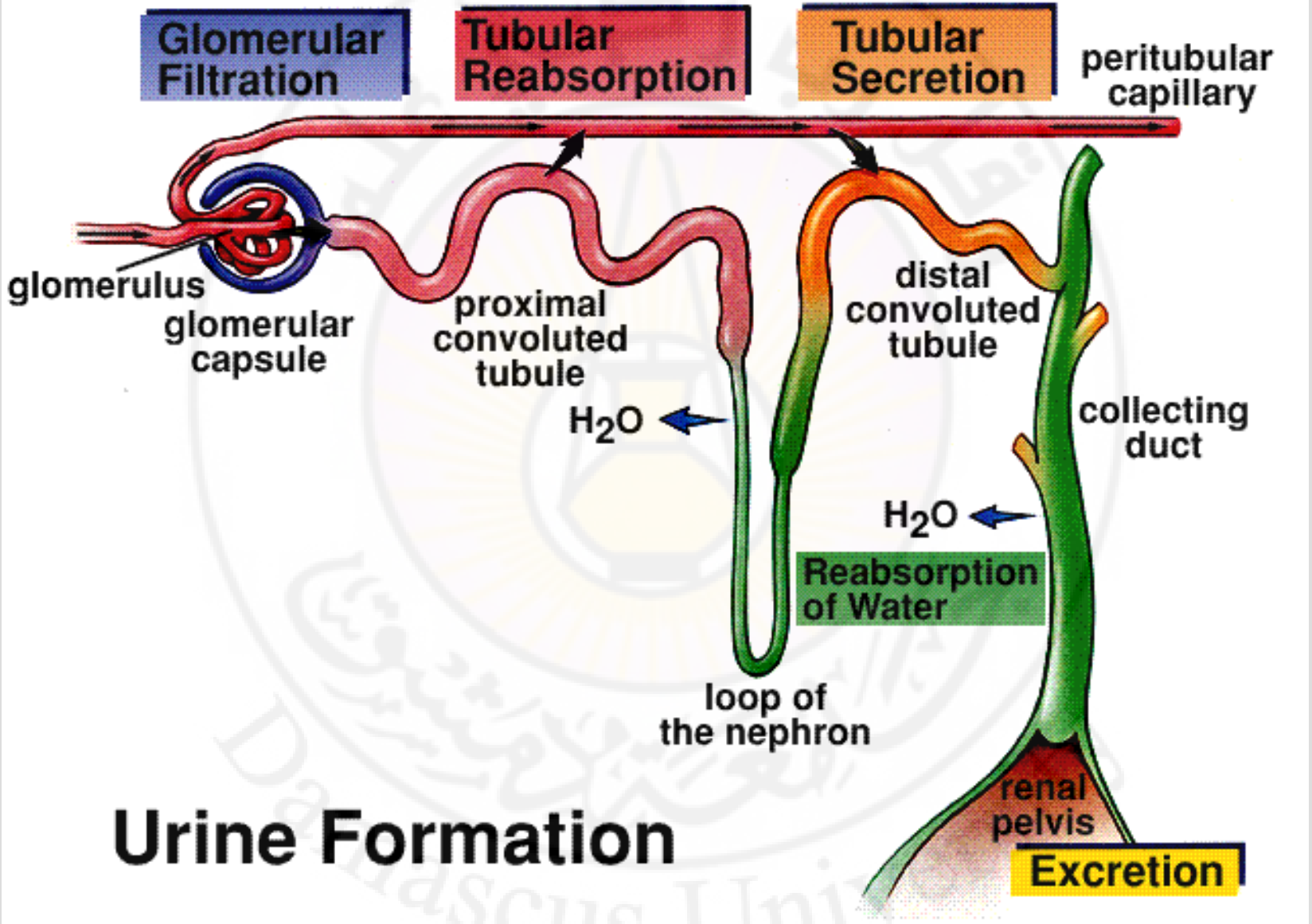
Each nephron consists of:

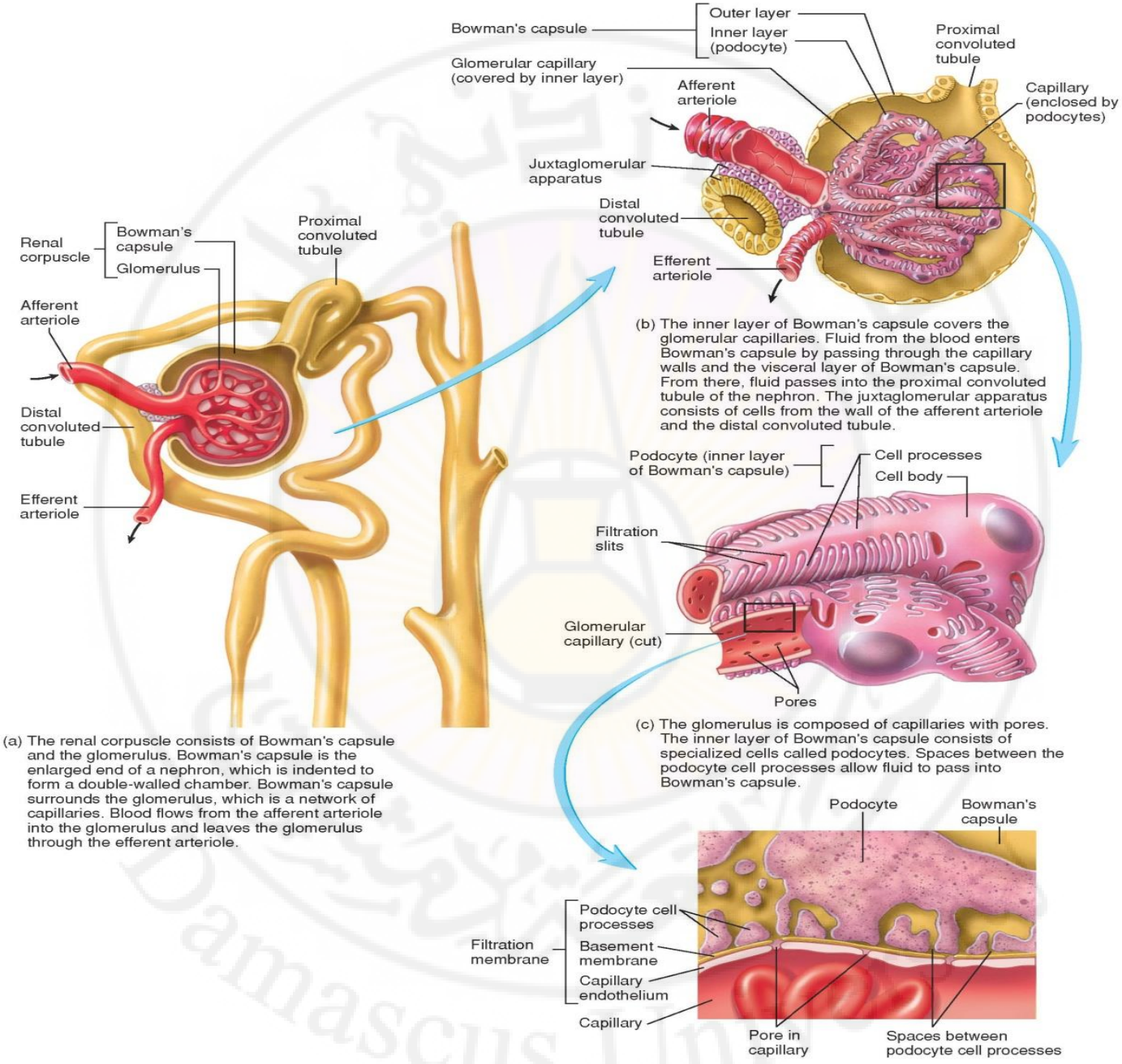
a renal corpuscle, a proximal convoluted tubule, a loop of Henle, and a distal convoluted tubule

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(a) The renal corpuscle consists of Bowman's capsule and the glomerulus. Bowman's capsule is the enlarged end of a nephron, which is indented to form a double-walled chamber. Bowman's capsule surrounds the glomerulus, which is a network of capillaries. Blood flows from the afferent arteriole into the glomerulus and leaves the glomerulus through the efferent arteriole.

(b) The inner layer of Bowman's capsule covers the glomerular capillaries. Fluid from the blood enters Bowman's capsule by passing through the capillary walls and the visceral layer of Bowman's capsule. From there, fluid passes into the proximal convoluted tubule of the nephron. The juxtaglomerular apparatus consists of cells from the wall of the afferent arteriole and the distal convoluted tubule.

(c) The glomerulus is composed of capillaries with pores. The inner layer of Bowman's capsule consists of specialized cells called podocytes. Spaces between the podocyte cell processes allow fluid to pass into Bowman's capsule.

(d) The filtration membrane consists of the glomerular capillary endothelium, a basement membrane, and the podocyte cell processes. Fluid passes from the capillary through the filtration membrane into Bowman's capsule.

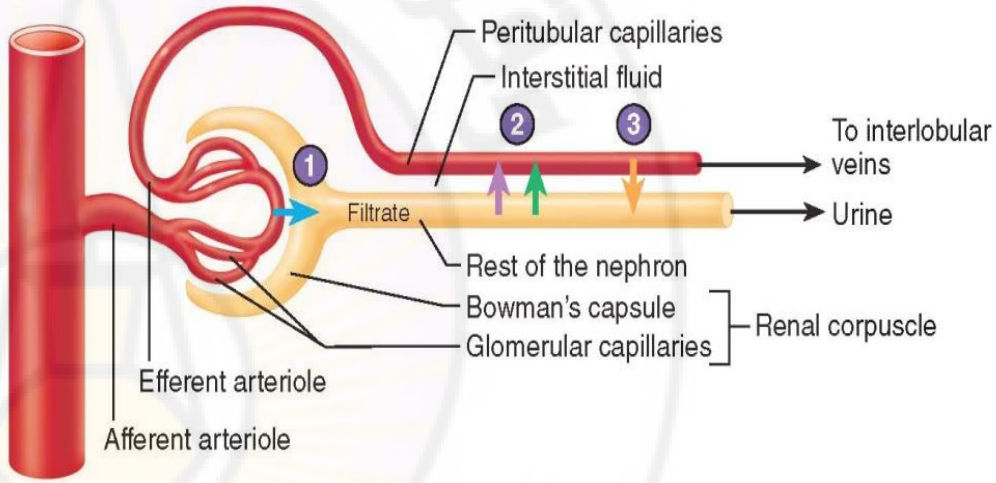
Figure 18.5 Renal Corpuscle and Filtration Membrane

Urine forms through the following three processes:

1. **Filtration.** Filtration (*blue arrow*) is the movement of materials across the filtration membrane into Bowman's capsule to form filtrate.

2. **Tubular reabsorption.** Solutes are reabsorbed (*purple arrow*) across the wall of the nephron into the interstitial fluid by transport processes, such as active transport and cotransport. Water is reabsorbed (*green arrow*) across the wall of the nephron by osmosis. Water and solutes pass from the interstitial fluid into the peritubular capillaries.

3. **Tubular secretion.** Solutes are secreted (*orange arrow*) across the wall of the nephron into the filtrate.



PROCESS Figure 18.7 Urine Formation

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Functions of the urinary system

The major function of the urinary system is:

to control the composition and volume body fluids.

It perform this function through multiple processes.

Functions

1. Excretion
2. Control Blood volume and blood pressure
3. pH regulation
4. Concentration of solutes
5. Vitamin D production
6. Red blood cell synthesis

Functions of the Kidneys

- **Erythropoietin Release**
  - ***If a patient has chronic renal failure, what condition will occur?***
  - ***WHY???***



Functions of the Kidneys

- **Activate Vitamin D**
  - **Necessary to absorb Calcium in the GI tract.**

If a patient has renal failure, what will happen to the patient's serum calcium level?

_____

Hormonal Mechanisms

- Three major hormonal mechanisms are involved in regulating urine concentration and volume
- 1- The renin angiotensin aldosterone mechanism
- 2- The antidiuretic hormone ADH mechanism
- 3- The atrial natriuretic hormone ANH mechanism

Each mechanism is activated by different stimuli, but work together to achieve homeostasis

Both renin angiotensin aldosterone and ANH are more sensitive to changes in blood pressure, whereas ADH is more sensitive to changes in blood concentration.

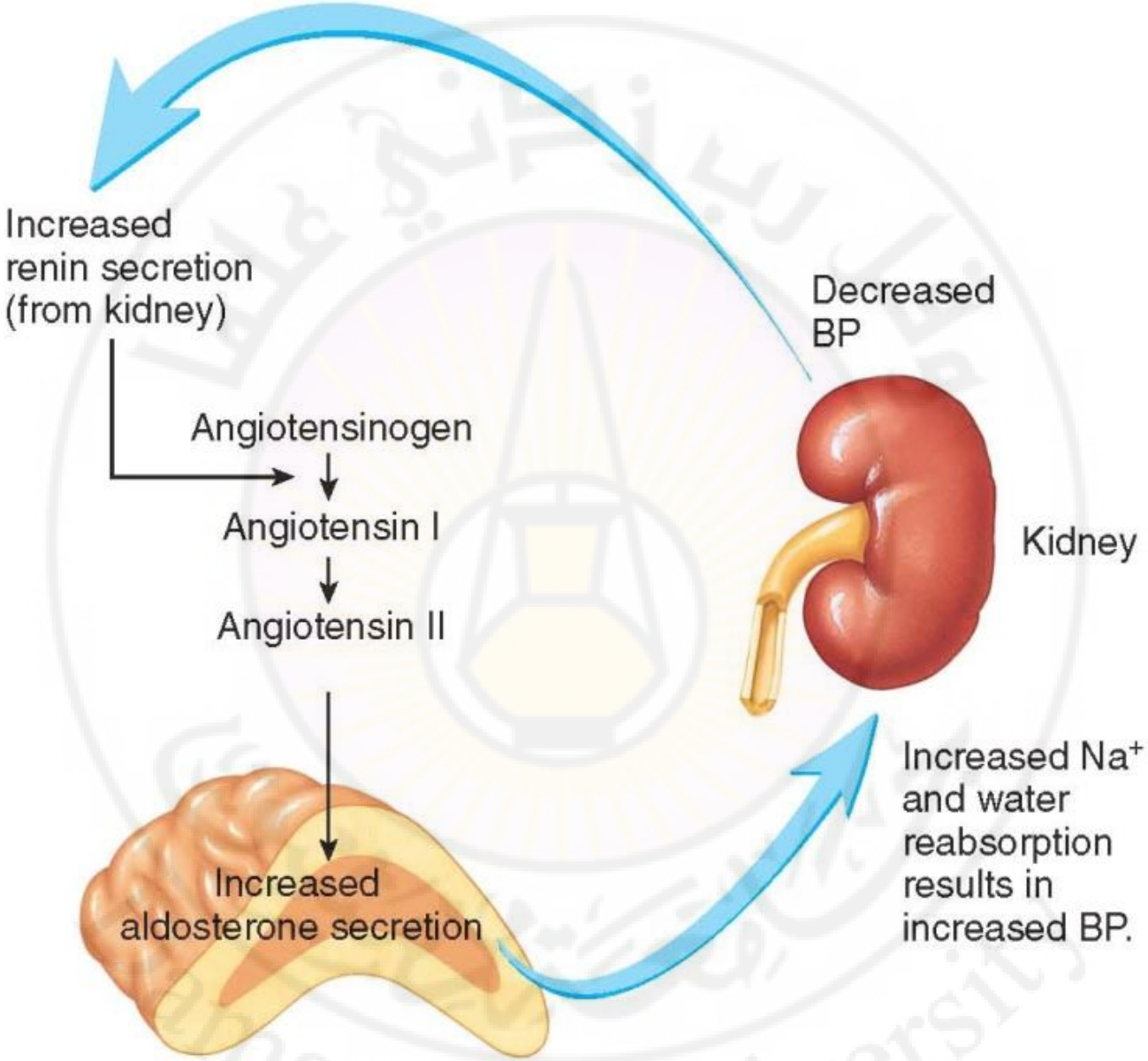


Figure 18.14 Aldosterone and the Regulation of Na^+ and Water in Extracellular Fluid

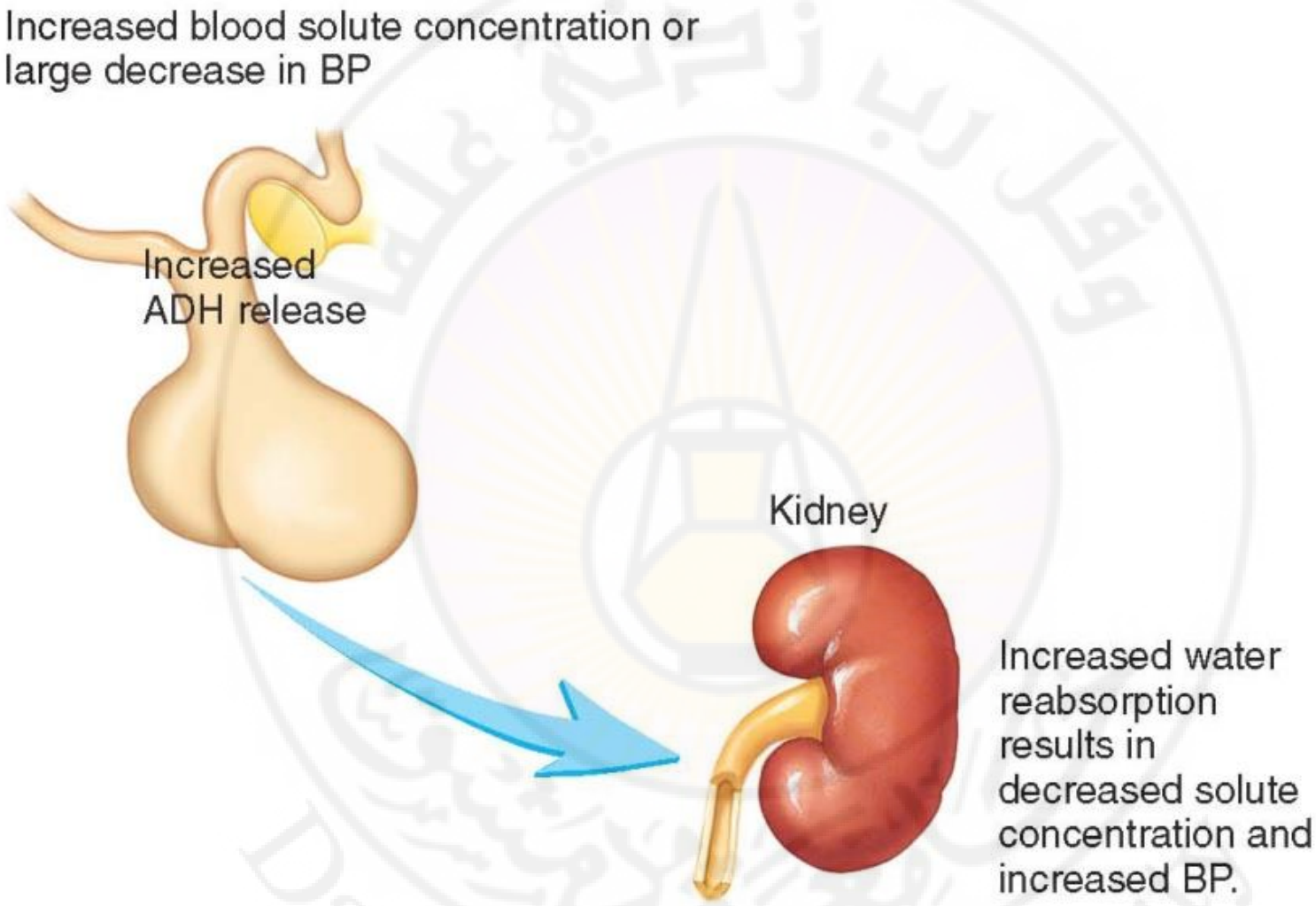


Figure 18.15 ADH and the Regulation of Extracellular Fluid Concentration

Increased blood solute concentration affects hypothalamic neurons, and decreased blood pressure affects baroreceptors. As a result of these stimuli, the posterior pituitary secretes ADH, which increases water reabsorption by the kidney.

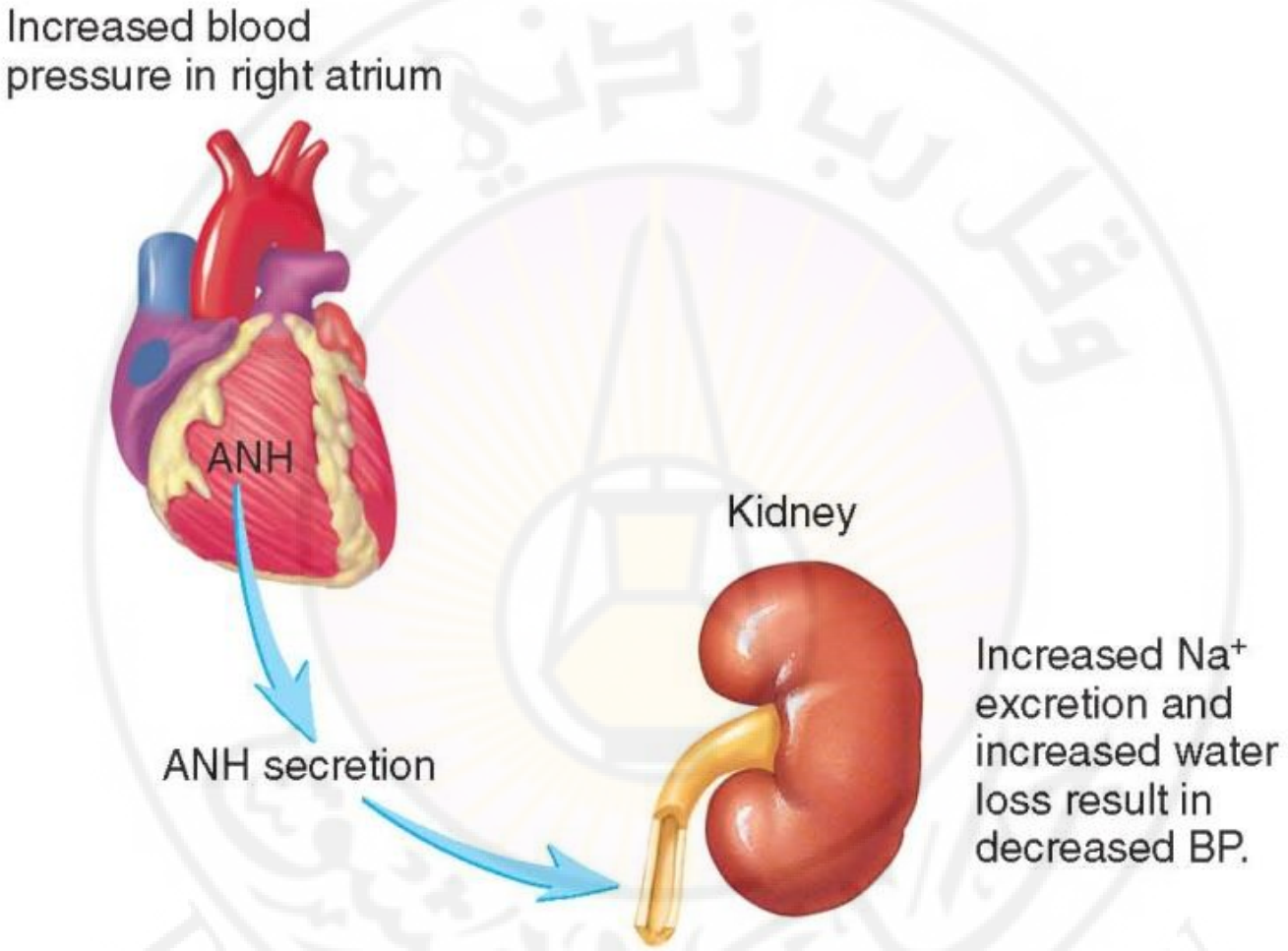
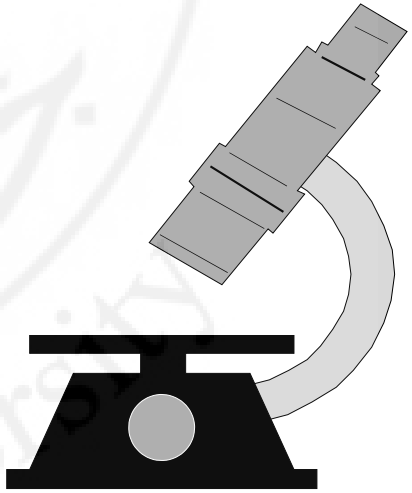


Figure 18.16 ANH and the Regulation of Na^+ and Water in Extracellular Fluid

Increased blood pressure in the right atrium of the heart causes increased secretion of ANH, which increases Na^+ excretion and water loss in the form of urine.

Diagnostic Tools for Assessing Renal Failure

- Blood Tests
  - BUN
  - Creatinine
  - K+
  - PO_4
  - Ca
- Urinalysis
  - Specific gravity
  - Protein
  - Creatinine clearance



BUN

- Normal 10-40 mg/dl
- Nitrogenous waste product of protein metabolism
- Reliable in measurement of renal function

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Creatinine

- A waste product of muscle metabolism
- Muscle contains creatine phosphate a high energy compound for the rapid formation of adenosine triphosphate (ATP)
- Creatine phosphate+ADP+H+→ creatine+ATP↔creatinine
- Every day, up to 20% of total muscle creatine spotaneously dehydrates and cycles to form creatinine.

- Normal value 0.5 - 1.5 mg/dl
- 2 times normal = 50% damage
- 8 times normal = 75% damage
- 10 times normal = 90% damage

Elimination of Nonprotein Nitrogen compounds

1. **Urea**: makes up the majority (more than 75%) of the NPN waste excreted daily as a result of the oxidative catabolism of protein. Urea synthesis occurs in the liver ,proteins are broken down to amino acid, which are then deaminated to form ammonia. Amonia is readily converted to urea. 40%-60% of urea is reabsorbed. Molecular weight 60 Da.

- Creatinine: Muscle contains creatine phosphate which is catalyzed by CK to form creatinine. Creatinine levels are a function of muscle mass, M.w is 113 Da, is not reabsorbed

- **Uric Acid:** it is the primary waste product of purine metabolism. The purine, adenine, guanine, are precursors of nucleic acids,ATP,GTP.
- M.w is 168 Da. Only 6%-12% is excreted .
- At pH>5.75 it exists in ionized and more soluble form.
- At pH <5.75 it is undissociated. This fact has clinical significance in the development of urolithiasis and gout.

Analytical procedures

- Several tests are avalaibl that assess the various aspects of nephron function , including glomerular filtration and proximal and distal tubular secretion and reabsorption Analytical procedures When the same test is performed on various individuals, we find that the mean of each person's results is not the same.

- Clearance measurementt: The rate at which creatinine and urea are removed or cleared from the blood into the urine is termed clearance
- Clearance is defined as the volume of plasma from which a measured amount of substance can be completely eliminated into the urine per unit of time expressed in milliliters per minute Measurement of clearance is used to estimate the rate of glomerular filtration

- Creatinine: is a realy ideal substance for the measure of clearance. It is an endogenous product synthesized at a constant rate for a given individual and cleared essentially only by glomerular filtration, it is not reabsorbed and is only slightly secreted by the proximal tubule.

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Estimation Glomerular Filtration Rate(GFR) :

1. be calculated each time a serum creatinine level is reported. The equation is used to predict GFR and is based on a serum creatinine ,age, body, size, gendere, without the need add a urine creatinine.

2. **Urea**: is freely filtered at the glomerulus and approximately 40% reabsorbed by the tubules.

- **Cystatin C:** is a low molecular weight protein(13.3 k. dalton) produced by nucleated cells. It is freely filtered by the glomerulus, reabsorbed, and catabolized by the proximal tubule. Produced at a constant rate. Levels remain stable, if kidney function is normal.
- Plasma concentration appear to be unaffected by gender, age, and muscle mass.

- A rise in cystatin C is often detectable before there is a measurable decrease in GFR or increase in creatine.
- Cystatin C levels have been reported to be altered in patients with cancer, thyroid dysfunction[, and glucocorticoid therapy in some but not all situations. Other reports have found that levels are influenced by cigarette smoking and levels of C-reactive protein.

- Several studies have found that increased levels of cystatin C are associated with the risk of death, several types of cardiovascular disease (including myocardial infarction, stroke, heart failure, peripheral arterial disease and metabolic syndrome) .
- It also seems to play a role in brain disorders involving amyloid (a specific type of protein deposition), such as Alzheimer's disease.

- As a result, creatinine is more helpful in monitoring renal function over time for a given individual whereas, cystatin C is potentially more useful for detecting minor renal impairment.

- **Urine Electrophoresis:** When the efficiency of renal glomerular filtration and tubular reabsorption normal, urinary protein excretion is only about 50-150 mg/24h.

- Proteinuria may develop when there are defects in renal reabsorption or glomerular capillary permeability or when there is a significant increase in serum immunoglobulins.

- As a result, urine electrophoresis is used primarily to distinguish between acute glomerular nephropathy and tubular proteinuria. It also used to screen for abnormal monoclonal or polyclonal globulins.

- **Conditions with proteinuria as a sign**
- Proteinuria may be a feature of the following conditions:[Nephrotic syndromes (i.e. intrinsic renal failure)
- Pre-eclampsia
- Eclampsia
- Toxic lesions of kidneys

- Amyloidosis
- Collagen vascular diseases (e.g. systemic lupus erythematosus)
- Dehydration
- Glomerular diseases, such as membranous glomerulonephritis
- Diabetes mellitus

- β2-Microglobulin: is a small nonglycosylated pepetide (m.w 11.800Da) found on the surface of most nucleated cells.

- Levels of β2-Microglobulin remain stable in normal patients, elevated levels in serum indicate incresaed cellular turnover as seen in myeloproliferative and lymphoproliferative disorders, inflammation.

- β2-Microglobulin is easily filtered by the glomerulus, about 99.9% is then reabsorbed by the proximal tubules and catabolized.
- Measurement of serum β2-Microglobulin is used clinically to assess renal tubular function in renal transplant patients, elevated levels indicating organ rejection.

- **Myoglobin:** is a low m.w protein(16,900Da) associated with acute skeletal and cardiac muscle injury.

- In rhabdomyolysis, myoglobin release from skeletal muscle is sufficient to overload the proximal tubules and cause acute renal failure

- Microalbumin: Urine microalbumin measurement is important in the management of patients with diabetes ,who are at serious risk of developing nephropathy .
- Type1 has a 30%- 45% risk , and type 2 has a 30% risk.
- Urinary albumin concentrations of 50-200mg/24h are predictive of diabetic nephropathy.
- A random urine sample that uses a ratio of albumin to creatinine 20-30 mg/g is indicative of microalbuminuria.

- **Urinanalysis:(** UA)
- permits a detailed assessment of renal status with an easily obtained specimen.
- UA serves as a quick indicator of an individual's glucose status and hepatic – biliary

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- Routine UA includes assessment of physical characteristic, chemical analyses, and a microscopic examination of the sediment from a urine specimen. (specimen collection, Visual appearance, odor, turbidity, volume, specific gravity, pH, chemical analysis: glucose and ketones, protein, nitrite, bilirubin/urobilinogen, hemoglobin/, blood cells, cells, crystals.

Pathophysiology

- Glomerular Diseases:
- Disorders that directly damage the renal glomeruli may, exhibit normal tubular function, with time, disease progression involves the renal tubules

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- Acute Glomerulonephritis: (AG): Histologic examination shows large inflamed glomeruli with decreased capillary lumen. Abnormal laboratory findings usually include hematuria, and proteinuria, decreased GFR, anemia, elevated blood urea nitrogen, and serum creatinine, oliguria, sodium and water retention .and sometimes , congestive heart failure is typical.
-

- A.G is often related to recent infection by group A and B hemolytic streptococci.
- Possible causes include drug-related exposures, acute kidney infection due to other bacterial,or viral, and other systemic immune complex diseases as systemic lupus erythematosus (SLE)and bacterial endocarditis.

- **Chronic Glomerulonephritis**

  - Lengthy glomerular inflammation may lead glomerular scarring and the eventual loss of functioning nephron.

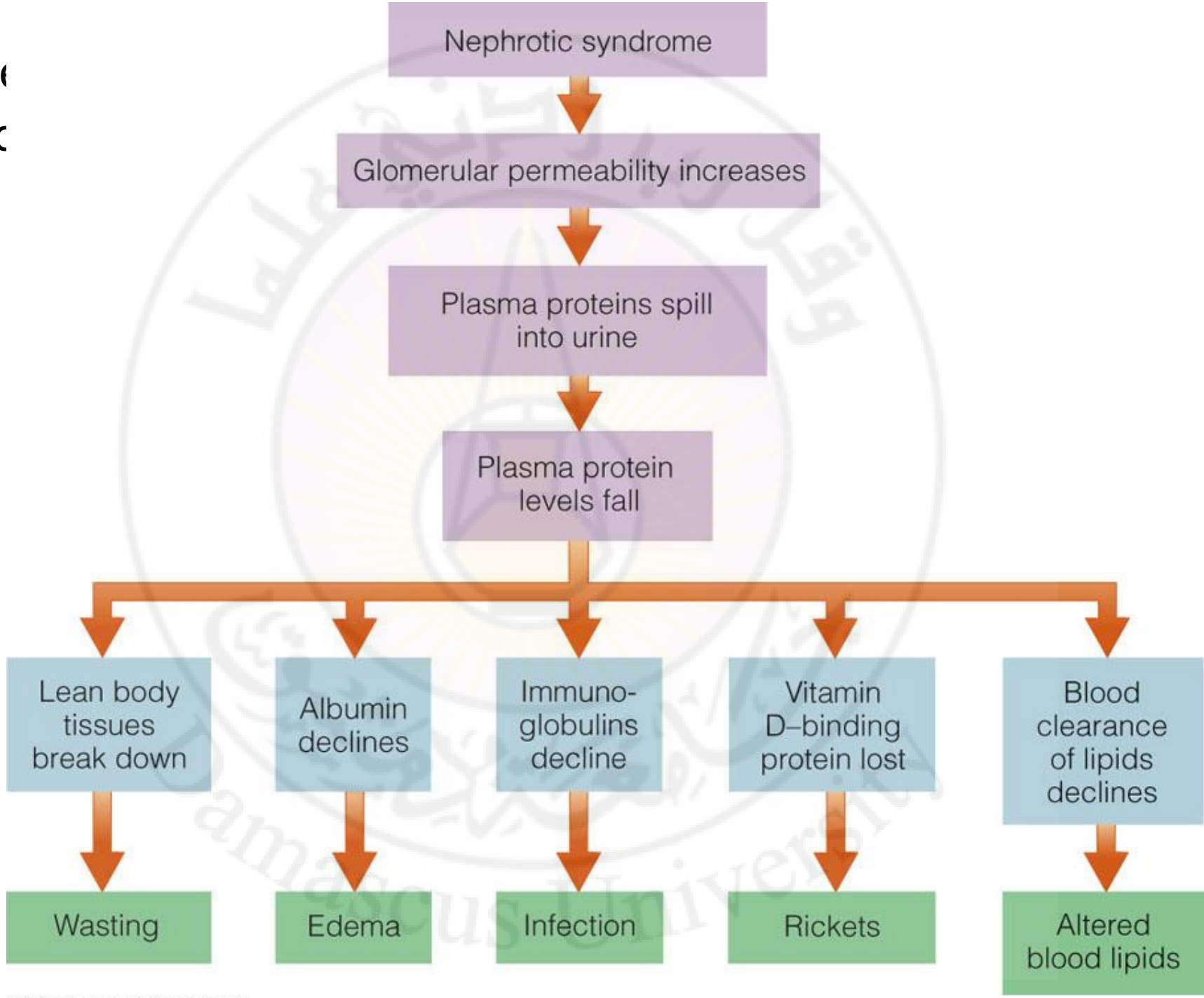
- Nephrotic syndrome: can be caused by several different disease that result in injury and increased permeability of the glomerular basement membrane.
- This defect yield several abnormal findings, such massive proteinuria >3.5 g/day and resultant hypoalbuminemia.
- That causes generalized edema

Nephrotic Syndrome

- Possible causes
  - Infections
  - Chemical damage
  - Immunological & hereditary disorders
  - Diabetes mellitus
- Clinical findings
  - Proteinuria
  - Low serum albumin
  - Edema
  - Elevated blood lipids
  - Blood coagulation disorders

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Consequences

- Disturbances in protein metabolism
- Edema
  - Loss of albumin
  - Sodium retention
- Risk of CVD
  - Elevated LDL, VLDL & lipoprotein(a)
  - Loss of blood clotting proteins
- Loss of antibodies
- Loos of antithrombine-3
- Decreased vitamin D-binding protein
  - Lower D & calcium levels

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Treatment

- Medications
  - Anti-inflammatory drugs, ACE inhibitors, antihypertensives, immunosuppressants, lipid-lowering drugs, diuretics
- Protein & energy
  - 0.8-1.0 grams/day
  - 35 kcalories/kg
- Fat
  - Low saturated fat, cholesterol, & refined sugars
- Sodium
  - 2-3 g/day
- Vitamin D & calcium
- Multivitamin

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- **Tubular diseases**

  Tubular diseases occur to a certain extent in the progression of all renal disease as the GFR falls. The result is decreased excretion/reabsorption of certain substances or reduced urinary concentrating capability.

- Clinically, the most important defect is renal tubular acidosis (RTA),:
- the primary tubular disorder affecting acid-base balance. This disease can be classified into two types ,depending on the nature of the tubular defect –

- Distal tubules(RTA), in which the renal tubules are unable to keep up the vital pH gradient between the blood and tubular fluid,

  (amylodosis, high calcium in blood, SLE, immunologie disorders).

- Proximal tubules(RTA), (Fanconi syndrome) in which there is decreased reabsorption of small molecules as glucose, phosphate, amino acid, uric acid, bicarbonate reabsorption,(resulting in hyperchloremic acidosis).

- In general, reduced reabsorption in the proximal tubule is manifested by finding of abnormally low serum values for phosphate, uric acid,..
- In addition, there may be some proteinuria(usually <2g/day).

- Acute inflammation of the tubules may occur as a result of analgesic drugs or radiation toxicity, renal transplant rejection, and viral-fungal-bacterial infections.
- Characteristic clinical findings are: decreases in GFR, urinary concentrating ability, leucocytes in the urine.

- Urinary tract infection/ obstruction
- Infection
- The site of infection may be either in the kidneys or in the urinary bladder. Bacteriuria, hematuria,and pyuria, are all frequently encountered abnormal laboratory results

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- Obstruction
- Renal calculi : or kidney stones , are formed by the combination of various crystallized substances, calcium oxalate stones are the most commonly encountered(cystin, uric acid, calcium phosphate).

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Renal Failure

Acute Renal Failure:

Is a sudden decline in renal function as a result of an acute toxic or hypoxic to the kidneys, defined as occuring when the GFR is reduced to less than 10ml/min. This sydrom is subdivided into three types , depending on the location of the precipitating defect.

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- - Prerenal failure: The defect lies in the blood supply before it reaches the kidney. Causes can include cardiovascular system failure, and consequent hypovolemia.
- - Primary renal failure: The defect involves the kidney. The most commun cause is acute tubular necrosis, vascular obstruction/inflammations , and glomerulonephritis.

Postrenal failure: The defect lies in the urinary tract after it exits the kidney. Generally, as a consequence of lower urinary tract obstruction or rupture of urinary bladder.

Toxic insults to the kidney that are severe enough to initiate acute renal failure include hemolytic transfusion reactions, myoglobinuria due to rhabdomyolysis, heavy metal/solvent poisoning. These conditions directly damage the renal tubules.

- The most commonly symptoms of acute renal failure are: oliguria, and anuria<400ml/day.
- Leading to peripheral edema, hypertension, and congestive heart syndrome.
- In the case of irreversible renal damage, progression to chronic renal failure.

Acute Renal Failure

- Function rapidly deteriorates
  - Reduced urine output
  - Build up of nitrogenous wastes
- Mortality rates are high

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Causes

- *Prerenal*
  - Heart failure
  - Shock
  - Blood loss
- *Intrarenal*
  - Infections
  - Toxins
  - Drugs
  - Direct trauma
- *Postrenal*
  - Factors preventing excretion of urine
  - Urinary tract obstructions

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Consequences

- Oliguria < than 400 mL urine/day
- Sodium retention
- Elevated potassium, phosphate, & magnesium
- Edema
- Uremia
  - BUN, creatinine & uric acid accumulate in blood
  - Fatigue, lethargy, confusion, headache, anorexia, metallic taste, diarrhea

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Treatment

- Drug therapy
  - Diuretics
  - Potassium exchange resins
  - calcium
  - Insulin, glucose
  - Bicarbonate
- Protein
  - Depends on kidney function, degree of catabolism, use of dialysis
- Fluids
  - Measure output and add 500 mL
  - Can increase if on dialysis
- Electrolytes
  - Restrict potassium, phosphorus, sodium

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Chronic Renal Failure

Chronic kidney disease is a clinical syndrome that occurs when there is a gradual decline in renal function over time. The conditions that can precipat acute renal failure also may lead to chronic renal failure.

- Increasing Incidence of Chronic Kidney disease:
- There is an increasing incidence due to the increase in diabetes, obesity, and metabolic sydrom.
- Approximately 45% of patients with type 1 diabetes will develop progressive deterioration of kidney function within 15-20 years after diagnosis.
- Typically, diabetes affect the kidneys by causing them to become glucouric, polyuric, and nocturic. Microalbuminuria often develops between 10-15 years the original disease.

The metabolic sydrom, characterized by the presence of at least three of the following risk factors:

Abdominal obesity, hypertension, low high density lipoprotein cholesterol level, hypertriglyceridemia, or hyperglycemia.

- Renal Hypertension:
- Renal disease-induced hypertension can be caused by either decreased perfusion to all or part of the kidney (ischemia).
- Lack of perfusion may be caused by traumatic injury of an artery or intrarenal arteriols. Chronic ischemia of any kind results in nephron dysfunction and eventual necrosis.

The resulting changes in blood and body fluid volumes within the kidney trigger the activation of the renin- angiotensin-aldosterone system, setting of vasoconstruction that is manifested as persistent hypertension.

As a result of the effect of aldosterone , increased serum Na, decreased serum K, and increased urine K.

Causes of Chronic Renal Failure

- Diabetes
- Hypertension
- Glomerulonephritis
- Cystic disorders
- Developmental - Congenital
- Infectious Disease

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Causes of Chronic Renal Failure

- Neoplasms
- Obstructive disorders
- Autoimmune diseases
- Hepatorenal failure
- Scleroderma
- Amyloidosis
- Drug toxicity

TABLE 22-4 Evaluation of Chronic Renal Disease

Stage of Disease	Description	GFR[a] (mL/min per 1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 (or undergoing dialysis)

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Therapy of acute renal failure:

- Dialysis:

In patient with acute renal failure, uremic symptoms, uncontrolled hyperkalemia, and acidosis have traditionally been indications that the kidneys are unable to excrete the body‘s waste products and a substitute method in the form of dialysis was necessary.

Arterial blood and dialysate are pumped at high rates (150-250mL/min) and 500ml/min, respectively in opposite directions.

The diffusion of low-molecular-weight solutes<500Da), into the dialysate is favored by this process, but mid molecular weight solutes 500-2000 Da are inadequately cleared.

The most efficient hemodialysis techniques provide only 10%-20% of the small solutes removal of two normal kidneys and considerably less removal of large solutes.

Renal transplantation is form a compatible donor to a recipient suffering from irreversible renal failure.

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Dialysis

- Removes excess fluid & wastes from blood
- Blood is circulated thoug a dialyzer
- Blood is bathed by dialysate
- Hemodialysis & peritone dialysis



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Medical Nutrition Therapy

- Energy
  - Enough to maintain healthy weight & prevent wasting
- Low-protein diet
  - Can increase when on dialysis
- Lipids
  - Restrict saturated fat & cholesterol
- Fluids
  - Not restricted until output decreases
- Sodium
  - Mild restriction
- Potassium
  - May need to restrict high-potassium foods

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Medical Nutrition Therapy

- Calcium & vitamin D needs increase
- May need phosphorus restrictions
  - Restrict protein
  - Restrict milk & milk products
- Dietary supplements
  - Generous folate and B_6
  - Recommended amounts of water-soluble vitamins except vitamin C
  - IV iron administration
- Intradialytic parenteral nutrition

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Prevention & Treatment

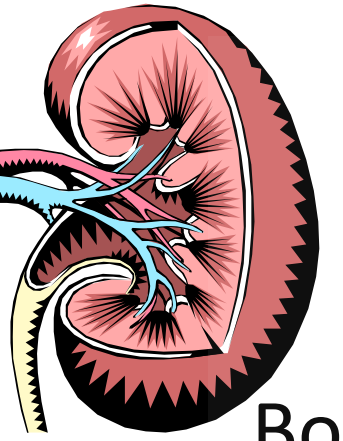
- Drink 12-16 cups of fluids/day
- Tea, coffee, No banana or grapefruit juices

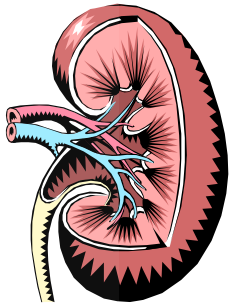
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Other Dietary Measures

- Consume enough calcium to control oxalate absorption
- Restrict dietary oxalate & purine
- Moderate protein intake
- Sodium restriction

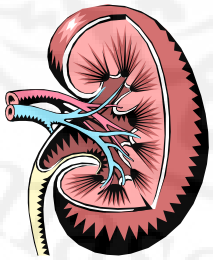
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Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep without immediate danger to survival. But -- should kidneys fail.... neither bone, muscle, nor brain could carry on.

Homer Smith, Ph.D.



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Stages of Chronic Renal Failure
Old System

- Reduced Renal Reserve
- Renal Insufficiency
- End Stage Renal Disease (ESRD)

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Stages of Chronic Renal Failure

NKF Classification System

Stage 1:

GFR >/= 90 ml/min despite kidney damage

Stages of Chronic Renal Failure

NKF Classification System

Stage 2: Mild reduction

(GFR 60 – 89 ml/min)

1. GFR of 60 may represent 50% loss in function.
2. Parathyroid hormones starts to increase.

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During Stage 1 - 2

- No symptoms
- Serum creatinine doubles
- Up to 50% nephron loss

Stages of Chronic Renal Failure

NKF Classification System

Stage 3: Moderate reduction

(GFR 30 – 59 ml/min)

1. Calcium absorption decreases
2. Malnutrition onset
3. Anemia
4. Left ventricular hypertrophy

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Stages of Chronic Renal Failure

NKF Classification System

Stage 4: Severe reduction

(GFR 15 – 29 ml/min)

1. Serum triglycerides increase
2. Hyperphosphatemia
3. Metabolic acidosis
4. Hyperkalemia

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During Stage 3 - 4

- Signs and symptoms worsen if kidneys are stressed
- Decreased ability to maintain homeostasis

During stages 3 - 4

- 75% nephron loss
- Decreased: glomerular filtration rate, solute clearance, ability to concentrate urine and hormone secretion
- Symptoms: elevated BUN & Creatinine, mild azotemia, anemia

Stages of Chronic Renal Failure

NKF Classification System

Stage 5: Kidney failure (GFR < 15 ml/min)

1. Azotemia

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During Stage 5
End Stage Renal Disease

- Residual function < 15% of normal
- Excretory, regulatory and hormonal functions severely impaired.
- Metabolic acidosis
- Marked increase in: BUN, Creatinine, Phosphorous
- Marked decrease in: Hemoglobin, Hematocrit, Calcium
- Fluid overload

During Stage 5

- Uremic syndrome develops affecting all body systems
  - can be diminished with early diagnosis & treatment

- Last stage of progressive CRF
- Fatal if no treatment

Manifestations of Chronic Uremia

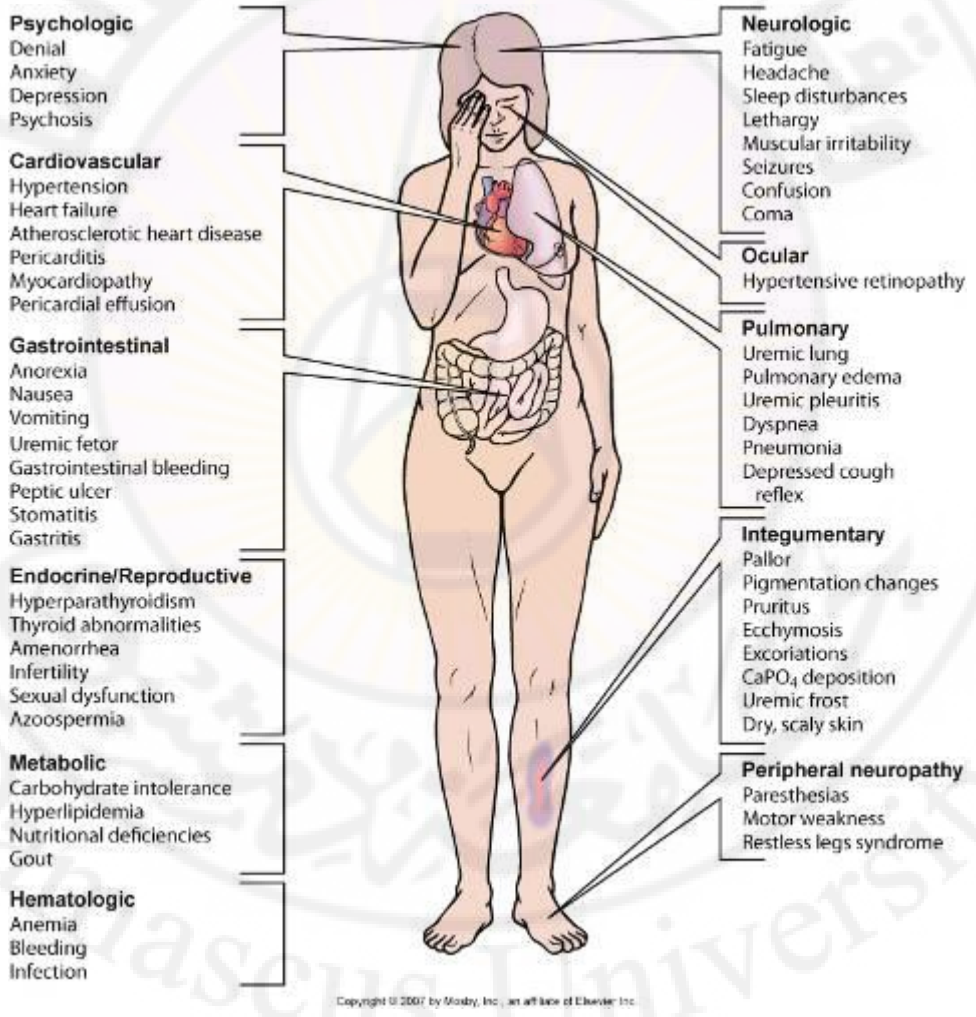


Fig. 47-5

What happens when the kidneys don’t function correctly?



Manifestations of CRF
Nervous System

- Mood swings
- Impaired judgment
- Inability to concentrate and perform simple math functions
- Tremors, twitching, convulsions
- Peripheral Neuropathy

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Manifestations of CRF
Skin

- Pale, grayish-bronze color
- Dry scaly
- Severe itching
- Bruise easily
- Uremic frost

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Manifestations of CRF
Eyes

- Visual blurring
- Blindness

Manifestations of CRF
Fluid - Electrolyte - pH

- Volume expansion and fluid overload
- Metabolic Acidosis
- Change in urine specific gravity
- Electrolyte Imbalances
  - Potassium
  - Magnesium
  - Sodium

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Manifestations of CRF
GI Tract

- Uremic
- Anorexia, nausea, vomiting
- GI bleeding

Manifestations of CRF Hematologic

- Anemia
- Platelet dysfunction

Manifestations of CRF Musculoskeletal

- Muscle cramps
- Soft tissue calcifications
- Weakness
- Related to calcium phosphorous imbalances
- RENAL OSTEODYSTROPHY

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Manifestations of CRF
Heart - Lungs

- Hypertension
- Congestive heart failure
- Pericarditis
- Pulmonary edema
- Pleural effusions
- Atherosclerotic vascular disease*
- Cardiac dysrhythmias

Manifestations of CRF Endocrine - Metabolic

- Erythropoietin production decreased
- Hypothyroidism
- Insulin resistance
- Growth hormone decreased
- Gonadal dysfunction
- Parathyroid hormone and Vitamin D_3
- Hyperlipidemia

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Treatment Options

- Conservative Therapy
- Hemodialysis
- Peritoneal Dialysis
- Transplant
- Nothing

Conservative Treatment Goals

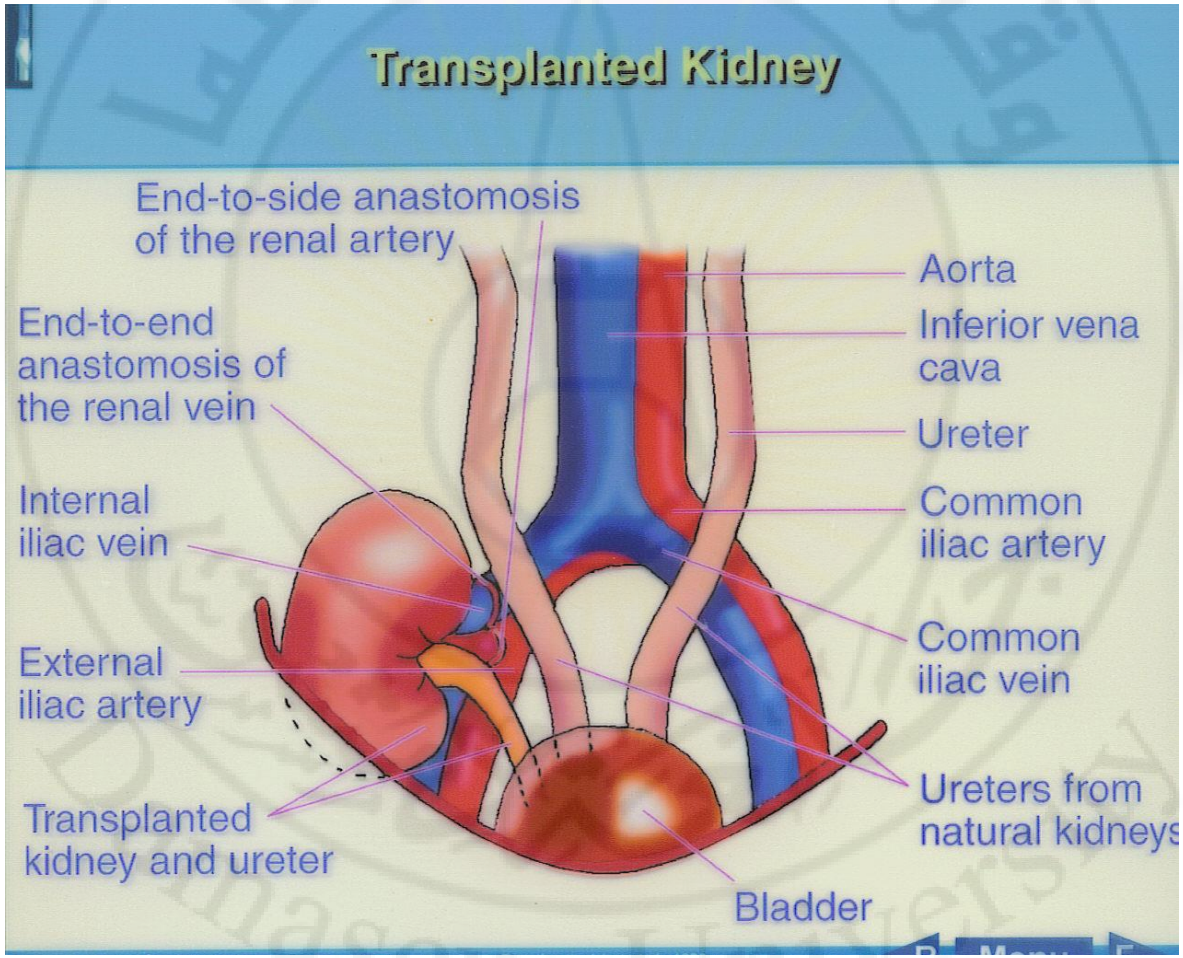
GOALS:

- Detect & treat potentially reversible causes of renal failure
- Preserve existing renal function
- Treat manifestations
- Prevent complications
- Provide for comfort

Conservative Treatment

- Control
  - Hyperkalemia
  - Hypertension
  - Hyperphosphatemia
  - Hyperparthryoidism
  - Hyperglycemia
  - Anemia
  - Dyslipidemia
  - Hypothyroidism
  - Nutrition

Transplanted Kidney



Advantages

- Restoration of “normal” renal function
- Freedom from dialysis
- Return to “normal” life
- Reverses pathophysiological changes related to Renal Failure
- Less expensive than dialysis

Disadvantages

- Life long medications
- Multiple side effects from medication
- Increased risk of tumor
- Increased risk of infection
- Major surgery

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Kidney Stones

- Affects 12% of men & 5% of women
- Crystalline mass in urinary tract
  - Severe pain
  - Can obstruct tract
- *Formation* is promoted by:
  - Reduced urine volume
  - Blocked urine flow
  - Increased concentrations of stone-forming substances

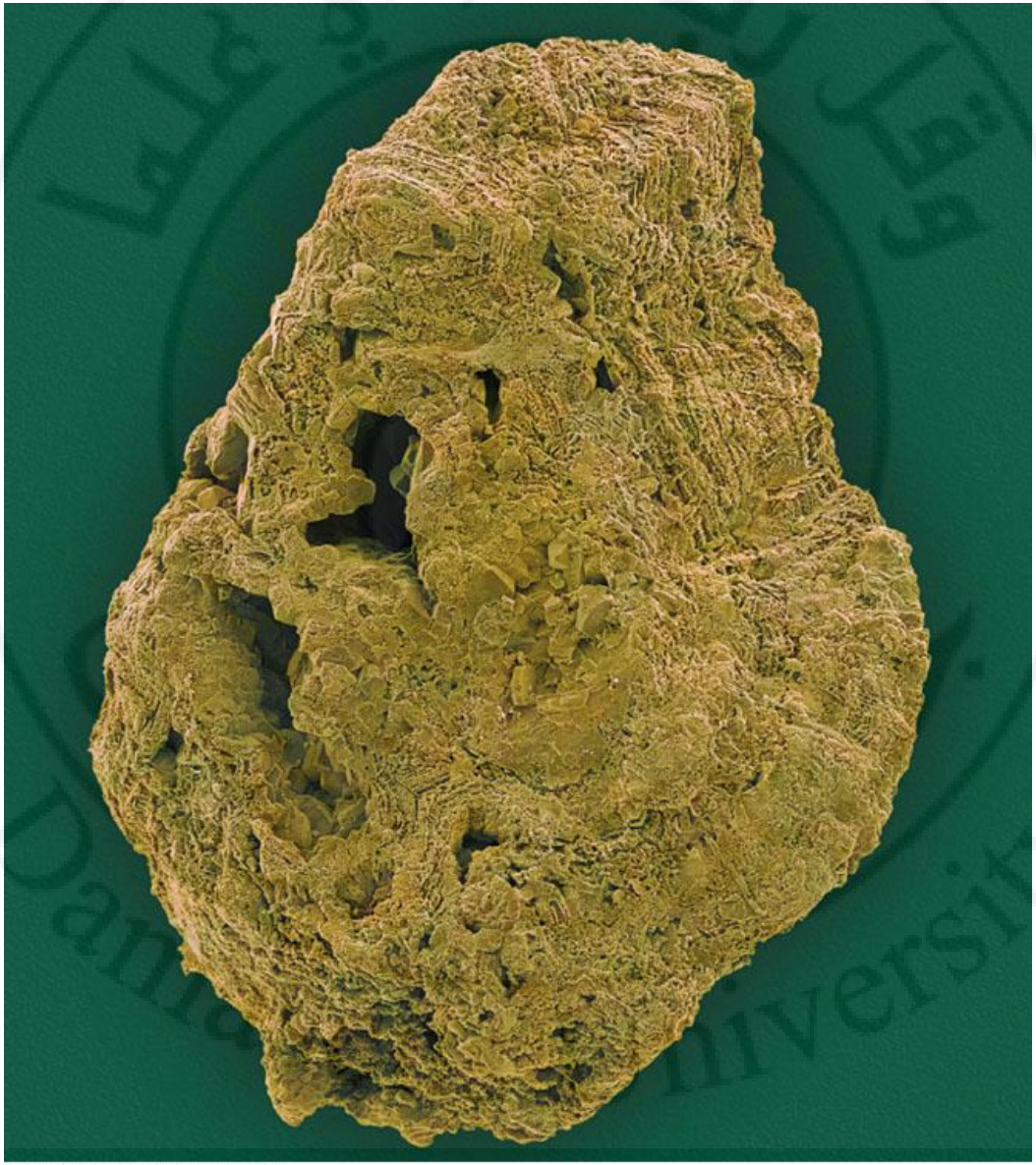
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Types of Stones

- Calcium oxalate stones
  - Most common
  - Reduce intake of oxalate
  - Avoid vitamin C supplements
- Uric acid stones
  - Abnormally acidic urine
  - Associated with gout
  - Low-purine diet
- Cystine stones
  - Inherited disorder *cystinuria*
- Struvite stones
  - Form in alkaline urine

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Calcium Oxalate Stone

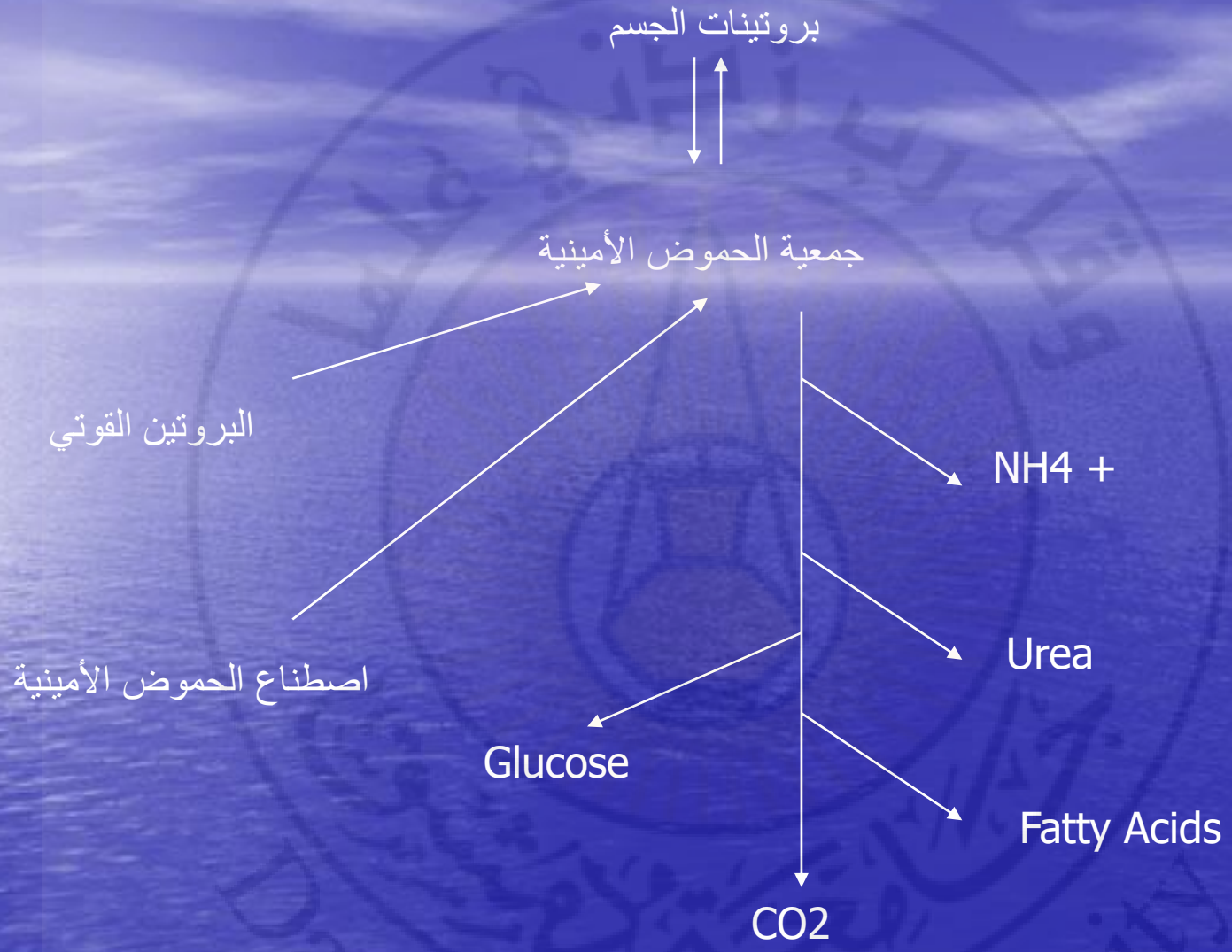


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اضطراب استقلاب الحموض الأمينية

تصطنع وتتدرك معظم البروتينات في الجسم بشكل دائم ومتكرر وتبقى الكمية الاجمالية لبروتين الجسم عند البالغين الأصحاء مستقرة طالما ان معدل اصطناع البروتين متوازن مع كمية البروتين المتدركة.

يتغير معدل انقلاب البروتين بشكل كبير تبعاً لنوعية البروتين مثلاً تتحطم بروتينات البلاسما بشكل سريع حيث تملك نصف عمر من ساعات إلى أيام بينما تكون بعض البروتينات (الكولاجين) مستقرة استقلابياً وتمتلك نصف عمر لعدة سنوات.


بروتينات الجسم
جمعية الحموض الأمينية
البروتين القوتي
اصطناع الحموض الأمينية
NH4 +
Urea
Glucose
Fatty Acids
CO2

بيلة الحموض الأمينية :

لا يطرح سوى كميات ضئيلة من الحموض الأمينية في البول السوي وذلك لارتفاع العتبة الكلوية لها في الأنابيب البولية.

وتتراوح بيلة الحموض الأمينية من 0-200 ملغ / بول 24 ساعة يحيث أن الغليسين , الغلوتامين , الهستدين تطرح بكميات من 25-200 ملغ / بول 24 ساعة بينما الأرجنين واللوسين والسيرين تطرح من 0-25 ملغ / بول 24 ساعة.

تصنيف بيلة الحموض الأمينية

- A - بيلة حموض أمينية فائض:

وتحصل بسبب ارتفاع تراكيز الحموض الأمينية في البلاسما بحيث تعجز النبيبات الكلوية عن عودة امتصاصها وقد تكون لأسباب عديدة

-أمراض كبدية : خاصة في القصور الكبدي حيث يعجز الكبد فيها عن تقويض الحموض الأمينية وتحويلها إلى هياكل كربونية ليتم استقلابها إلى مكونات أخرى , أو قد يعجز عن نزع أمينها التأكسدي مما يؤدي إلى تراكمها في الدم.

أسباب وراثية : نتيجة عوز في أحد أنزيمات الداخلة في التدرك الاستقلابي لحمض أميني محدد

B - بيلة حموض أمينية لأسباب كلوية نذكر منها :

- أمراض وراثية تؤدي إلى زيادة طرح بعض الحموض الأمينية (أمراض نبيبية)

- أذية كلوية وقصور كلوي يؤدي إلى طرح الحموض الأمينية بكميات كبيرة في البول.

1-فرط الفنيل ألانين الوراثي:

هو مرض وراثي جسدي متنحي Transmission autosomal recessive أو ما يسمى بمرض FOLLIMG وبنسبة تصل 1 لكل 12000 مولود (أوربا) لذلك يتم التحري عنه عند حديثي الولادة بشكل الزامي .

الفنيل ألانين هو حمض أميني ضروري وهو مولد للسكر والكيتون معاً وهو طليعة precursors للتيروزين .

الأفة الكيميائية الحيوية : هي عوز في أنظيم فنيل ألانين هدروكسيلاز وهو أنظيم موجود فقط في الكبد .

عند الولادة يبدو الطفل طبيعي غالباً ما يكون (شعر أشقر وعينان زرقاوان ورأس صغير) ولكن سرعان مايبدي اضطرابات عصبية, أفات جلدية , اضطرابات هضمية ومع تقدم العمر وبغياب أية معالجة يؤدي الى تخلف عقلي شديد .

يتم دراسة العوز الانظيمي على الأنسجة الكبدية ويمكن أن يكون بنمطين :

1- عوز بانظيم فنيل ألانين هدروكسيلاز والتي تتوسط تحول الفنيل ألانين إلى تيروزين وهذا الأكثر تواتراً (1)

2- عوز في انظيم بيوبترين المرجعة – biopterine reductase التي تتوسط التفاعل (2) وهو أكثر ندرة.

وهذا أكثر خطورة لأن هذه الجملة تلعب دور في نقل جذر الهدروكسيل في الاصطناعات الحيوية للحموض الدسمة والستيروئيدات واستقلابات أخرى.

مهما كان سبب عدم هدركسلة الفنيل ألانين فإننا بالمحصلة نحصل على ثلاث نتائج :

a- تراكم الفنيل ألانين في الخلايا وفي السوائل الحيوية في الجسم وخاصة في الدم .

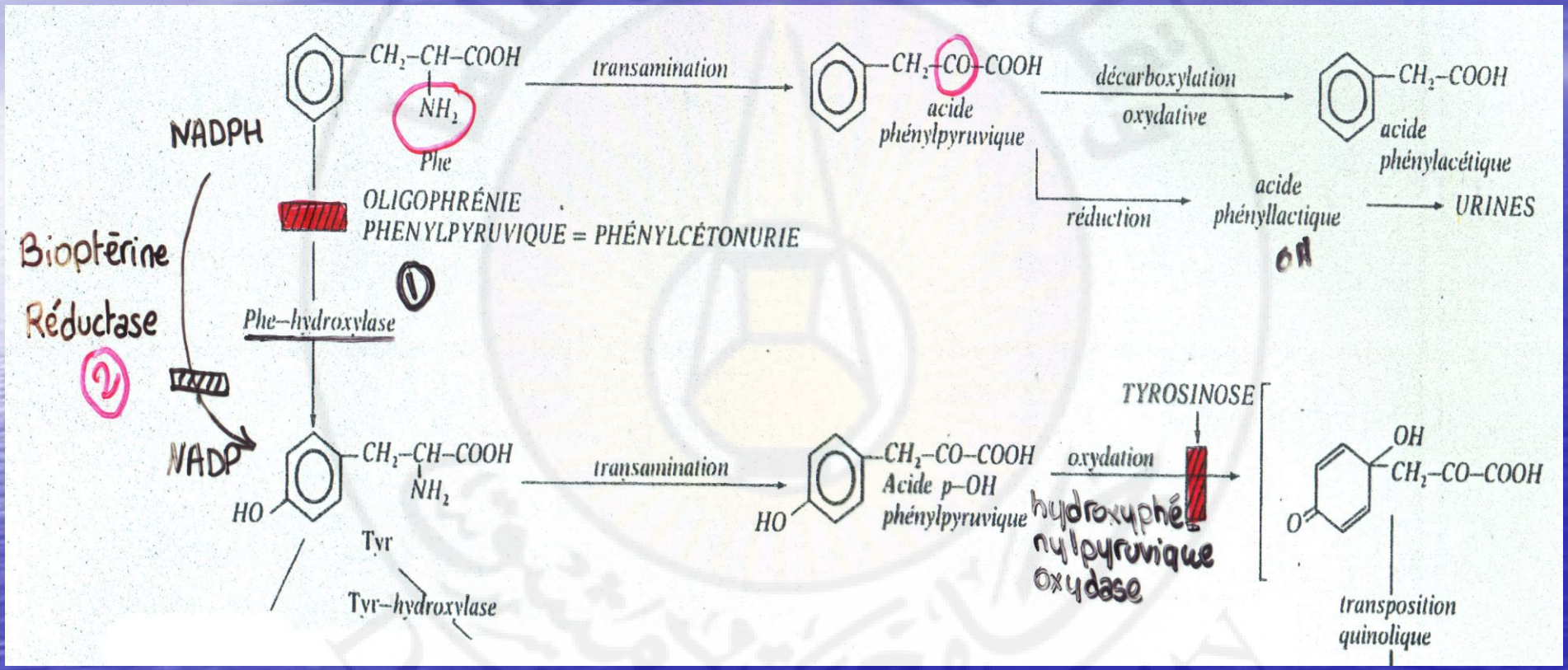
b- الحصول على مشتقات استقلابية أخرى وبكمية كبيرة تمر إلى الدم وتطرح بشكل كبير في البول

c- اضطراب في الاستقلابات الأخرى والتي يتدخل فيها من التيروزين :

- انخفاض في اصطناع السيروتونين اعتباراً من التربتوفان

- انخفاض في اصطناع حمض أمينو البوتريك اعتباراً من حمض الغلوتاميك butyric amino acide

- إنخفاض في اصطناع الكاتيكولامين والميلانيين اعتباراً من التيروزين.


NADPH
Biopterine
Réductase
2
NADP
CH2–CH–COOH
NH2
Phe
transamination
CH2–CO–COOH
acide
phénylpyruvique
décarboxylation
oxydative
CH2–COOH
acide
phénylacétique
réduction
acide
phényllactique
URINES
OH
OLIGOPHRÉNIE
PHENYLPYRUVIQUE = PHÉNYLCÉTONURIE
1
Phe–hydroxylase
HO
Tyr
Tyr–hydroxylase
transamination
Acide p–OH
phénylpyruvique
oxydation
TYROSINOSE
hydroxyphénylpyruvique oxydase
OH
O
transposition
quinolique

التشخيص :Diagnostic

يتم التشخيص مبكراً في اليوم السادس بعد الولادة أو على الأكثر قبل أن يصبح عمره شهرين وذلك لتجنب ظهور أي أعراض أو اضطرابات عصبية . يلجأ في حال عوز أنزيم الفنيل ألانين هدروكسيلاز الى اتباع حمية غذائية فقيرة بالفنيل ألانين .

هذه الحمية يجب أن تتبع وبشدة لعدة سنوات على الأقل لمدة 5 سنوات لحين التطور الكامل للجهاز العصبي .

يتم التشخيص باجراء معايرة كمية بطريقة الفلورة وكل نتيجة أعلى من 240 مكرومول / لتر يجب أن تعاد مرة ثانية لأنه قد تكون هذه الزيادة ناتجة عن عدم اكتمال نضج كامل النظام الانظيمي .

وفي حال ثبوتها نبدأ بحمية فقيرة بالفنيل الانين حيث توجد مستحضرات غذائية جاهزة .

يعطي البول رائحة مميزة لوجود مركبات خلونية فنيلية phenylketonuria (وجود حمض الفنيل الخلي , حمض الفنيل اللبني , فنيل بيروفيك).

المجال الطبيعي للفنيل ألانين في المصل عند حديثي الولادة الطبيعين هو 70-200 مكرومول / لتر 1.2-3.4 ملغ / دلتر .

المعالجة :

يضبط فنيل ألانين الدم في مستوى طبيعي بواسطة تغذية المريض بمستحضرات بروتنية منخفضة الفنيل ألانين وذلك لمدة خمس سنوات منذ الولادة مع معايرة اسبوعية للفنيل ألانين . ويجب ألا تتجاوز 600مكرومول /ل لأن بعدها تظهر الأعراض العصبية –النفسية وألا تقل عن 180 مكرومول /ل حيث قد يؤدي إلى حصول عوز في هذا الحمض الأميني الضروري .

لايمكن الكشف عن العوز في مرحلة قبل الولادة لأن الفنيل ألانين هدروكسيلاز هي انظيم متوضعة في الكبد ولا تواجد في السائل الأمينوسي .

ولكن يمكن دراستها في الكيميائية الوراثية .

لايمكن اصطناع التيروزين عند هؤلاء المرضى لذلك يجب أن يزود في القوت .

b- بيلة كيتونية جزئية :

ينجم عن عوز جزئي في انظيم الفنيل ألانين هدروكسيلاز وأحياناً تظهر في البول المركبات الاستقلابية المترتبة على ذلك : حمض البيروفيك , فنيل حمض الخل

2- فرط التيروزين الوراثي :

وهو مرض نادر يعود لعوز انظيم

Fumaryl acetroacetase وبالتالي تتوقف العمليات الاستقلابية التي يخضع لها تيروزين

يتشارك هذا المرض مع تشمع كبدي وأمراض كلوية شديدة مع بيلة سكرية بروتنية .

غالباً ما يحدث الموت بعد عدة سنوات لقصور كبدي حاد .

نجد في المصل كمية عالية من التيروزين (الفلورة) .

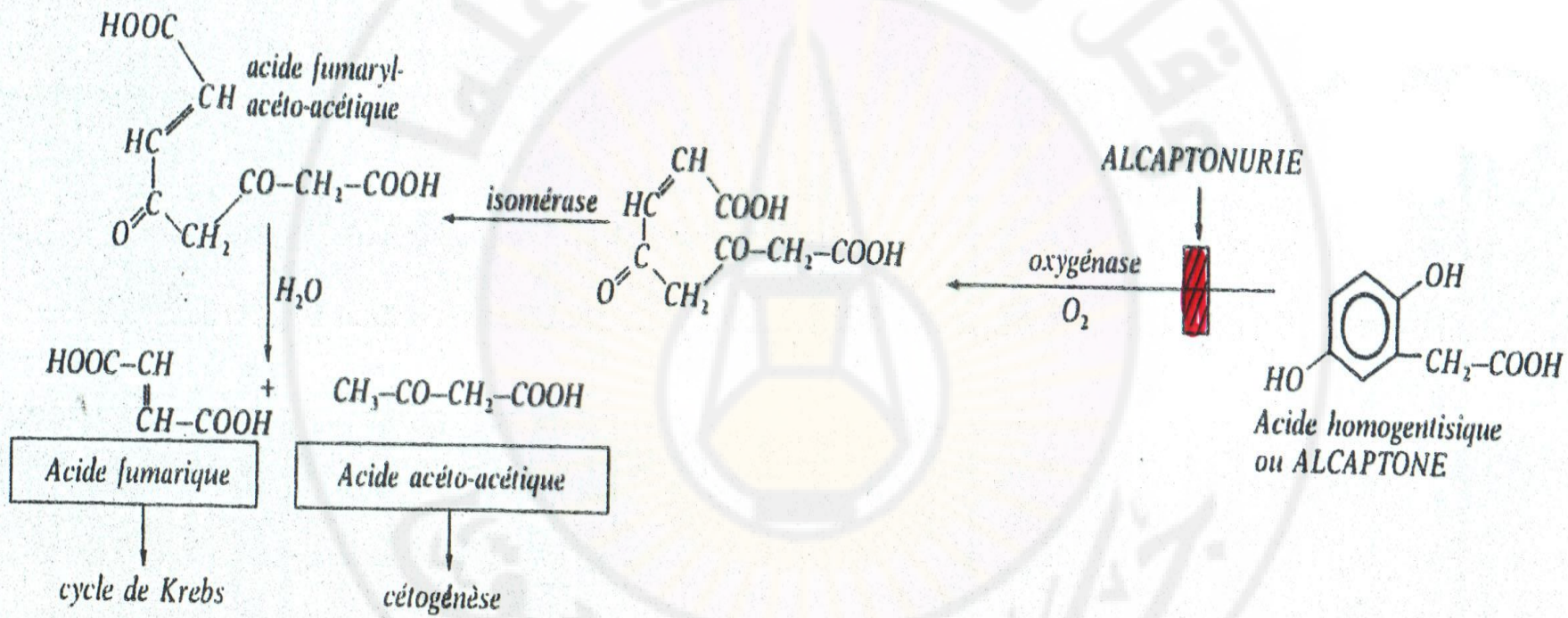
كذلك نجد قيم عالية من α-foetoproteine .

يستقلب حمض (HGA) بسرعة إلى فومارات وأسيتو أستات , قد يكون هناك عوز في الأنزيمات المتوسطة لهذا الاستقلاب مما يؤدي إلى فرط التيروزين .

3- بيلة الألكابتون Alcaptonurie

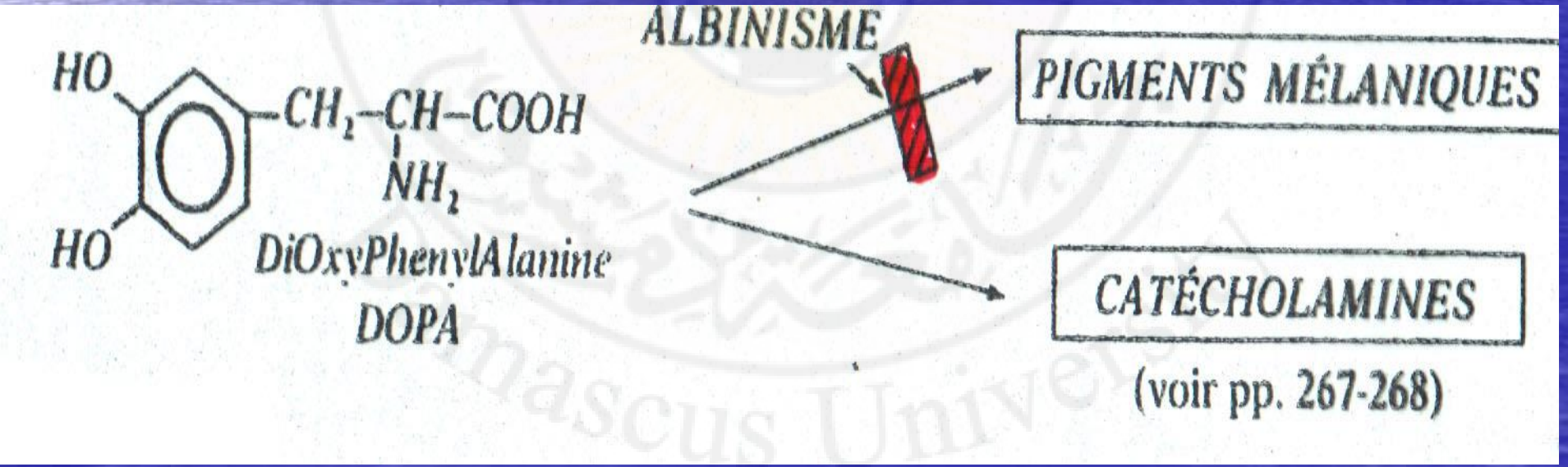
سببه عوز في انظيم oxygenase homogentise فيمنع تحـــول homogentisique إلــى دورة كريبس . أو يســـمى acide (alcaptone) أو حلقــة cetogenese

وبالتالي ينطرح هذا الحمض في البول معطياً لون أسود عند تأكسده ويسمى مرض البول الأسود حيث نجد كمية كبيرة من هذا الحمض في البول .


HOOC
acide fumaryl-acéto-acétique
CH
HC
CO–CH₂–COOH
C
O
CH₂
isomérase
CH
HC
COOH
C
CO–CH₂–COOH
O
CH₂
ALCAPTONURIE
oxygénase
O₂
OH
HO
CH₂–COOH
Acide homogentisique ou ALCAPTONE
H₂O
HOOC–CH
CH–COOH
+
CH₃–CO–CH₂–COOH
Acide fumarique
Acide acéto-acétique
cycle de Krebs
cétogénèse

4- البهق Albinisme

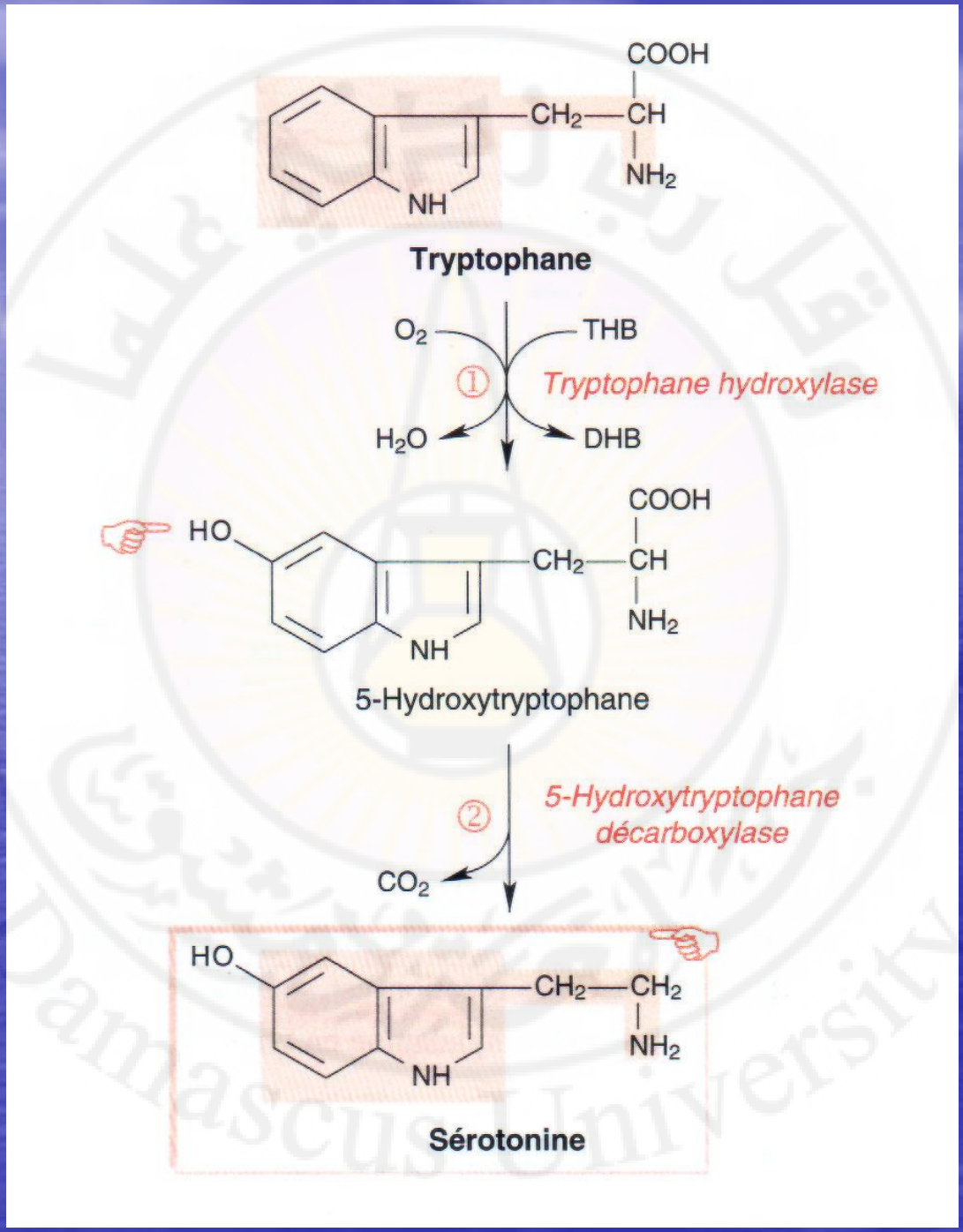
سببه عوز في الأنظيمات التي تتوسط تحول Dopa إلى أصبغة ميلانية مما يعطي اللون الأبيض الغير طبيعي للجلد وقد يؤدي أحياناً هذا العوز إلى حدوث سرطان للجلد .



5- البيلة التربتوفانية : Tryptophonuria

هي اضطراب استقلابي وراثي ينتج عنه اضطراب في تحول التربتوفان إلى السيروتونين

وسببه عوز إما في أنزيم بيوبترين ريدكتاز المسؤولة عن تحول THB إلى DHB أو عوز في أنزيم تربتوفان هدروكسيلاز


COOH
CH2—CH
NH2
NH
Tryptophane
O2
THB
①
Tryptophane hydroxylase
H2O
DHB
HO
COOH
CH2—CH
NH2
NH
5-Hydroxytryptophane
②
5-Hydroxytryptophane
décarboxylase
CO2
HO
CH2—CH2
NH2
NH
Sérotonine

الأعراض السريرية :

اضطرابات جلدية – فقدان التوازن – اضطرابات نفسية وفي بعض الحالات قد يؤدي إلى تخلف عقلي .

6- مرض هارتنب : Hartnup

هومرض وراثي ينتقل بصفة متنحية وعلى الصبغي الجسدي ينتج عنه اضطراب عودة في امتصاص التربتوفان وطرحه عن طريق البول مع مجموعة من الحموض الأمينية المعتدلة .

كذلك يحدث اضطراب في اصطناع النياسين (vit pp) أو vit B3 والذي يشتق من التمامة الأنظمية NAD و NADH .

الأعراض السريرية :

تبدأ الأعراض منذ الطفولة وتتمثل بطفح جلدي وخاصة في المناطق المعرضة للضوء مع الشعور بحرقة في المكان المعرض للضوء.

كما يترافق بنزع الطبقة الجلدية السطحية .(المرضى غالباً لهم عينان زرقاوان , شعر دقيق وقامة قصيرة) .

كذلك تترافق الأعراض بالتهاب في اللسان والتهابات في الأغشية المخاطية مع ضعف عضلي , فقدان التوازن , فقدان الوعي وفي حالات نادرة قد يحصل تخلف عقلي واضطرابات نفسية .

المعالجة :

تغذية جيدة ,اعطاء الفيتامين PP طوال الحياة والحماية من الشمس .

7- فرط الهستدين في الدم :

مرض وراثي ناتج عن عوز في أنزيم الهستيداز Histidase والذي يحول الهستدين إلى حمض اليورو كاني acide urocanique مما يؤدي إلى زيادة تركيز الهستدين في البلاسما (المقدار الطبيعي 11 ملغ / لتر)

أنزيم الهستيداز أنزيم كبدي وكذلك نجده في الأدمة الجلدية .

وبعوز هذا الأنزيم نجد كميات كبيرة من الهستدين في البول وكذلك مركباته الاستقلابية .

الأعراض السريرية :

تخلف عقلي مع صعوبة في الكلام يعتمد التشخيص على معايرة الهستيداز في الخزعات الجلدية .

كذلك نجد تراكيز عالية من الهستدين في البلاسما والبول وقد يصل إلى 900 ملغ / بول 24 ساعة

ونجد في البول أيضاً زيادة طرح حمض ايميدازول البيروفي – حمض ايميدازول اللبني – حمض ايميدازول الخلي .

ويتم الكشف عنه باجراء معايرة كمية للهستدين في الدم وكذلك إجراء معايرة نسيجية للهستدين في خزعة جلدية .

تظهر الاعراض : تخلف عقلي – اضطراب في الكلام والنطق مع اندفاعات تحسسية حين التعرض لأشعة الشمس

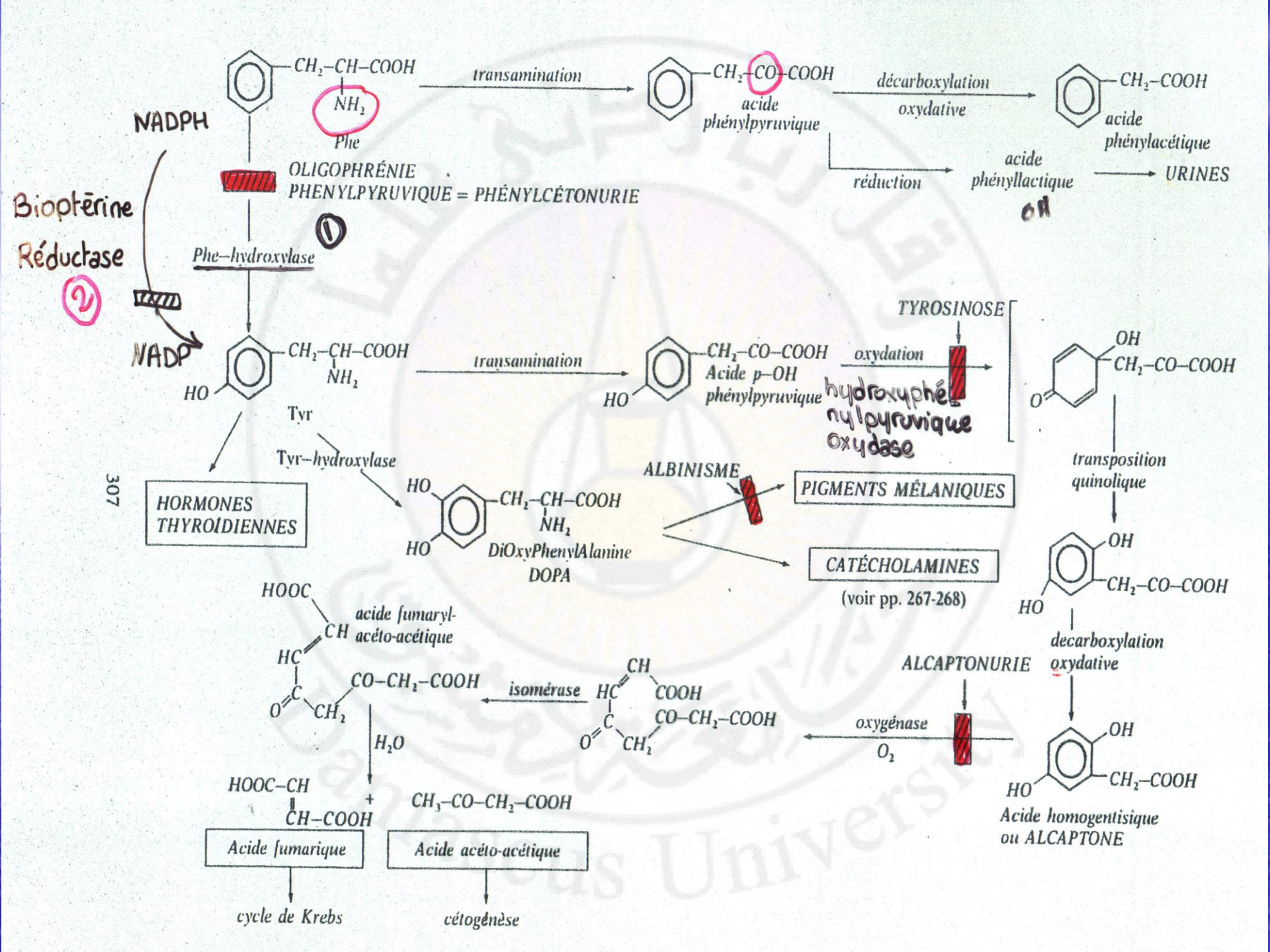
8- فرط السيستئين البولي :

هو اضطراب وراثي يؤدي إلى زيادة طرح السيسئين في البول لاصابات وراثية في الأنابيب الكلوية ويؤدي أيضاً إلى زيادة في طرح الليزين والأرجنين والاورنثين .

ويمكن لهذا السيستئين أن يحدث حصيات سيستنية تبدو بوضوح على مسير الحالبين وفي الكلتين وقد يسبب تلراكم السيستئين في البول تحصي سيستيني في الكلتين .

وعند فحص الراسب البولي نجد بللورات سيستئين سداسية شفافة ذات حواف سوداء وأرضية لماعة .

المقدار الطبيعي في البول < 150 ملغ / بول 24 ساعة .


NADPH
Biopterine Réductase (2)
NADP
Phe
transamination
acide phénylpyruvique
décarboxylation oxydative
acide phénylacétique
URINES
réduction
acide phényllactique
OH
OLIGOPHRÉNIE PHENYLPYRUVIQUE = PHÉNYLCÉTONURIE
(1)
Phe–hydroxylase
Tyr
transamination
Acide p–OH phénylpyruvique
TYROSINOSE
oxydation
hydroxyphénylpyruvique oxydase
transposition quinolique
HORMONES THYROÏDIENNES
Tyr–hydroxylase
DiOxyPhenylAlanine
DOPA
ALBINISME
PIGMENTS MÉLANIQUES
CATÉCHOLAMINES
(voir pp. 267-268)
ALCAPTONURIE
oxygénase
O_2
decarboxylation oxydative
Acide homogentisique ou ALCAPTONE
acide fumaryl-acéto-acétique
isomérase
H_2O
Acide fumarique
Acide acéto-acétique
cycle de Krebs
cétogénèse

Understanding Diabetes Mellitus and the complications relating to the disease.

Diabetes Mellitus and the Associated Complications

What is Diabetes

- Diabetes is a complete or relative lack of insulin.
- First noted in 1552BC
- Diabetes (Greek) – siphon of water
- Mellitus (Latin) – honeysweet
- 11th Century detected by urine drinking
- 19th Century pancreas noted as the cause

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Why is diabetes significant?

- People with diabetes have a high risk of heart disease, stroke, blindness, kidney disease and amputations.
- They are five times more likely than the general population to suffer heart failure.
- It is the leading cause of blindness in the working age population.
- Across the UK one thousand people with diabetes start kidney dialysis every year.



According to the World Health Organization (WHO), the number of global cases of DM is expected to increase in the next 25 years from 135 million to nearly 300 million people.

Most of these people will come from areas of the world where unhealthy diets, aging, obesity, and sedentary lifestyles will contribute to the onset of Diabetes.

Diabetes Mellitus

Most Costly Disease In the Modern World
$132 Billion Medical Expense

5% of All Health Care Dollars Spent On **Unnecessary** Diabetes Complications

Significantly Higher Average Annual Health Care Costs
$13,243/Year – Diabetes Patients
$2,560/Year – Non-diabetes Patients

Diabetes Mellitus

The diabetes epidemic



- 366 million affected in 2011
- 552 million in 2030

- UK – 2.9 million diagnosed
- 850,000 Undiagnosed
- 400 per day
- 17 per hour
- 3 every 10 minutes

IDF Diabetes Atlas

Diabetes is the decreased use of or shortage of insulin , which plays an active part in the metabolism of fat and proteins.

Sugar is glucose and used as fuel or an energy source for the body.

Insulin is a hormone. The pancreas secretes insulin to the blood. The liver and muscles store glucose.

When not controlled, glucose and fats remain in the blood and damage vital organs.



Diabetes Mellitus

Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Gestational Diabetes Mellitus (GDM)
- Other specific types of diabetes
  - Monogenic diabetes syndromes
  - Diseases of the exocrine pancreas, e.g., cystic fibrosis
  - Drug- or chemical-induced diabetes

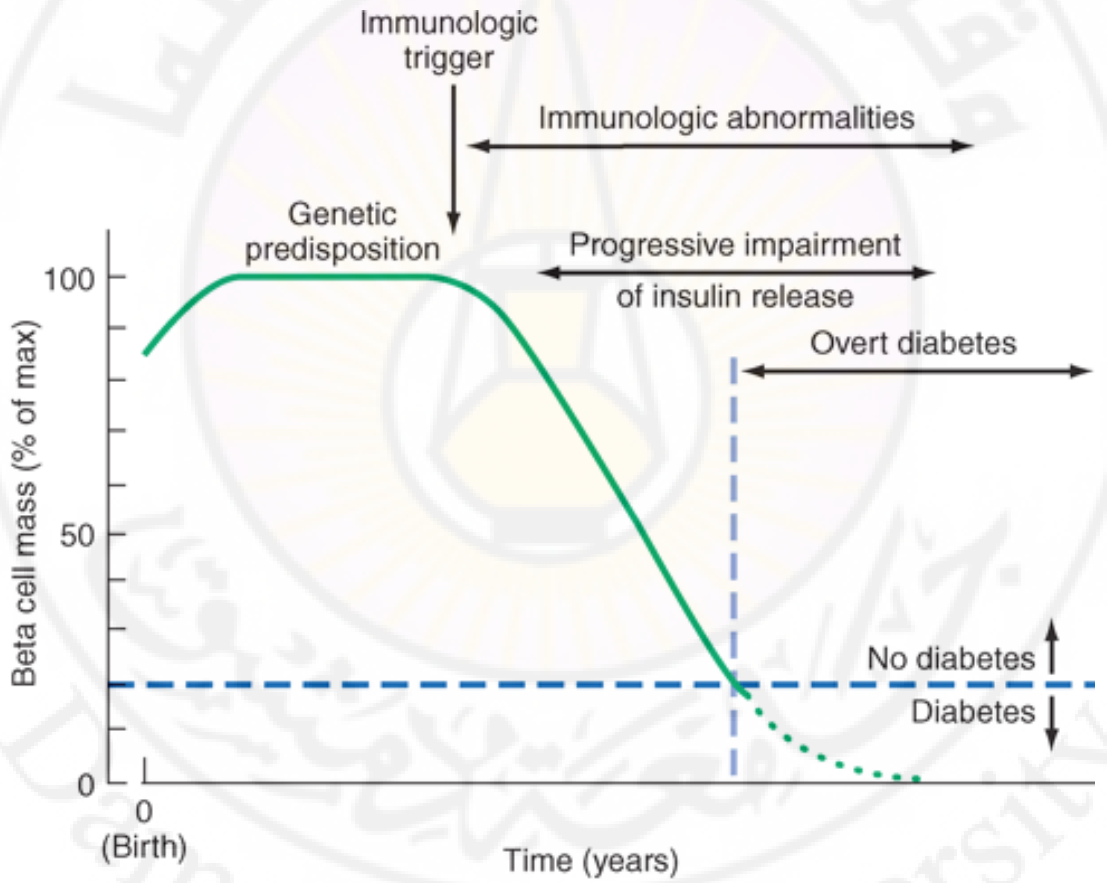
Diabetes

- Group of metabolic disorders that share a common feature of **HYPERGLYCEMIA**
  - Type 1 DM: absolute deficiency of insulin cause by beta cell destruction
  - Type 2 DM: combination of peripheral resistance to insulin action and inadequate secretory response
- Results from defects in Insulin secretion, action or most commonly both
- Leading cause of end stage renal disease, adult onset blindness and non traumatic lower extremity amputation

Pathogenesis of Type 1 DM

- Lack of insulin is caused by an immunologically mediated destruction of the beta cells
- Genetic susceptibility.
- The autoimmune occurs, 80-90% b cell destruction.

Development of Type 1 Diabetes



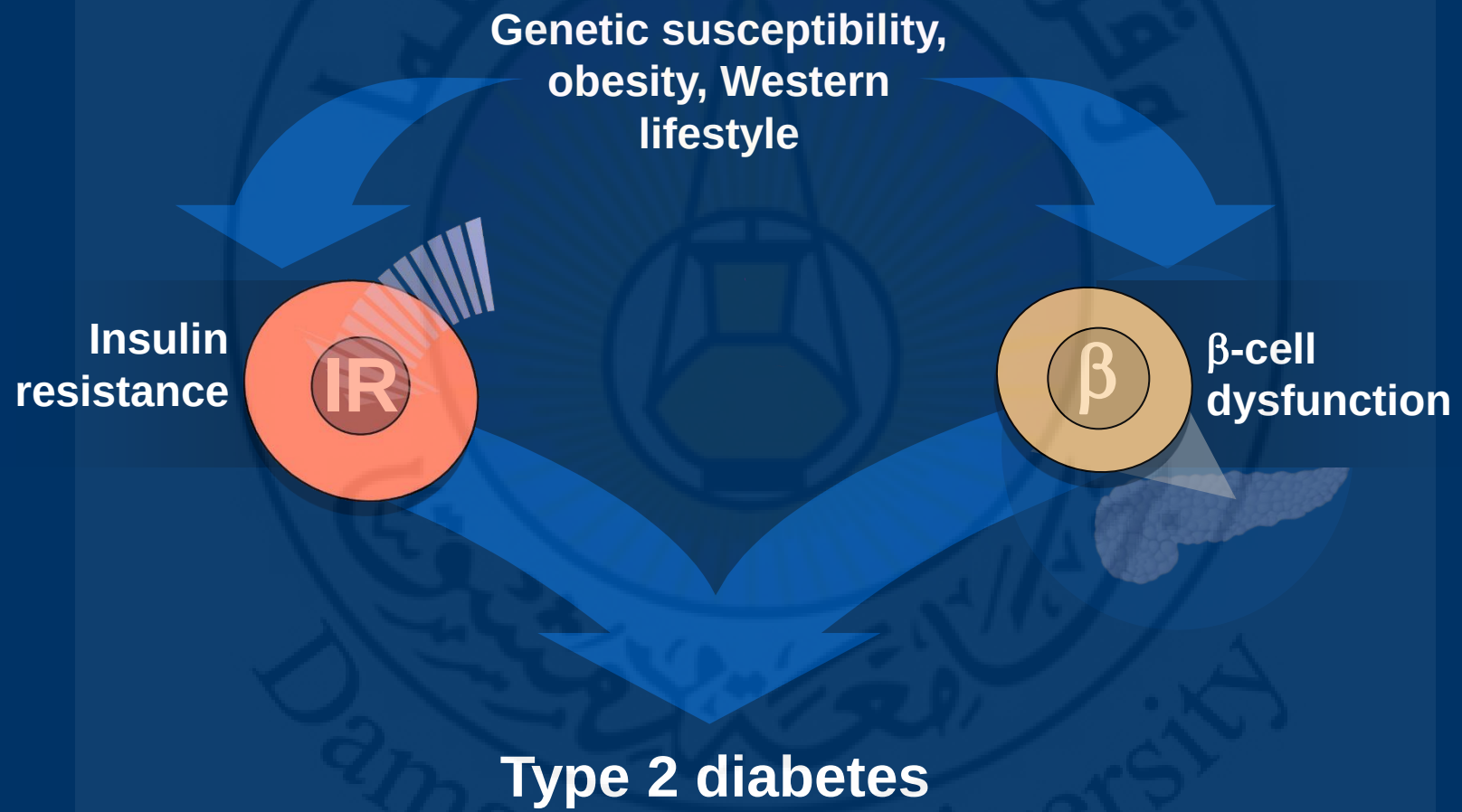
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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Pathogenesis of Type 2 DM

- Environmental factors play a large role (lifestyle, dietary habits etc.)
- 2 Metabolic defects
  - Decreased ability of peripheral tissues to respond to insulin
  - b-cell dysfunction that is manifested as impaired insulin secretion

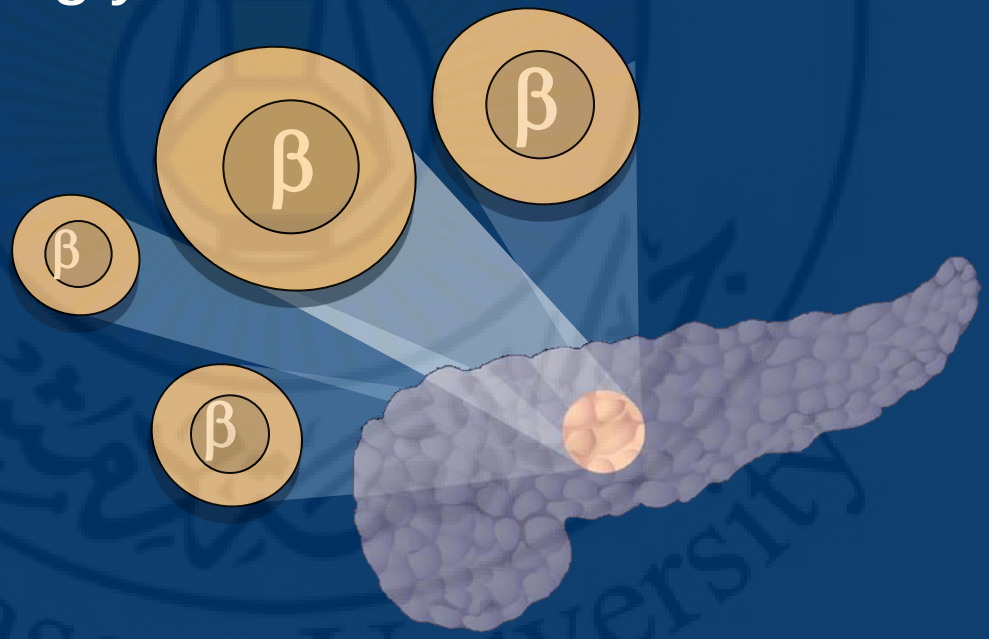
Insulin resistance and β-cell dysfunction are core defects of type 2 diabetes



Rhodes CJ & White MF. *Eur J Clin Invest* 2002; 32 (Suppl. 3):3–13.

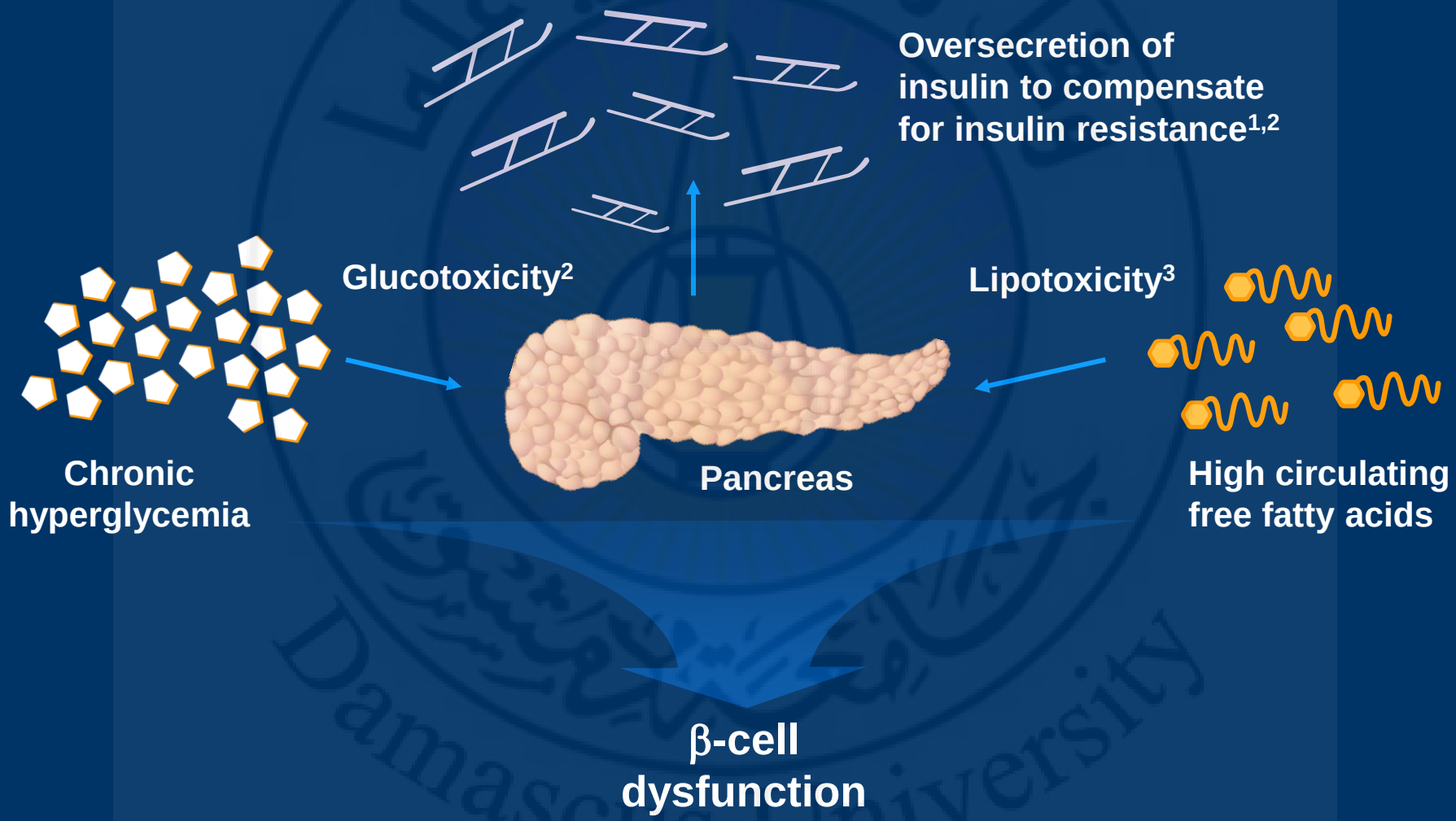
What is β-cell dysfunction?

- Major defect in individuals with type 2 diabetes
- Reduced ability of β-cells to secrete insulin in response to hyperglycemia



DeFronzo RA, *et al. Diabetes Care* 1992; 15:318–354.

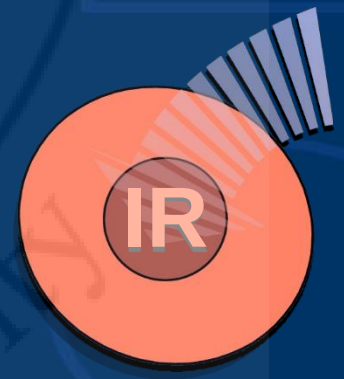
Why does the β-cell fail?



[1]Boden G & Shulman GI. *Eur J Clin Invest* 2002; 32:14–23.
[2]Kaiser N, *et al. J Pediatr Endocrinol Metab* 2003; 16:5–22.
[3]Finegood DT & Topp B. *Diabetes Obes Metab* 2001; 3 (Suppl. 1):S20–S27.

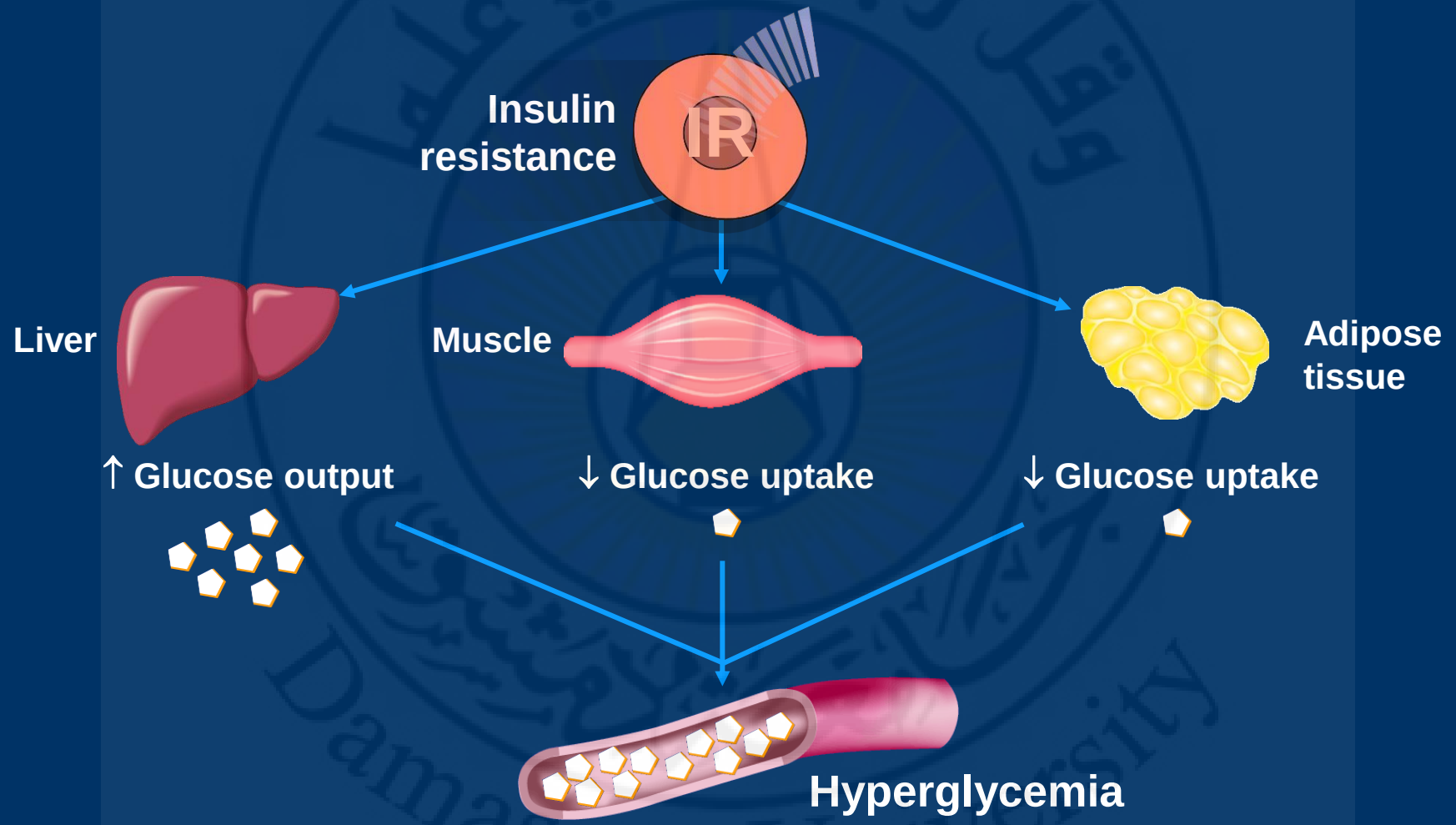
What is insulin resistance?

- Major defect in individuals with type 2 diabetes[1]
- Reduced biological response to insulin[1–3]
- Strong predictor of type 2 diabetes[4]
- Closely associated with obesity[5]

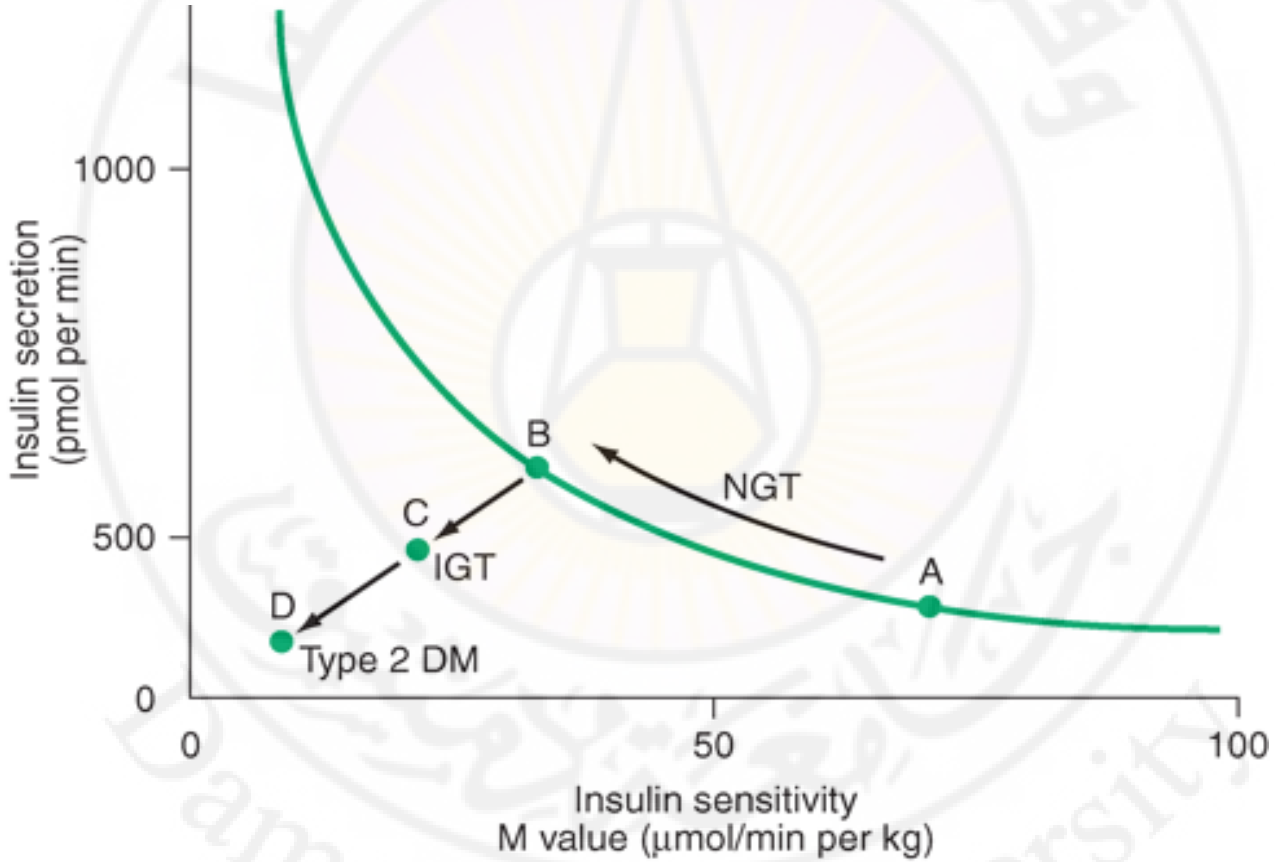


[1]American Diabetes Association. *Diabetes Care* 1998; 21:310–314.
[2]Beck-Nielsen H & Groop LC. *J Clin Invest* 1994; 94:1714–1721. [3]Bloomgarden ZT. *Clin Ther* 1998; 20:216–231.
[4]Haffner SM, *et al. Circulation* 2000; 101:975–980. [5]Boden G. *Diabetes* 1997; 46:3–10.

Insulin resistance – reduced response to circulating insulin



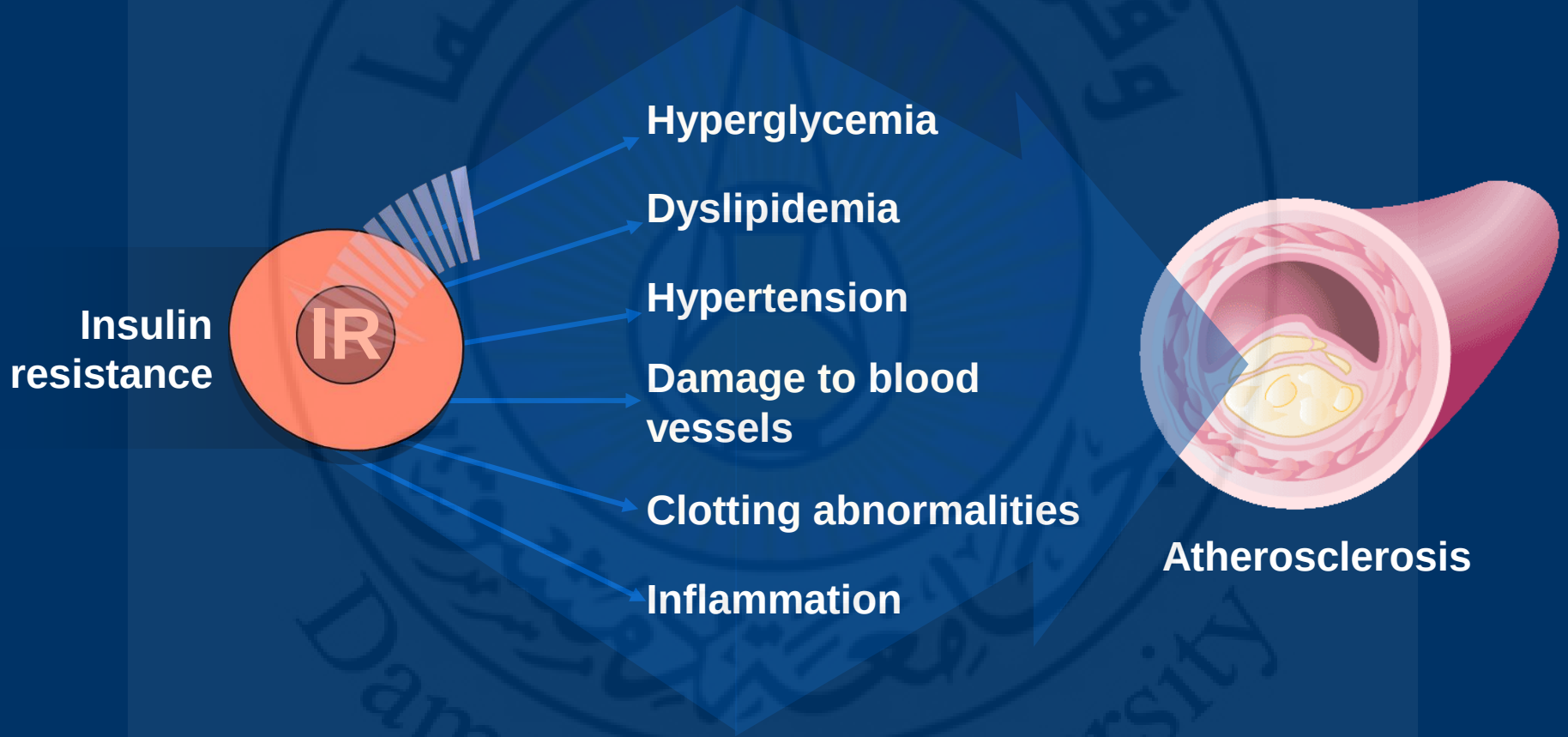
Development of Type 2 Diabetes



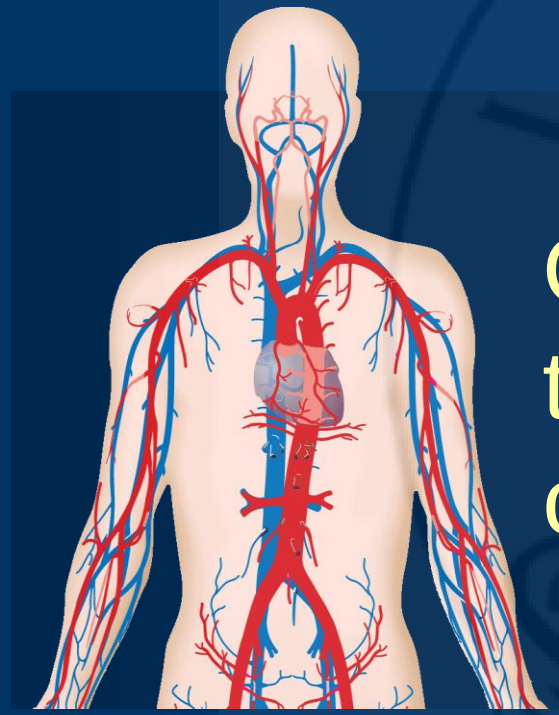
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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Insulin resistance is linked to a range of cardiovascular risk factors



Zimmet P. *Trends Cardiovasc Med* 2002; 12:354–362.



Overall, 75% of patients with type 2 diabetes die from cardiovascular disease

Gray RP & Yudkin JS. Cardiovascular disease in diabetes mellitus. In *Textbook of Diabetes* 2nd Edition, 1997. Blackwell Sciences.

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG)
≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL
(11.1 mmol/L) during an OGTT/oral Glucose Tolerance test

OR

A1C ≥6.5%

OR

Classic diabetes symptoms + random plasma glucose
≥200 mg/dL (11.1 mmol/L)

American Diabetes Association.

Recommendations: Type 1 Diabetes

- Blood glucose rather than A1C should be used for type 1 diabetes in symptomatic individuals.

- Screening for type 1 diabetes with an antibody panel is recommended only in the setting of a clinical research study or in a first-degree family members with type 1 diabetes.

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American Diabetes Association.

Recommendations: Prediabetes

- Screening for prediabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults.
- Testing should begin at age 45 for all people.
- Consider testing for prediabetes in asymptomatic adults of any age w/ BMI ≥25 kg/m2 or ≥23 kg/m2 (in Asian Americans) who have 1 or more add'l risk factors for diabetes.
- If tests are normal, repeat at a minimum of 3-year intervals.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

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Recommendations: Prediabetes (2)

- FPG, 2-h PG after 75-g OGTT, and A1C, are equally appropriate for prediabetes testing.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

American Diabetes Association.

Prediabetes*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

* For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

American Diabetes Association.

Recommendations: Testing for Type 2 Diabetes

- Screening for type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults.
- Consider testing in asymptomatic adults of any age with BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans who have 1 or more add'l dm risk factors.
- For all patients, testing should begin at age 45 years.
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable.

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Risk factors for Prediabetes and T2D

- A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
- first-degree relative with diabetes
- high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- women who were diagnosed with GDM
- history of CVD
- hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- women with polycystic ovary syndrome
- physical inactivity
- other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).

www.diabetes.org/are-you-at-risk

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Comparisons of Type 1 & Type 2

Type 1 (5-10%)

- Sudden onset
- Severe symptoms
- Weight loss
- Lean
- Ketosis
- Absent C-peptides
- Markers of autoimmunity present
- Family history uncommon
- Onset usually in the young

Type 2 (90-95%)

- Gradual onset
- May be Asymptomatic
- Often no weight loss
- Usually obese
- Not ketotic
- C-peptide detectable
- No markers of autoimmunity present
- Family history
- Onset usually >40 years old

Immune-Mediated Diabetes (T1a Diabetes)

β-Cell Destruction

- Variable rate
  - Rapid in infants and children (primarily)
  - Slow in adults (primarily)

Immune Markers

- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b

When fasting hyperglycemia is first detected, 85% – 90% of individuals have ≥1 autoantibody

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

- GAD is an enzyme (glutamic acid decarboxylase) that helps the body produce a specific neurotransmitter called gamma-aminobutyric acid (GABA).

- Neurotransmitters are chemical messengers that carry information and instructions from the brain to the rest of the body via the nervous system.

- GABA is an amino acid that reduces the amount of communication to and from the nerves.

- GAD is present in the pancreas and the nervous system, and its roles include relaxing the muscles and helping the pancreas function, among other processes.

- GAD can also trigger the immune system to produce autoantibodies against healthy cells.

- These pancreatic cells produce insulin. Diabetes occurs when the immune system treats these cells as though they were foreign, harmful material and destroys them.

T1D: Clinical Course

- Typically characterized by the acute onset of the classic symptoms of diabetes
  - Polyuria, polydipsia, weight loss
- Course of autoimmune diabetes characterized by ongoing β-cell destruction
- Exogenous insulin required for survival
  - T1D should be identified as soon as possible to avoid high morbidity due to a delay in insulin treatment

T1D, type 1 diabetes.

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Ketoacidosis in T1D/T2

- First manifestation of T1D in many patients, especially children and adolescents
- May be precipitated by infection or environmental triggers
  - Rapid change from modest fasting hyperglycemia to severe hyperglycemia
- In some patients (especially adults), residual β-cell function may prevent ketoacidosis for many years
  - Once patients become insulin dependent (with low or undetectable plasma C-peptide), they are at risk for ketoacidosis

T1D and Obesity

- Although T1D patients are rarely obese when they present, the presence of obesity is not incompatible with T1D

T1D and Susceptibility to Other Autoimmune Diseases

- Addison’s disease
- Autoimmune hepatitis
- Graves’ disease
- Hashimoto’s thyroiditis
- Pernicious anemia
- Vitiligo

Idiopathic Diabetes (Type 1b Diabetes)

- No known etiology
- Strongly inherited
  - No immunological evidence for β-cell autoimmunity and no HLA association
  - More common with African or Asian ancestry
- Patient presentation
  - May have permanent insulinopenia
  - Prone to ketoacidosis, with varying degrees of insulin deficiency between episodes

Fulminant T1D

- Presentation
  - Extremely high glucose levels with diabetic ketoacidosis
  - On average only 4 days of hyperglycemia
  - Normal or near-normal A1C
- Often preceded by common cold–like and gastrointestinal symptoms
- Sometimes associated with pregnancy
- Pancreatic enzymes often elevated, absent C-peptide levels, but virtually no detectable autoantibodies against constituents of pancreatic beta cells.
- The death of the patient is likely to occur within 24 h.

- The number of patients presumably amounts to 5,000-7,000 in Japan. The involvement of both, genetic background and viral infection, has been suggested in the pathogenesis of this disease. (2012)

Recommendations: Detection and Diagnosis of GDM

- Test for undiagnosed T2DM at the 1st prenatal visit in those with risk factors.
- Test for GDM at 24–28 weeks of gestation in women not previously known to have diabetes.
- Screen women with GDM for persistent diabetes at 4–12 weeks postpartum, using the OGTT.

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One-Step Strategy

- At 24-28 weeks gestation in women not previously with diabetes
- 75-g OGTT; Measure plasma glucose at fasting and at 1 and 2 hours.
- GDM when plasma glucose exceeds:
  - Fasting: 92 mg/dL (5.1 mmol/L)
  - 1 h: 180 mg/dL (10.0 mmol/L)
  - 2 h: 153 mg/dL (8.5 mmol/L)

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

American Diabetes Association.

Recommendations: Monogenic Diabetes Syndromes

- All children diagnosed with diabetes in the first 6 months of life should have genetic testing for neonatal diabetes.
- Children and adults, diagnosed in early adulthood, who have diabetes not characteristic of T1D or T2D that occurs in successive generations should have genetic testing for MODY. :

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

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Genetic Defects of β-Cell Function

- Chromosome 12, HNF-1α (hepatocyte nuclear factor 1 (MODY3)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 20, HNF-4α (MODY1)
- Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
- Chromosome 17, HNF-1β (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Mitochondrial DNA

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ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Recommendations: Cystic Fibrosis–Related Diabetes (CFRD)

- Annual screening for CFRD with OGTT should begin in all patients with cystic fibrosis
- A1C is not recommended as a screening test for CFRD.
- Patients with CFRD should be treated with insulin to attain individualized glycemic goals.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

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Diagnosis of Diabetes

Diagnosis cannot be made from:

- Blood glucose strips read visually or by a meter.



- Urine testing

- Glycosalated Haemoglobin - HbA1c

Diagnosis of Diabetes

Two pieces of evidence required

- Symptoms

- Random Venous Plasma Glucose ≥ 11.1 mmol/L

- Fasting Venous Plasma Glucose ≥ 7.0 mmol/L

- 2 Hour Venous Plasma Glucose ≥ 11.1 mmol/L

WHO

Glucose Tolerance Test

- 3 days of unrestricted diet and exercise
- Evening meal as normal the night before
- Overnight fast of 8-14 hours

TEST

- Fasting blood on the morning
- Drink 75g of anhydrous glucose in 250-300ml water over 5 mins
- Blood sample 2 hours later
- No smoking during the test

DIAGNOSIS AFTER AN OGTT

	Impaired Fasting Glucose (IFG)	Impaired Glucose Tolerance (IGT)	Diabetes
Fasting Venous Plasma Glucose	6.1 mmol/l to 6.9 mmol/l	<7.0 mmol/l	≥ 7.0 mmol/l
2 hr post	< 7.8 mmo/l	≥7.8 mmol/l up to 11.1 mmol/l	≥11.1 mmol/l (WHO,2006)

Impaired Glucose Regulation

- Impaired Glucose Tolerance (IGT)
  - Abnormalities in glucose regulation in the post-prandial state.
  - More common in women

- Impaired Fasting Glucose (IFG)
  - Elevated fasting glucose concentrations, but lower than those required to diagnose diabetes
  - More common in men

Do not use HbA1c

- Under 18yrs
- Possible Type 1
- Where glucose may rise rapidly e.g.: steroids, antipsychotics.
- Reduced red cell survival e.g. haemolytic anaemia
- Gestational Diabetes
- Pancreatic damage/surgery
- Anaemia/Haemoglobinopathy

- Type 1 diabetes signs and symptoms can appear relatively suddenly and may include:

- Increased thirst
- Frequent urination
- Extreme hunger
- Unintended weight loss
- Irritability and other mood changes
- Fatigue and weakness
- Blurred vision

Complications of Diabetes: An Overview of the Pathophysiology

OBJECTIVES

1. To understand the pathophysiology of acute complications of DM due to:
   - Diabetic Ketoacidosis
   - Hyperosmolar state
2. To understand the pathophysiology of chronic complications of DM due to hyperglycemia (micro vascular and macro vascular complications)
3. To gain an understanding of the mechanisms that lead to glucose induced vascular damage.

Complications of Diabetes

Though the pathogenesis of DM differs, the complications are the same and are the main cause of mortality and morbidity

Acute complications due to hyperglycemia

- Diabetic ketoacidosis
- HHS

Chronic complications due to vascular damage

- Microvascular complications:
  - Neuropathy, Nephropathy, Retinopathy
- Macrovascular complications:
  - Coronary artery disease, peripheral vascular disease, stroke

Diabetic Ketoacidosis

- MEDICAL EMERGENCY!!!
- Due to lack of insulin
- Most often seen in Type 1 DM but also can be present in Type 2 DM who have predominantly secretory defects
- Common in younger patients (<65), Women>Men
- Mortality 5%
  - Most often due to the underlying illness and not the metabolic complications

Hyperosmolar Hyperglycemic State

- Less common than DKA
- Seen in Type 2 DM
- Age group is often older (>65 years)
- Mortality 5-20%!
- Often present with altered level of consciousness due to hyperosmolar state (when sOsm > 300mosm/kg)

HHS

- Hyperglycemia, hyper osmolality and dehydration *without* ketosis
- Most frequent precipitants:
  - Acute Stressors
  - Renal Failure
  - Hyperglycemic inducing medications

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Precipitating Factors

- Acute stressors or illness increase the secretion of glucagon, cortisol and epinephrine precipitating hyperglycemia
  - Infection
  - Infarction
  - Insulin
  - Ischemia
  - Intoxication (alcohol, drug abuse)

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Regulatory Hormones

- 2 main hormones responsible to hyperglycemia and ketoacidosis
  - Insulin - deficiency or resistance
  - Glucagon - excess

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Normal Response

- Glucose is ingested during a meal, stimulates the release of Insulin from b-cells of the pancreas
- Insulin action is to restore normoglycemia:
  - Decreasing hepatic glucose production
  - Inhibiting glycogenolysis and gluconeogensis
  - Increases the skeletal muscle and adipose tissue uptake
  - Inhibits glucagon secretion and production

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Hyperglycemia

- Overall net reduction in effective circulation insulin with a net increase in counter regulatory hormones (epinephrine, cortisol, glucagon)
- Hyperglycemia is due to:
  - Impaired peripheral utilization in tissue (post prandial)
  - Increased gluconeogenesis (fasting state)
- Insulin deficiency is more prominent in DKA over HHS
  - Glucose levels are much higher in HHS than in DKA

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Ketoacidosis

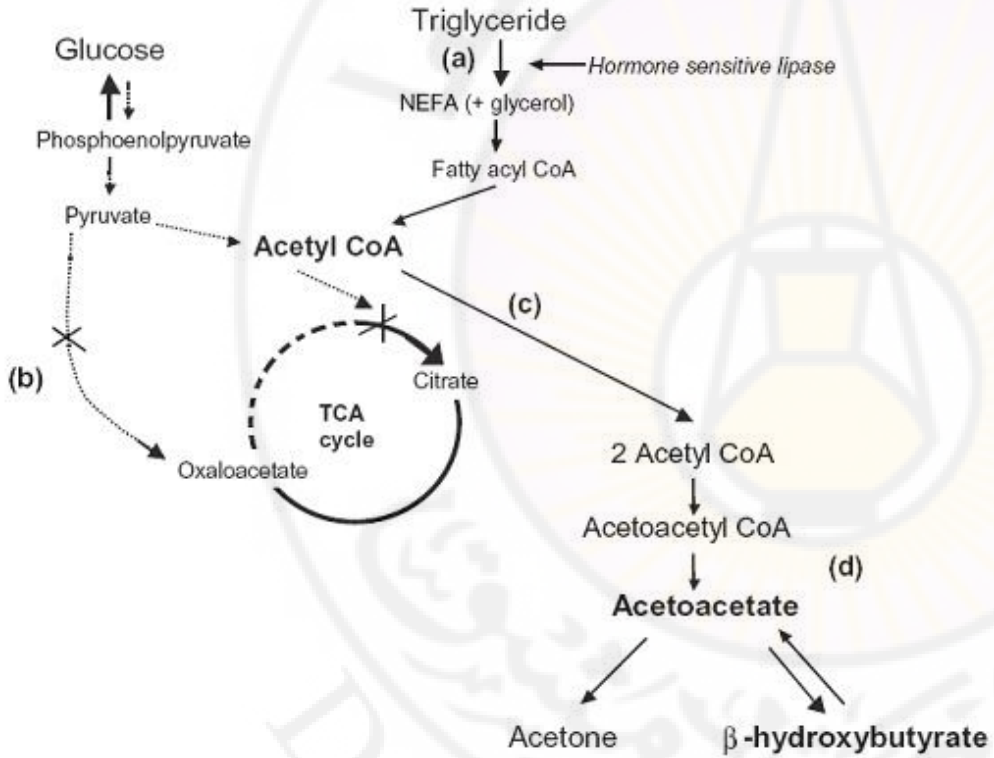
- Insulin deficiency results in loss of uptake of glucose by peripheral glucose transporters → Hyperglycemia
- Insulin deficiency activates hormone dependent lipase → Increased lipolysis (unregulated)
- This leads to conversion of triglycerides to free fatty acids and glycerol

Fatty acids are converted to acetyl CoA which is shuttled into

1) Krebs cycle (insulin dependent)

2) Ketones bodies (without insulin) including BHB and acetoacetate.

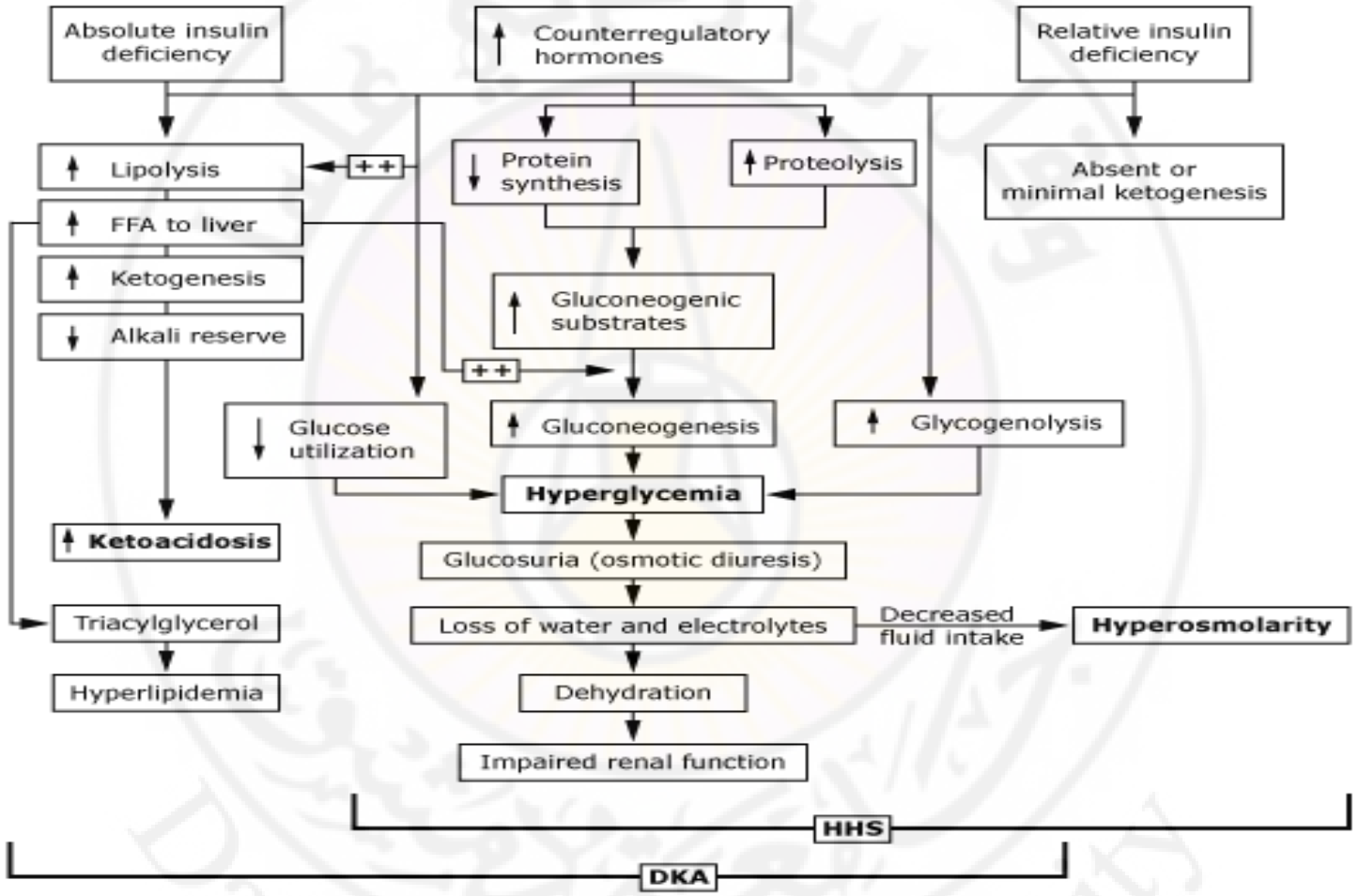
Ketoacidosis



[14]

- Inadequate insulin leads to energy stores from fat and muscle to be broken down into fatty acids and amino acids
- These precursors are transported to the liver for conversion to glucose and ketones

Pathogenesis of DKA and HHS



++: Accelerated pathway.

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UpToDate

Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>18
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)•	Variable	Variable	Variable	>320
Anion gapΔ	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

* Nitroprusside reaction method.
• Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.
Δ Calculation: (Na+) - (Cl- + HCO3-) (mEq/L). See text for details.
Copyright © 2006 American Diabetes Association From Diabetes Care Vol 29, Issue 12, 2006. Information updated from Kitabchi, AE, Umpierrez, GE, Miles, JM, Fisher, JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335.
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Pathophysiology of Chronic Complications

Macrovascular Complications

- Main cause of mortality
- large and medium vessel disease due to accelerated atherosclerosis

Microvascular Complications

- Significant source disability and decrease in quality of life
- Capillary dysfunction in target organs

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Macrovascular Complications

- Coronary Artery Disease
  - 2-4 times increased risk compared to general population
  - Greater incidence of “Silent MI”
    - May present as CHF
- Peripheral Vascular Disease
- Cerebrovascular disease

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Microvascular Complications

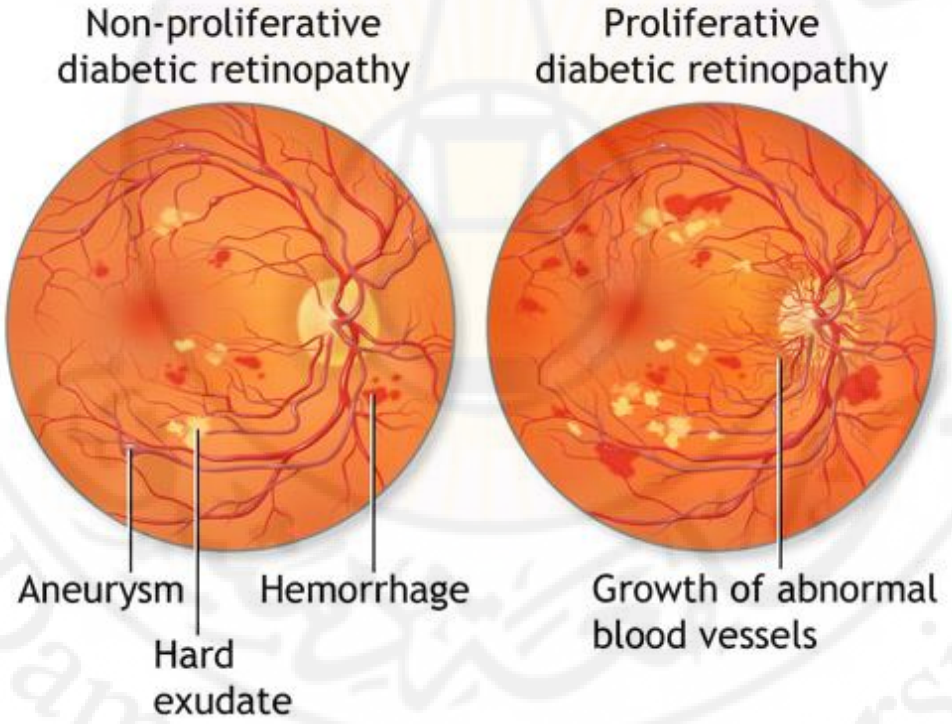
- Retinopathy
- Neuropathy
- Nephropathy

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Retinopathy

- Diabetes is the most common cause of blindness in the US
- Retinopathy has the highest correlation with severity and duration of diabetes
- Hyperglycemia is the primary cause of diabetic retinopathy but the specific pathophysiologic mechanisms are not well understood.
  - Growth factors have been implicated in the development of the next phase - proliferative retinopathy.
    - Vascular Endothelium Growth Factor (VGEF)

Classification of Diabetic Retinopathy



Nephropathy

- **Near euglycemia can decrease the development of microalbuminuria and progression of diabetic nephropathy**.
- However, tight glycemic control has no effect in reducing proteinuria or improving GFR if clinical nephropathy is present.
- Early recognition of nephropathy is crucial

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Neuropathy

- Diabetic neuropathy can present as mononeuropathy or polyneuropathy and can also be divided in sensory, motor and autonomic.
- The pathogenesis is not well elucidated, but it is believed that the mononeuropathies, such as the acute cranial nerve palsies and diabetic amyotrophy, are due to ischemic infarction of the peripheral nerves.
- The peripheral sensori-motor neuropathies and autonomic neuropathies may be caused by a metabolic factor or osmotic toxicity secondary to hyperglycemia.

- **Foot damage.** Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated, cuts and blisters can become serious infections that may ultimately require toe, foot or leg amputation.

Hyperglycemia Induced Complications

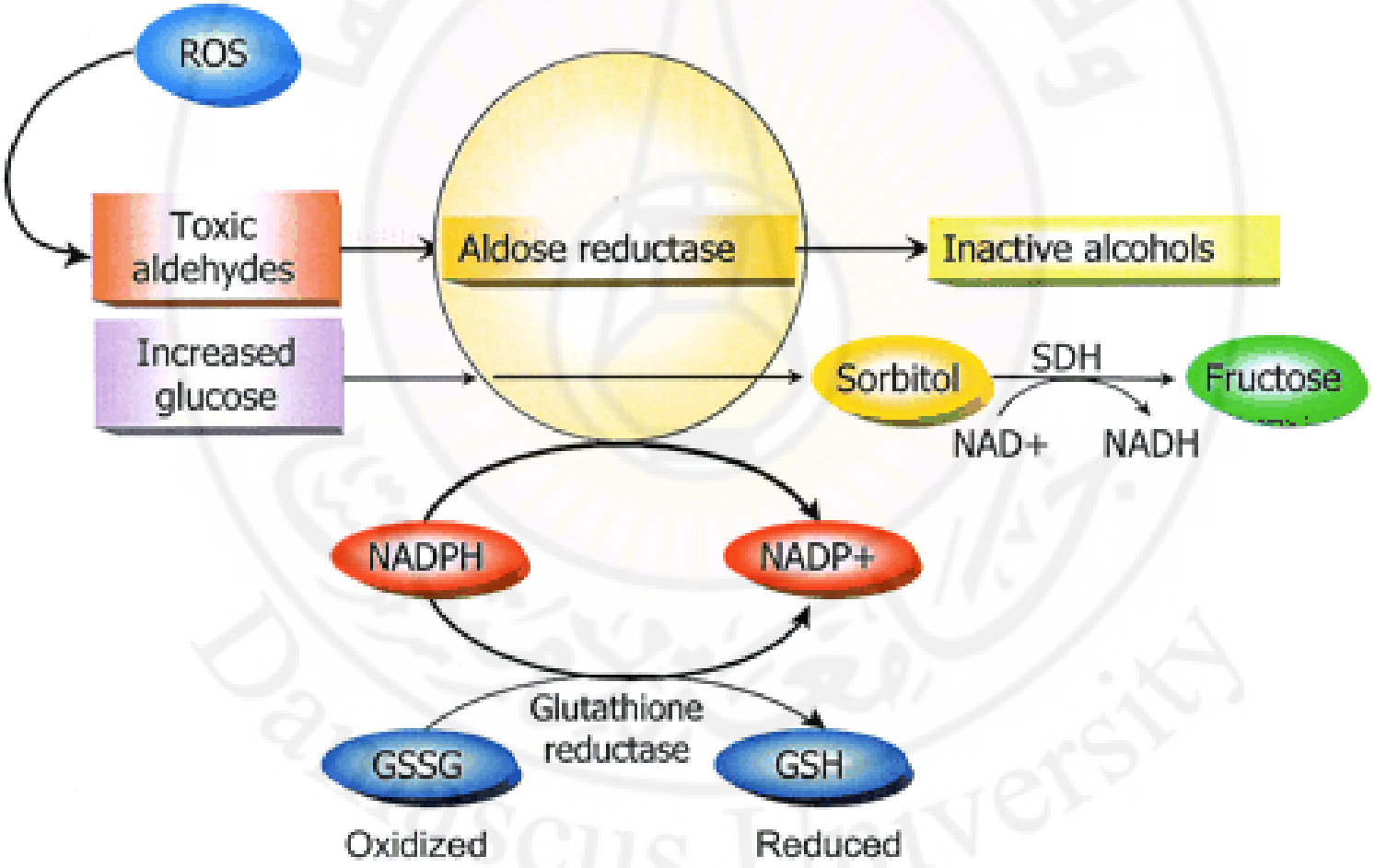
- Many proposed mechanisms of vascular damage from hyperglycemia
  - Aldose reductase pathway
  - Reactive Oxygen Species
  - Advanced Glycation Endproducts theory
  - Protein Kinase Theory

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Aldose reductase pathway

- Certain cells are unable to regulate glucose uptake in hyperglycemic states (ex. Endothelial cells)
- In a hyperglycemic state glucose is metabolized intracellularly by an enzyme aldose reductase into sorbitol and eventually into fructose
- Intracellular NADPH is used as a cofactor in the pathway but is also used to regenerate glutathione
  - Glutathione is an antioxidant which prevent which decreases cellular susceptibility to oxidative stress

Aldose Reductase Pathway

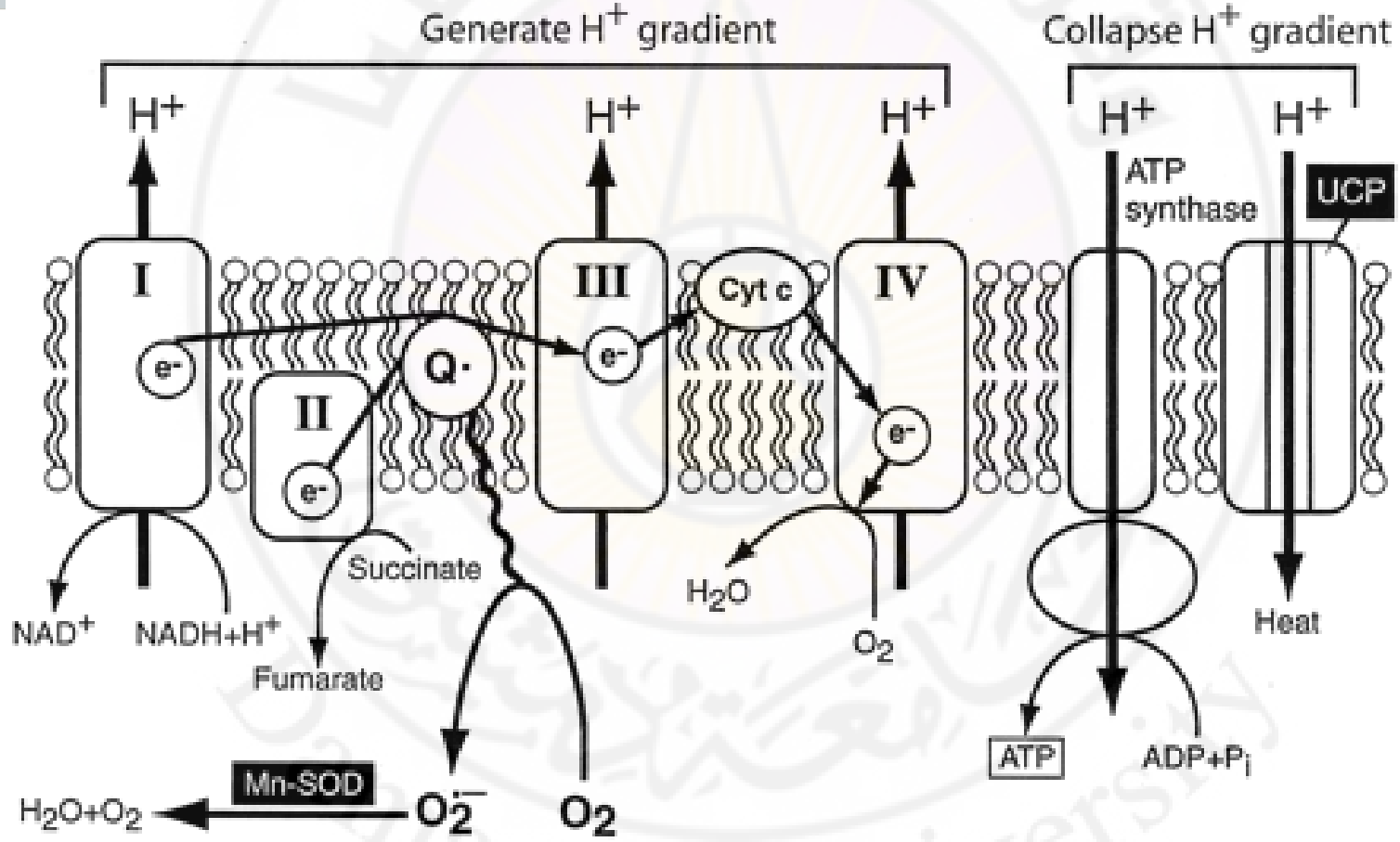


Reactive Oxygen Species

- The depletion of NADPH by aldose reductase leads to inability to regenerate GSH leading to oxidative stress reactions and cell death
- Increased Sorbitol causes a decrease in nitric oxide – vasoconstriction in neuronal tissue and eventually ischemia

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Hyperglycemia-induced production of superoxide by the mitochondrial electron transport chain.



Advanced Glycation End products theory

- Sorbitol may also glycate nitrogens on proteins, such as collagen, and the products of these glycations are referred-to as AGEs - advanced glycation endproducts.
- AGEs are thought to cause disease in the human body, one effect of which is mediated by RAGE (receptor for advanced glycation endproducts) and the ensuing inflammatory responses induced.

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Advanced Glycation End products theory

- AGE's are formed from **nonenzymatic** reactions between high levels of intracellular glucose, defects in the glucose metabolism pathway due to reactive oxygen species and build up of precursors
- AGE's effect extracellular matrix (collagen, laminin) – causes cross link between polypeptides and abnormal matrix and interrupts normal cell interactions
  - Ex: cross linking type 1 collagen in large vessels may lead to increase endothelial injury and atherosclerotic plaque build up
  - Ex: Cross linking type IV collagen in basement membrane decreases endothelial adhesion and increases fluid filtration.
  - On the other hand, the structural impairment in collagen alters the osteoblast differentiation leading to bone remodeling and skeletal fragility

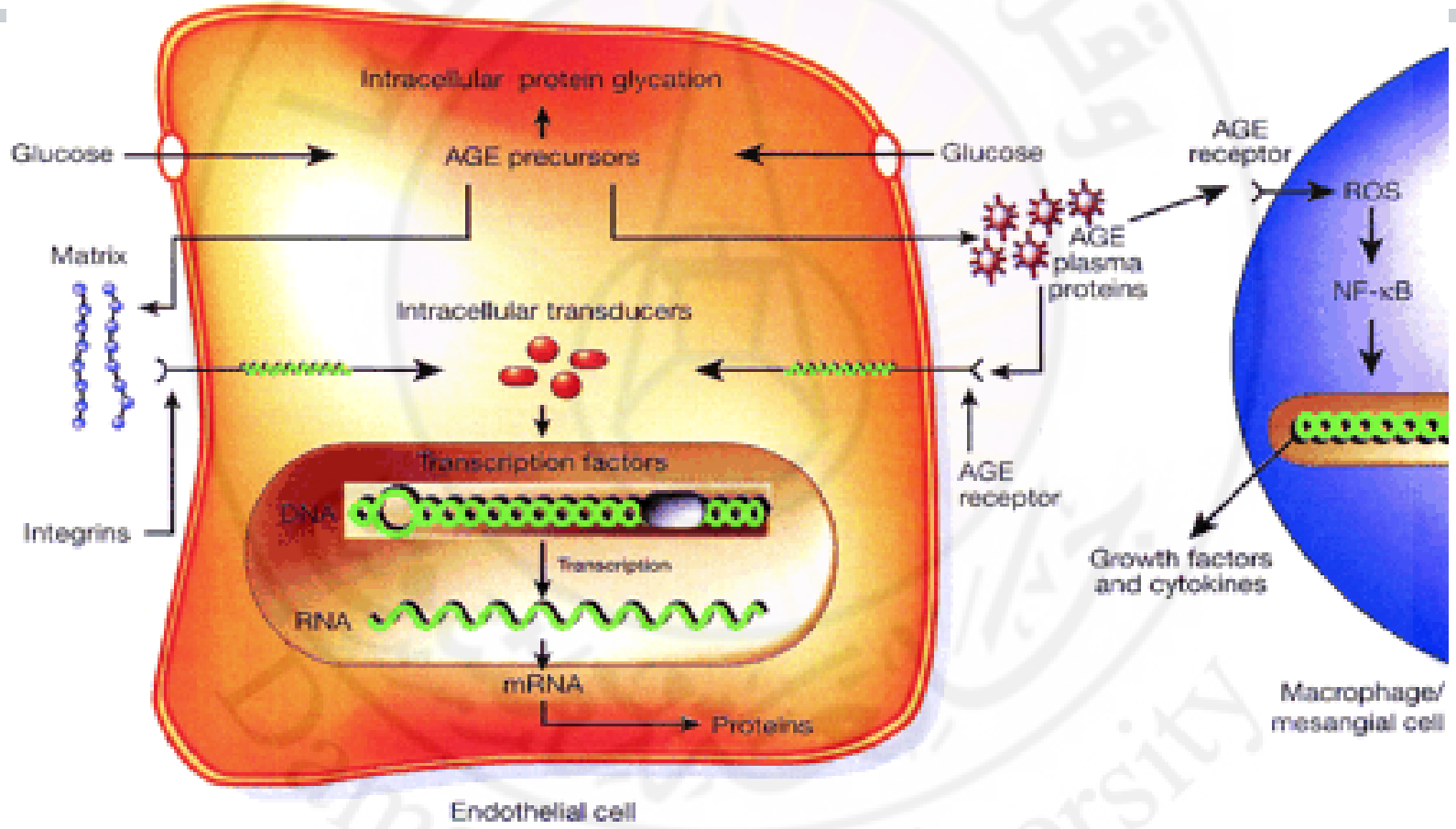
AGE effects on Protein

- AGE's cross link proteins – causing them to be resistant to degradation
  - Increases protein deposition
  - Plasma proteins may bind to glycated basement membrane – may cause increased basement membrane thickness seen in nephropathy
  - proteins bind to AGE receptors and activate nuclear transcription of NF-Kb, cytokines, inflammatory markers

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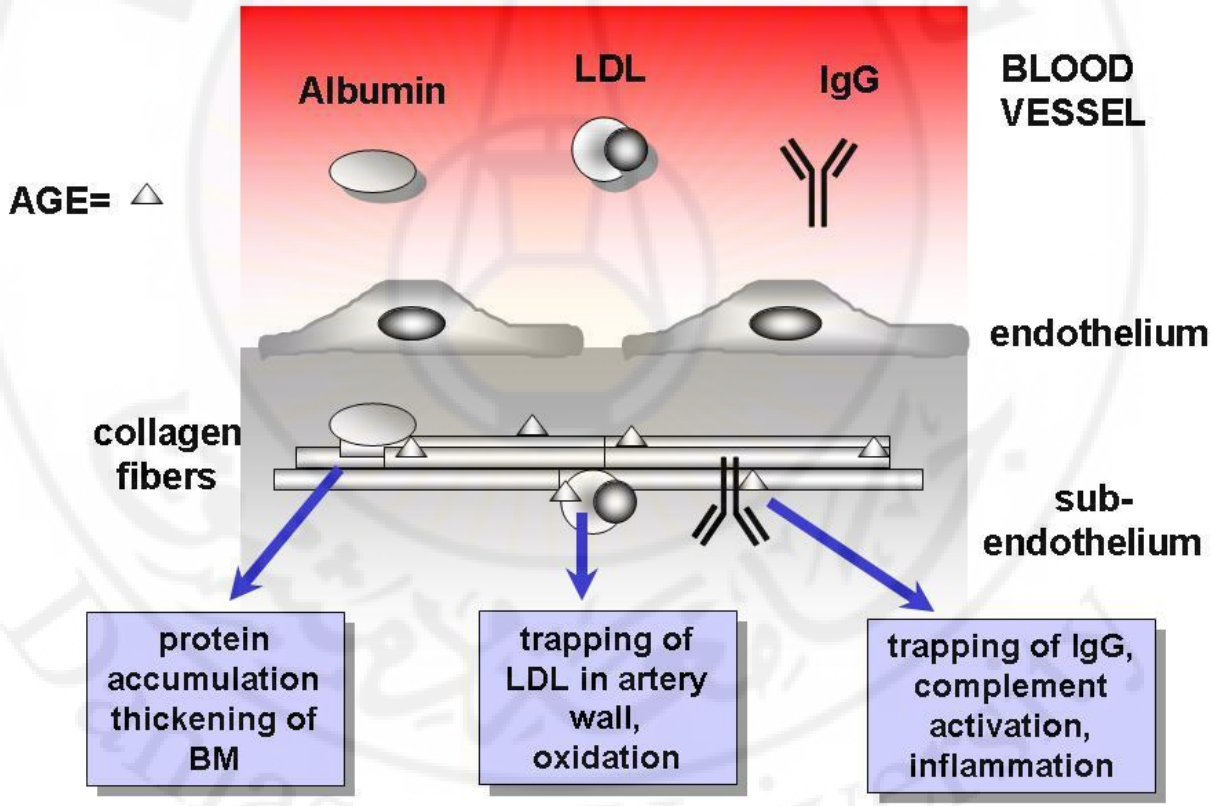
- AGEs form intra- and extracellular cross linking not only with proteins, but with some other endogenous key molecules including lipids and nucleic acids to contribute in the development of diabetic complications.
- Recent studies suggest that AGEs interact with plasma membrane localized receptors for AGEs (RAGE) to alter intracellular signaling, gene expression, release of pro-inflammatory molecules and free radicals.

- The glycation of plasma proteins such as albumin, fibrinogen, globulins and collagen to form different types of AGEs. Furthermore, the role of AGEs in the pathogenesis of diabetic complications including retinopathy, cataract, neuropathy, nephropathy and cardiomyopathy is also discussed.


Intracellular protein glycation
Glucose
AGE precursors
Glucose
AGE receptor
ROS
NF-κB
Matrix
AGE plasma proteins
Intracellular transducers
Transcription factors
DNA
Transcription
RNA
mRNA
Proteins
Integrins
AGE receptor
Growth factors and cytokines
Endothelial cell
Macrophage/ mesangial cell

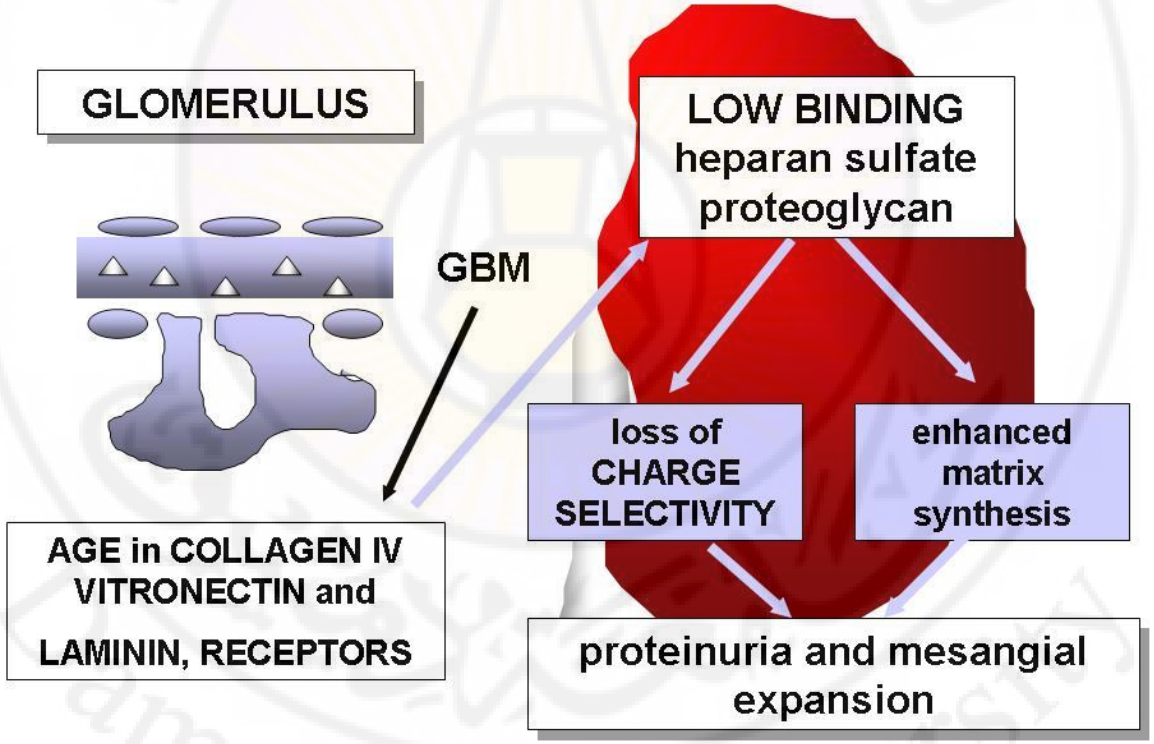
Advanced glycation products in vascular pathology.

Fig 3



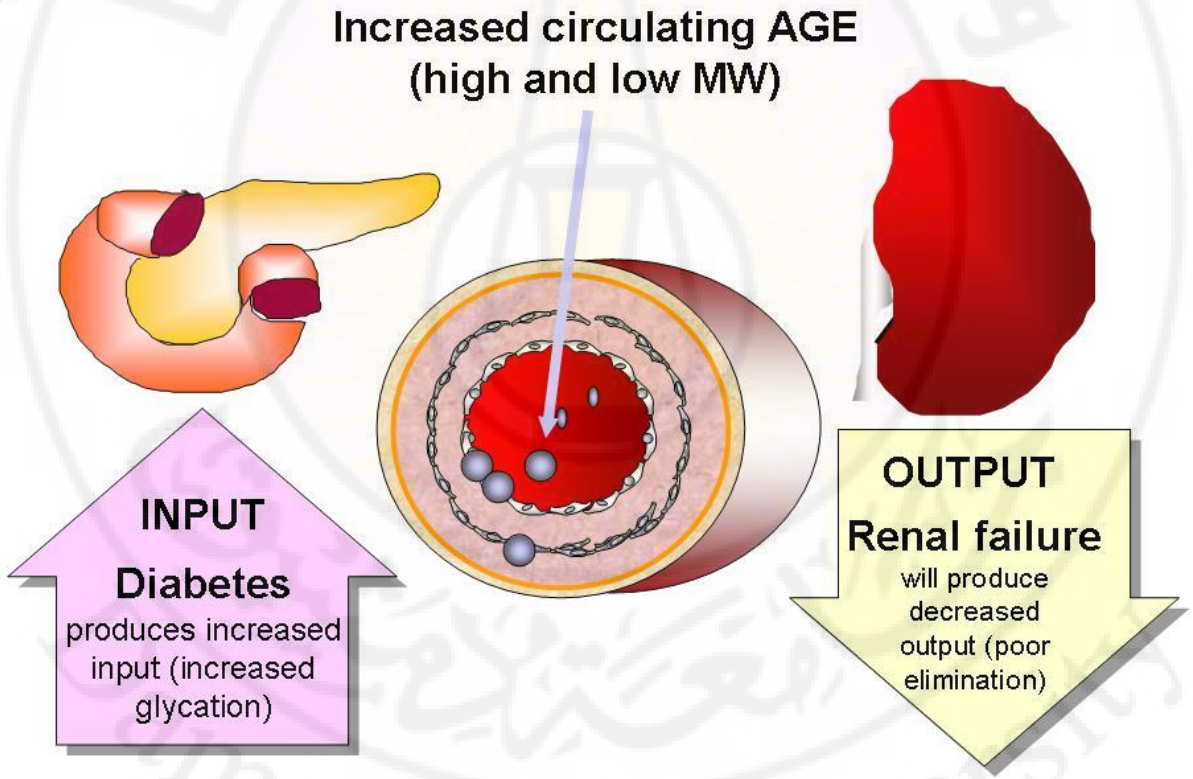
Advanced glycation products in nephropathy

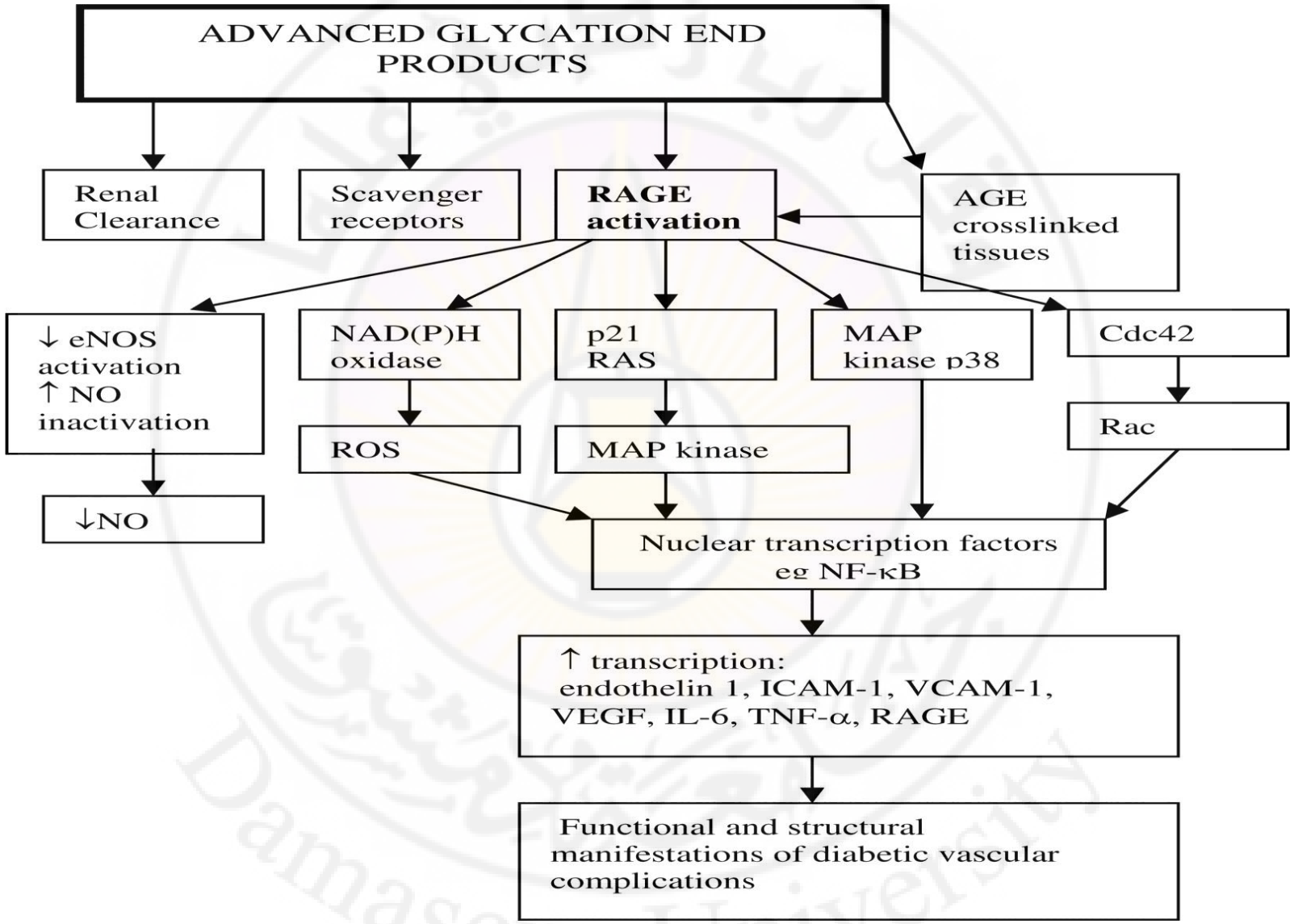
Fig 4



Advanced glycation products are metabolized to small peptides

Fig 8





Goh S , Cooper M E JCEM 2008;93:1143-1152

©2008 by Endocrine Society

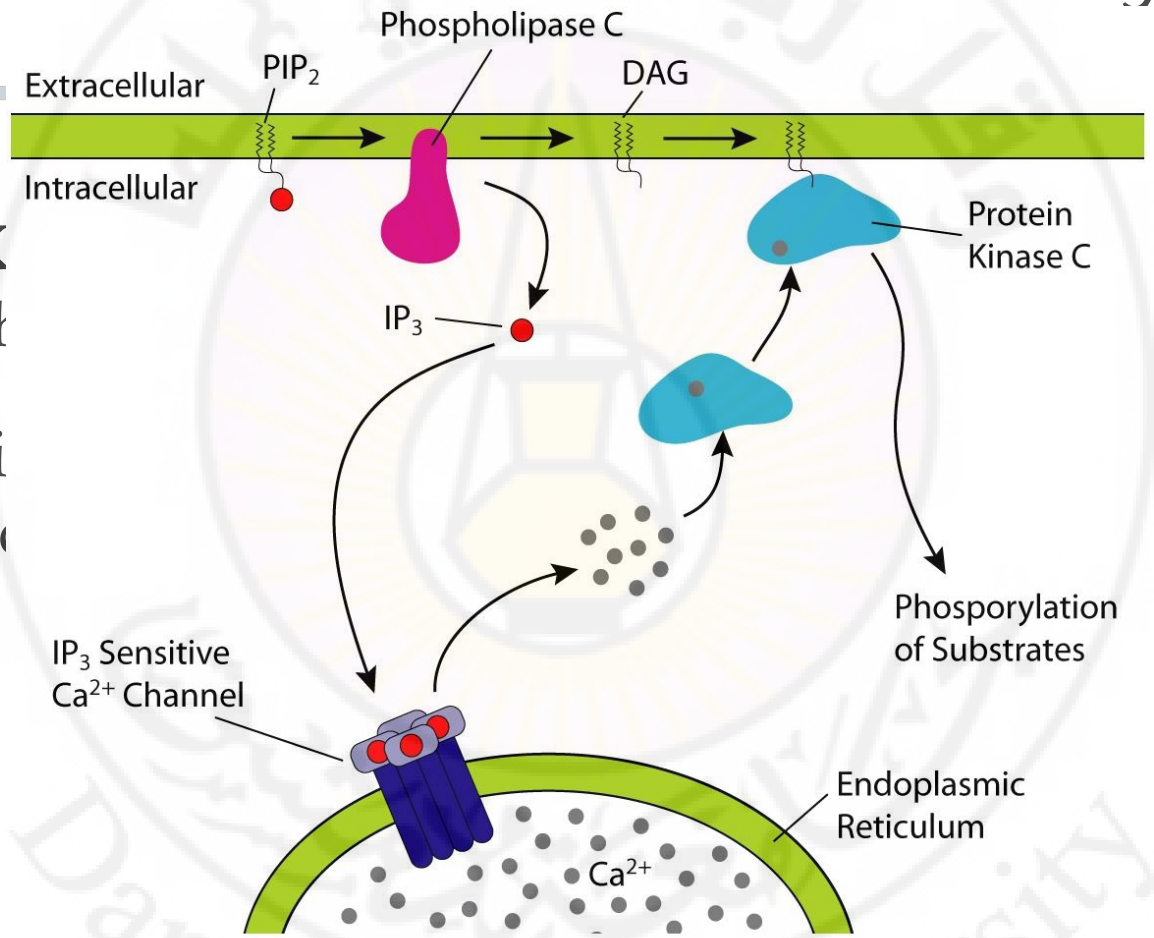
Biological effects of Activating AGE receptors

- Release cytokines and growth factors from macrophages (VEGF, IGF-1)
- Increases endothelial permeability
- Increases procoagulant activity
- Enhances proliferation of synthesis of extracellular matrix by fibroblasts and smooth muscle cells

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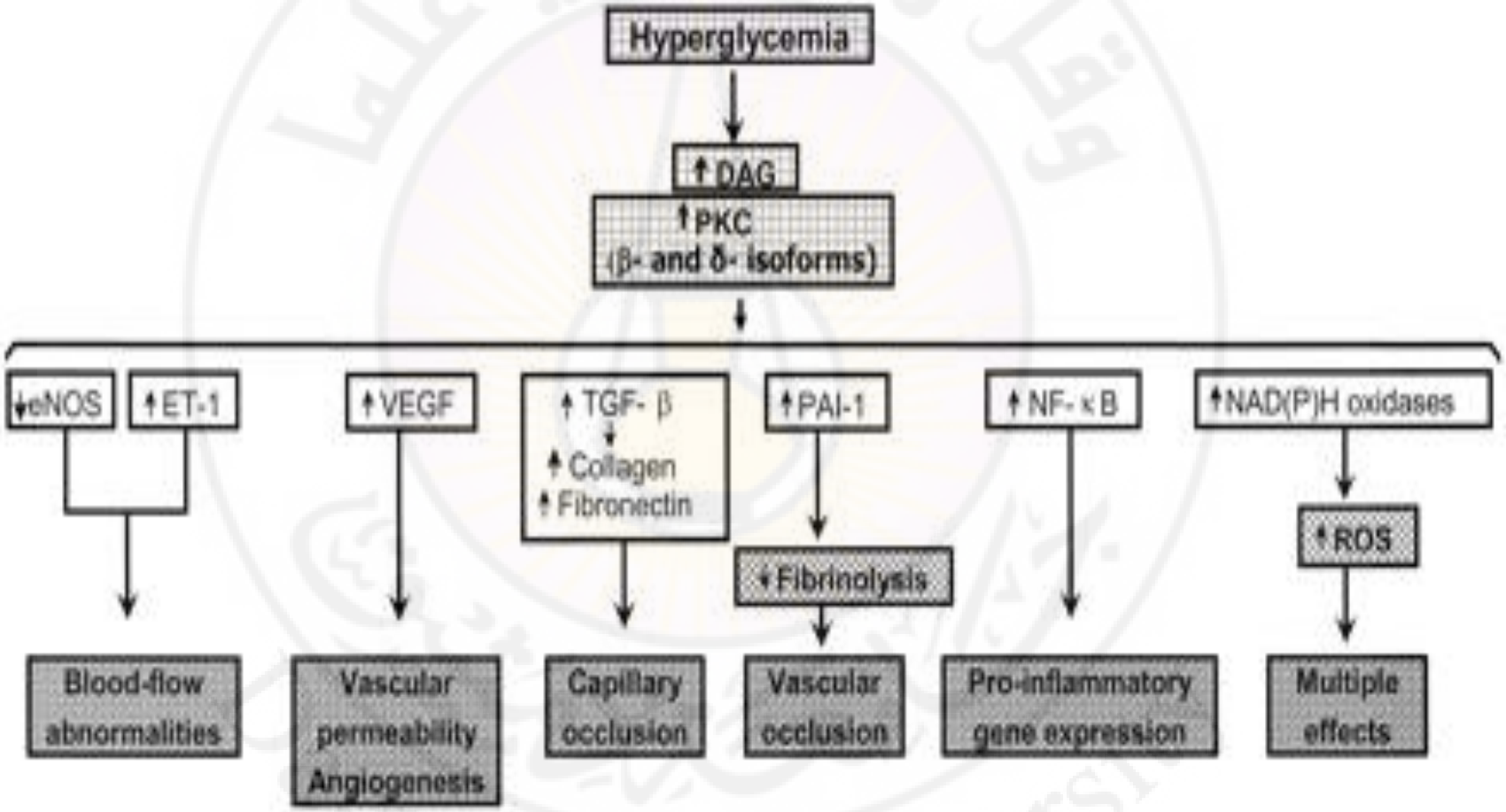
Protein Kinase Theory

- Activating PK important signalling path
- Hyperglycemi G and causes unregulated a

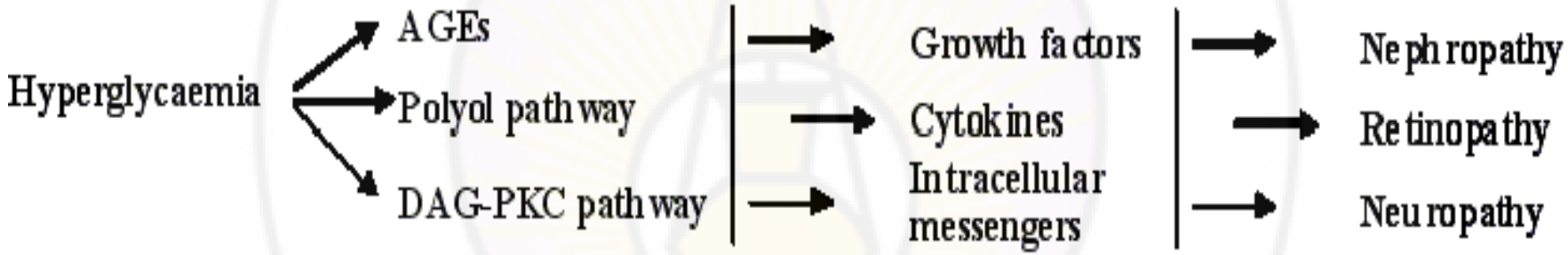


Effects of PKC activation

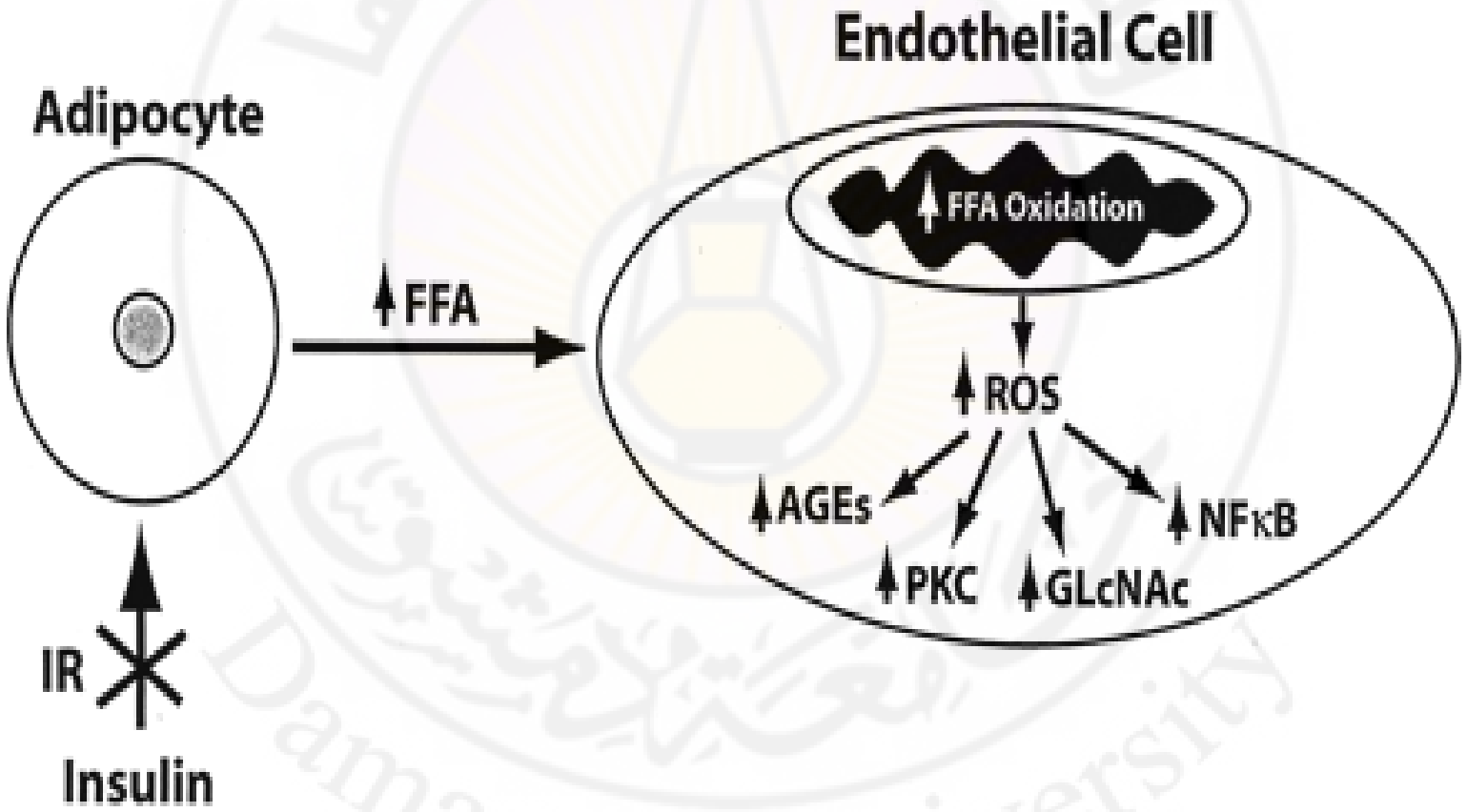
- Produ
  retinc
- Increa
  NOsy
- Produ
  matri
- Procc
  fibrin
- Produ



Pathways of micro vascular complications initiated by hyperglycemia. AGEs, advanced glycation end products; DAG, diacylglycerol; PKC, protein kinase C.

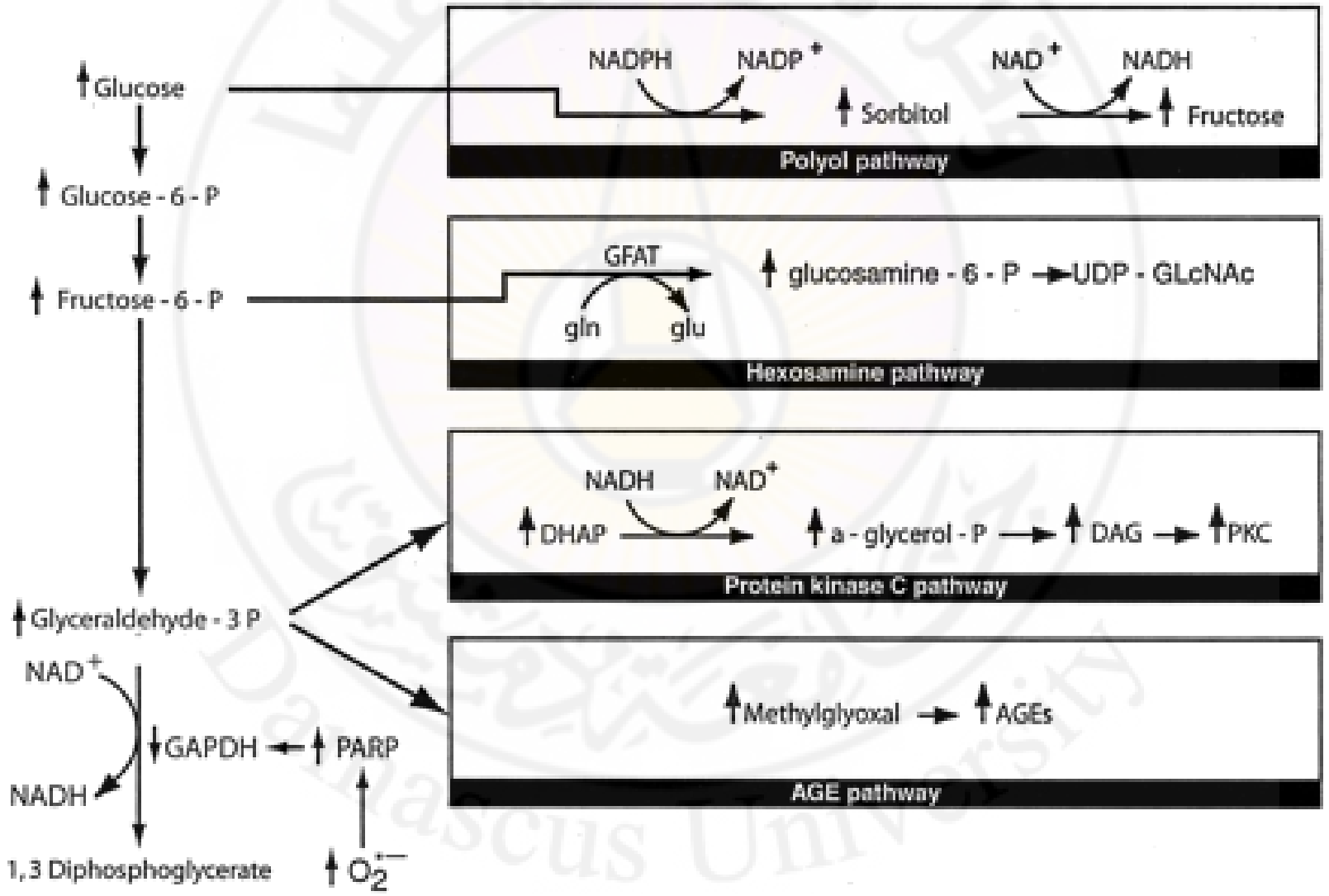


Insulin resistance causes mitochondrial overproduction of ROS in macrovascular endothelial cells by increasing FFA flux and oxidation.



Hyperglycemic damage by inhibiting NAPDH.

From Brownlee M: Biochemistry and molecular cell biology of diabetic complications. *Nature* 414:813–820, 2001.



Hypoglycaemia (Hypo)

- Hypoglycaemia is the most common complication in diabetes
- It occurs when the bloods glucose falls below 4mmol/l
- The symptoms vary from child to child and are documented within their individual health care plan

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Definition of Hypoglycemia

1. Development of neurogenic or neuroglycopenic symptoms

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty Concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision Changes
Nausea	Difficulty Speaking
	Dizziness

2. Low blood glucose (<4 mmol/L if on insulin or secretagogue)
3. Response to carbohydrate load

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Classification of Hypoglycemia

Table 6.3—Classification of hypoglycemia (61)

Level	Glycemic criteria	Description
Glucose alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

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American Diabetes Association.

Severity of Hypoglycemia

- **Mild**
  - Autonomic symptoms present
  - Individual is able to self-treat
- **Moderate**
  - Autonomic and neuroglycopenic symptoms
  - Individual is able to self-treat
- **Severe**
  - Requires the assistance of another person
  - Unconsciousness may occur
  - Plasma glucose is typically <2.8 mmol/L

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Hypoglycaemia (causes)

Too much insulin

Missed food

Delayed food

Too much or too intense exercise

Unscheduled exercise

Hot weather

Alcohol / Vomiting /Reduced sugar intake by not eating

There may be no obvious cause

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Mild Hypoglycaemia symptoms



- Hunger
- Shakiness
- Weakness
- Paleness
- Personality change
- Dizziness
- Sweating
- Drowsiness
- Anxiety
- Irritability

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Risk factors for severe hypoglycemia in people treated with sulfonylureas or insulin

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of insulin therapy
- Autonomic neuropathy
- Chronic kidney disease
- Low economic status, food insecurity
- Low health literacy
- Preschool-age children unable to detect and/or treat mild hypoglycemia on their own
- Adolescence
- Pregnancy
- Elderly
- Cognitive impairment

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Steps to Address Hypoglycemia

1. **Recognize** autonomic or neuroglycopenic symptoms
2. **Confirm** if possible (blood glucose <4.0 mmol/L)
3. **Treat** with "fast sugar" (simple carbohydrate) (15 g) to relieve symptoms
4. **Retest** in 15 minutes to ensure the BG >4.0 mmol/L and **retreat** (see above) if needed
5. **Eat** usual snack or meal due at that time of day or a snack with 15 g carbohydrate plus protein

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Recommendations: Hypoglycemia

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter.
- Glucose (15–20 g) preferred treatment for conscious individual with blood glucose ≤ 70 mg/dL.
- Glucagon should be prescribed for those at increased risk of clinically significant hypoglycemia, defined as blood glucose < 54 mg/dL, so it is available if needed.
- Hypoglycemia unawareness or episodes of severe hypoglycemia should trigger treatment re-evaluation.

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

American Diabetes Association.

Recommendations: Hypoglycemia (2)

- Insulin-treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised to raise glycemic targets to strictly avoid further hypoglycemia for at least several weeks, to partially reverse hypoglycemia unawareness, and to reduce risk of future episodes.
- Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition and/or declining cognition is found.

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

American Diabetes Association.

Consequences

- Renal colic
  - Severe, continuous pain
  - Begins in the back & travels toward bladder
  - Nausea & vomiting
- Urinary tract complications
  - Urgency
  - Frequency
  - Inability to urinate
  - Obstruction
  - Infection

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استقلاب حمض البول

Metabolism of Uric acid

- إن تقويض النيكليوتيدات البورينية عند الإنسان تعطي في نهاية المطاف حمض البول و الذي يتم طرحه عن طريق البول.
- ماهي النيكليوتيدات: هي حجر الأساس لاصطناع الحموض النووية.

و هي تتكون من: أساس آزوتي

Purine

Pyrimidine

+

Ribose

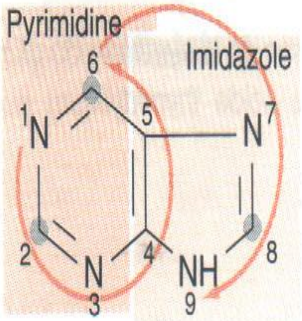
Pentose+

Desoxyribose

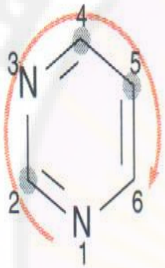
3 Phosphates

تساهم البورينات في اصطناع وحدة البناء الاساسية لاصطناع الحموض النوويةDNA and RNA كذلك فهي تساهم في استقلاب الطاقة ونقل الاشارة وذلك من خلال دخولها في تركيب بعض الكوانزيمات كما انها تشارك في الوظائف الحيوية الفيزيولوجية للصفيحات الدموية.

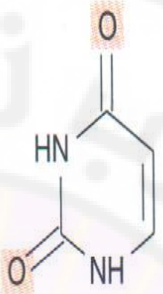
Phosphate(s) — Pentose — Base



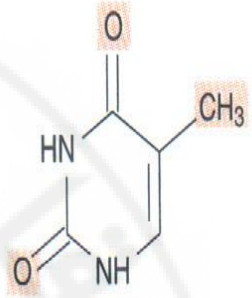
Purine



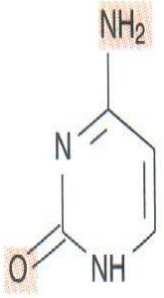
Pyrimidine



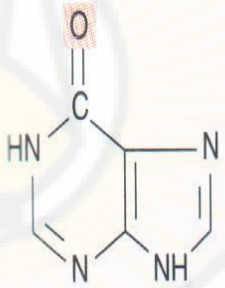
Uracile



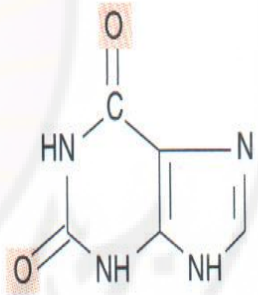
Thymine



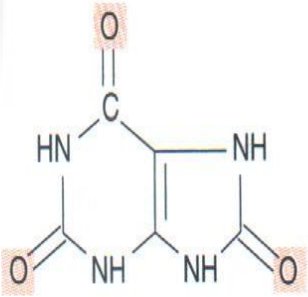
Cytosine



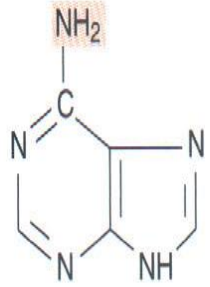
Hypoxanthine



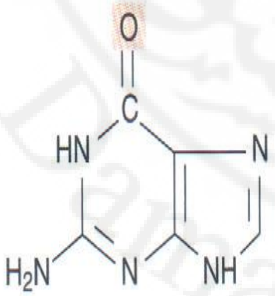
Xanthine



Acide urique

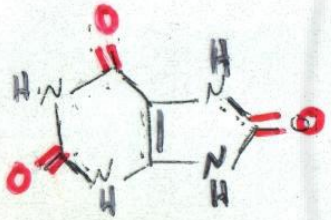


Adénine



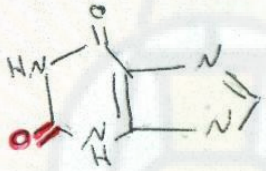
Guanine

DNA
RNA → (nucléase) Nucléosides-monophosphates puniques → (nucléotidase, Pi) Nucléosides → Base punique (adénine + Guanine)



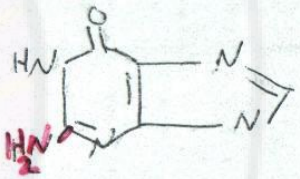
acide unique

← (xanthine oxydase)



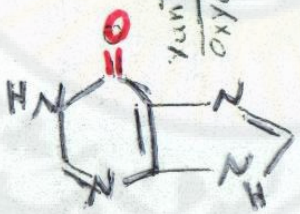
xanthine

→ (Guanine desaminase, H_2O, NH_3)



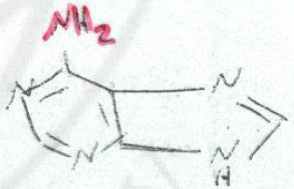
Guanine

← (xanthine oxydase)



Hypoxanthine

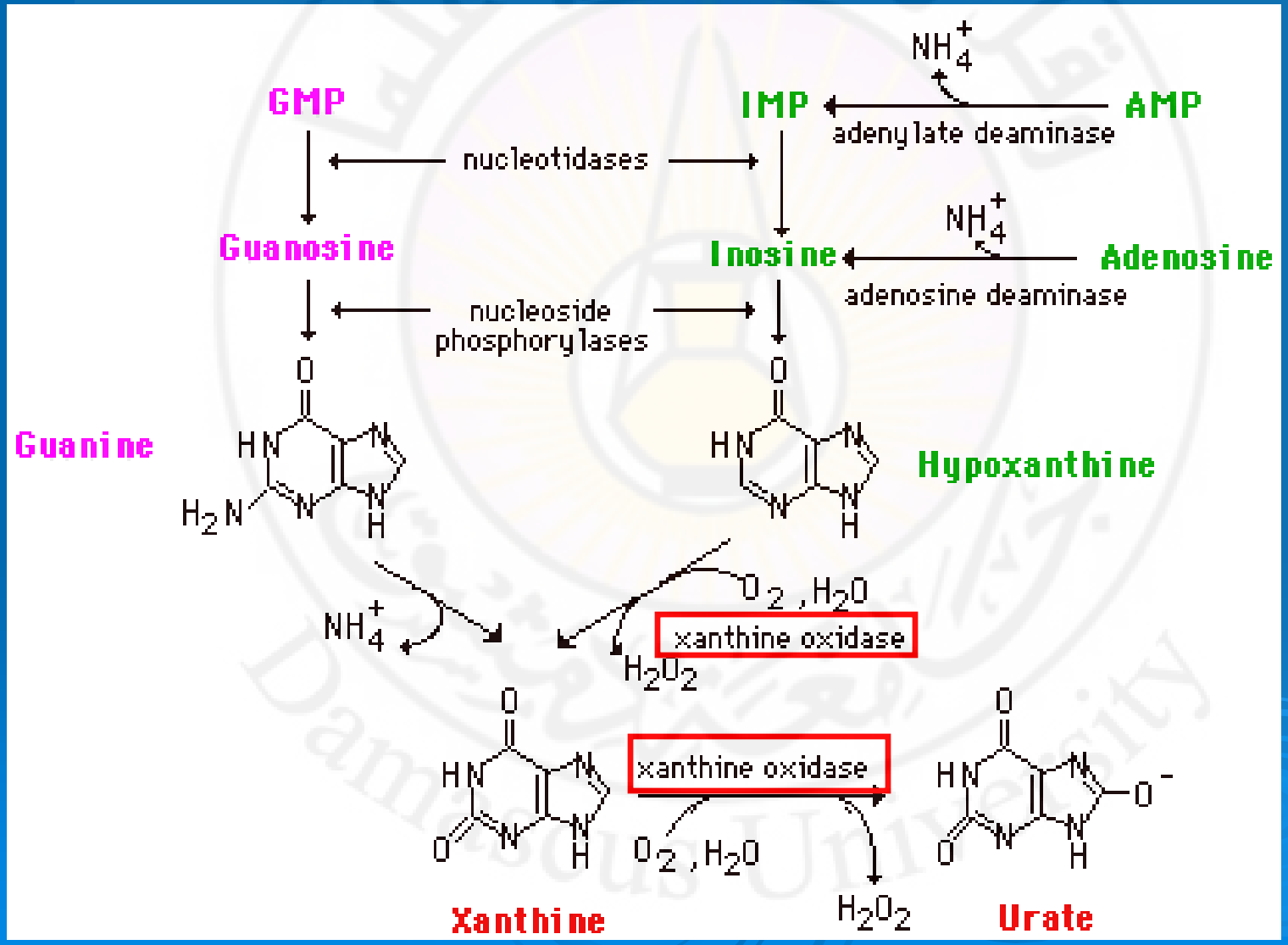
→ (adenine desaminase, H_2O, NH_3)

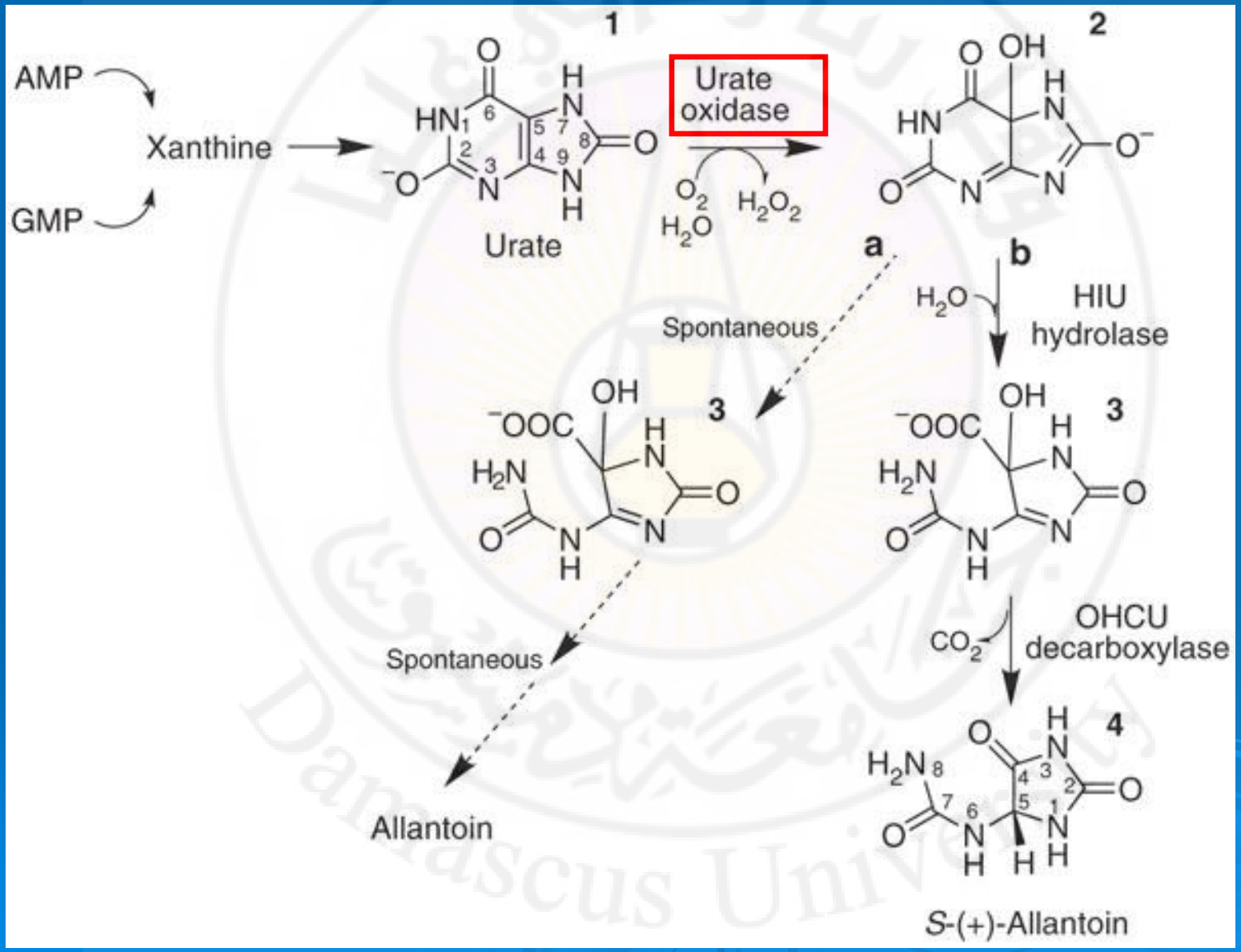


adénine

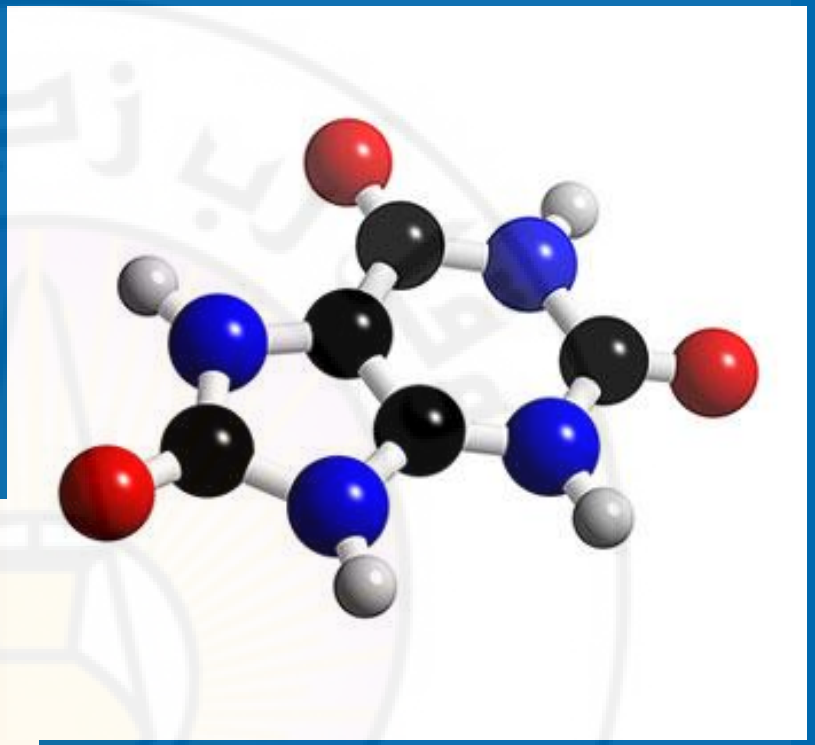
تنويض النيكليوتيدات البورينية

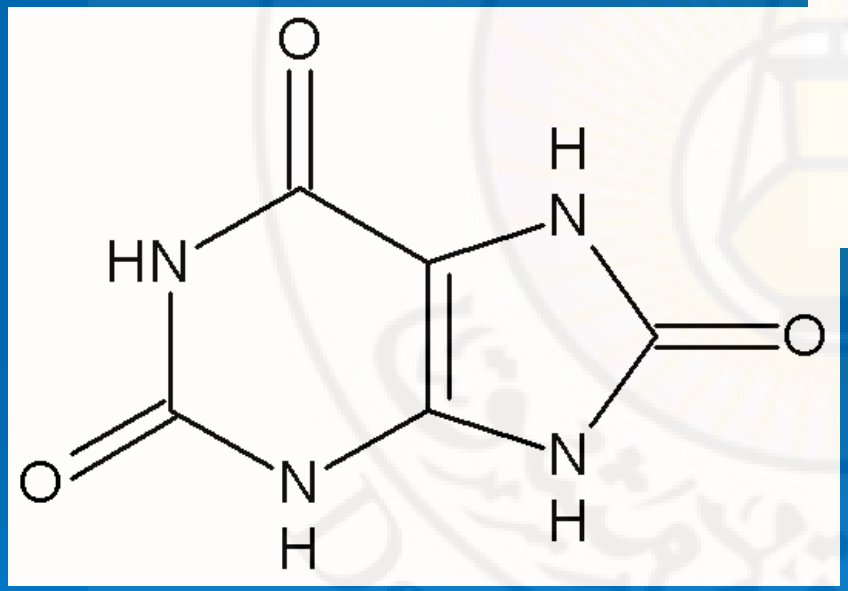
Uric acid is produced by xanthine oxidase from xanthine and hypoxanthine, which in turn are produced from purine. Mainly in liver, kidney, intestine.




AMP
Xanthine
GMP
1
Urate
Urate oxidase
O_2
H_2O
H_2O_2
2
a
b
H_2O
HIU hydrolase
Spontaneous
3
3
Spontaneous
CO_2
OHCU decarboxylase
Allantoin
4
S-(+)-Allantoin

- عنـد بعـض الحيوانـات هـذا التقـويض يسـتمر للحصـول علـى allantoine ومن ثم حمض acide allantoique ويصل أحيانـاً إلـى البولـة التـي يـتم تفكيكهـا بواسـطة أنظـيم Urease و الحصول بالنهاية على NH3 وCO2
- حمض البول هو 2-6-8-Trihydroxypurin قليل الانحلال بالماء ويطرح كما هو في البول.





Uric acid

- يتواجد حمض البول في البلاسما بشكل بولات و حيدة الصوديوم بتركيز ٥٠ – ٨٠ ملغ / ليتر عندما يزداد تركيزه في hyperuricemie فليس من الضرورة أن يترسب in urine لأن انحلالية بولات الصوديوم تزداد بوجود البروتينات في البول .
- يفرغ حوالي ٧٥ % من البولات في البول والباقي يطرح عن طريق البراز بعد أن يتم تقويضه من قبل الجراثيم المعوية.
- ترتشح اليولات من الكبيبات في البول الأولي ليعاد امتصاصها بشكل كامل تقريباً في النبيبات الدانية ثم يتم افرازها في النبيبات القاصية بشكل فعال.
- في البول يبقى حمض البول منحلاً بفضل التركيز العالي للفوسفات و أي تحمض للبول يؤدي الى ترسب حمض البول حيث يتناقص تركيز البولات القلوية لصالح حمض البول الحر.

- ويمكن التنوية هنا إلى تعاكس فعل الساليسيلات وبعض الأدوية على افراغ حمض البول بحسب تراكيز هذه الأدوية : فتراكيز قليلة من السيليسيلات(أقل من ٢,٥ غ/ اليوم) يثبط افراز حمض البول في النبيبات القاصية مما يؤدي إلى ارتفاع تركيزه في الدم . أما الجرعات المرتفعة من السيليسيلات(أعلى من ٣غ/ اليوم) فإنها تؤدي إلى زيادة عودة امتصاص حمض البول في النبيبات الدانية وزيادة افراغ حمض البول في البول وانخفاض تراكيزه في اليلاسما. بالمقابل فان تناول ٧٥ملغ/اليوم يؤدي الى ارتفاع تركيزه في البلاسما
- يعتبر قياس حمض البول في المصل من التحاليل الروتينية المطلوبة بكثرة فهي تعكس حالة الوظيفة الكلوية وكذلك معايرتها في البول وحساب التصفية الكلوية.

القيم الطبيعية و التغيرات المرضية:

- القيم الطبيعية :

- عند الرجال ٣٠٠ ± ٦٠ ميكرومول / لتر (٤ – ٦ ملغ / دل).

- عند النساء ٢٤٠ ± ٦٠ ميكرومول / لتر (٣,٥ – ٦ ملغ / دل).

- ارتفاع حمض البول في الدم:

ان ارتفاع حمض البول في الدم يعود الى آليتين مختلفتين:

١- اضطراب استقلاب البورينات (ازدياد في اصطناع البورينات).

٢- اضطراب في آلية طرح حمض البول عن طريق البول.

- كما ذكريتم ارتشاح اليورات من الكبيبات في البول الأولي ثم يعاد امتصاصها بشكل كامل تقريباً في الأنابيب البولية القربية ثم يتم افرازها في الأنابيب البعيدة ليتم طرحها.
- يثبط حمض اللبن و الأجسام الكيتونية هذه العملية بطريقة التنافس.
- مايحدث في حالة ارتفاع حمض البول هواما اضطراب نوعي في اعادة الامتصاص الأنبوبي لحمض البول أو اضطراب في طرح حمض البول.
- وغالباً مايكون هناك اضطراب في كلا الأمرين مما يؤدي الى حبس حمض البول في الجسم وخاصة فيما إذا تشارك مع اضطراب وراثي في استقلاب البورينات.
- مجموعة هذه العوامل و النتائج تؤدي الى تخرب الكلى عند المريض.

يمكن تصنيف امراضيات حمض البول الى أربع أصناف:

١- داء النقرس الأولي:

- و هو مرض وراثي ناتج عن اضطراب استقلاب الأسس البورونية يصيب الذكور بنسبة ٩٠% وعند العائلات المصابة بداء النقرس واحد من خمسة لديه ارتفاع في حمض البول.
- تتدخل مجموعة من المورثات في هذا المرض من ناحية ازدياد اصطناع الأسس البورينية مع اضطراب في طرح البولات المتشكلة.
- تبدأ الأعراض شديدة بآلام مفصلية ليلية خاصة مع مجموعة من الدلالات الاحتقانية الشديدة وترفع حروري سرعة التثفل عالية مع ازدياد بمعدل عدد الكريات البيضاء.
- نجد توضعات في اليورات تحت الجلد (Tophi) تدعى التوفي وعند فحص السائل المفصلي بعد اصابته تشاهد بلورات من يورات الصوديوم المبلوعة من الكريات البيض (المعتدلات) وكذلك نجد بللورات منحلة تحت تأثير أنظيمات البيروكسيداز الموجودة ضمن الكريات البيضاء.

خلال هذه الإمراضية هناك خطرين كبيرين:

- أخطار وعائية: من نمط احتشاء دماغي أو قلبي – التهاب الشرايين وخاصة في الأطراف السفلية.
- أخطار كلوية: تشكل الحصيات البولية مما يؤدي الى حصول القصور الكلوي.

٢- داء النقرس الأنزيمي:

أو مايسمى بارتفاع حمض البول Nyhan-Lesch وهو مخالف لسابقه حيث أن السبب محدد تماماً و هو عوز أنزيم (HGPRT)

Hypoxanthine – guanine – phosphoribosyl – Transferase

وهو مرض وراثي نادر يصيب الذكور ينتقل بشكل متنحي ومرتبط بالجنس.ينتج عن طفرة mutation تصيب المورثة gene :HPRTالمتوضع على الصبغي X

وفي هذه الحالة لا يمكن للهيوكزانتين ولا للغوانين أن يتحولا الى نيكلوتيدات وبالتالي يتم استقلابهم الى حمض البول الذي يرتفع في الدم وفي البول .

الأعضاء الأكثر تضرراً وإصابة هي الجملة العصبية و الكلى.

تكـون الأعـراض العصـبية أكثـر خطـورة و إيضـاحاً: تخلـف عقلـي – تهيجـات عصـبية – بالإضـافة الـى تشـكل حصـيات بوليـة تـؤدي الـى حصول قصور كلوي شديد.

كـــذلك ان العـــوز فـــي هـــذا الانـــزيم يـــؤدي الـــى انخفـــاض فـــي تراكيزفيتامينB12 لذلك فان بعض المرضى يمكن ان يبدوا فاقة دم كبيرة الخلايا megaloblastic

قد نجد مثل هذه الأعراض من (ارتفاع حمض البول + حصيات + اضطراب عصبية) عند الإنسان البالغ و هذا يعود الى عوز جزئي في تنظيم الـ HGPRT.

٣- ارتفاع حمض البول الثانوي :

- اخطاء غذائية : ان السمنة وتناول كميات من الأغذية تشارك على تحريض اصطناع الأسس البورينية وتؤدي الى ارتفاع حمض البول. يسبب الصيام وتناول الكحول والجهد العضلي الشديد زيادة في حمض البول في الدم مع نقصان انطراحه البولي.
- ان اي تحمض (تنفسي او استقلابي) يعتبر مثبط لطرح حمض البول في البول.

- التخرب الخلوي :

يزداد تشكل حمض البول في التخرب و الانحلال الخلوي بالاضافة الى ما يرافقها من تحمضن في الدم وبالتالي مما يؤدي الى حبس حمض البول في الجسم.

- القصور الكلوي:
- مهما كان مصدره أو سببه فانه يؤدي الى ارتفاع حمض البول في الدم، وخاصة في حال وجود حصاة بولية او ورم في البروستات.
- أول المعالم الحيوية التي يمكن أن تظهر هي زيادة حمض البول في الدم وانخفاض شديد في تصفية حمض البول والتي هم أهم فحص يمكن أن يفيد في التشخيص.

أولاً لأن يكون المشعر الأول (PLUS PRECOE) والأكثر أمانة PLUS FIDELE من ارتفاع البولة الدموية .

- الأمراض الدموية : مهما كان نوع الأمراض الدموية فانها جميعاً تزيد من حمض البول في الدم وذلك بسبب زيادة تدرك النيكليوتيدات البروتينية الخلوية.
- أهم هذه الأمراض: احمرار الدم الأساسي.

احمرار الدم الأساسي polyglobulies essentielle

ابيضاض الدم النقوي leucemie myeloide

فاقات الدم الانحلالية المزمنة anemies hemolytic chronic

ابيضاض الدم النقوي المتعدد multiple myelome

بشكل عام الأمراض السرطانية سريعة التطور وخاصة عند المعالجة بالأدوية الحالة cytolytic أو بالأدوية الكورتيزونية cortison حيث تؤدي الى تشكل كميات كبيرة من حمض البول. بالاضافة الى مشاركتها في زيادة تشكل الحصيات البولية.

٤– مجموعة من الأمراض يمكن أن تصاحب زيادة حمض البول مع انخفاض في طرحه نتيجة لتحمضن البول

- النمط I من تدرك الغلوكوجين الكبدي (عوز الغلكوز ٦ فوسفاتاز).
- ارتفاع الضغط الشرياني بسبب كلوي.
- التسممات مع زيادة في حمض اللبن في الدم.
- فرط نشاط الدرق
- الداء السكري
- بالاضافة الى مجموعة من الأدوية cortison – cytolytic المدرات التيازيدية diuretic thiazidic التي تثبط طرح حمض البول.

المظاهر السريرية لداء النقرس : يمر بثلاث مراحل:

- المرحلة الحادة: نوبات ألم مفصلية غالباً ما تكون في ابهام القدم الذي يبدو متوذماً ومتهيجاً.
- المرحلة ما بين النوبات: وتكون هادئة لا أعراض فيها
- المرحلة المزمنة : يترسب حمض البول في المفاصل والأنسجة مما يؤدي الى زيادة في عدد الكريات البيضاء نتيجة الاحتقان الذي تسببه زيادة حمض البول (inflamation) هذه المحصلة تؤدي الى زيادة حمض اللبن الذي يؤدي بدوره الى تحمضن الدم فينشط بذلك ترسب حمض البول في المفاصل والنسج.

دراسة كيميائية حيوية للسائل الدماغي الشوكي

Etude biochimique du liquide Cephlo – rachidien

- هو سائل يحيط بالجهاز العصبي المركزي عبارة عن مزيج من الترشيح المستدق للبلاسما (كمية قليلة من البروتينات و الشوارد) يبلغ حجمه 130 مل والذي يقوم بحماية الجملة العصبية.
- جمع السائل الدماغي الشوكي:

يتم الحصول عليه بواسطة البزل القطني Ponction Lombaire مابين الفقرة القطنية الرابعة والخامسة وهو عبارة عن عمل طبي خطر يجب عدم اجراءه عند ارتفاع الضغط داخل القحف Hypertension intra – cranienne مما يؤدي إلى خطر الموت.

- الأمر الأكثر شيوعاً الذي يحدث أثناء عملية البزل هو إدخال الإبرة في وعاء دموي مما يؤدي الى الحصول على LCR زهري أو مدمى.

يتم عادة جمع السائل في ثلاثة أنابيب معقمة:

الأول لإجراء الزرع و التحري الجرثومي

الثاني لإجراء تعداد الخلايا

الثالث للفحص الكيميائي

يعتبر فحص السائل الدماغي الشوكي من الفحوص الاسعافية التي يجب اجراؤها فور وصولها إلى المخبر قد تتخرب الخلايا اضافة الى تحلل الغلوكوز بسرعة.

المعطيات الفيزيائية:

- إن السائل الدماغي الشوكي سائل شفاف رائق تماماً كالماء eau de roche يحتوي على أقل من 5 خلايا / ميكروليتر و إن وجود كريات بيضاء تؤدي الى ظهور عكر > 300 خلية في الميكرو ليتر.
- إن السائل الدماغي الشوكي عديم اللون و يصبح ملوناً في الحالات التالية:

1- يعطي لون زهري أو مدمى: قد يكون السبب عن اصابة وريد وعائي اثناء عملية البزل وقد يظهر ذلك اذا كان الانبوب الأول هو الأكثر لوناً بينما الأخير فقير أو عديم اللون.

ولكن قد يكون السائل مدمى و ذلك في النزف السحائي أو في كسور العمود الفقري . وأي سائل مدمى لايمكن اجراء الفحوص الكيمائية عليه : معايرة البروتينات الكلية ـ الغلكوز ـ الكلور ←نتائج خاطئة .

كما يمكن معرفة منشأ الكريات الحمراء بتثفيل السائل ومراقبة الطبقة الطافية فإذا كان عديم اللون دل على ذلك على نزف حديث أي اصابة وريد وعائي

2- اصفرار السائل LCR Jaune وقد يكون لأحد الأسباب التالية :

a- انصباب دموي مضى عليه عدة أيام (نزف سحائي ـ كسور)

b- وجود كميات كبيرة من الخلايا أو الكريات البيضاء ←سائل عكر ومصفر قليلاً.

c وجود أورام دماغية ويكون السائل لزج وقد يصل إلى مر حلة التخثر فور بزل السائل وذلك لوجود الفيبرنوجين بكميات كبيرة.

d- يؤدي ارتفاع البيلوروبين في المصل في الحالات الشديدة والمزمنة إل تلون السائل بلون أصفر .

3- سائل بشكل ماء الرز (eaude riz) حيث يكون السائل عكر بشدة أو قيحي ويكون التشخيص بالتهاب سحايا حاد meningite aigue وفي هذه الحالة نجد عدد الكريات البيضاء > 300 كرية بيضاء أو خلية / مكرولتر .

في هذه الحالة هناك ضرورة اسعافية لاجراء الفحص الجرثومي والزرع وكذلك إجراء زرع للدم hemoculture إن البحث عن هوية الجرثوم المسبب وإجراء فحص الصادات الحيوية antibiogramme يجب اجراؤه خلال ساعات قليلة من عملية البزل وعندها يجب البدء بالمعالجة بالصادات الحيوية مباشرة .

4- إذا كان للسائل الدماغي الشوكي مظهر طبيعي يجب أن يخضع لفحص خلوي – جرثومي لأننا قد نكون أمام التهاب سحايا مع سائل طبيعي اللون meningite liquide claire وهذا ما نجده غالباً في التهاب السحايا السلي Tuberculeuses أو التهاب السحايا الفيروسي virales

الاختبارات المطبقة على السائل الدماغي الشوكي

- كما ذكرنا يتم على الأنبوب الأول فحص جرثومي وزرع وإجراء التحسس للصادات الحيوية .
- يتم على الأنبوب الثاني فحص مجهري لاجراء تعداد الخلايا من الطبيعي وجود حتى 5 خلايا / مكرولتر كحد أعظمي عند الإنسان البالغ أما عند حديثي الولادة فإنه يقبل حتى 20 كرية لمفاوية .
- وإذا كان عدد الكريات البيضاء كبير فإنه يتم التعداد كما هو الحال في عد الكريات البيضاء الموجودة في الدم
- كذلك يتم دراسة الصيغة الدموية وتحديد نسب الكريات البيضاء قد يكون التهاب ناتج عن سبب فيروسي أو جرثومي أو يكون فطري cryptococcus خاصة نجده عند المرضى المصابين بنقص المناعة حيث تطهر الفطور بشكلها المبرعم أوغير المبرعم تحت المجهر وتبدو كالكريات البيضاء ولتميزها يستعمل الحبر الصيني فتبدو الفطور بشكل كريات منيره على أرض سوداء .

يتم على الانبوب الثالث التحاليل الكيمائية وهي :

- معايرة البروتينات يحتوي السائل الدماغي الشوكي على كمية قليلة من البروتينات ما يقارب 0.2 غ/ لتر ويعود ذلك إلى كبر جزيئات البروتين مما يعيق انتقالها إلى السائل من البلاسما 70 غ/لتر
- ترتفع كمية البروتين في السائل في الحالات التالية

وجود نزف دموي ← بروتينات البلاسما والهيموغلوبين

وجود كريات قيحية ← في الحالات الالتهابية ← زيادة في النفوذية

التهاب غير جرثومي : التهاب السحايا السلي ـ التهاب السحايا الفطري ـالتهاب الدماغ ـ التهاب الأعصاب المتعدد.

- كما ان انسداد قناة السائل الدماغ الشوكي تؤدي إلى زيادة تركيز البروتينات بسبب اضطراب النقوذية الغشائية وعودة الامتصاص.
- ان السائل الدماغي الشوكي لا يحتوي على فيبرينوجين Fibrinogene . ويمكن تصنيف البروتينات الموجودة في السائل الدماغي الشوكي بشكل طبيعي إلى الاصناف التالية Fractions :
- الألبومين -α1 α2- ß1 - ß2 - γ غلوبيلين، مع اختلاف بنسبها بالمقارنة مع مثيلاتها في البلاسما، حيث نجد جزء هام أو كبير نسبياً بما يسمى ما قبل الالبومين prealbumine والجزء α1 مكون كبير أيضاً يسمى antitrypsine في البلاسما.

- نسبة IgG اقل من تلك الموجودة في البلاسما ، بينما IgA وIgM تكون بكميات قليلة (آثار) Traces
- لتحري بروتينات السائل الدماغي الشوكي نلجأ الى اجراء : رحلان بروتينات للسائل , مع معايرة البروتينات الكلية والألبومين وIgG هذا التحري يسمح بدراسة مختلف التغيرات الحاصلة على تركيب البروتينات fractions وتعطي فكرة عن حالة الحاجز الدموي ـ الدماغي

Barriere hemato- encephalique

وكذلك فكرة عن الحالة المناعية للسائل.

- هذه الدراسة يجب ان تكون مترافقة مع دراسة البروتينات في المصل.
- يجري الرحلان على هلام استات السللوز او على الأغاروز نجد فيه ستة أجزاء :

- ما قبل الألبومين prealbumine (4-8%) أي ما يعادل 10.7-23.9 ملغ/لتر. تزداد نسبتها في التهاب الدماغ أما انخفاضها فهو دلالة على انسداد قناة السائل الدماغي الشوكي

- الألبومين: Albumine (52-66%) أي ما يعادل 116 -194 ملغ/لتر) تزداد نسبتها في حال وجود اضطراب في الحاجز الدموي ـ الدماغي حيث نترك البلاسما لتتجه الى السائل الدماغي الشوكي.

α1 globulines (3-6%) و α2 globuline (3- 6%)

تزداد الأولى في الاصابات النزفية الدماغية أما الثانية تزداد في الالتهابات والاحتقانات inflamaton .

- مكونات α2 :

antithrombine Ceruleoplasmine -macroglobiline haptoglobine

- مكونات ß-globilines:

ß1-glolulines (7-13%) ß2-globilines(4-8%).

تزاد ß1 في الحالات النزفية الدماغية اما ß2 فترتفع في الأمراض Degeneratives (العته، ومرض الزهايمر).

يحتوي ß على Transferine

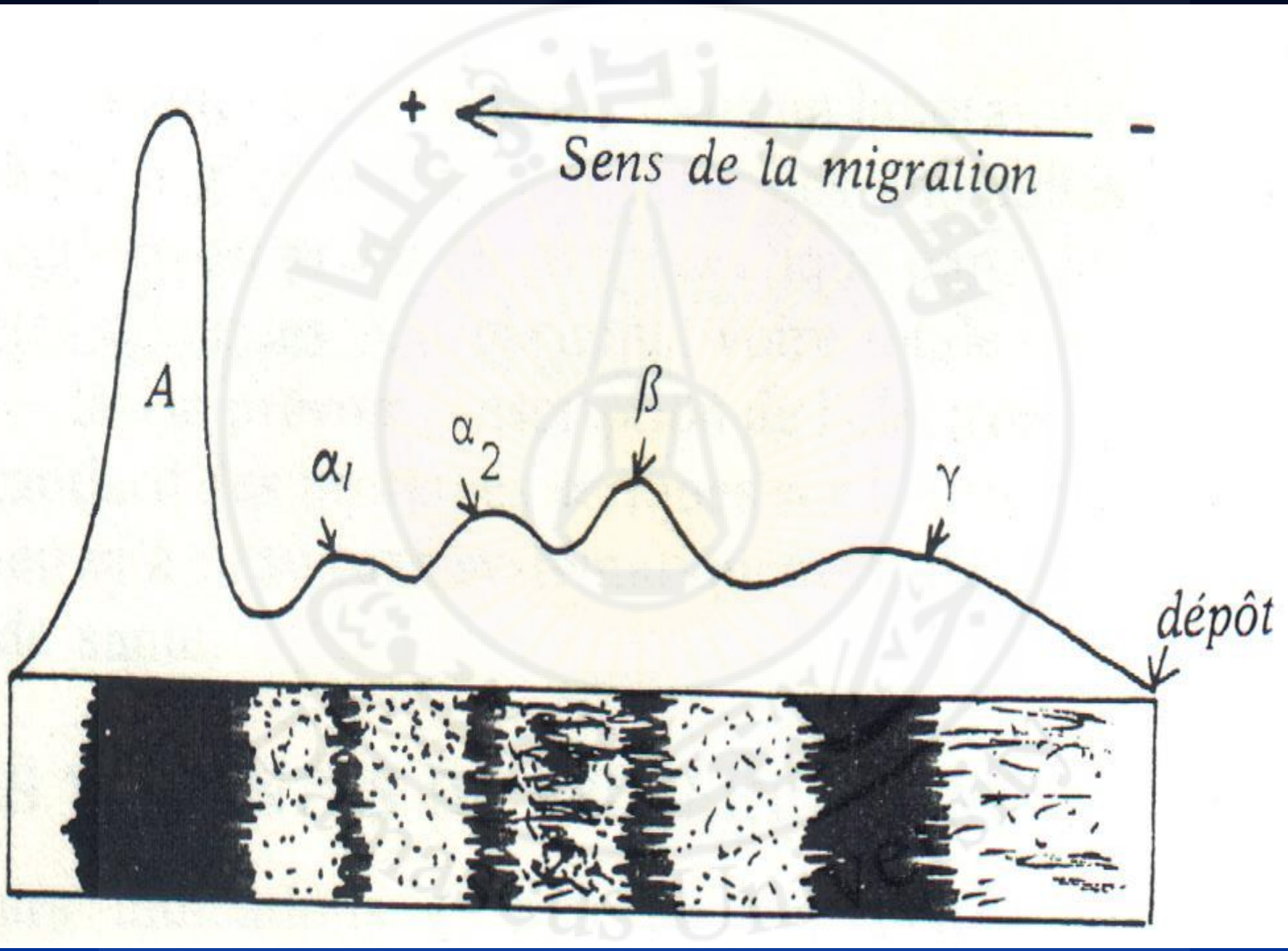
γ-globulines (7- 12%) في الحالة الطبيعة تمثل جميعها IgG (10-40ملغ/لتر) ويتم انتشارها بسهولة من الدم الى السائل الدماغي الشوكي. لذلك فحين زيادتها يجب معرفة السبب لهذه الزيادة:

والتي يمكن ان تكون:

اضطراب في الحاجز الدموي ـ الدماغي أو زيادة اصطناعها.

ان دراسة هذا الجزء له فائدة كبيرة فظهور قمة محددة وعالية pic point دليل على وجود مرض مناعي، اما ظهور عدة قمم في منطقة γ فهذا دليل على وجود عديد من الأمراض أهمها:

- التصلب الصفيحي sclerose en plaques السفسلس ـوأمراض مناعية متعددة.
- معايرة انظيم اللاكتات دي هيدروجيتاز (LDH) ان قياس فعالية انظيم LDH في السائل الدماغي الشوكي ومقارنتها مع مثيلها في البلاسما تفيد في تشخيص التهاب السحايا الفيروسي عن التهاب السحايا الجرثومي فهي ترتفع في الالتهابات الفيروسية.


+
Sens de la migration
-
A
α1
α2
β
γ
dépôt

- ألفا 1 أنتي تربسين : هو عبارة عن غلكوبروتين يصنع في الكبد وله تأثير مضاد لحلمهة البروتينات Anti Proteolyse يحمي الأنسجة من الأنظيمات الحالة للبروتينات في نسج متعددة خاصة في المعدة وفي الرئتين. تركيزة في البلاسما من 1-2 غ \ لتر.
- بيتا 1 ترانسفيرين هو عبارة عن غليكوبروتين يصنع في الكبد ينقل الحديد من الخلايا البالعة النقوية إلى أرومة الكريات الحمراء أو يقوم بنقل الحديد من البلاسما إلى الكبد (Hepatocyte).ويعتبر هو الناقل الوحيد الذي يمكن أن ينقل الحديد إلى أرومة الكريات الحمراء حيث يوجد على أغشيتها مستقبلات غشائية خاصة.
- نسبة اصطناعة تتناسب عكساً مع كمية الحديد ينقل الترانسفيرين النحاس والزنك وله دور هام في تنظيم الامتصاص المعوي للحديد والنحاس والزنك.
- ألفا 2 ماكروغلوبولين : هو عبارة عن غلكوبروتين يحمل الزمرة الدموية وله تاثير مثبط للأنظيم التربسين.

- ألفا 2 هابتوغلوبولين : هو عبارة عن غلكوبروتين يصنع في الخلايا الكبدية له دور هام في الإنحلالات الفيزيولوجية حيث يقوم بإلتقاط جزيئات الهيم مشكلاً معقداً ويختفي من الدوران العام خلال عشرون دقيقة حيث يقوم بنقله إلى الكبد الذي يحرر الحديد من المعقد ويخزنه في الخلايا الكبدية.
- بيتا 2 ميكروغلوبولين : هي عبارة عن ببتيدات صغيرة تصنع من الخلايا اللمفاوية ومن الوحيدات.
- يؤدي غيابه إلى عدم تعرف اللمفاويات T إلى مولدات الأضداد السرطانية مما يؤدي إلى عدم تشكل المستضدات الموافقه لها. أما ارتفاع تركيزة في المصل فهو دليل على تحريض مناعي نتيجة تحرر الأنترفرون أو مركبات السيتوكينات الأخرى كذلك فهو يزداد في مرض نقص المناعة المكتسب الإيدز وفي الأمراض المناعية الذاتية Syndrom lyamphatic Proliferative.
- الغاما غلوبولين : هو عبارة عن غلكوبروتين يفرز من بلاسموسيت Plasmocyte وهو مولد الضد وله خمسة أصناف :

IgG, IgA, IgM, IgD, IgE.

ويتكون من سلسلتين خفيفتين κ - λ

ومن سلسلتين ثقيلتين α - γ - ε - δ - μ

C- معايرة الغلكوز:

تتراوح نسبة الغلكوز في السائل الدماغي الشوكي من 40 – 60% من تركيز الغلكوز في الدم. يتم غالباً اجراء المعايرة بالطريقة الانظيمية: يجب اجراء المعايرة بسرعة لأنه يحدث تحلل للسكر.

ينخفض تركيز السكر في السائل في الحالات التالية:

التهاب السحايا: حيث تستهلك الجراثيم والفطور والكريات البيضاء السكر عند ارتفاعه في الدم.

D- معايرة الكلور في السائل الدماغي الشوكي:

ان تركيز الكلور في السائل هو أعلى مما هو عليه في البلاسما فهو في السائل127 ممول/لتر بينما في البلاسما 103 ممول /لتر وله دور في التوازن التحالي للسائل equilibre osmotique

هناك معايرات كيمائية اخرى يمكن اجراؤها على السائل كالبولة والكالسيوم ولكنها دون فائدة علمية.

اهم التغيرات المرضية لبعض معاير فحص السائل الدماغي الشوكي.

A-التهاب السحايا : نميز هنا التهاب السحايا الحاد او تحت الحاد، الجرثومي الفيروسي أو نتيجة الاصابة بالسفلس. تشترك المعايرة الكيمائية بانخفاض السكر والكلور بينما يرتفع تركيز البروتين ليصل الى 2- 1غ/لتر hyperproteinemie وكذلك يزداد التعداد الخلوي الموجود في السائل.

في التهاب السحايا الجرثومي يرتفع تركيز البروتين في LCR أكثر بكثير مما هو في حالة التهاب السحايا الفيروسي أو السلي (قد يسمى التهاب سحايا بسائل رائق).

B- العلاقة بين الألبومين والتعداد الخلوي:

عندما يحصل ضغط نقوي Compressions medullaires ومهما كان منشؤه خارجي extrinseque (كسور) أو داخلية intrinseque (أورام نقوية) فان الذي يحصل هو ارتفاع كبير في تركيز البروتين قد يصل الى 10غ/لتر أو حتى 20غ/لتر بينما لا يزيد التعداد الخلوي كثيراً وقد يصل الى 10 – 100 خلية / مكرولتر.

- هذه الترسبات تؤدي إلى تشوهات مفصلية وندبات نسيجية.
- قد تحدث هذه الهجمات حتى ولو لم يتجاوز تركيز حمض البول ٧ ملغ / دسل في المصل وهذا يدل على أن حدوث النقرس لا يتعلق فقط بتركيز حمض البول في المصل وإنما بمجموعة من العوامل الأخرى المساعدة في الجسم.
- أما تواتر هذه الهجمات فهو يتراوح ما بين ٢٠ – ٣٠ % عند الرجال الذين تجاوز عندهم تركيز حمض البول ٧ ملغ / دسل

Electrolytes

Dr. SAHAR SHAMAA

Electrolytes

- Ions capable of carrying an electrical charge.
- Anion: (-) → Anode
- Cation : (+) → Cathode
- Processes necessary for electrolyte involvement in the body.

1. Volume and Osmotic pressure (Na, K, Cl)
2. Myocardial rhythm and contraction (K, Mg, Ca)

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3. Cofactors in enzyme activation (Mg, Ca, Zn).
4. Regulation of ATPase ion pump (Mg)
5. Acid/Base balance (pH)- HCO3, K, Cl)
6. Coagulation (Mg, Ca)
7. Neuromuscular excitability (K, Mg, Ca)
8. Production and Utilization of ATP from glucose (Mg, PO4)

All activities work together to keep an electrolyte balance in the body.

Water

- Average water content 40-70% total body weight.
- Solvent for all body processes
- Transport system for all nutrients
- Regulates cell volume
- Removes waste products
- Coolant

All occurs intracellular and extracellular of the cells.

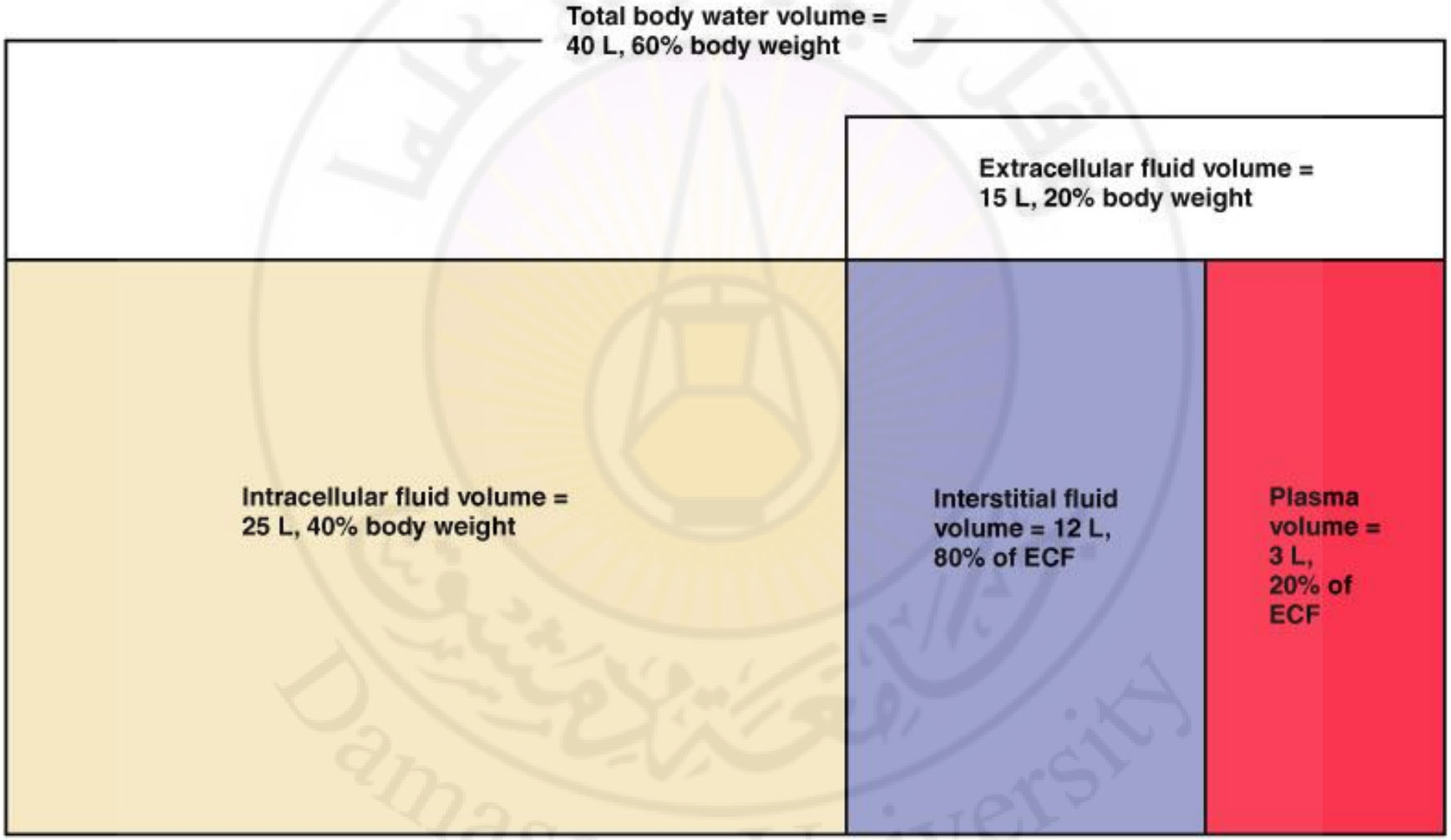
Body Water Content

- Infants have low body fat, low bone mass, and are 73% or more water
- Total water content declines throughout life
- Healthy males are about 60% water; healthy females are around 50%
- This difference reflects females':
  - Higher body fat
  - Smaller amount of skeletal muscle
- In old age, only about 45% of body weight is water

Fluid Compartments

- Water occupies two main fluid compartments
- Intracellular fluid (ICF) – about two thirds by volume, contained in cells
- Extracellular fluid (ECF) – consists of two major subdivisions
  - Plasma – the fluid portion of the blood
  - Interstitial fluid (IF) – fluid in spaces between cells
- Other ECF – lymph, cerebrospinal fluid, eye humors, synovial fluid, serous fluid, and gastrointestinal secretions

Fluid Compartments



Composition of Body Fluids

- Water is the universal solvent
- Solutes are broadly classified into:
  - Electrolytes – inorganic salts, all acids and bases, and some proteins
  - Nonelectrolytes – examples include glucose, lipids, creatinine, and urea
- Electrolytes have greater osmotic power than nonelectrolytes
- Water moves according to osmotic gradients

Electrolyte Concentration

- Expressed in milliequivalents per liter (mEq/L), a measure of the number of electrical charges in one liter of solution
- mEq/L = (concentration of ion in [mg/L]/the atomic weight of ion) × number of electrical charges on one ion
- For single charged ions, 1 mEq = 1 mOsm
- For bivalent ions, 1 mEq = 1/2 mOsm

Extracellular and Intracellular Fluids

- Each fluid compartment of the body has a distinctive pattern of electrolytes
- Extracellular fluids are similar (except for the high protein content of plasma)
  - Sodium is the chief cation
  - Chloride is the major anion
- Intracellular fluids have low sodium and chloride
  - Potassium is the chief cation
  - Phosphate is the chief anion

Extracellular and Intracellular Fluids

- Sodium and potassium concentrations in extra- and intracellular fluids are nearly opposites
- This reflects the activity of cellular ATP-dependent sodium-potassium pumps
- Electrolytes determine the chemical and physical reactions of fluids

Extracellular and Intracellular Fluids

- Proteins, phospholipids, cholesterol, and neutral fats account for:
  - 90% of the mass of solutes in plasma
  - 60% of the mass of solutes in interstitial fluid
  - 97% of the mass of solutes in the intracellular compartment

uids

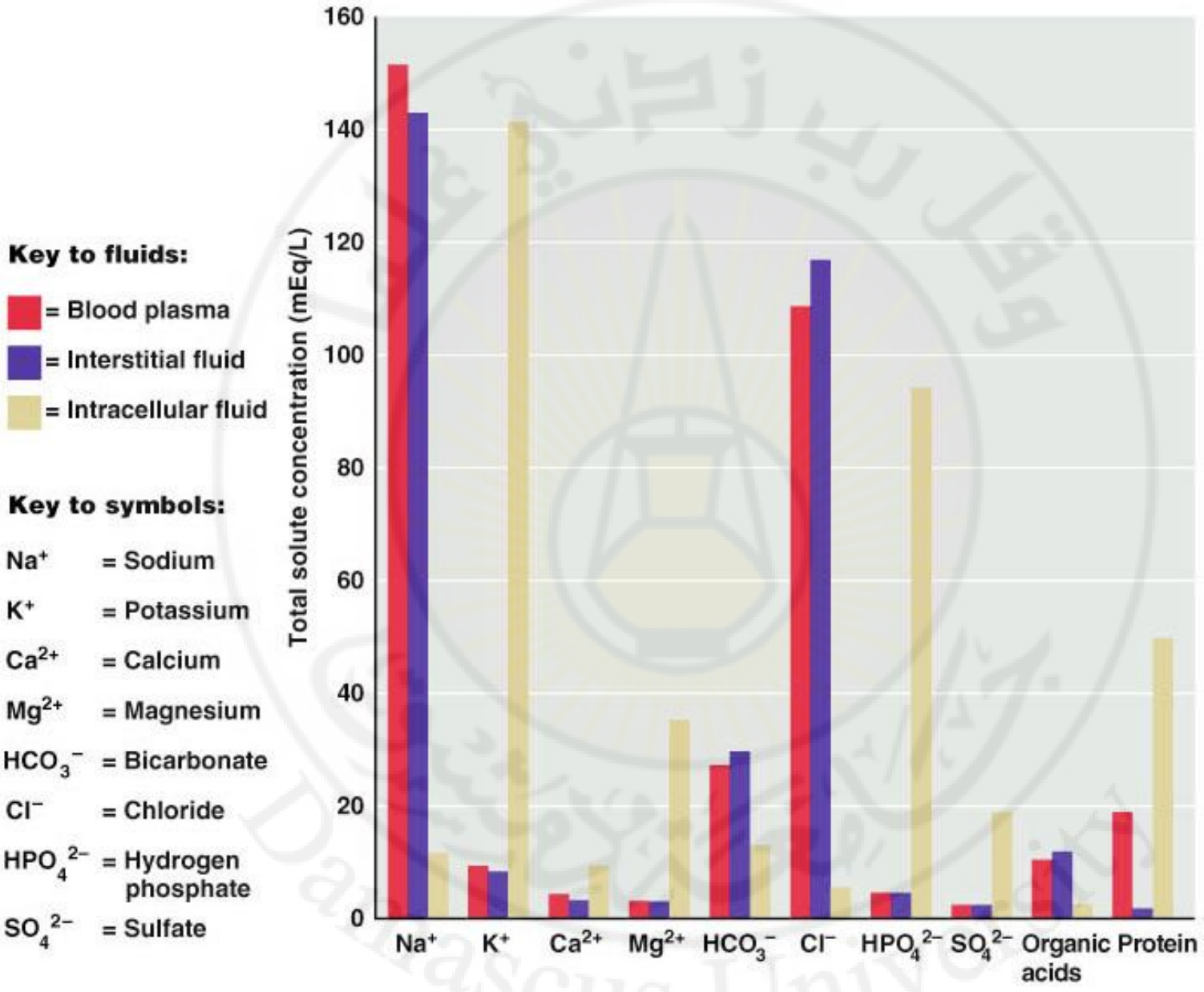


Figure 26.2

Fluid Movement Among Compartments

- Compartmental exchange is regulated by osmotic and hydrostatic pressures
- Exchanges between interstitial and intracellular fluids are complex due to the selective permeability of the cellular membranes

Extracellular and Intracellular Fluids

- Ion fluxes are restricted and move selectively by active transport
- Nutrients, respiratory gases, and wastes move unidirectionally
- Plasma is the only fluid that circulates throughout the body and links external and internal environments
- changes in solute concentrations are quickly followed by osmotic changes

PLAY

InterActive Physiology®:
Fluid, Electrolyte, and Acid/Base Balance: Introduction to Body Fluids

Continuous Mixing of Body Fluids

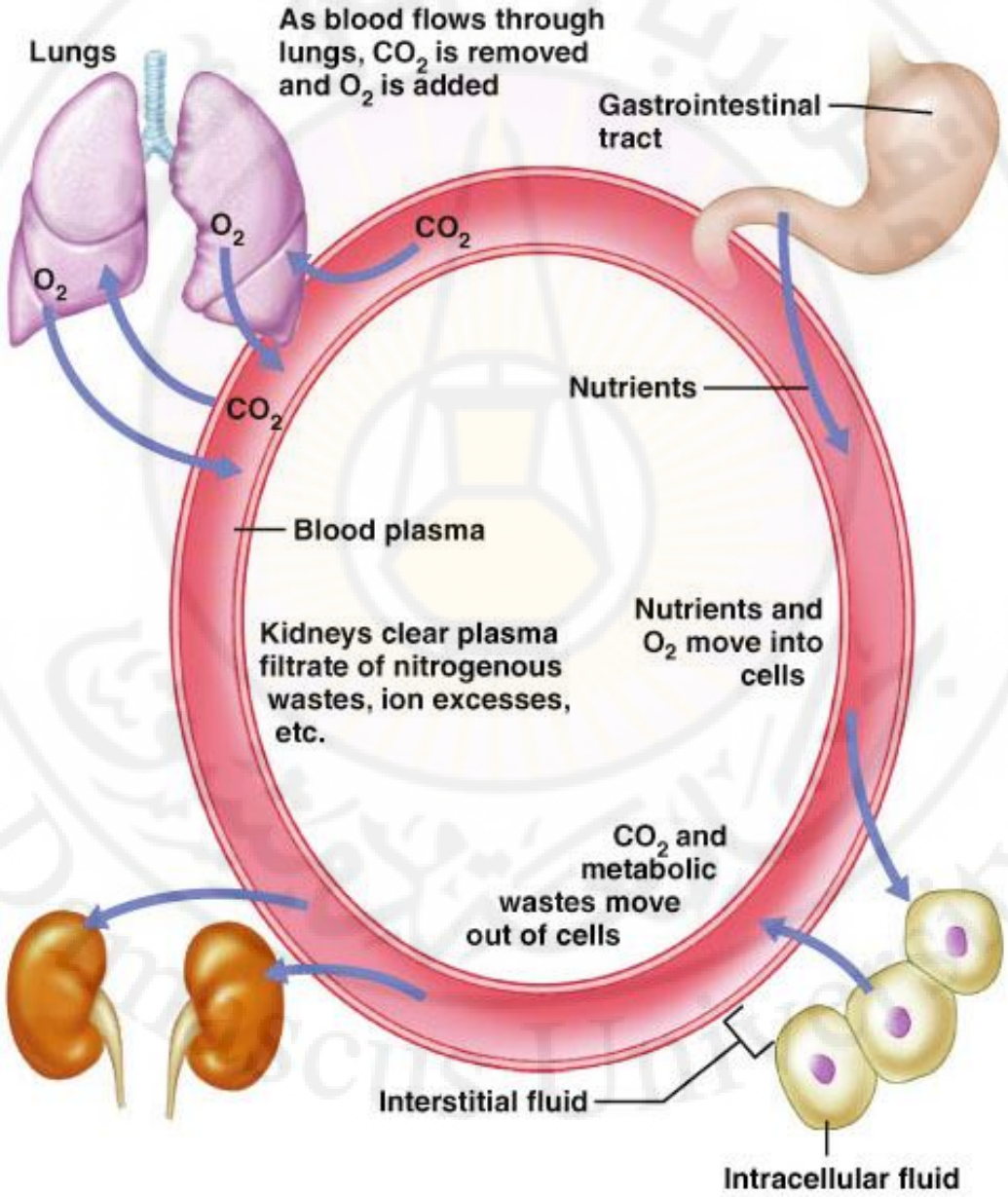


Figure 26.3

Water Balance and ECF Osmolality

- To remain properly hydrated, water intake must equal water output
- Water intake sources
  - Ingested fluid (60%) and solid food (30%)
  - Metabolic water or water of oxidation (10%)

Water Balance and ECF Osmolality

- Water output
  - Urine (60%) and feces (4%)
  - Insensible losses (28%), sweat (8%)
- Increases in plasma osmolality trigger thirst and release of antidiuretic hormone (ADH)

Regulation of Water Intake

- The hypothalamic thirst center is stimulated:
  - By a decline in plasma volume of 10%–15%
  - By increases in plasma osmolality of 1–2%
  - Via baroreceptor input, angiotensin II, and other stimuli

- Concentration of ions within the cells and plasma maintained by:

1. Energy consumption Active transport (Mechanism that requires energy to move ions across the cellular membrane.)
2. Diffusion: Passive movement of ions across the membrane.

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- Osmolality: Physical property of a solution based on the concentration of solutes per kilograms of solvent.
- The natural response to the thirst is the consume more fluids increasing the water content of the ECF and decreasing the osmolality.
- ADH (Antidiuretic Hormone) and thirst are stimulated by the hypothalmus in response to an increased osmolality of body
- ADH is secreted by the posterior pituitary gland, acts on the cells in the kidneys to increase water reabsorption .
-

- ADH: increasing H2O content, diluting the elevated solute(Na) level in the blood which decreases the osmolality turning the ADH off.

Clinical significance: (osmolality)

- Osmolality is the parameter to which the hypothalamus responds. Osmoreceptors in the hypothalamus respond quickly to small changes in osmolality
- Effects Na concentration in plasma .Regulates blood volume through Na concentration.

- Normal osmolality 275-295 mOsm/kg of plasma.

- Renal function relate to Osmolality:
- Water load:

1- Kidneys respond to excess intake of water; decrease in osmolality

- 2.Both ADH and thirst are suppressed –excess urine produced and excreted.
- Water deficit:

1. Decrease water intake; increases plasma osmolality, as a result ADH increase secretion and induces thirst.
2. Thirst is the major defense against hyperosmolality and hypernatremia.

Role of ADH (antidiuretic hormone)

- Synthesized in the hypothalamus and stored in the posterior pituitary

- Released in response to plasma hyperosmolality and decreased effective circulating volume

- Actions of ADH →
  1. Increases the water permeability of the collecting tubule
  2. Mildly decreases vascular resistance

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Regulation of blood volume:

- Blood volume is essential to maintain blood pressure and ensure good perfusion to all cells and tissue.
- Regulation of both sodium and water are inter-related in controlling blood volume.
- Renin-angiotensin-aldosterone: system of hormones that respond to decrease in blood volume and help maintain the correct blood volume.

Renin-Angiotensin-Aldosterone Axis



Angiotensin II → 1. Stimulates production of aldosterone

2. Acts directly on arterioles to cause vasoconstriction

3. Stimulates Na^+/H^+ exchange in the proximal tubule

Aldosterone → 1. Stimulates reabsorption of Na^+ and excretion of K^+ in the late distal tubule

2. Stimulates activity of H^+ ATPase pumps in the late distal tubule

- Changes in blood volume regulated by receptors in the cardiopulmonary circulation , carotid sinus, aortic arch and glomerular arterioles- they activates effectors that restore volume.
- Factors effecting blood volume:

1. Atrial natriuretic Peptide (ANP) released from the myocardial atria in response to volume expansion, promotes Na excretion in the kidney .And BNP (B –type natriuretic peptide acts too in regulating blood pressure.
2. Volume receptors independent of osmolality stimulate the release of ADH.
3. Glomerulus filtrate rate (GFR) increases with volume expansion and decreases with volume depletion

Determination of Osmolality

- Serum or urine sample
- Based on properties of a solution related to the number of molecules per kilogram of solvent present in sample.

Measured by:

- Freezing Point osmometer:
- Standardized method using NaCl reference solution.
- Specimen is super cooled to -7ºC, to determine freezing point.
- An increase in osmolality decreases the freezing point temperature.

- Calculation of osmolality:
- 2Na + Glucose(mg/dl)/20 + Bun(mg/dl)/3
- Or
- 1.86 Na + Glucose/18 + Bun/2.8 +9

Electrolytes

Sodium:

- Most abundant extracellular cation- 90%
- ATPase ion pump: the way the body moves sodium and potassium in and out of cells.
- Three sodium ions pump out of the cell for every two potassium ions pumped in to convert ATP to ADP.

Reference Ranges: Sodium

- Serum
  - 136-145 mEq/L or mmol/L
- Urine (24 hour collection)
  - 40-220 mEq/day

Regulation of sodium balance:

The plasma Na concentration depends on the intake and excretion of water:

- 1-Thirst to increase intake of water
- 2-Excretion of water largely affected by ADH release, in response to changes in blood volume or osmolality .

- 3-Blood volume status which affects sodium excretion through aldosterone, angiotensin II, and ANP.
- The kidneys have the ability to conserve or excrete large amounts of sodium ,depending on the Na content of the ECF and the blood volume .
- 60-75 % of sodium that is filtered is reabsorbed by or in proximal tubules.

Hyponatremia:

- Hyponatremia: result of excess Na loss, increased water retention ,or water imbalance
- Increased Na loss in the urine occur with decreased aldosterone production, certain diuretics, Ketonuria, salt -losing nephropathy, potassium depletion, prolonged vomiting, or diarrhea.
- Increased water retention causes dilution of serum sodium as with acute or chronic renal failure .

- In nephrotic syndrome and hepatic cirrhosis plasma proteins are decreased resulting in a colloid osmotic pressure in which intravascular fluid migrates to the tissue .The low plasma volume causes ADH to be produced , causing fluid retention also see in CHF.
- In syndrome of inappropriate ADH secretion causes an increase in water retention because of increased ADH production .It is observed in pulmonary diseases, malignancies ,infection or trauma.

Hyponatremia/Osmolality

- Normal Osmolality (275 – 295 mOsm / kg)

- Isotonic

pseudohyponatremia; hemolysis

Hyperproteinemia (>10 mg / dl); myeloma.

Hyperlipidemia (severe)

Hyperkalemia ,hypermagnesemia,hypercalcemia

-High osmolality :hyperglycemia

- - Low osmolality:increased sodium loss/increassed water retention.

Hyponatremia

- Sodium: Normal 135 – 145 mmol/L
- Symptoms usually begin <130 mmol/L.
  - Nausea
  - Muscle cramp
  - Psychosis
  - Seizure
  - Coma
  - Death

Hypernatremia:

increased sodium concentration. results from excess loss of water relative to Na+ loss; decrease water intake; or increased Na+ intake or retention.

- Result of excess water loss in the presence of sodium excess.(diabetes)
- Loss of fluid by: kidneys, sweating or intestinal loss, fever, burns, heat exposure, diseases (Diabetes insipidus)
- Chronic hypernatremia: involves hypothalamic disease
- Excess ingestion of salts.

Hypernatremia

- Sodium: Normal 135 – 145 mmol/L
  - Altered mental status
  - coma
  - Muscle cramp
  - Psychosis
  - Seizure
  - Nausea
  - Death
  - More than 160mmol/L, mortality rate of 60-75%

The Homeostatic Regulation of Normal Sodium Ion Concentrations in Body Fluids

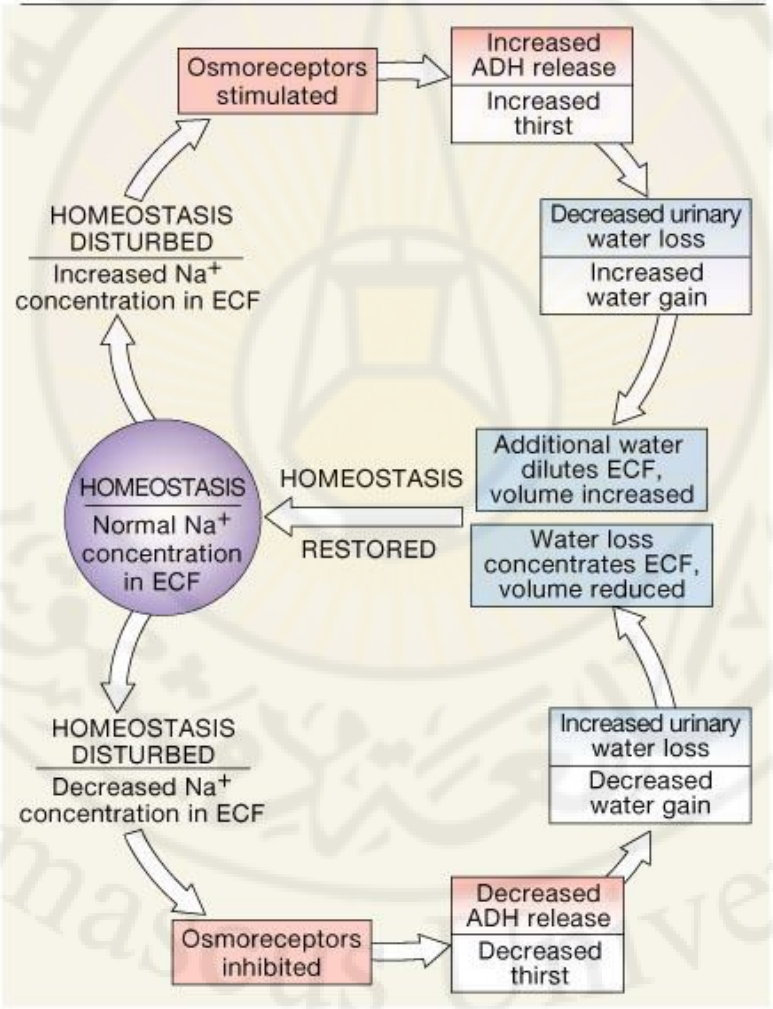


Figure 27.4

The Integration of Fluid Volume Regulation and Sodium Ion Concentrations in Body Fluids

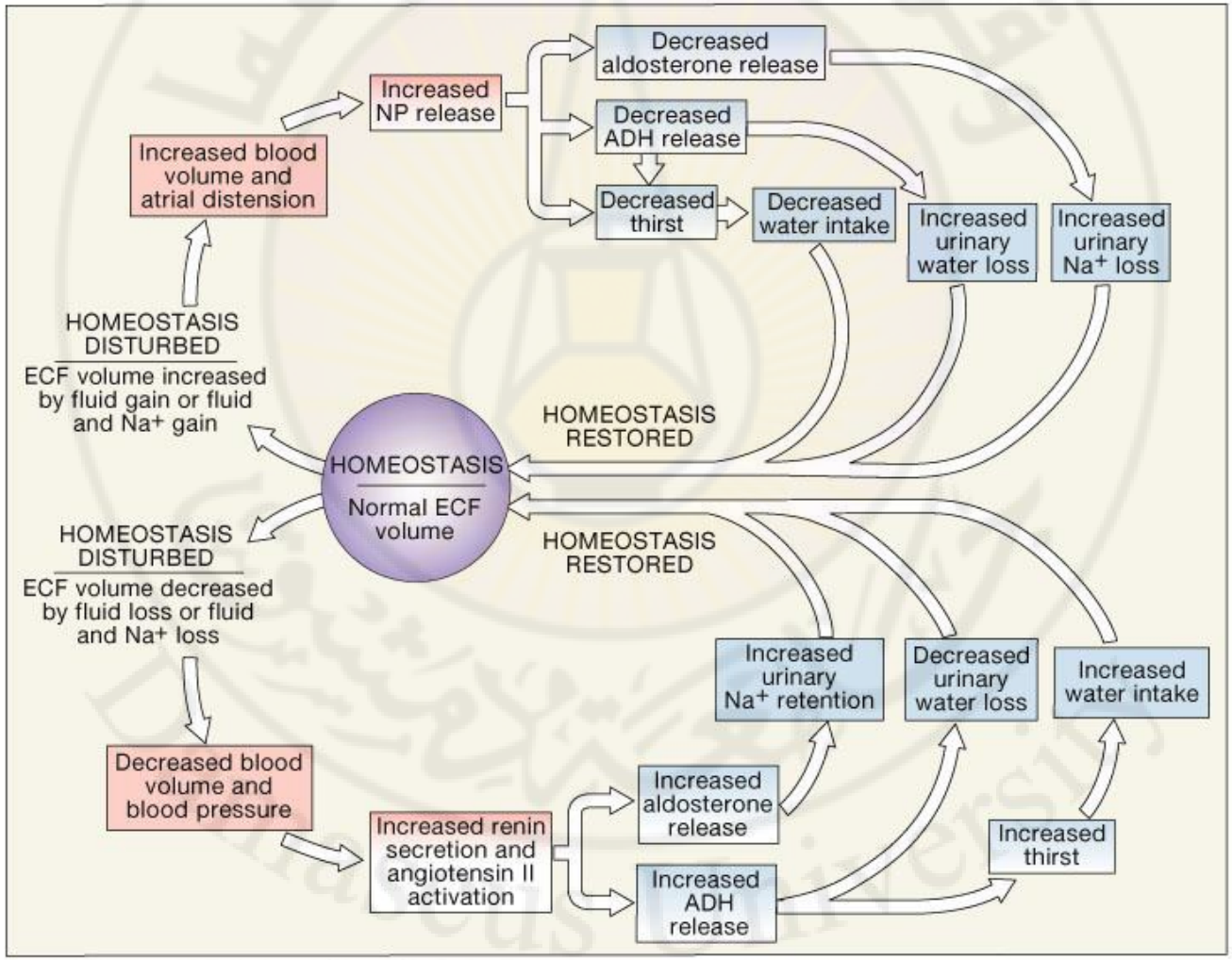


Figure 27.5

Potassium

- Major intracellular cation
- 20X greater concentration in the cell vs. outside the cell.
- 2% of the bodies potassium circulates within the plasma.

Function:

- Regulates neuromuscular excitability
- Hydrogen ion concentration.
- Intracellular fluid volume.

Reference Ranges

- Serum (adults)
  - 3.5 - 5.0 mEq/L or mmol/L
- Newborns
  - 3.7 - 5.9 mEq/L
- Urine (24 hour collection)
  - 25 - 125 mEq/day

Effects on Cardiac muscle:

- Increase plasma potassium; slows the heart rate by decreasing the resting membrane potential of the heart,
- Decrease extracellular potassium; cause arrhythemia or paralysis.

Potassium role in hydrogen concentration

- In general acidemia is associated with increased plasma potassium concentration (hyperkalemia), alkalemia (increased blood pH) is associated with reduced plasma potassium concentration (hypokalemia).
- A frequently cited mechanism for these findings is that acidosis causes potassium to move from cells to extracellular fluid (plasma), and alkalosis causes the reverse movement of potassium and hydrogen ions.

Regulation of potassium

- Kidneys regulate the potassium balance.
- Reabsorption of potassium occurs in the proximal tubules
- Influenced by aldosterone- potassium secreted in the urine exchange for sodium.
- Three factors influence the distribution of K between cells and ECF are:
- K loss occurs whenever Na/K ATP ase pump is inhibited as hypoxia, digoxin over dose therapeutic, hypomagnesemia.

- Insulin promotes acute entry of K into skeletal muscle and liver by increasing activity Na/K ATP ase.
- Cathecholamines promote cellular entry of K+(epinephrine,β- stimulator), whereas propranolol(β- blocker) impairs cellular entry of K+.

Hypokalemia

- Decrease of serum potassium caused by:

1. GI loss: diarrhea, vomiting,
2. Renal Loss: renal tubular acidosis (RTA) tubular excretion of H+ decreases, K+ excretion increases.
3. Renal Loss: also occurs with acute leukemia, acute myelomonocytes leukemia.
4. certain diuretics (thiazide).
5. Decrease intake, malabsorption.

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- 6. Increased K loos in the stool occurs with certain tumors.
- 7. Hypomagnesemia : by promoting urinary loss of K+, diminishes the activity of Na+/K+ ATP ase , and enhances the secretion of aldosterone.
- 8. Alkalemia and insulin increase the cellular uptake of K+.
- Plasma K+ decrease by about 0.4mmol/L per 0.1 unit rise in pH.
- Symptoms: muscle weakness, cardiac arrhythmia, paralysis
- Treat: potassium replacement.

Hypokalemia

- Normal K level: 3.5 – 5.0 mmol/L
- Clinical manifestations
  - Fatigue
  - Cramps
  - Constipation
  - Weakness / Paralysis
  - Parasthesias
  - Arrhythmias

Hyperkalemia

- Increase potassium serum levels 5-5.5 mmol/L
- levels exceeding 8.5 mEq/L can cause respiratory paralysis or cardiac arrest and can quickly be fatal.
- Associated with diseases such as renal, diabetes and metabolic acidosis.
- Results of inability to remove potassium sufficiently.

The most common cause of hyperkalemia in hospitalized patients is due to therapeutic K+ administration.

- **Caused by:**

  - Decreased renal excretion ,hypoaldosteronism ,diuretic.

    Cellular shift ,acidosis, cellular injury, chemeotherapy, transfusion.

Increased intake, exercise, various drugs as captopril(inhibits angiotensin converting enzyme), nonsteroidal anti-inflammatory agents(inhibits aldosterone),digoxin(inhibits Na,K pump), cyclosporine(inhibits renal response to aldosterone, and heparine(inhibits aldosterone secretion).

- In diabetes mellitus, insulin deficiency promotes cellular loss of K+
- Hyperglycemia also can contributes by producing a hyperosmolar plasma that pulls water and K+ from cells, promoting loss of K+ into the plasma.

- In banked blood, K+ is gradually release from erythrocytes during storage often causing elevated K+ concentration in plasma supernatant.

- Patients may develop mild elevations in plasma K+ during warming after surgery because warming causes cellular release of K+. Hypothermia causes movement of K+ into cells.

- exercise: K+ is released from cells during exercise, by 0,3-1,2mmol/L and 2-3 mmol/L with exhaustive exercises.

- Hyperkalemia can lead to cardiac arrhythmias and possible cardiac arrest.
- may alter the electrocardiogram, and concentrations more than 8mmol/L may cause fatal cardiac arrest.

- **Collection of samples:** analysis is extremely important:
- First: the coagulation process releases K+ from platelets(0.1-0.7mmol/L) if thrombocytosis
- Second: if a tourniquet is left on the arm too long during blood collection.
- Third hemolysis :Determination anticoagulant –
- Stored blood on ice promotes the release of K+ from cells, whole blood samples for K+ determinations should be stored at room temperature (never iced).

- Fourth, if hemolysis occurs after the blood is collect, K+ may be falsely elevated .
- Slight hemolysis =50mg/dL of hemoglobin can cause an increase of approximately 3% while gross hemolysis ≥500mg/dL of Hb can cause an increase of up to 30%.

- Symptoms: weakness and cardiac arrhythmia
- Treatment: calcium given to ameliorate cardiac toxicity Insulin and bicarbonate.

Chloride

- Major extracellular anion 98-107 mmol/L
- Urine 24H : 110-250mmol /Day, varies with diet.
- It is involved in maintaining osmolality, blood volume, and electric neutrality.
- Cl ion is secondary to sodium and bicarbonate movement in and out of cells
- Ingested in diet and absorbed in the intestines- become part of HCl.

- Cl- is then filtered out by the glomerulus and passively reabsorbed, in conjunction with Na+, by the proximal tubules.
- Excess Cl- is excreted in the urine and sweat. Excessive sweating stimulates aldosterone secretion, which acts on the sweat glands to conserve Na+ and Cl-.

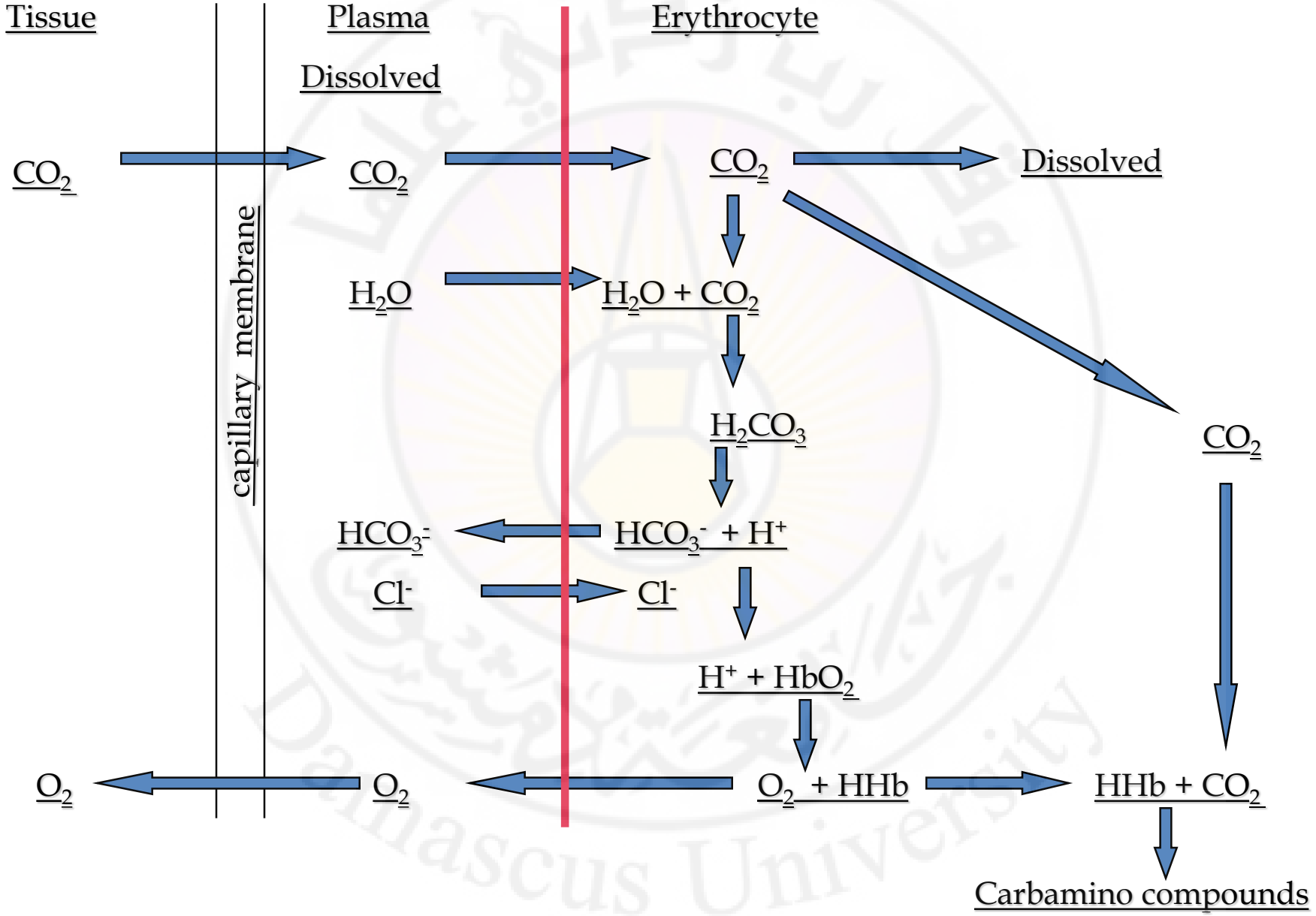
Electric Neutrality

Cl- maintains electrical neutrality in two ways:

1. Na reabsorbed with Cl in proximal tubules. Cl acts as the rate –limiting component ,the Na reabsorption is limited by the amount of Cl available.
2. Electroneutrality is also maintained by Cl- through the Chloride shift

   CO_2 generated in RBC from carbonic acid. Splits to hydrogen and bicarbonate, the bicarbonate diffuses out into the plasma and Cl diffuses into the red cell to maintain electrical balance of the cell..

Hemoglobin--reactions at the tissue level



Disorders

- Cl- disorders are often a result of the same causes that distrub Na+ levels because Cl- passively follows Na+.

- Hyperchloremia: increased loss of bicarbonate as GI losses, metabolic acidosis, RTA.
- Hypocholremia: decreased level of Cl vomiting, diarrhea, salt-losing renal diseases, diabetic ketoacidosis, aldosterone deficiency.
- A low serum level of Cl- may also be occurs in association with high serum HCO3- concentrations , such as metabolic alkalosis.

- Determination : specimen serum or plasma may be used, with lithium heparin being the anticoagulant of choice. Hemolysis does not cause a significant change in serum or plasma value.
- However, with marked hemolysis, levels may be decreased as a result of a dilutional effect.
- The specimen of choice in urine Cl- analysis is 24 hours collection.

- Sweat is also suitable for analysis. mucoviscidosis; is an autosomal recessive inherited disease that affects the exocrine glands and causes electrolyte and mucous secretion abnormalities.

Bicarbonate

- 2nd most abundant anion of ECF.
- Major component of the buffering system.
- Buffering system: $NaHCO_3/H_2CO_3$, Phosphate, hemoglobin and plasma proteins.
- Balanced by the conversion of

$$H2O + CO2 \rightarrow H2CO3 \rightarrow HCO3^{-} + H^{+}$$

- Total CO_2 comprise the bicarbonate ion(HCO_3^-), carbonic acid (H_2CO_3), and dissolved CO_2, with HCO_3^- accounting for more than 90% of the total CO_2 at physiologic pH.
- Because HCO_3^- compose the largest fraction of total CO_2, total CO_2 measurement is indicative of HCO_3^- measurement.

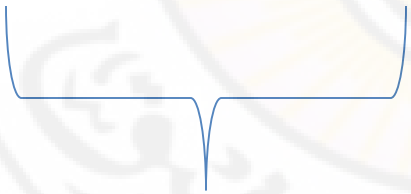
Specimen Collection: Bicarbonate ion

- heparinized plasma
- arterial whole blood
- fresh serum
- Anaerobic collection preferred

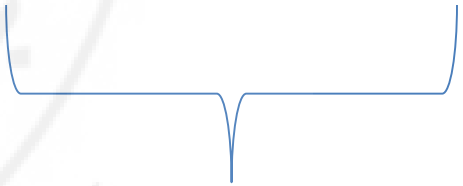
Regulation of Bicarbonate ion

Reaction: $CO_2 + H_2O \leftrightharpoons H_2CO_3 \rightarrow H^+ + HCO^-_3$

carbonic anhydrase



Pulmonary Control



Renal Control

Reference Range: Bicarbonate ion

- ***Total*** Carbon dioxide (venous)
  - 23-29 mEq/L or mmol/L
    - includes bicarb, dissolved and undissociated H_2CO_3 - carbonic acid (bicarbonate)

- Bicarbonate ion (HCO_3^-)
  - 22-26 mEq/L or mmol/L

Regulation

- Kidneys: 85% of bicarbonate ion is reabsorbed by the proximal tubules; 15% reabsorbed by the distal tubules as CO_2.

Because tubules are only slightly permeable to HCO_3^-, it is usually reabsorbed as CO_2 . This happens as HCO_3^-, after filtering into the tubules ,combines with H^+ to form carbonic acid, which then dissociated into H_2O and CO_2. The CO_2 readily diffuses back into the ECF.

Regulation

1. In Alkalosis :with a relative increase in HCO3- compared to CO2, the kidney increase excretion of HCO3- into the urine , carrying along a cation as Na+, this loos of bicarbonate from the body helps correct pH .

1. In Acidosis: The response of the body is an increased excretion of H+ into the urine, in addition bicarbonate reabsorption is virtually complete, with 90% of the filtered HCO3- reabsorbed in the proximal tubule and the rest in the distal tubule.

Magnesium

- 4th most abundant cation in the body and second most abundant intracellular ion.
- The average human body 70Kg contains 1 mole (24g)of Mg2+.
- 53 % of Mg found in the bone, 46 % in muscle and tissue, <1% is present in the serum.
- The Mg circulating in serum is in the bound form (one third-bound to albumin), of the remaining two thirds-(61%) is in the free or ionized form, 5 % bound to phosphate and citrate.
- Free form is physiologically active.

- The most significant findings are the relationship between abnormal serum Mg levels and cardiovascular, metabolic, and neuromuscular disorders.
- Although serum levels may not reflect total body stores of Mg, serum levels are useful in determining acute changes in the ion.

- Role in the body is of an essential cofactor of more than 300 enzymes(glycolysis, transcellular ion transport, synthesis of carbohydrates ,proteins ,lipids, and nucleic acids, and release to certain hormones…..).
- Regulated by dietary intake, sm. intestine may absorb 20-65 % of dietary intake and body needs.
- Kidneys regulate reabsorption and excretion of Mg:
- The overall regulation of body Mg is controlled largely by the kidney, which can reabsorb Mg in deficiency states or readily excrete excess in overload states.

- Abnormal levels related to cardiovascular, metabolic, and neuromuscular disorders.
- Aldosterone and thyroxine have opposite effect of PTH in the kidney, increasing the renal excretion of Mg.
- PTH increases the renal reabsorption of Mg and enhances the absorption in the intestine

Hypomagnesemia

- Hypomagnesaemia: most frequently observe in hospital patients, especially those receiving diuretics or digitalis therapy.

  - Normal: Magnesium 1.7 – 2.4 mg / dl
  - 0.6-1.1 mmol/L

Result of:

1. Reduce intake: chronic alcoholism,
2. Decreased absorption: surgical, vomiting, congenital, Laxative

- Increased excretion : tubular disorder, Hyperaldosteronism, Hyperparathyroidism, and Hypercalcemia can cause increased renal excretion, Diabetic Ketoacidosis, diuretic, Antibiotic.

- A chronical congenital hypomagnesemia with secondary hypocalcemia(autosomal recessive disorder) has also reported, molecular studies have revealed a specific transport protein defect in the intestine.
- In persons with diabetes, excess urinary loss of Mg is associated with glycosuria.
- Hypomagnesemia can aggravate the neuromuscular and vascular complications commonly found in this disease.

- Excess serum Na+ levels caused by hyperaldosteronism may also cause increased renal excretion of Mg+.
- A pseudohypomagnesemia may also be the result of hyperaldosteronism caused by increased water reabsorption.
- Some studies have shown a relationship between Mg deficiency and insulin resistance.

- Several drugs, including diuretics, gentamicin, and cyclosporine increase renal loss of Mg.
- Excess lactation has been associated with hypomagnesemia as a result of increased use and loss through milk production.
- Mild deficiencies have been reported in pregnancy, which may cause a hyperexcitable uterus, and insomnia.
- Asymptomatic until serum levels fall below 0.6mmol/L: Cardiovascular, neuromuscular psychiatric.

- The cardiovascular and neuromuscular symptoms result primarily from the ATP ase enzyme`s requirement for Mg. Mg loss leads to decreased intracellular K+ levels because of a faulty Na+/K+ pump.
- Muscle contraction also requires Mg and ATP ase for normal calcium uptake following contraction.
- Normal nerve and muscle cell stimulation requires Mg to assist with the regulation of acetylcholine, a potent neurotransmitter.

- Hypomagnesemia can cause a variety of symptoms from weakness to tremors, tetany, paralysis.
- The CNS can also be affected, metabolic disorders are associated with hypomagnesemia.

- Hypermagnesemia less frequently seen.
- The most common is renal failure (GFR≤30 mL/min).
- The most severe elevation are usually a result of the combined effects of decreased renal function and increased intake of commonly prescribed Mg+2 containing medication such as antacids.

- Caused by:

1. Decreased excretion: Hypoaldosteronism,
2. Increased intake: Therapeutic:

MgSO4 may be used with preeclampsia, cardiac arrythmia , or myocardial infarction.

Mg is a vasodilator and can decrease uterine hyperactivity in eclampsia state and increase uterine blood flow.

This therapy can lead to maternal hypermagnesemia, as well as neonatal hypermagnesemia due to the immature kidney of the newborn.

- Studies have shown that IV Mg+2 therapy in myocardial infarction patients may reduce early mortality.
- Dehydration can cause peudohypermagnesemia.
- In individuals with multiple myeloma or, bone metastases, a serum Mg elevations can occurs.
- Symptoms do not occur until the serum level exceeds 1,5 mmol/L.

- Symptoms: cardiovascular , dermatology, GI, neurological, metabolic, Hemostatic abnormalities.
- Such as : hypotension, bradycardia, skin flushing, nausea, vomiting.
- Elevated Mg levels inhibits PTH release and target tissue response.
- This may lead to hypocalcemia and hypercalcuria.

- Normal hemostasis is a calcium dependent process that may be inhibited as a result of competition between levels of Mg and Ca ions.

Phosphate: H_2PO_4

- Element found everywhere, participates in various biochemical processes.
- Most significant: ATP, Creatine Phosphate, phosphoenolpyruvate reactions,
- Important compound in the release of O_2 from Hb.
- The genetic materials DNA,RNA are complex phosphodiesters.

Regulation

- Absorbed in the intestine through diet, released from cells regulated into the blood, regulated by renal excretion or reabsorption.
- Renal regulation is effected by factors such as
- Vit. D, calcitonin, growth hormone, acid-base balance act to increase phosphate in the blood. PTH, which lowers blood concentrations by increasing renal excretion.

- Vitamin D acts to increase phosphate in the blood. Vitamin D increases both phosphate absorption in the intestine and phosphate reabsorption in the kidney.
- Growth hormone increases phosphate concentration in the blood by decreases renal excretion.

Distribution: two forms

1. Organic
2. inorganic

- Distribution:
- The concentration of all phosphate in blood is about 12mg/dl, most of that is organic and only about 3-4mg/dl is inorganic.
- About 80% of the total body pool is contained in bone,20% in soft tissues and less than 1% is active in serum/plasma.

Clinical application

- Hypophosphatemia:

Decreased level of phosphate in blood: diabetes, Ketoacidosis, malignancy, inflammatory bowel disease, alcoholism, long treatment with total parenteral nutrition.

- Hypophosphatemia can also be caused by increased renal excretion, as with hyperparathyroidism, and decreased intestinal absorption, as with vitamin D deficiency or antacid use.

Hypophosphatemia

- Phosphorus: Normal 2.6-4.5 mg / d
- Occurs in 1%-5% of hospitalized patients, and to20-40% in patients with following disorders:
  - Hyperglycemic states
  - Alcoholism
  - Respiratory alkalosis
  - GI abns
  - malignancy
  - inflammatory
  - Renal wasting as hyperparathyroidism
  - Decreased intestinal absorption as with vitamin D deficiency.

- Hyperphoshatemia:

patients with acute and chronic renal failure are at the greatest risk for condition.

Hyperphosphtemia

- An increased intake
- Increased breakdown of cells : infection, neoplastic disorders(lymphoblastic) , or intravascular hemolysis, laxative.
- Acute or chronic renal failure
- Neonate are especially susceptible to hyperphosphatemia caused by increased intake. Such as from cow's milk

Electrolyte Summary

- ***cations (+)***
  - ***Na 142***
  - ***K 5***
  - ***Ca 5***
  - ***Mg 2***

  154 mEq/L

- ***anions (-)***
  - ***Cl 105***
  - ***HCO3- 24***
  - ***HPO4- 2,2***
  - ***SO4-2 1***
  - ***organic acids 6***
  - ***proteins 16***

  154 mEq/L

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Lactate

- Is the by-product of emergency mechanism that produces a small amount of ATP when O2 delivery is diminished- leads to accumulation of excess NADH.
- Regulated by the liver- through gluconeogenesis

Reference range 0.5-1.6 m.mol/L Arterial

0.5-2.2 m.mol/L Venous

Clinical Application

- There are two types of lactic acidosis .
- Type A is associated with hypoxic conditions such as myocardial infarction ,severe congestive heart failur, severe blood loss.
- Type B is of metabolic origin ,such as severe infection, diabets, liver or renal disease and toxins (ethanol, methanol, salicylate poisoning).

Assay

- Serum or plasma, collected on ice
- Enzymatic method: use lactate dehydrogenase with cofactors NAD to convert Lactate to Pyruvate with the formation of NADH.

Anion Gap

- Use to evaluate electrolytes :Na, K, Cl, HCO3.
- Difference between measured anions and measured cations.
- Formula: AG=(Na + K)- (Cl + HCO3)
- Reference range of 10-20 m.mol/L
- There is never a gap between total cationic charges and anionic charges
- Consistently abnormal anion gap in serum from healthy persons may indicate an instrument problem.

Functions of the Anion Gap

- Increased ***AG***
  - uncontrolled diabetes (due to lactic & keto acids)
  - severe renal disorders
  - Hypernatremia
  - lab error

- Decreased ***AG***
  - a decrease AG is rare, more often it occurs when one test/instrument error
- ***May be seen with hypoalbuminemia***

Calcium Physiology

- Ionic calcium in ECF is important for:
- - They act as a second messenger, in neurotransmitter release from neurons, in contraction of all muscle cell types, and in fertilization.
  - Blood clotting
  - Cell membrane permeability
  - Enzymatic regulation
  - Hormonal secretion

- $[Ca^{2+}]_{cyt}$ is approximately $1/1000^{th}$ of extracellular concentration
  - Stored in mitochondria and ER
  - $[Ca^{2+}]$ in blood is 5,000-10,000 times higher than in the cytosol of cardiac or smooth muscle cells.

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- Binding of calcium to albumin is pH dependent
- Acute alkalosis increases calcium binding to protein and decreases ionized calcium
- Patients who develop acute respiratory alkalosis have increased neural excitability and are prone to seizures due to low ionized calcium in the extracellular fluid which results in increased permeability to sodium ions.

Calcium in blood and bone

- Ca^{2+} normally ranges from 8.5-10 mg/dL in the plasma.(2.1-2.6 mmol/l)
- About 98% of the 1200 g of calcium in the adult is in the form of hydroxyapatite in the skeleton
- In blood the active free ionized Ca^{2+} is only about 48%, 46% is bound to protein in a non-diffusible state while 6% is complexed to salt.
- Only free, ionized Ca^{2+} is biologically active.
- ["Corrected" Ca (mmol/L) = Ca measured (mmol/L) + 0.020 or 0.025 (40 - albumin (g/L))].

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Regulation

- Three hormones: PTH, Vitamin D, and Calcitonin, are known to regulate serum Ca++ by altering their secretion rate in response to changes in ionized Ca+2.

- **Hypocalcemia:**
  - Increases excitability
  - Causes muscle tetany
- **Hypercalcemia:**
  - Weakness, depression, lethargy, coma.
  - Constipation ,nausea, vomiting, nephrolithiasis.
  - May cause heart arrhythmias

Regulation of Calcium and Phosphate

- PTH promotes increase inionized calcium levels by targeting:
  - Bones – PTH activates osteoclasts to break down bone matrix
  - Small intestine – PTH enhances intestinal absorption of calcium
  - Kidneys – PTH enhances calcium reabsorption and decreases phosphate reabsorption
- Calcium reabsorption and phosphate excretion go hand in hand

- Vitamin D increases Ca+2 absorption in the intestine and enhances the effect of PTH on bone resorption.
- Calcitonin exerts its ca+2 lowering effect by inhibiting the actions of both PTH and vitamin D.
- Although calcitonin is not secreted during normal regulation of the ionized Ca+2 concentration in blood, it is secreted in response to a hypercalcemia stimulus.

- Hypocalcemia:
- When PTH is not present as with primary hypoparathyroidism, serum Ca+2 levels are not regulated.
- Hypomagnesemia may cause hypocalcemia by three mechanisms:1- it inhibits the secretion of PTH 2- it impairs PTH action at its receptor site on bone, and 3- it causes vitamin D resistance.

- Hypocalcemia can appear with hypoalbuminemia: chronic liver disease, nephrotic syndrome, malnutrition.
- The patients with acute pancreatitis develop hypocalcemia: the cause appears to be a result of increased intestinal binding of Ca+2 as increased intestinal lipase activity.

- Patients with renal disease caused by glomerular failure often have altered concentrations of ca+2, Po4-, albumin, Mg+2, and H+.

- Hypercalcemia:
- Primary hyperparathyroidism is the main cause of hypercalcemia.
- Also is associated with various types of malignancy, many tumors produce PTH – related peptide which binds to normal PTH receptors and causes increased Ca+2 levels.

- A rare, benign familial hypocalciuria has reported.
- Thiazide diuretics increase Ca+2 reabsorption, leading to hypercalcemia.
- Prolonged immobilization may cause increased bone resorption.

Regulation of calcium and phosphate

- High or normal ECF calcium levels inhibit PTH secretion:
  - Release of calcium from bone is inhibited
  - Larger amounts of calcium are lost in feces and urine
  - More phosphate is retained

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Influence of calcitonin

- Released in response to rising blood calcium levels
- Calcitonin is a PTH antagonist, but its contribution to calcium and phosphate homeostasis is minor to negligible

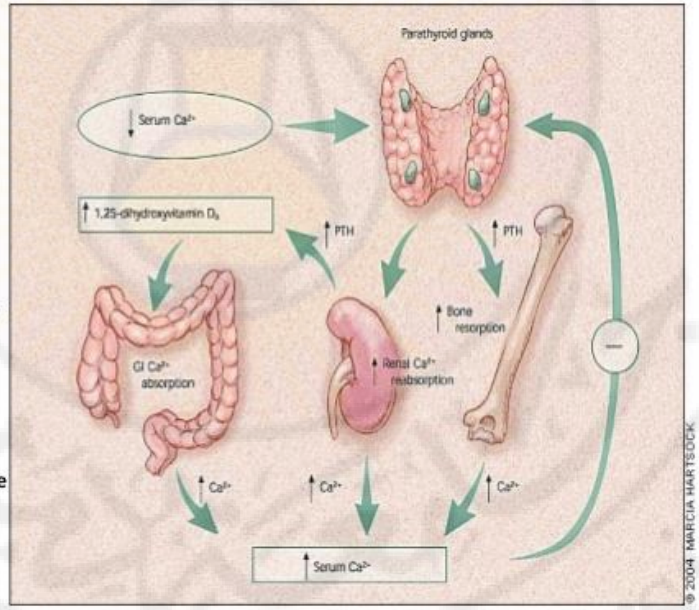
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PTH/Calcium Homeostasis

Low circulating serum calcium concentrations stimulate the parathyroid glands to secrete PTH, which mobilizes calcium from bones by osteoclastic stimulation.

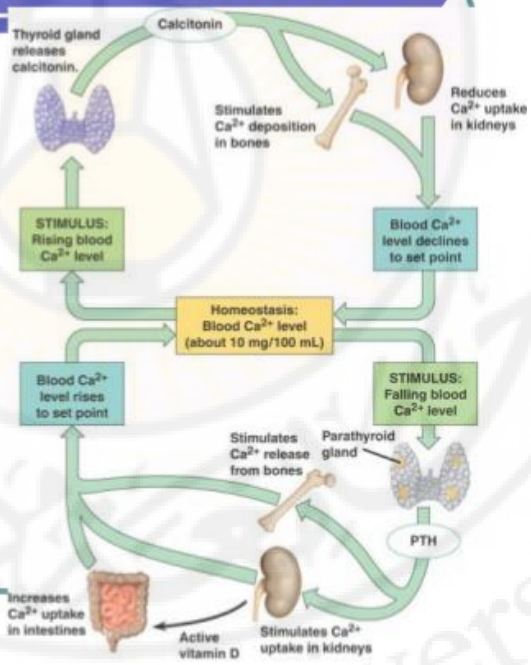
PTH also stimulates the kidneys to reabsorb calcium and to convert 25-hydroxyvitamin D3 (produced in the liver) to the active form, 1,25-dihydroxyvitamin D3, which stimulates GI calcium absorption.

High serum calcium concentrations have a negative feedback effect on PTH secretion.



Calcium Homeostasis

- Two antagonistic hormones, **parathyroid hormone (PTH)** and **calcitonin**, play the major role in calcium (Ca^{2+}) homeostasis in mammals.



Chapter 14

Blood Gases, pH, and Buffer system

Part 2

Dr. SAHAR SHAMAA

What Is a Blood Gas Test?

- A blood gas test measures the amount of oxygen and carbon dioxide in the blood . It may also be used to determine the pH of the blood, or how acidic it is.
- The test is commonly known as a blood gas analysis or arterial blood gas (ABG) test.

- Imbalances in the oxygen, carbon dioxide, and pH levels of blood can indicate the presence of certain medical conditions. .These may include:
- kidney failure
- heart failure
- uncontrolled diabetes
- hemorrhage
- chemical poisoning
- A drug overdose- Shock -

Blood Gases:

- Determining blood pH to diagnose acidosis vs. alkalosis and to determine the origin (respiratory or metabolic)
- Evaluated by determining O2 and CO2 exchange by measuring partial pressure of O2 along with pH.
- Specimen collected is arterial blood

First some definitions---

acidemia---decreased pH in the blood

acidosis---decreased pH in the tissues

alkalemia---increased pH in the blood

alkalosis---increased pH in the tissues

Definitions

- hypoxemia---decreased PaO_2 in the blood
- hypoxia---decreased PO_2 in the tissues
- hypercarbia, hypercapnia---increased PCO_2; CO_2 retention
- ***acute***---a condition in which there has been no compensation by the body to rectify the abnormality
- ***chronic***---a condition in which there has been compensation by the body to rectify the abnormality

Oxygen Transport :Hemoglobin

A large protein structure having a molecular weight near 65,000, comprised of 4 heme units and globin

The globin portion is a protein molecule, made up of 2 α and 2 β polypeptide chains.

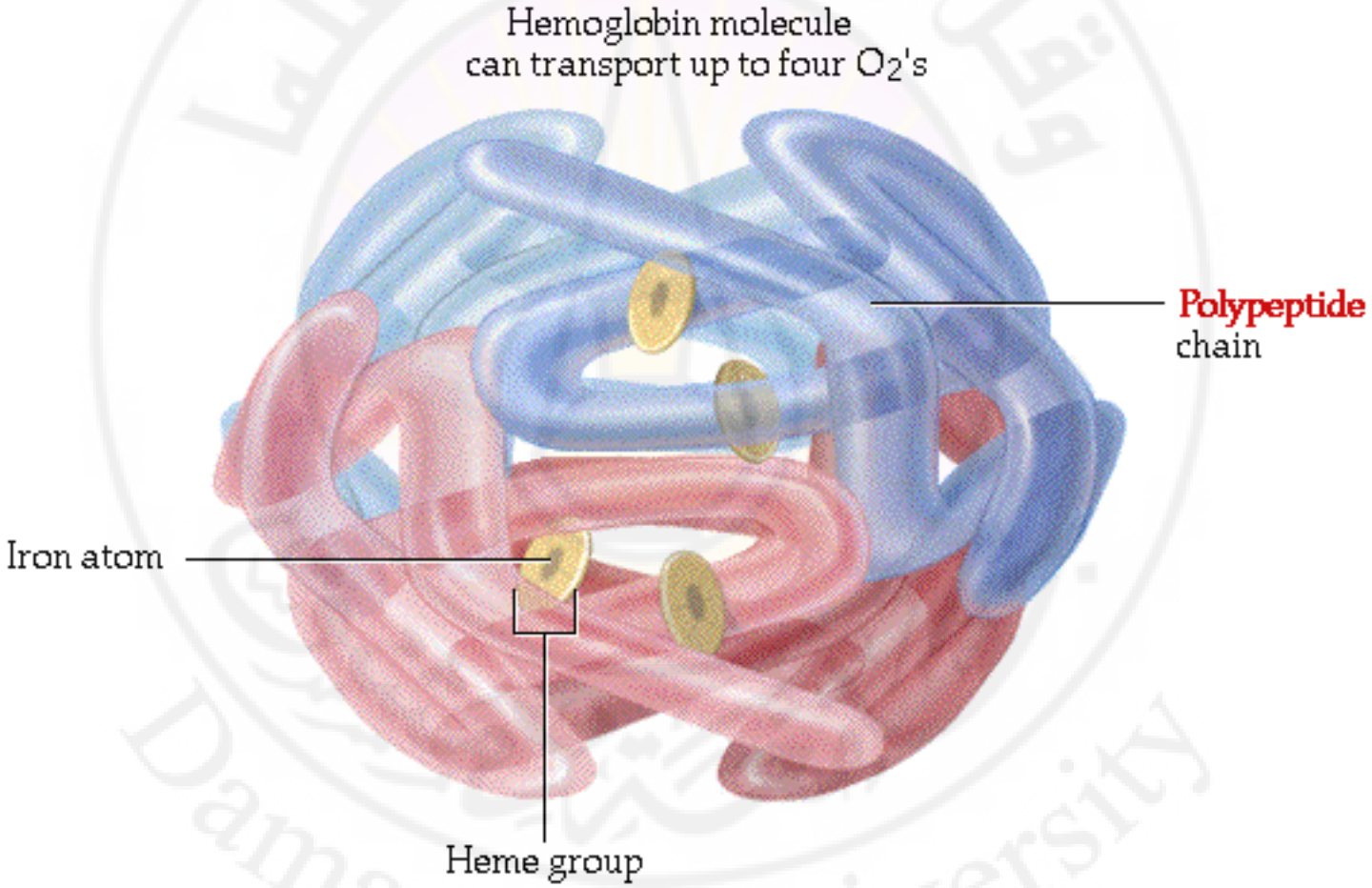
Each of these chains is bound to an iron (heme) moiety. The iron attaches at a histidine residue in both the alpha and beta chains.

Hemoglobin is a *metalloporphyrin* , that is, porphyrin combined with a metal, in this case, iron.

Hemoglobin-a simplified structure



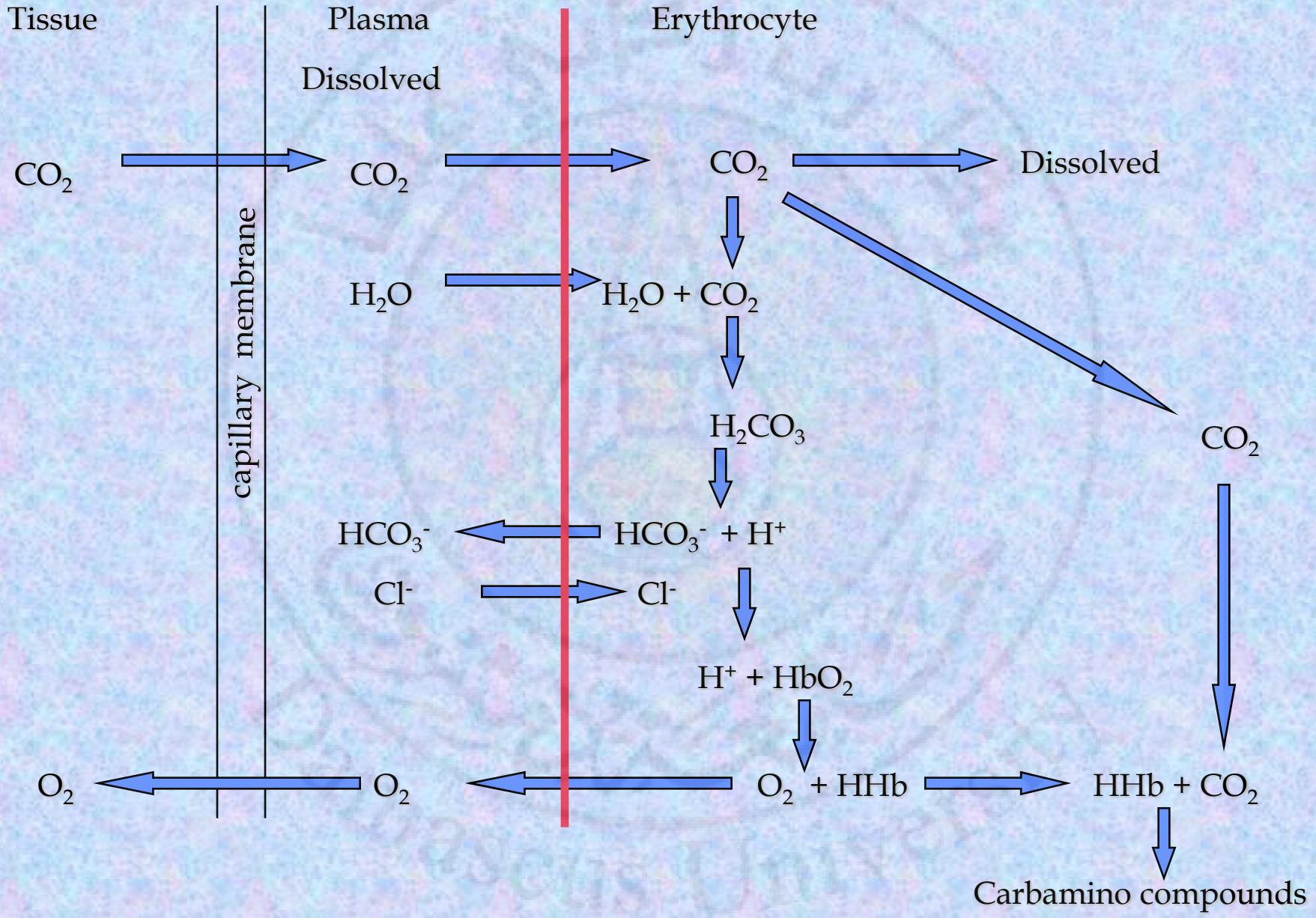
HEMOGLOBIN


Hemoglobin molecule
can transport up to four O_2's
Polypeptide
chain
Iron atom
Heme group

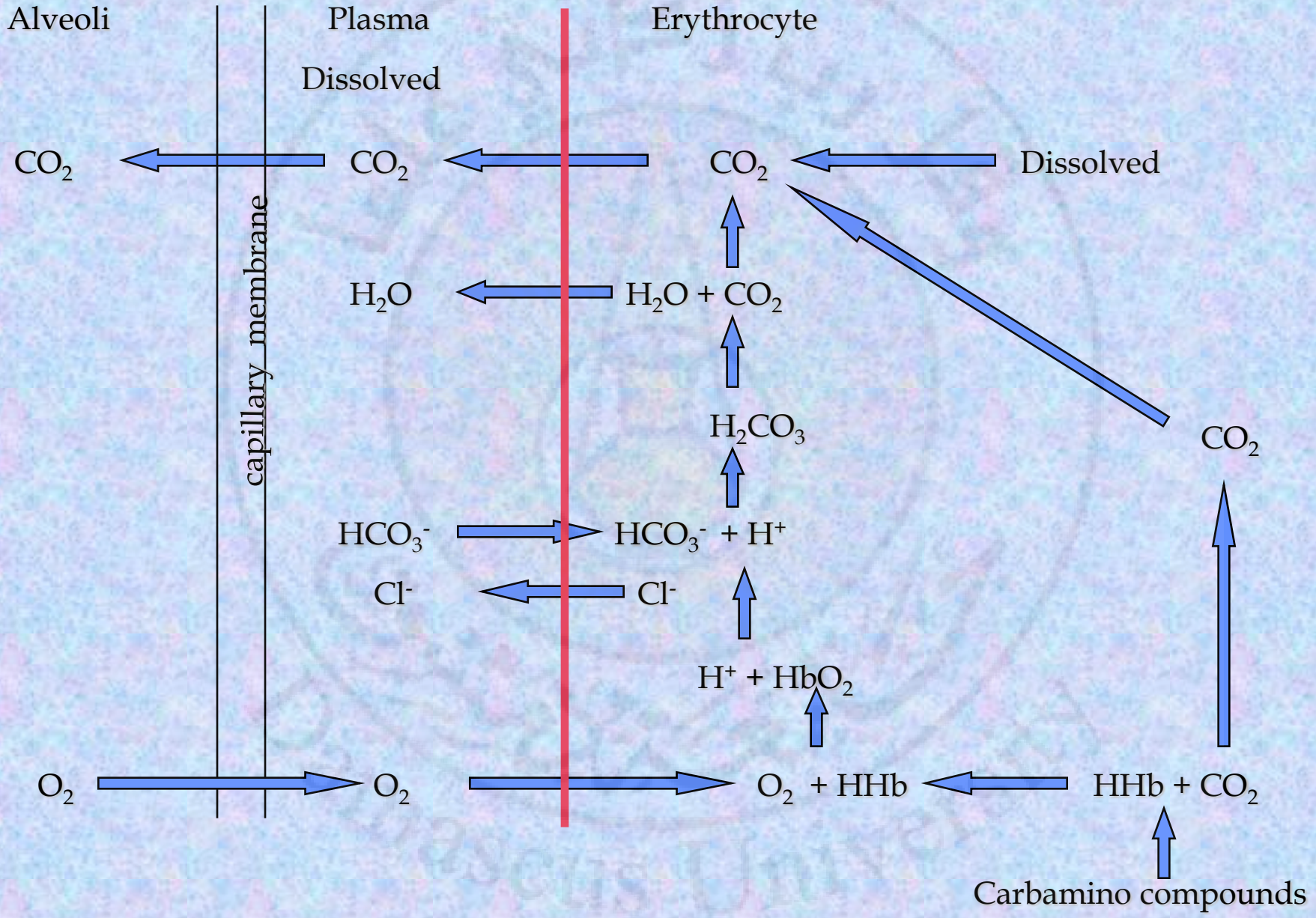
The amount of O2 loaded onto Hb depends on the: -
concentration and types of Hb,
the presence of interfering substances, such as carbon monoxide,
the pH, the temperature of the blood, and
the levels of PCO2, and 2,3 – DPG.
With adequate atmospheric and alveolar O2 available, and
with normal diffusion of O2 ,
more than 95% of functional Hb will bind O2.

- Normally blood Hb exists in one of four condition:
- Oxyhemoglobin(O2Hb) reversibly bound to Hb
- Deoxyhemoglobin (HHb) reduced Hb which is Hb not bound to O2.
- Carboxyhemoglobin COHb , the bound is reversible, but is greater than 200 times as HbO2
- Methemoglobin MetHb, which is Hb unable to bind O2; iron is an oxidized. The Fe+3 can be reduced by the enzyme methemoglobin reductase, which is found in red blood cells.

Hemoglobin--reactions at the tissue level



Hemoglobin--reactions at the alveolar level



PARTIAL PRESSURES

- In a mixture of gasses, the total pressure distributes among the constituents proportional to their percent of the total

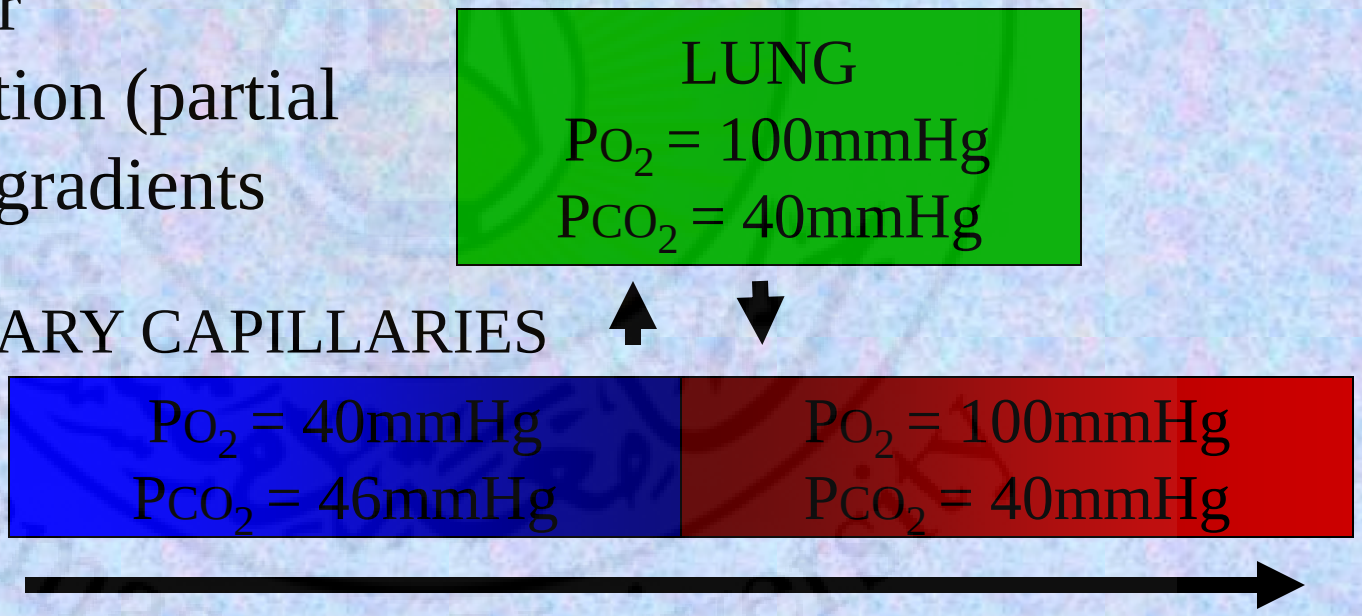
- The concentration of a gas can therefore be expressed as its partial pressure

GAS EXCHANGE ACROSS PULMONARY CAPILLARIES

Inspired Air P_{O_2} = 149mmHg

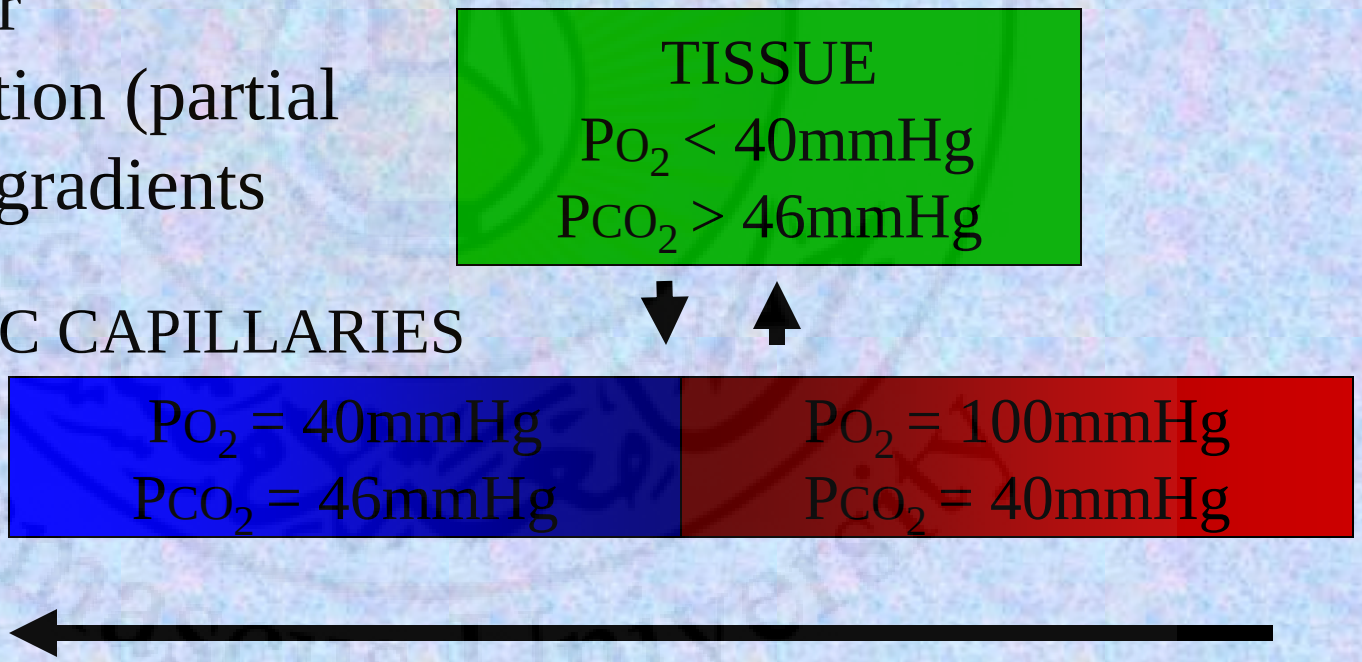
P_{CO_2} = 0.2mmHg

- Both oxygen and carbon dioxide diffuse down their concentration (partial pressure) gradients

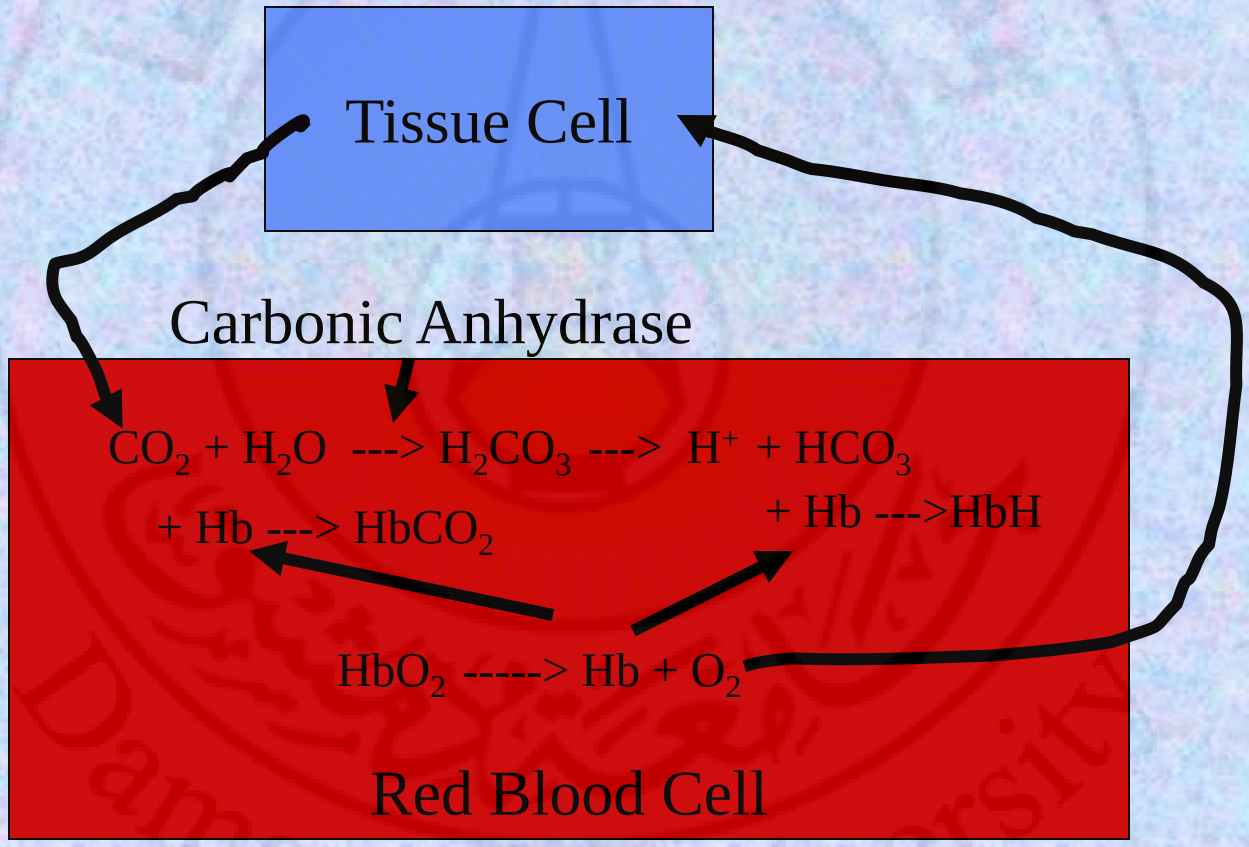


GAS EXCHANGE ACROSS SYSTEMIC CAPILLARIES

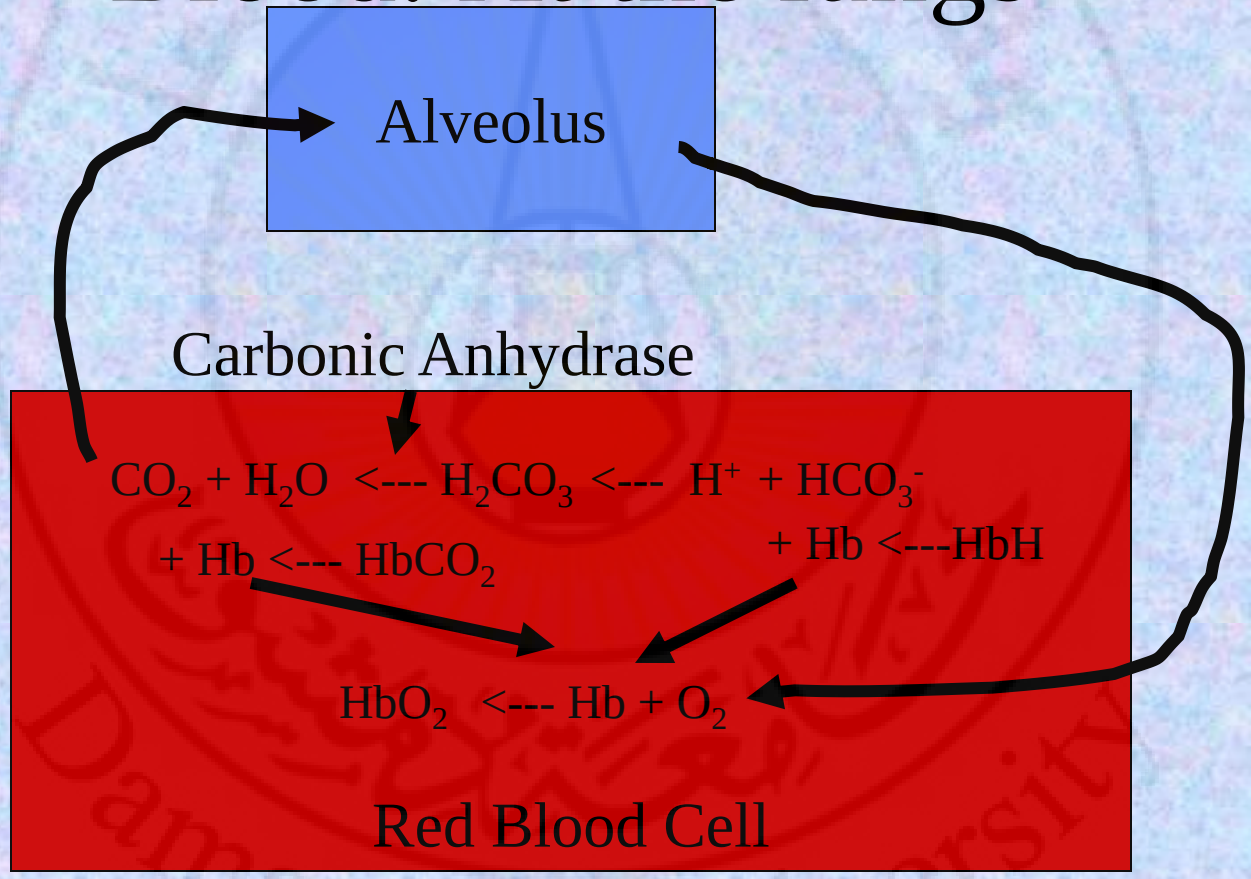
- Both oxygen and carbon dioxide diffuse down their concentration (partial pressure) gradients



Carbon Dioxide Transport in the Blood: At the tissues



Carbon Dioxide Transport in the Blood: At the lungs



The Haldane Effect

- Removal of oxygen from hemoglobin increases hemoglobin's affinity for carbon dioxide
- This allows carbon dioxide to "ride" on the empty hemoglobin

Normal Arterial Blood Gas Values*

pH	7.35 - 7.45
$PaCO_2$	35 - 45 mm Hg
PaO_2	70 - 100 mm Hg **
SaO_2	93 - 98%
HCO_3^-	22 - 26 mEq/L
%MetHb	< 2.0%
%COHb	< 3.0%
Base excess	-2.0 to 2.0 mEq/L
CaO_2	16 - 22 ml O_2/dl

* At sea level, breathing ambient air

** Age-dependent

Hemoglobin--Carbon Dioxide

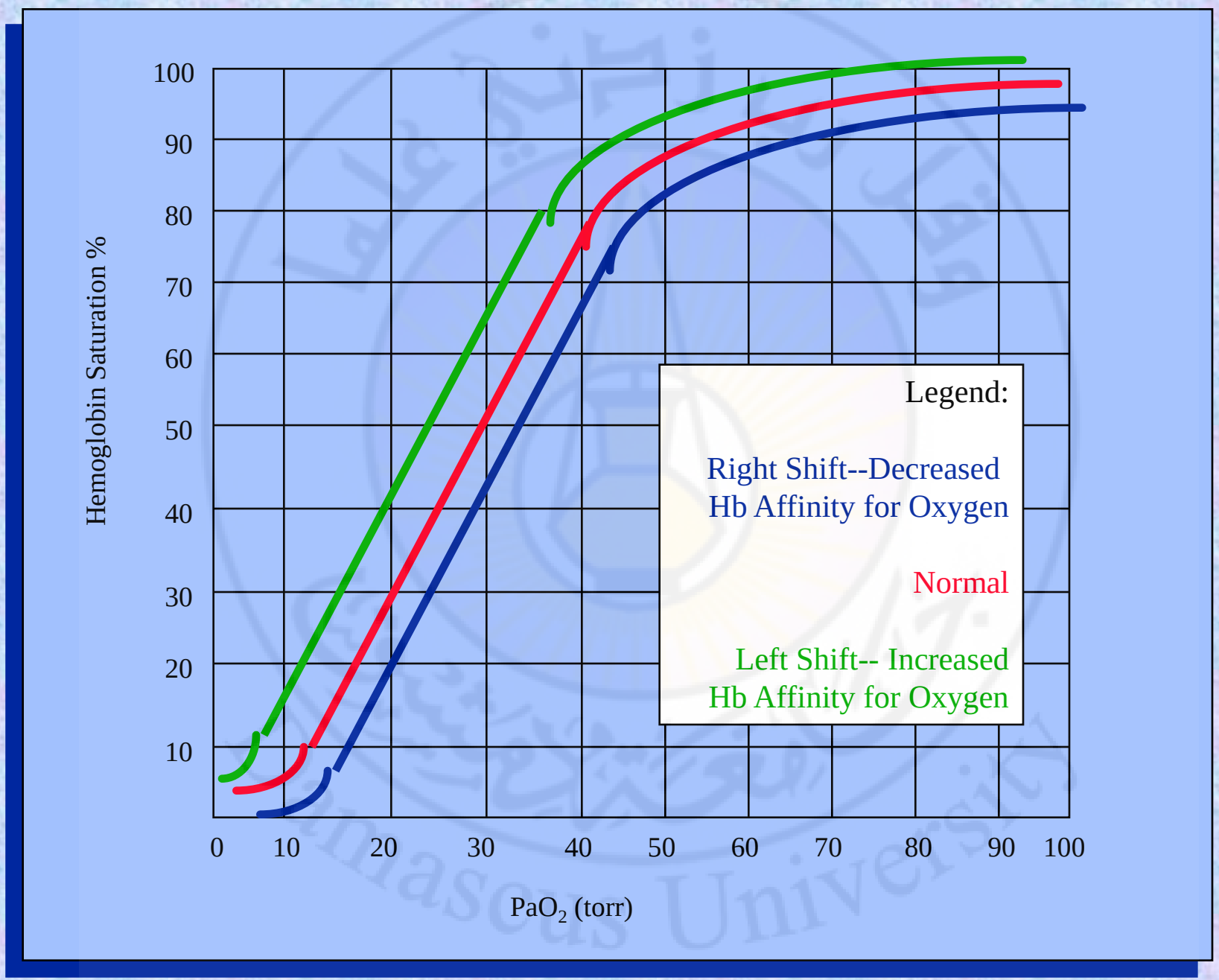
- Attaches to the terminal amine groups of the globin chains, not to heme as oxygen does
- The reaction is reversible and is rapid, similar to oxygen

Hemoglobin--The Oxygen Dissociation Curve

.Oxygen dissociates from adult Hb, the result curve is sigmoid or slightly s-shaped.

Increased Hemoglobin Affinity for Oxygen--a left shift of the curve...easy to load oxygen...difficult to unload

Decreased Hemoglobin Affinity for Oxygen-- a right shift of the curve...difficult to load...easy to unload


Hemoglobin Saturation %
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
100
PaO2 (torr)
Legend:
Right Shift--Decreased Hb Affinity for Oxygen
Normal
Left Shift-- Increased Hb Affinity for Oxygen

Hemoglobin & Myoglobin

Myoglobin

- 1 heme, 1 globin chain
- Dissociation curve--hyperbolic
- attach--1 molecule O_2
- oxygen release: < 40 torr

Hemoglobin

- 4 heme units, 1 globin chain
- Dissociation curve: sigmoid
- attach: 4 molecules O_2
- oxygen release: < 60 torr

Blood Oxygen Transport

Oxygen is carried by blood in two forms

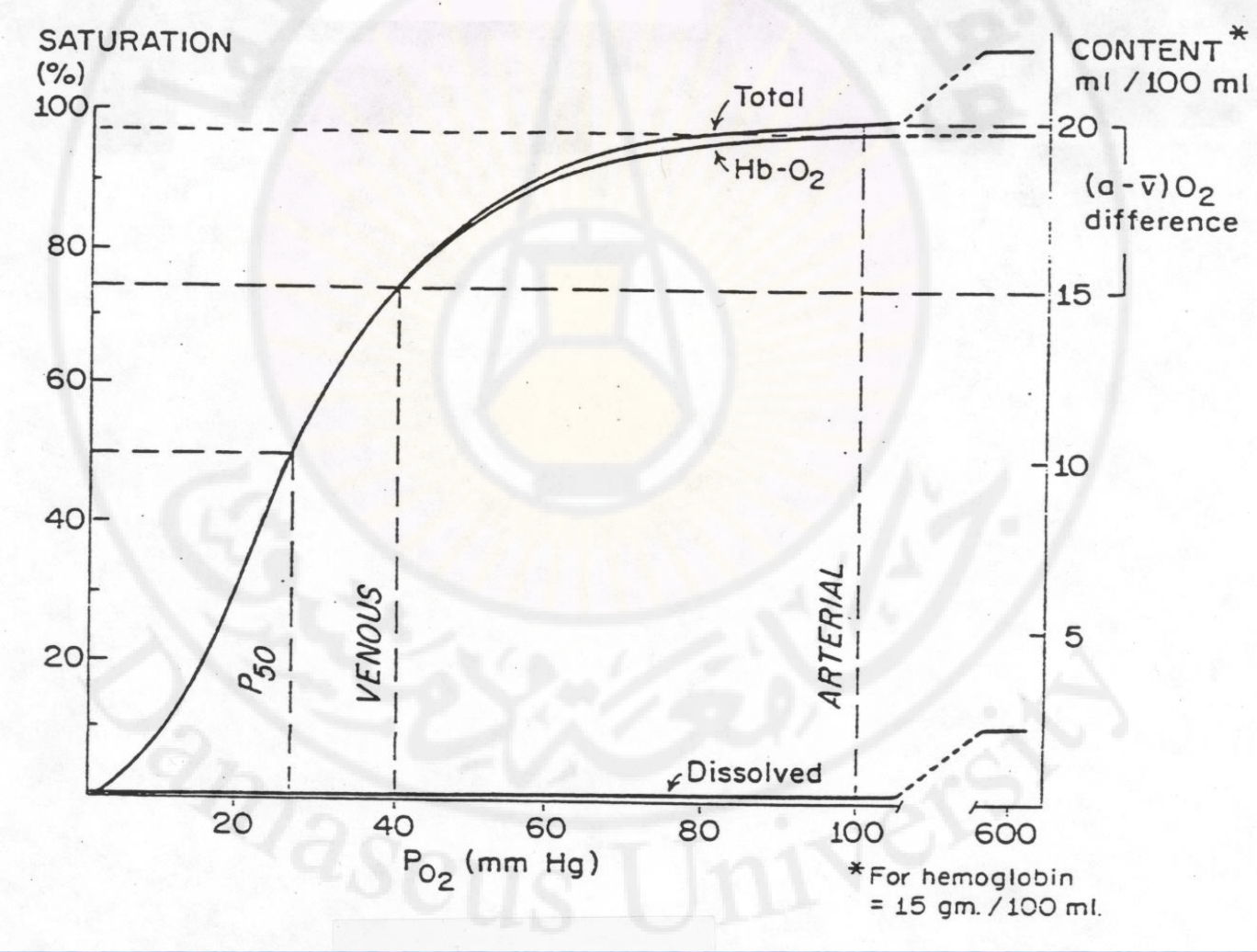
Dissolved in physical solution (both in plasma and RBCs)

- **in direct proportion to partial pressure**
- **PO_2 = partial pressure of oxygen - mmHg**

Bound to hemoglobin in red cells

- **non-linear binding with respect to PO_2**
- **saturable**

Blood Oxygen Transport



Blood Oxygen Transport

Oxygen bound to red cell hemoglobin

Special Features

non-linear relationship between PO_2 and amount bound to Hb

saturation possible

Relationship between PO_2 and HbO_2 content

hemoglobin saturation: SO_2 %

= (HbO_2 content / total HbO_2 capacity) x 100%

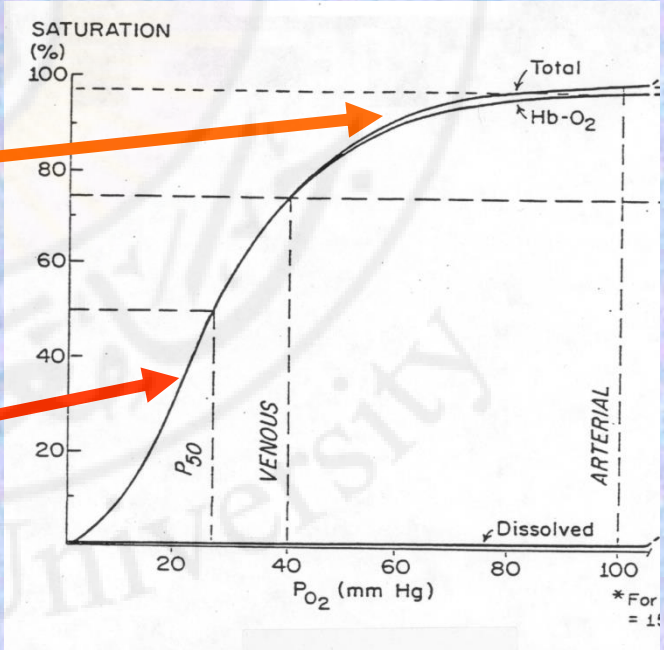
Blood Oxygen Transport

Oxygen bound to red cell hemoglobin

Hb-O_2 dissociation curve is non-linear (S-shaped) sigmoid-shaped curve has physiological advantages

in the arterial range (60-100 mmHg)
% sat changes are small

in the venous range (20-40 mmHg)
% sat changes are large

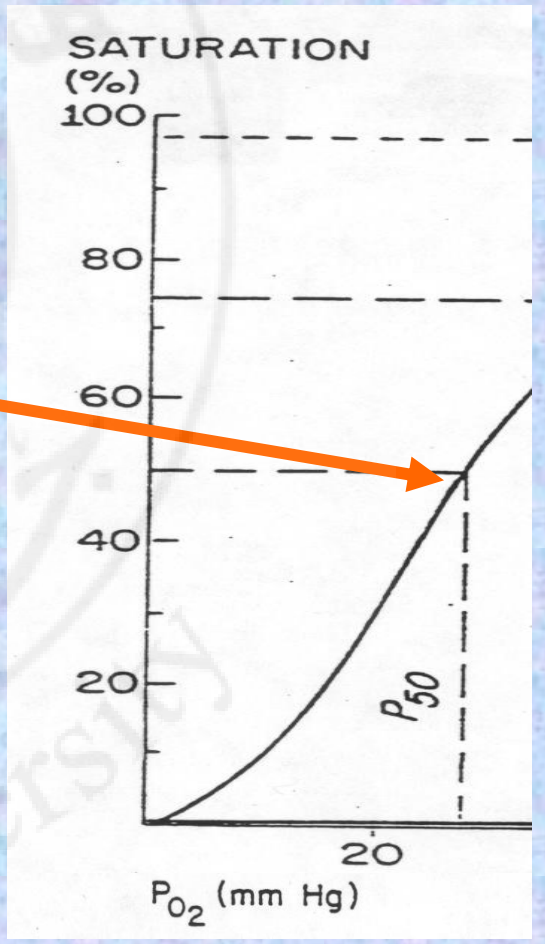


Blood Oxygen Transport

Hemoglobin affinity for oxygen

Relative affinity for O_2 is described by P_{50}

P_{50} = PO_2 at which hemoglobin is 50 % saturated



decreased P_{50} = increased O_2 affinity

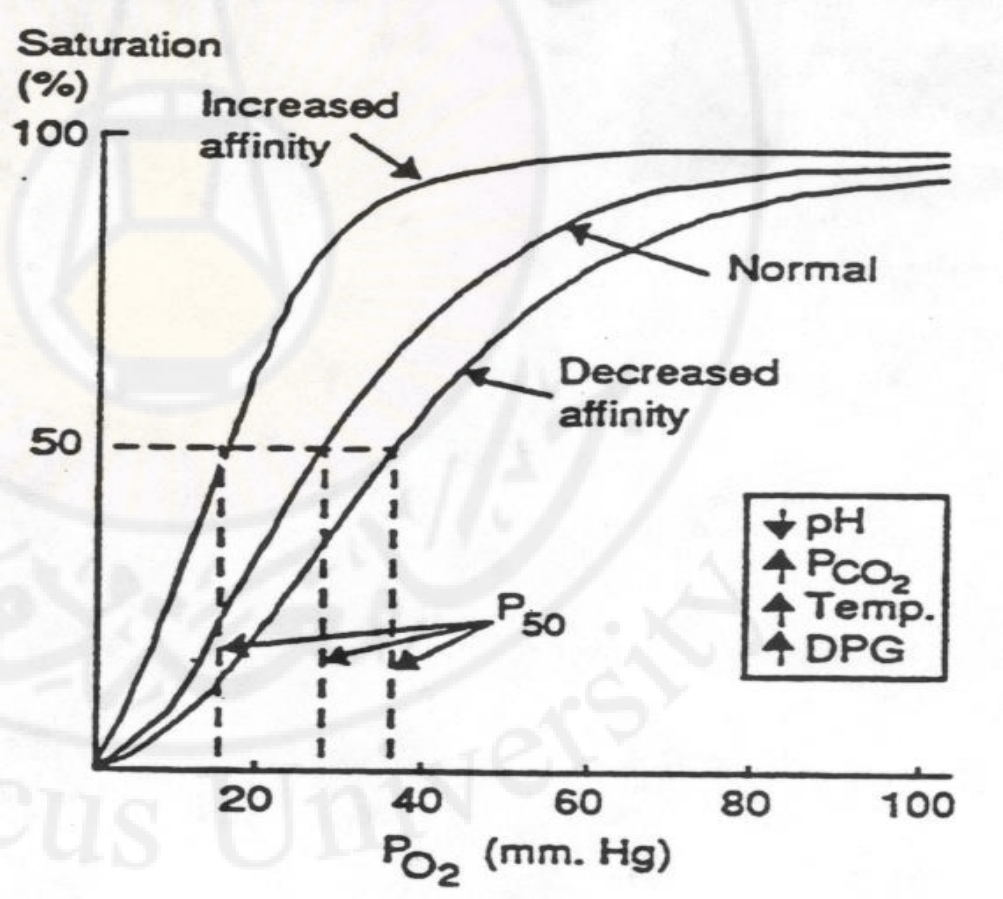
increased P_{50} = decreased O_2 affinity

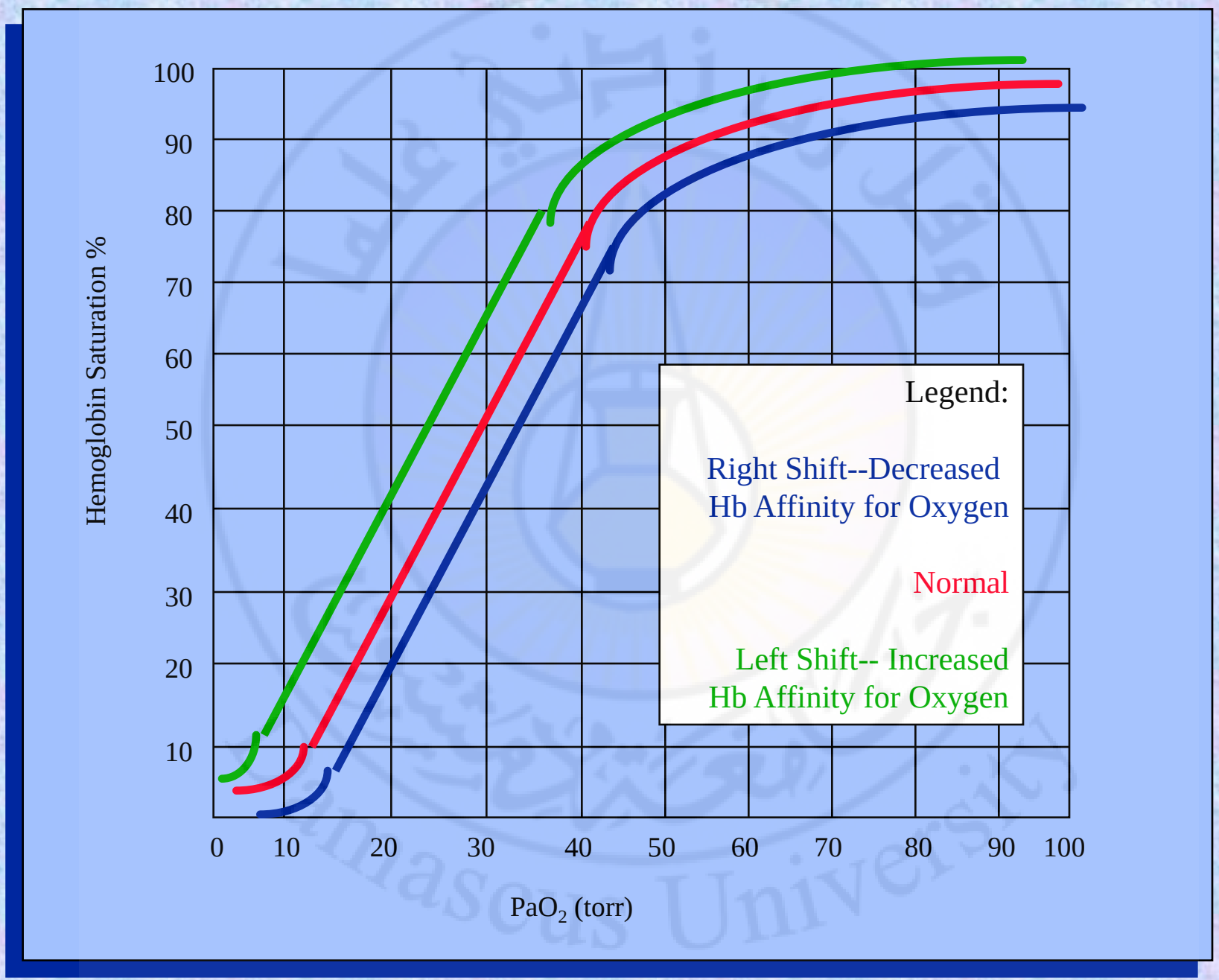
Blood Oxygen Transport

Relative affinity for O_2 is described by P_{50}

decreased P_{50}
- **increased O_2 affinity**
- **left shifted curve**

increased P_{50}
- **decreased O_2 affinity**
- **right shifted curve**




Hemoglobin Saturation %
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
100
PaO2 (torr)
Legend:
Right Shift--Decreased Hb Affinity for Oxygen
Normal
Left Shift-- Increased Hb Affinity for Oxygen

Factors Affecting Oxyhemoglobin Dissociation

- pH:
  - The more acidic the blood, the more readily hemoglobin gives up oxygen and the higher the PaO_2
  - With alkalosis, hemoglobin binds more tightly to oxygen
  - A rise or fall in pH of 0.10 causes a fall or rise in the PaO_2 of about 10%, respectively

Factors Affecting Oxyhemoglobin Dissociation

- Partial pressure of CO_2
  - CO_2 entering blood from tissues shifts the curve to the right
  - Oxygen is displaced from the hemoglobin and delivers oxygen at a higher PO_2 than normal

Factor Affecting Oxyhemoglobin Dissociation

- Temperature
  - With a rise in blood temperature, hemoglobin releases oxygen more readily, which increases the PO_2 in the plasma

Temp Effect on Change of ABG values

- Iced sample maintains values for 1-2 hours
- Uniced sample quickly invalid within 15-20minutes
- PaCO2 ↑ 3-10mmHg/hours
- pH change every 10min at 37C: 0.01 ↓
- pH change every 10min at 4 C: 0.001 ↓
- PCO2 change every 10min at 37C: 1mmHg↑
- PCO2 change every 10min at 4C; 0.1mmhg ↑
- PO2 change every 10min at 37C: 0.1mmHg ↓
- PO2 change every 10 min at 4C: 0.01mmH/g ↓

- Leucocytosis: ↓pH and PO2, and ↑PCO2
- Excessive heparin: dilution effect on results ↓PCO2, ↓HCO3
- Only 0.05 mL heparin required for 1 mL blood.

Factors Affecting Oxyhemoglobin Dissociation

- Exercise
  - With exercise, muscles release large amounts of CO_2 and acids
  - Muscle temperature can rise 3-4ºC
  - Combined, these shift the oxyhemoglobin dissociation curve to the right, which releases O_2 more readily

Factors Affecting Oxyhemoglobin Dissociation

- 2,3-Diphosphoglycerate (2,3-DPG)
  - With prolonged hypoxia over several hours, 2,3-DPG quantities increase, which shifts the dissociation curve to the right
  - If the concentration of 2,3-DPG falls, such as in banked blood or sepsis, the curve shifts left and the PaO_2 falls

Causes of O_2 Curve Shifts

- ***Left Shifts***

  ↓Hydrogen ion (Increased pH)

  ↓$PaCO_2$

  ↓Temperature

  ↓2,3-DPG

  Abnormal Hb's

- ***Right Shifts***

  ↑Hydrogen ion (Decreased pH)

  ↑$PaCO_2$

  ↑Temperature

  ↑2,3-DPG

  Abnormal Hb's

Errors: any error that normally occurs with the use of a Spectrophotometer.

Saturation O2 determines the ability of the lungs to carry O2 by measuring how much O2 is found in the RBC, how saturated it is. The most accurate results are obtained when:

- Ventilation is stabilized
- Reframe from smoking at least 4hrs.
- Collect anaerobically
- Mix properly with anticoagulant
- Analyze immediately

- Errors: Protein build-up, debris, change in temperature.
- Sample handling: Do not expose to room air and an increase in WBC can increase metabolic activity and decrease PO2.