CLINICAL LABORATORY TESTS AND INTERPRETATION

- ✓ Laboratory tests are per formed for multiple purposes, including discovering a disease, confirming or differentiating a diagnosis, stage or classifying a disease, and monitoring effectiveness of therapy.

LABORATORY TESTS ARE CLASSIFIED AS SCREENING OR DIAGNOSTIC

- ✓ Screening tests are used in patients with no signs or symptoms of a disease (e.g. serum cholesterol for assessing cardiovascular disease risk).
- ✓ Diagnostic tests are done in patients with signs and symptoms of disease or with an abnormal screening test.

MONITORING DRUG THERAPY

- ➢ Laboratory test results are used to investigate potential problems with a patient's anatomy or physiology. Pharmacists usually monitor laboratory tests to
  - ✓ **Assess the therapeutic and adverse effects of a drug**
    E.g. monitoring the serum uric acid level after allopurinol is administered, checking for increased liver function test values after administration of isoniazid
  - ✓ **Determine the proper drug dose**
    E.g. assessment of the serum creatinine or creatinine clearance value before use of a renally excreted drug
  - ✓ **Assess the need for additional oral ternate drug therapy**
    E.g. assessment of white blood cell count after an antibiotic is administered
  - ✓ **Prevent test misinterpretation resulting from drug interference**
    E.g. determination of a false-positive result for a urine glucose test after cephalosporin administration

DEFINITIONS

- ✓ Laboratory test abnormalities are values outside of the normal range for a population.
- ✓ True abnormalities are reproducible, and they are usually associated with signs and symptoms consistent with a disease state.
- ✓ Laboratory test abnormalities are not in themselves diseases, but increases or decreases in values are associated with various diseases.
- ✓ Abnormal values may be caused by drugs, including test interference, side effects, or therapeutic effects.
- ✓ Diseases associated with laboratory tests discussed include, but are not limited to, renal and liver dysfunction, diabetes mellitus, hyperuricemia/gout, myocardial infarction (MI), pancreatitis, malnutrition, malignancies, inflammatory diseases, anemia, blood dyscrasias, infections, and bleeding/clotting disorders.

GENERAL PRINCIPLES

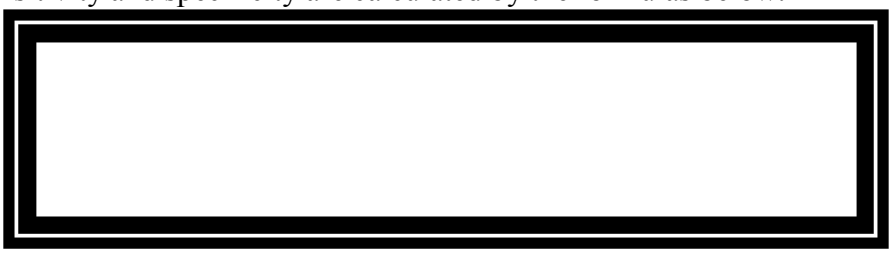
➢ SPECIMEN COLLECTION

- ✓ Blood and urine are the most common body fluids used for analytic purposes.
- ✓ Phlebotomists should be familiar with the test being performed, know the appropriate container for collection, and how the collection procedure may affect the results.
- ✓ Verification that computer-printed labels match requisitions at the nurses' station and the patient's wristband is essential.
- ✓ Specimens should never be drawn without first identifying the patient.
- ✓ Proper techniques help avoid hemolysis and bacterial contamination.
- ✓ Particular attention should be given to tests where timing is important (e.g., in relation to ingestion of food or drugs).

- ✓ Special precautions are necessary for blood cultures and specimens obtained from indwelling catheters, especially central venous access catheters.
- ✓ Urine collection must also follow a very strict procedure to insure valid results.
- ✓ A freshly obtained urine specimen is crucial when testing for bilirubin, red blood cells, and white blood cells, as these undergo decomposition if left standing at room temperature.
- ✓ Nonpreserved urine specimens are also predisposed to microbial overgrowth at room temperature.
- ✓ A good rule for all specimens is to deliver them to the laboratory within 1 hour of collection or refrigerate them.

➢ METHODS OF ANALYSIS

- ✓ Several methods are available in the clinical laboratory to assay desired substances in body fluids.
- ✓ Two commonly used techniques are chromatography and immunoassays.
- ✓ The type of compound to be measured determines which assay is used.
- ✓ Certain methods are used for qualitative measurements and others for quantitative measurements.
- ✓ Qualitative measurements only detect that the substance is present and not the quantity of the substance.
- ✓ A urine toxicology screen is an example of a qualitative test in which knowing if a substance is present is usually more important than knowing its amount.
- ✓ **Sensitivity** and **Specificity** are important aspects of a clinical laboratory test.
  - **Sensitivity is commonly defined as the lowest detectable value of a substance** and
  - **Specificity as the ability to differentiate the substance of interest in the presence of other interfering substances**.
- ✓ Sensitivity and specificity are calculated by the formulas below.



- ✓ Ideally, sensitivity and specificity should each be at least 95%.
- ✓ Most clinical laboratories have strict performance criteria set for their assay techniques.
- ✓ These criteria vary widely among institutions and can greatly affect the interpretation of individual patient results.
- ✓ Most clinical laboratories use the most accurate method with the best automation at a reasonable cost.
- ✓ For each individual clinical laboratory, particular attention to accuracy, precision, and quality control are essential for reliable reproducible results.

- **REFERENCE VALUES**
  - ✓ Normal ranges are provided as a guideline, but individual laboratory results may vary considerably.
  - ✓ Values outside of the quoted normal range may be considered abnormal but not clinically important, whereas certain values in the normal range with a particular disease state are actually abnormal (e.g., normal hemoglobin in a patient with chronic obstructive airway disease).
  - ✓ Laboratories may evaluate substances with different assays that are more or less precise.
  - ✓ Certain tests are time dependent and the time the sample is drawn is crucial in determining if the patient sample is truly within the reference range.
  - ✓ This is especially true for most serum drug concentrations.
- **DRUG INTERFERENCE**
  - ✓ Medications affect laboratory test results in two major ways.
  - ✓ Due to a drug's intrinsic pharmacokinetic, pharmacologic, or toxicologic properties, it may alter the formation, regulation, release, or elimination of the substance being tested.
    - E.g., hydrochlorothiazide blocks the tubular secretion of uric acid, exogenous insulin affects serum glucose, or toxic acetaminophen concentration affects serum transaminases.
  - ✓ Medications may also directly interfere with the assay used to detect the substance
    - E.g., ascorbic acid causes false-negative results with urine glucose by the glucose oxidase method.
  - ✓ Each laboratory test discussed in this chapter will include a brief section on common medications that affect the test results.

SYSTEM INTERNATIONAL D'UNITS

- ✓ The basis for converting all measurements of body fluid substances to a molar concentration unit is that substances in the body interact on a molar basis.
- ✓ It also standardizes units internationally.
- ✓ Certain societies including the American College of Physicians and their official journal (*Annals of Internal Medicine*) have adopted the System International D'Units (SI units) as their preferred reference standard.
- ✓ Other journals still accept both sets of units.
- ✓ Reference laboratories in most hospitals and most clinicians in the United States have not accepted this change willingly and still use the old conventional reference standards.
- ✓ To convert from conventional units to SI units, multiply the results in conventional units by the conversion factor.

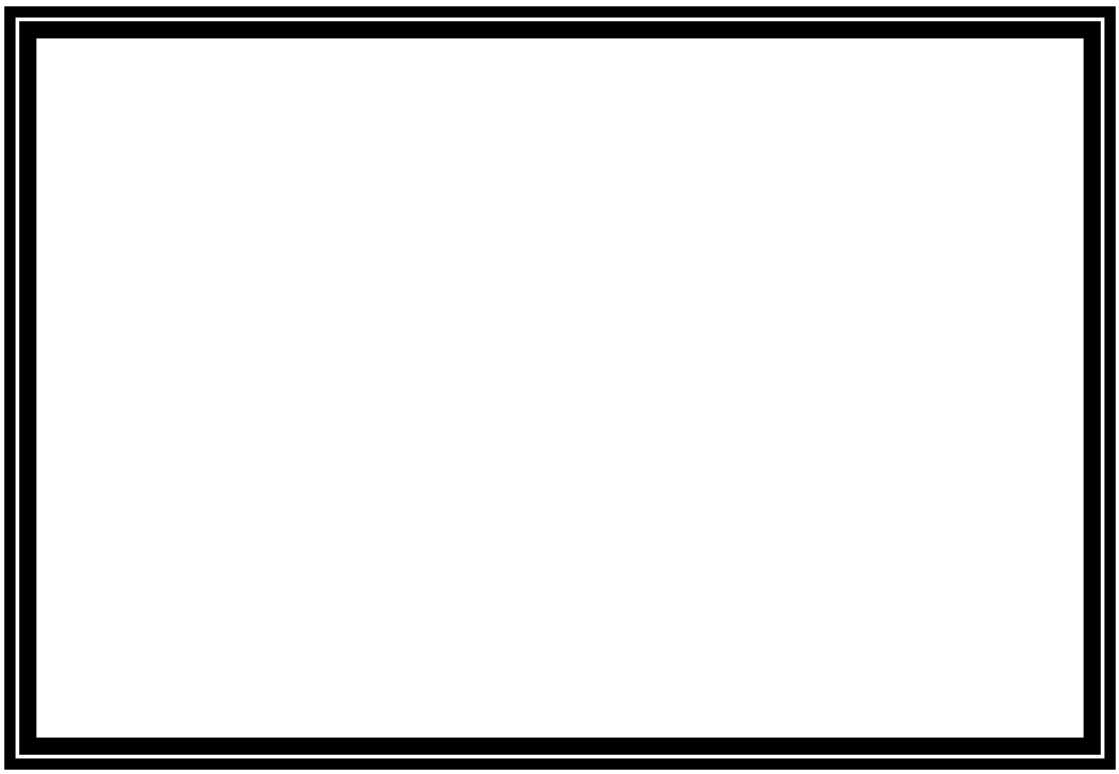
VARIOUS LABORATORY TESTS FOR DIFFERENT DISORDERS	
DISORDER	**TESTS**
Renal disorder	Serum Creatinine
	Blood Urea Nitrogen
	Uric Acid
Diabetes Mellitus	Glucose
	Oral Glucose Tolerance Test (OGTT)
	Insulin
	C-peptide
	Glycosylated hemoglobin
Cardiovascular disorders	Creatine kinase
	Lactate dehydrogenase
	Troponin
Liver disorder	Transaminase 1. Aspartate transaminase (SGOT) 2. Alanine Aminotransferase (SGPT)
	γ-glutamyl transpeptidase
	Phosphatase
	Bilirubin
	Albumin
General	Protein
	Water/Electrolyte balance
	Haematological data 1. Total and differential count, Blood count 2. Haemoglobin 3. Hematocrit 4. Reticulocytes 5. Erythrocyte Sedimentation Rate (ESR) 6. Leucocytes 7. Coagulation tests

Biochemical data: typical normal adult reference values measured in serum	
Laboratory test	**Reference range**
Urea & Electrolyes	
Sodium	135-145mmol/L
Potassium	3.4-5.0 mmol/L
Calcium (Total)	2.12-2.60 mmol/L
Calcium (Ionized)	1.19-1.37 mmol/L
Phosphate	0.80-1.44 mmol/L
Creatinine	75-155 μmol/L
Urea	3.1-7.9 mmol/L
Glucose	
Fasting	3.3-6.0 mmol/L
Non-fasting	<11.1 mmol/L
Glycated haemoglobin	<5.5%
Liver Function	

Albumin	34-50 g/L
Bilirubin (total)	<19 µmol/L
Bilirubin (Conjugated)	<4 µmol/L
Enzymes	
Alanine transaminase	<45 U/L
Aspartate transaminase	<35 U/L
Alkaline phosphatase	35-120 U/L
γ-glutamyl transpeptidase	<70 U/L
Ammonia Men Female	 15-50 µmol/L 10-40 µmol/L
Amylase	<100 U/L
Cardiac markers	
Cardiac troponin (cTnT)	<0.1 µg/L
Other tests	
Osmolality	282-295 mosmol/kg
Uric acid	0.15-0.47 mmol/L
Parathyroid hormone (adult with normal calcium)	10-65 ng/L
25-Hydroxyvitamin D	10-75 nmol/L

TESTS FOR RENAL DISORDERS

- **SERUM CREATININE (SCr)**
  - ✓ **Men = 0.6 to 1.2 mg/dL, 0.1 mg/dL lower for women**
    SI units: males = 50 to 110 µmol/L, women = 10 µmol/L lower,
    Conversion factor (CF) = 88.40
  - ✓ Serum creatinine (SCr) is a peptide formed as a waste product of creatine, an important energy storage substance in muscle metabolism.
  - ✓ Creatinine is an anhydride of creatine and is not used in the body.
  - ✓ Formation of creatinine is relatively constant with about 1.6% to 1.7% of creatine transformed to creatinine each 24 hours.
  - ✓ This in turn depends on the total muscle content of creatine and creatine phosphate.
  - ✓ **Factors that affect creatine levels**, such as diet, fever, and muscle damage, do not readily influence SCr level.
  - ✓ The serum concentration of creatinine is also relatively constant, and urinary excretion is the result of glomerular filtration and proximal tubular secretion.
  - ✓ The SCr level is a more reliable indicator of renal function than the blood urea nitrogen (BUN).



- ✓ SCr concentration increases in the presence of impaired renal function.
- ✓ Since up to 50% of renal function is lost before the SCr level becomes abnormally elevated, it is not a good indicator of early renal dysfunction.
- ✓ Several methods exist for the rapid estimation of creatinine clearance based on the patient's age, ideal body weight, and SCr level.
- ✓ A steady-state SCr level is necessary for an accurate estimation.
- ✓ **Certain methods are more inaccurate in the elderly and in patients with decreased muscle mass.**
- ✓ **Drugs that may cause an increased SCr level due to interference with tubular secretion** of creatinine are cephalosporins, cimetidine, salicylates, and trimethoprim.
- ✓ **Drugs** such as acetohexamide, ascorbic acid, flucytosine, levodopa, lidocaine, methyldopa, p-aminohippurate, and phenolsulfonphthalein may cause **increases by interference with the analytical methodology of the SCr determination.**

- ➢ **BLOOD UREA NITROGEN (BUN)**
  - ✓ **Normal Range: 8 to 18 mg/dL**
  - ✓ **SI units = 3.0 to 6.5 mmol/L,**
  - ✓ **CF = 0.357**
  - ✓ Urea is the predominant product of protein and amino acid catabolism and is made in the liver through the urea cycle.
  - ✓ It is the main **Nonprotein nitrogen (NPN)** constituent in the blood.
  - ✓ Other NPN substances include amino acids, uric acid, creatinine, and ammonia.
  - ✓ Total NPN determinations are no longer used clinically.
  - ✓ Urea is distributed to all intra- and extracellular fluids and is freely diffusible across most cell membranes.

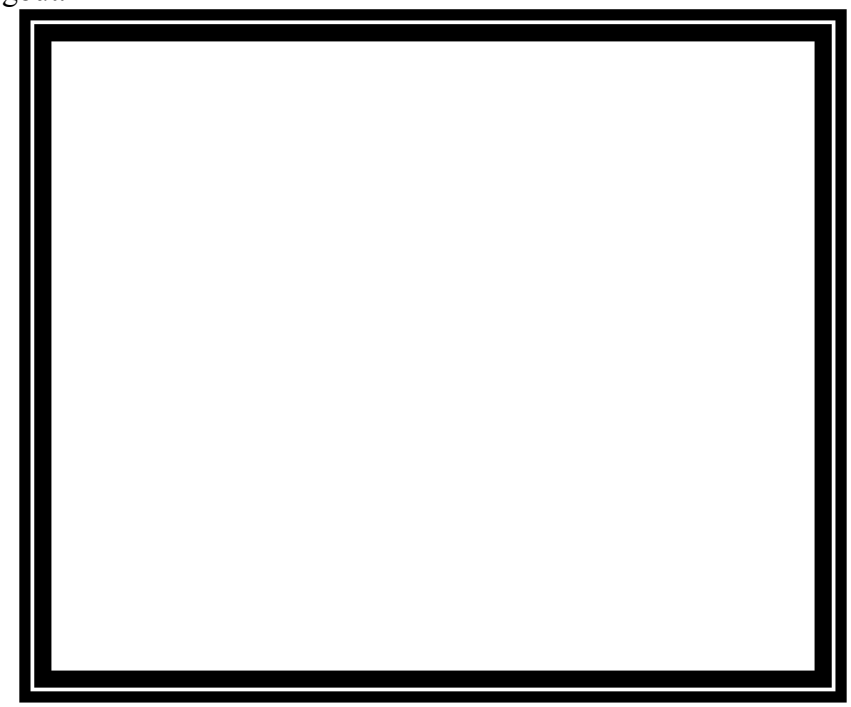
- ✓ Urea is excreted mostly by the kidneys, with only small amounts excreted in sweat and in the intestines.
- ✓ When there is a **large increase of nonprotein compounds**, such as urea in the blood, the condition of **azotemia** is present.
- ✓ **Azotemia** can be categorized as prerenal, renal, and postrenal.
    - **Prerenal azotemia**
        - ✓ Prerenal azotemia is the result of inadequate perfusion of the kidneys with otherwise normal renal function.
        - ✓ Causes of prerenal azotemia include dehydration, decreased blood volume, shock, and heart failure.
    - **Renal azotemia**
        - ✓ Renal azotemia refers to decreased glomerular filtration because of acute or chronic renal disease including glomerulonephritis, interstitial nephritis, and tubular necrosis.
    - **Postrenal azotemia**
    - ✓ Postrenal azotemia is most commonly the result of urinary tract obstruction.
- ✓ **The extreme form of azotemia, known as Uremia**, is a constellation of symptoms resulting from severe elevations in BUN (100 to 200 mg/dL) and other substances not adequately cleared by the kidney.
- ✓ **Uremic symptoms** include acidosis, water and electrolyte imbalance, nausea, vomiting, and neuropsychiatric changes including stupor or deep coma.
- ✓ Agents that are noted for causing acute interstitial nephritis usually accompanied with an allergic reaction include allopurinol, cephalosporins, penicillins, nonsteroidal antiinflammatory agents, and phenytoin.
- ✓ Common agents that may cause **acute tubular necrosis** include aminoglycosides, amphotericin B, angiotensin converting enzyme (ACE) inhibitors, carboplatin, cisplatin, cyclosporine, diuretics, gold salts, ifosfamide, intravenous contrast media, lithium, pentamidine, tacrolimus, tetracyclines, and vancomycin.
- ✓ Agents that may increase the **risk of Urolithiasis** include allopurinol, calcium salts, carbonic anhydrase inhibitors, indinavir, sulfonamides, triamterene, and zonisamide.
- ✓ Nephrolithiasis occurs in 1% to 3% with lamivudine-zidovudine combination, but may increase to as high as 4 to 12% with the addition of indinavir.
- ✓ BUN can be used as an estimate of renal function.
- ✓ As with creatinine levels, a clinically important elevation will not be observed until glomerular filtration is decreased by at least 50%.
- ✓ **A decreased BUN is usually not clinically significant; however, a few conditions may cause a significant decrease.**
- ✓ These include **poor nutrition, high fluid intake, and severe liver disease** where urea synthesis is decreased.
- ✓ **Drugs that may increase BUN** by methodologic interference are chloral hydrate, ammonium salts, acetohexamide, and sulfonylureas, while those that **decrease** it include chloramphenicol and streptomycin.
- ✓ BUN and SCr concentrations may be evaluated simultaneously.
- ✓ To yield more information than either alone, the BUN is divided by the SCr.

- ✓ This is termed the BUN to creatinine ratio; the normal ratio ranges from 10 to 20:1.
- ✓ Table indicates clinical causes of elevated BUN and SCr with increased or normal BUN:creatinine ratios.
- ✓ Specific causes of prerenal, renal, and postrenal azotemia can be further delineated using the BUN to SCr ratio, fractional excretion of sodium (FENa), free water clearance, and urinalysis.

BUN:CREATININE RATIO	
RATIO	**CONDITION**
≥20:1	Prerenal azotemia (e.g., heart failure, dehydration) Postrenal azotemia (e.g., obstructive uropathy) Impaired renal function plus excess protein intake or tissue breakdown Drugs such as tetracycline and glucocorticosteroids
<20:1	Prerenal azotemia in hepatic cirrhosis Renal dialysis Renal failure in muscular patients Decreased urea production (e.g., low protein intake, severe diarrhea or vomiting)

- **URIC ACID**
  - ✓ **Normal Range: 2.0 to 7.0 mg/dL**
  - ✓ **SI units = 120 to 420 µmol/L,**
  - ✓ **CF = 59.48**
  - ✓ Uric acid is the end product of purine metabolism.
  - ✓ The major rate-limiting step in the synthesis of uric acid is the intracellular concentration of 5-phosphoribosyl-1-pyrophosphate (PRPP).
  - ✓ Uric acid serves no biologic function.
  - ✓ **Approximately two thirds of uric acid is excreted by the kidneys and one-third through the gastrointestinal tract.**
  - ✓ Assuming that the uric acid filtered through the glomerulus equates to 100%, 98% to 100% of this glomerular filtrate is reabsorbed in the proximal portion of the proximal convoluted tubule.
  - ✓ Fifty percent of the original amount is secreted into the distal portion of the proximal convoluted tubule, but 40% to 44% is subsequently reabsorbed, and 6% to 12% of the original glomerular filtrate eventually excreted.
  - ✓ **HYPERURICEMIA**
    - It is due to an overproduction of uric acid (increased destruction of nucleoproteins, high protein diet, or inborn enzymatic defects) or an under excretion (renal defect).
    - Since the serum is saturated with urate at a concentration of 7 mg per dL (420 µmol/L), as serum urate concentrations exceed this saturation point, monosodium urate crystals deposit in and around the joints and cartilage and in the kidneys, sometimes eliciting the disease known as **Gout**.
    - As urinary pH is increased, the solubility of uric acid is increased; decreasing urinary pH may precipitate urate nephrolithiasis in patients with high urine uric acid concentrations.
    - Asymptomatic hyperuricemia is classified as an elevated serum uric acid without symptoms of acute gouty arthritis.

- With increasing uric acid levels, there is an increased risk of developing acute gout.



- ✓ Agents that have a cytotoxic effect causing an **increased** turnover of nucleic acids may increase uric acid concentrations.
  - E.g., antimetabolite and chemotherapeutic agents used to treat neoplastic diseases, such as methotrexate, busulfan, vincristine, prednisone, and azathioprine.
- ✓ Agents that **decrease the renal clearance or block tubular secretion** may cause a substantial elevation in serum urate concentrations
  E.g., thiazide and loop diuretics, pyrazinamide, and ethambutol
- ✓ Some agents, such as salicylates, probenecid, and sulfinpyrazone, inhibit the tubular secretion of urate at low doses, but at high doses also inhibit tubular reabsorption, inducing a marked uricosuric effect.
- ✓ Tacrolimus and cyclosporine may cause hyperuricemia in more than 3% of patients through an unknown mechanism.
- ✓ **Allopurinol therapeutically lowers serum uric acid** by inhibiting xanthine oxidase (enzyme that converts xanthine to uric acid in purine metabolism), while uricosuric agents, such as probenecid, are also used therapeutically to lower serum uric acid by blocking proximal tubular reabsorption.
- ✓ Ascorbic acid, caffeine, glucose, levodopa, methyldopa, and theophylline may interfere with the analytical technique and cause false high results.

TESTS FOR LIVER DISORDERS

- **ASPARTATE AMINOTRANSFERASE(AST)**
  - ✓ **Normal Range: 0 to 35 IU/L**
  - ✓ **SI units = 0 to 0.58 µkat/L,**
  - ✓ **CF = 0.01667**

- ✓ Aspartate aminotransferase (AST), formerly known as **Serum glutamic oxaloacetic transaminase (SGOT)** is one of several transaminases responsible for transfer of amino groups in gluconeogenesis.
- ✓ AST is responsible for transferring an amino group from aspartate to α, β-glutaric acid forming glutamate and oxaloacetate.
- ✓ The highest concentrations of AST are located in cardiac and hepatic tissues.
- ✓ AST usually appears within 6 to 8 hours after myocardial injury, peaking in 24 hours, and returning to baseline in 4 to 6 days.
- ✓ AST rises in virtually all types of hepatic diseases.
- ✓ Its peak concentration and ratio to other enzymes reflect the type of hepatic damage.
- ✓ **Several medications** may cause elevations in AST levels by direct hepatocellular damage or cholestasis.
- ✓ Cholinergic drugs and opioids cause elevation of transaminases due to spasm of the sphincter of Oddi.
- ✓ Several agents (commonly isoniazid and rifampin) may cause transient elevations in transaminase levels.
- ✓ Initially, **dye-binding techniques** were used to assay for transaminases, which accounted for several drug interferences including isoniazid, but with newer **ultraviolet techniques**, there is very little interaction with the assay.

➢ **ALANINE AMINOTRANSFERASE**

- ✓ **Normal Range: 0 to 35 IU/L**
- ✓ **SI units = 0 to 0.58 µkat/L,**
- ✓ **CF = 0.01667**
- ✓ Alanine aminotransferase (ALT), formerly known as **Serum glutamate pyruvate transaminase (SGPT)**, transfers an amino group from alanine to α-ketoglutarate forming glutamate and pyruvate.
- ✓ ALT is very specific for hepatic tissue and is almost always absent in acute MI.
- ✓ It is much more sensitive to hepatic damage, and levels rise faster and higher than those of AST in most types of hepatocellular damage.

➢ **γ-Glutamyl Transferase (GGT)**

- ✓ **Normal Vaule: Men: 9-69 IU/L, SI units: 0.15-1.15 µkat/L**
  Women: 3-33 IU/L, SI units: 0.05-0.55 µkat/L
- ✓ **CF = 0.01667**
- ✓ γ-Glutamyl transferase (GGT) catalyzes the transfer of a γ-glutamyl group from one peptide to another.
- ✓ The kidneys, liver, and pancreas contain large quantities of GGT.
- ✓ Several isoenzymes of GGT have been isolated, but to date, no clinical use for them has been found.
- ✓ The elevation of GGT parallels that of alkaline phosphatase and raises higher in cholestatic and obstructive diseases than in acute hepatocellular diseases.
- ✓ **It is always elevated in acute pancreatitis, and its rise is faster and greater than that of alkaline phosphatase in obstructive jaundice.**
- ✓ GGT is the **most sensitive biochemical indicator of alcohol exposure**, since elevation exceeds that of other commonly monitored liver enzymes.
- ✓ In alcoholic hepatitis, GGT is usually the enzyme that rises fastest and has the highest peaks.

- ✓ Agents such as phenytoin and phenobarbital that induce the cytochrome P450 enzyme system may cause elevations in GGT.

➢ **PHOSPHATASES**

- ✓ Phosphatases are primarily responsible for catalyzing cleavage of monophosphate esters and may be A**cid** or **Alkaline**.

- **ACID PHOSPHATASES**
  - ✓ **Normal Range: 0 to 5.5 IU/L**
  - ✓ **SI units = 0 to 90 nkat/L,**
  - ✓ **CF = 16.67**
  - ✓ It is primarily found in prostate, erythrocytes, and platelets. Approximately 60% to 75% of men with prostate cancer have elevated acid phosphatase concentrations.
  - ✓ Acid phosphatases have optimal enzymatic activity at a pH of 5
- **ALKALINE PHOSPHATASE (ALP)**,
  - ✓ Normal Range: 30 to 120 IU/L
  - ✓ SI units = 0.5–2.0 µkat/L,
  - ✓ CF = 0.01667
  - ✓ Alkaline phosphatases have an optimal enzymatic activity at a pH of 9.17
  - ✓ It is found in most tissues but is derived predominantly from hepatic, osseous, and intestinal cells.
  - ✓ The placenta produces high concentrations of ALP in the third trimester because of high fetal osteoblastic activity.
  - ✓ Children in the active growth phase produce ALP at two to five times adult rates.
  - ✓ The osseous and hepatic isoenzymes of ALP can be readily identified in electrophoretic patterns of serum.
  - ✓ **ALP is elevated** in most disorders of bone involving osteoblastic activity.
  - ✓ Metastatic disease to bone may cause substantial elevations in ALP levels.
  - ✓ ALP is also elevated in acute fractures, hyperparathyroidism, renal bone disease, osteogenic sarcoma, and Paget disease.
  - ✓ ALP is secreted into bile, and an elevation may be the first clue to intra- or extrahepatic cholestasis.
  - ✓ The diagnosis of intra- or extrahepatic disease cannot be determined by the peak height of the serum ALP concentration.
  - ✓ When biliary obstruction is complete, ALP serum concentrations are almost always three to eight times normal; whereas, with incomplete obstruction, concentrations are only two to three times normal.

➢ **AMYLASE**

- ✓ **Normal Range: 0 to 130 IU/L**
- ✓ **SI units = 0 to 2.17 µkat/L,**
- ✓ **CF = 0.01667**
- ✓ Amylase enzymatically cleaves large polysaccharides into oligo- and monosaccharides in the gastrointestinal tract through salivary and pancreatic secretions.
- ✓ Amylase is present as α-, β-, and γ-amylase, but only **α-amylase is of clinical interest**.

- ✓ Amylase is present in a variety of human tissues including the pancreas, salivary glands, muscle, adipose tissue, kidney, brain, lung, fallopian tubes, intestine, spleen, and heart.
- ✓ Normal serum amylase is composed of approximately 40% pancreatic isoenzyme (P-type isoamylase) and 60% salivary isoenzyme (S-type isoamylase).
- ✓ This percentage changes with age so that after the age of 70, P-type isoamylase comprises only 20% of total serum amylase.
- ✓ Serum amylase concentrations rise within 6 to 48 hours after the onset of acute pancreatitis in >80% of patients.
- ✓ Values over four times the upper limit of normal are highly suggestive of the diagnosis.
- ✓ This is a sensitive measure of acute pancreatitis, but it is not highly specific, since several other conditions may present with acute abdominal pain and elevated serum amylase levels, including biliary colic, perforated peptic ulcer, and mesenteric infarction.
- ✓ In acute pancreatitis, the urinary clearance of amylase is increased, possibly because of altered renal tubular function.
- ✓ A urinary amylase to creatinine ratio >0.04 suggests acute pancreatitis; however, this method is unreliable since elevated ratios may also be seen with other conditions, such as burns, renal insufficiency, and ketoacidosis.
- ✓ The usefulness of isoenzyme separation is limited since other intestinal sources also account for P-type isoamylase.
- ✓ Patients with acute alcoholic pancreatitis have normal serum amylase levels approximately 30% of the time.
- ✓ Parotitis and mumps cause elevations of S-type isoamylase.
- ✓ Chronic alcohol consumption may also increase S-type isoamylase.
- ✓ This is an important consideration because alcohol is the most common cause of acute pancreatitis.
- ✓ Macroamylase is a circulating complex of normal amylase bound to either IgG or IgA.
- ✓ Analysis of macroamylase reveals variable amounts of P-type and S-type isoamylase.
- ✓ Macroamylasemia is an acquired benign condition that must be separated from other causes of hyperamylasemia.
- ✓ **Medications** that cause spasm of the sphincter of Oddi, such as narcotics and cholinergic agents, may cause elevations in serum amylase.
- ✓ Agents definitely associated with causing pancreatitis include 5-aminosalicylic acid, asparaginase, azathioprine, didanosine, estrogens, furosemide, 6-mercaptopurine, methyldopa, metronidazole, pentamidine, sulfonamides, sulindac, tetracycline, thiazide diuretics, and valproic acid.
- ✓ Certain pancreatic enzyme preparations contain amylase and lipase that may elevate serum amylase and lipase values.

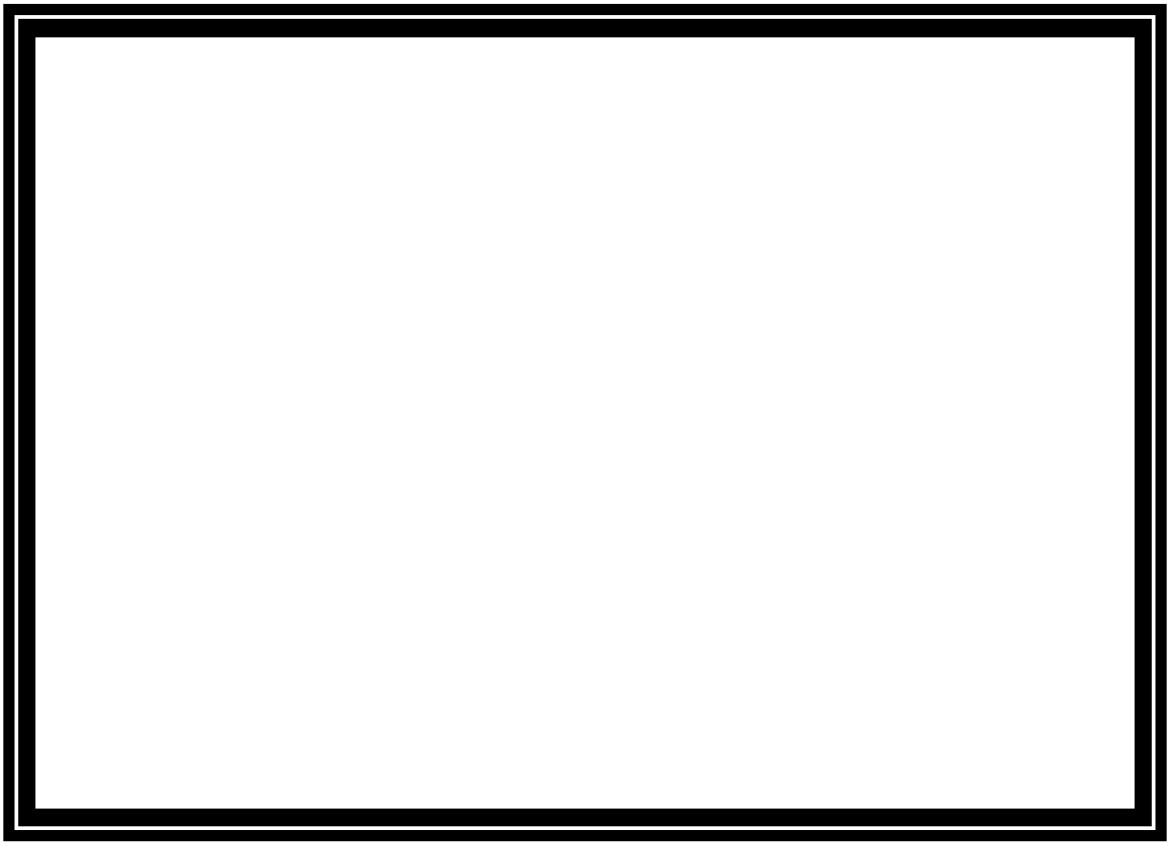
➢ **BILIRUBIN**

- ✓ **Normal Range: Total 0.1 to 1.0 mg/dL,**
  Direct 0 to 0.2 mg/dL
- ✓ **SI units = Total 2 to 18 µmol/L,**
  Direct 0 to 4 µmol/L,
- ✓ **CF = 17.10**

- ✓ Bilirubin is a metabolic byproduct of the lysis of heme by the reticuloendothelial system (RES).
- ✓ This production is predominantly from senescent erythrocytes (>85%).
- ✓ The RES catabolizes heme into free iron, globin, and biliverdin, which is rapidly converted to bilirubin.
- ✓ Unconjugated bilirubin is poorly soluble in serum; therefore, it is transported to the liver bound to albumin. This unconjugated form is also known as **Indirect or Prehepatic bilirubin**.
- ✓ In the liver, glucuronyl transferase conjugates bilirubin with two molecules of glucuronic acid forming bilirubin diglucuronide. This form of bilirubin is highly soluble in serum and is known as **Direct or Hepatic bilirubin**.
- ✓ **Direct bilirubin** is transported through the biliary tree with bile acids and stored in the gall bladder as bile.
- ✓ When bile is released during the digestive process, intestinal bacteria convert bilirubin into several compounds, collectively referred to as urobilinogen.
- ✓ An estimated 10% of urobilinogen is reabsorbed from the intestine into the bloodstream and resecreted by the liver.
- ✓ Small amounts of urobilinogen are then excreted in the urine, accounting for the urine's straw color.
- ✓ However, most urobilinogen is converted to stercobilin and eliminated in the feces, accounting for their characteristic dark brown color.
- ✓ The presence of bilirubin in the urine implies direct bilirubin, since indirect bilirubin is bound to serum albumin, which should normally not be filtered by the glomerulus.
- ✓ **δ-bilirubin** is a protein-bound pigment that may falsely raise total bilirubin measurements during hepatobiliary disease.
- ✓ Agents that may interfere with the bilirubin assay include ascorbic acid, dextran, intravenous contrast agents, propranolol, and rifampin.
- ✓ **Causes of hyperbilirubinemia** can be classified into **Three broad** categories:
  (a) Prehepatic (hemolysis),
  (b) Hepatic (defective removal of bilirubin from the blood or defective conjugation),
  (c) Posthepatic (obstruction of the extrahepatic biliary tree), also referred to as cholestatic or obstructive.
- ✓ **As serum bilirubin concentrations rise above approximately 2 mg per dL (34 µmol/L), classic scleral icterus and jaundice develop.**

- **PREHEPATIC HYPERBILIRUBINEMIA**
  - ✓ Hemolytic jaundice results from the rapid destruction of erythrocytes overwhelming the ability of the liver to process excess bilirubin.
  - ✓ Tissue hematomas or collection of blood in body cavities may increase the serum bilirubin.
  - ✓ Severe sepsis or malignancy-induced disseminated intravascular coagulation, sickle cell crisis, or certain medications may induce hemolytic anemia.
  - ✓ Drug-induced hemolytic anemia may also occur and is discussed later in this chapter under the section, “Erythrocytes.”
- **HEPATIC HYPERBILIRUBINEMIA**
  - ✓ Hepatocellular injury from viral hepatitis, alcoholic hepatitis, toxin-mediated hepatitis, or cirrhosis may elevate serum bilirubin concentrations.
  - ✓ Viral hepatitis usually causes elevations in direct bilirubin levels.

- ✓ Viral hepatitis may cause extreme elevations in transaminases **(10,000 to 20,000 IU/L, 167 to 334 µkat/L)**, with ALT levels usually greater than those of AST.
- ✓ Medications commonly reported to cause direct hepatocellular damage include acetaminophen, amiodarone, amsacrine, halothane, indinavir, irinotecan, tetracycline, valproic acid, isoniazid, rifampin, methyldopa, labetalol, and tacrine.
- ✓ Drug-induced hepatocellular damage may be indistinguishable from acute viral hepatitis.
- ✓ Alcoholic hepatitis presents in patients with acute or chronic alcohol ingestion.
- ✓ Transaminase elevations are only a fraction of those seen in viral or toxin-induced hepatitis.
- ✓ AST concentration is usually greater than ALT, but GGT levels may be markedly elevated due to the effects of alcohol on GGT release.



- **POSTHEPATIC HYPERBILIRUBINEMIA**
  - ✓ Patients with obstructive jaundice usually present with light clay-colored stools and dark cola-colored urine due to reabsorption of conjugated bilirubin from the biliary ducts with redistribution to the urine and lack of stercobilin in the stool.
  - ✓ The lack of bile acids in the gastrointestinal tract because of obstruction may cause steatorrhea.
  - ✓ Transaminase levels are usually only mildly elevated unless severe obstruction occurs causing hepatocellular damage.
  - ✓ ALP and GGT concentrations are usually quite high.
  - ✓ The most common cause of biliary obstruction is choledocholithiasis (gallstones) obstructing the common bile duct.

- ✓ Obese, middle-aged women are highly predisposed to choledocholithiasis; however, it may occur in both sexes at any age.
- ✓ Other causes of obstructive jaundice include pancreatitis, carcinoma of the head of the pancreas, or other neoplastic invasion of the papilla of Vater.
- ✓ Cholestatic changes may be due to an intrahepatic defect of the transport of bilirubin into hepatic canaliculi.
- ✓ Cholestatic jaundice closely resembles posthepatic biliary obstruction, except the stools are only somewhat lighter than normal due to less exclusion of bilirubin from the duodenum.
- ✓ Common medications that induce obstructive or cholestatic jaundice include C-17 alkyl steroids, estrogens, chlorpromazine, and erythromycin estolate.
- ✓ Other medications may cause a mixed picture of hepatic injury by an atypical (phenytoin) or granulomatous pattern (quinidine, allopurinol).

TEST FOR CARDIOVASCULAR DISORDER

- **CREATINE KINASE**
  - ✓ **Normal Range: 0 to 130 IU/L**
  - ✓ **SI units = 0 to 2.16 µkat/L,**
  - ✓ **CF = 0.01667**
  - ✓ **Creatine kinase (CK), formerly known as Creatine phosphokinase,** catalyzes the conversion of phosphocreatine to creatine releasing high-energy phosphate to skeletal and cardiac muscle.
  - ✓ Creatine is an unstable molecule and is converted very rapidly to creatinine.
  - ✓ CK is a dimer consisting of two subunits, M and B.
  - ✓ **Brain tissue yields approximately 90% BB (CK_1) and 10% MM (CK_3),**
  - ✓ **Cardiac tissue yields approximately 40% MB (CK_2) and 60% MM,**
  - ✓ **Normal serum contains virtually 100% MM as does skeletal muscle.**
  - ✓ Clinical conditions causing elevated serum CK primarily involve skeletal muscle or cardiac tissue.
  - ✓ The brain fraction is almost never observed in serum, even after a cerebrovascular accident, since the enzyme does not readily cross the blood–brain barrier.
  - ✓ Almost any damage to skeletal muscle will cause an elevation in serum CK.
  - ✓ Severe acute rhabdomyolysis secondary to trauma, prolonged coma, or overdoses of various drugs may cause dramatic rises of CK, ranging from 10,000 to 100,000 IU per L (167 to 1,670 µkat/L).
  - ✓ Other conditions damaging skeletal muscle such as progressive muscular dystrophy, polymyositis/dermatomyositis, delirium tremens, seizures, or hypothyroidism may cause significant elevations in CK.
  - ✓ **An MB fraction more than 6% of the total is indicative of myocardial injury.**
  - ✓ Intramuscular injections of medications may cause a variable increase in CK of 2 to 6 times the normal concentration.
  - ✓ These elevations return to normal within 48 hours after cessation of the injections.
  - ✓ CK rises in over 50% of patients receiving countershock or defibrillation but usually returns to normal in 48 to 72 hours.
  - ✓ **Several medications** have been reported to cause rhabdomyolysis in therapeutic and overdose situations, including opiates, cocaine, phencyclidine, amphetamines, theophylline, antihistamines, fibric acid derivatives, barbiturates, aminocaproic acid,

certain antibiotics, chloroquine, colchicine, corticosteroids, HMG-CoA reductase inhibitors, and vincristine.

- ✓ Patients receiving therapeutic doses of neuroleptics may rarely experience the neuroleptic malignant syndrome, which may cause severe elevations in CK.

➢ **LACTATE DEHYDROGENASE**

- ✓ **Normal Range: 100 to 190 IU/L**
- ✓ **SI units = 1.67 to 3.17 µkat/L,**
- ✓ **CF = 0.01667**
- ✓ Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate anaerobically to generate adenosine triphosphate (ATP).
- ✓ LDH is in high concentrations in cardiac and skeletal muscle, liver, kidney, lung parenchyma, and erythrocytes.
- ✓ **LDH can be separated into five distinct components**.
- ✓ The five LDH isoenzymes all have approximately the same molecular weight but have different charges.
- ✓ **LDH_5 has the greatest mobility and LDH_1 the least.**
- ✓ Serum LDH is almost always increased after an acute MI.
- ✓ Increased serum LDH level, with LDH_1 greater than LDH_2 (flipped enzymes), occurs in acute MI in approximately 80% of patients, but also occurs in acute renal infarction, pernicious anemia, and hemolysis.
- ✓ **In a large MI with biventricular failure, LDH_5 levels may also be elevated due to liver congestion.**
- ✓ LDH_5 may be markedly increased in hepatitis and may also be increased in other hepatic disorders.
- ✓ LDH elevations may occur 50% of the time with malignant tumors, usually with a nonspecific isoenzyme pattern.
- ✓ LDH is elevated in approximately 60% of patients with lymphomas and 90% of patients with leukemias.
- ✓ Marked increases in LDH_5 levels are seen in patients with skeletal muscle damage, extensive burns, and trauma.
- ✓ Pulmonary embolus and infarction may cause elevations in LDH_2 and LDH_3; if cor pulmonale is present, LDH_5 will also rise.
- ✓ In nephrotic syndrome, LDH_4 and LDH_5 will rise,
- ✓ In nephritis and renal infarction, LDH_1 and LDH_2 rise.
- ✓ All forms of hemolysis, including sickle cell crisis and drug-induced hemolysis, will cause elevations in LDH_1 and LDH_2.
- ✓ Serum LDH is usually elevated in patients with *Pneumocystis carinii* pneumonia particularly in human immunodeficiency virus (HIV) patients.However, LDH can also be elevated in multiple other pulmonary conditions including tuberculosis and bacterial pneumonia.
- ✓ All drugs causing damage to the above-mentioned tissues will cause elevations in LDH.
- ✓ Hepatotoxic agents and agents inducing hemolysis will increase serum LDH concentrations.

ELEVATED ISOENZYMES LEVELS IN VARIOUS CONDITIONS	
LDH_1	Acute myocardial infarction, Acute renal infarction, Pernicious anaemia, Hemolysis

LDH_2	Pulmonary embolus, Infarction, Hemolysis
LDH_3	Pulmonary embolus, Infarction, Hemolysis
LDH_4	Tumors, Nephrotic syndrome
LDH_5	Severe myocardial infarction with ventricular failure, Heratitis, Hepatic disorder, Skeletal muscle damage, trauma, Nephritic syndrome, Cor pulmonale

- **TROPONINS**
  - ✓ **Troponin I (cTnI) 0.7 to 1.5 ng/mL**
  - ✓ **SI units = 0.7 to 1.5 µg/L,**
  - ✓ **CF = 1.0**
  - ✓ Troponin is a complex of **three proteins**, Troponin T, Troponin C, and Troponin I.
  - ✓ Each troponin has its own specific function in the regulation of myosin and actin in the contractile process.
  - ✓ cTnI is very sensitive and specific for myocardial tissue.
  - ✓ After acute myocardial injury, cTnI starts to rise approximately 2 hours after myocardial damage (2 to 6 hours faster than myocardial bound CK [CKMB]) with peak elevations occurring at about 24 to 36 hours.
  - ✓ There is a 13-fold greater concentration of cTnI than CKMB in the heart and is at least as sensitive for the clinical detection of cardiac injury as CKMB.
  - ✓ **Cardiac troponin I is much more specific than CKMB for cardiac tissue** and is not elevated in skeletal muscle injury, chronic muscle disease, hypothyroidism, after endurance exercise, chronic renal failure, and postoperative patients without myocardial injury.
  - ✓ An elevation of cTnI greater than 2.0 ng per mL is indicative of acute myocardial injury.
  - ✓ Unlike CKMB, cTnI can also detect acute myocardial injury for up to 10 to 12 days without the lack of specificity and necessary isoenzyme separation of LDH.

TESTS FOR DIABETES MELLITUS

- **PLASMA GLUCOSE**
  - ✓ **Normal Range: 70 to 110 mg/dL**
  - ✓ **Fasting SI units = 3.9 to 6.1 mmol/L,**
  - ✓ **CF = 0.05551**
  - ✓ Laboratory determinations of glucose level are usually performed on venous plasma specimens.
  - ✓ Whole blood determinations are used only for capillary blood used in finger stick devices.
  - ✓ Serum and plasma glucose concentrations are identical and are 10% to 15% higher than whole blood measurements.
  - ✓ Glucose is one of the clinically important carbohydrates along with fructose and galactose.
  - ✓ Disorders of carbohydrate metabolism such as diabetes are evaluated in part by measurement of plasma glucose in the fasting state or after suppression or stimulation.
  - ✓ The concentration of glucose in the blood is regulated within narrow limits by hormones produced by the pancreas and through other mechanisms mediated by the adrenergic and cholinergic nervous systems.
  - ✓ Glucose is a major source of energy for brain, muscle, and fat.

- ✓ The brain is the only tissue that does not require insulin for glucose utilization.
- ✓ If glucose is not available exogenously (fasting state), the body, using hormonal mechanisms (counter-regulatory hormones: glucagon, epinephrine, cortisol, and somatostatin), will form its own glucose by tissue and hepatic gluconeogenesis and hepatic glycogenolysis.
- ✓ Glucose is therefore carefully regulated by glucagon and insulin secretion, which compensate for food ingestion and fasting states.
- ✓ **Methods for clinical determination of glucose are chemical or enzymatic.**
  - Chemical analysis is based on the reducing properties of glucose, and uses a color change reaction that is measured spectrophotometrically.
  - The Enzymatic method is based on the reaction of glucose and glucose oxidase. This is a very specific method and is generally inexpensive.
- ✓ Ascorbic acid can interfere with this method and result in decreased values.
- ✓ Elevated plasma glucose concentrations, or hyperglycemia, can be caused by a number of syndromes and diseases.
- ✓ **The classification of hyperglycemia is shown in Table.**

Hyperglycemia classified as	
Primary	
	Insulin-dependent diabetes mellitus Noninsulin-dependent diabetes mellitus
Secondary	
a	**Hyperglycemia resulting from disease of the pancreas:**
	Inflammation
	Acute pancreatitis (rare)
	Chronic pancreatitis
	Pancreatitis due to mumps
	Cell damage due to coxsackievirus B_4 infection
	Autoimmune disease
	Pancreatectomy
	Pancreatic infiltration
	Hemochromatosis
	Tumors
	Trauma to pancreas (rare)
b	**Hyperglycemia related to other major endocrine diseases**
	Acromegaly
	Cushing's syndrome
	Thyrotoxicosis
	Pheochromocytoma
	Hyperaldosteronism
	Glucagonoma
	Somatostatinoma
c	**Hyperglycemia caused by drugs**
	Corticosteroids, acetazolamide, thiazide diuretics, and beta agonists
	Pentamidine (late), tacrolimus, and protease inhibitors
d	**Hyperglycemia related to other major disease states**
	Chronic renal failure

	Chronic liver disease
	Infection
e	**Miscellaneous hyperglycemia**
	Pregnancy
	Related to insulin receptor antibodies (acanthosis nigricans)

- ✓ A fasting plasma glucose of 126 mg per dL (7.0 mmol/L) or greater is considered abnormal.
- ✓ **Hypoglycemia** is a syndrome of low plasma glucose with related symptoms.
- ✓ **In the adult**, an overnight fasting plasma glucose <45 mg per dL (2.5 mmol/L) is considered abnormal and more than 55 mg per dL (3.0 mmol/L) is considered the lower limit of normal.
- ✓ **In neonates**, less than 35 mg per dL (1.9 mmol/L) is abnormal
- ✓ **In infants** and **children**, less than 45 mg per dL (2.5 mmol/L) is abnormal.

Table shows the classification of common causes of hypoglycemia.

Hypoglycemia classified as		
I.	**No anatomic lesion present**	
	a	**Fasting plasma glucose normal**
		Reactive hypoglycemia
		Functional hypoglycemia
		Alimentary hypoglycemia
		Diabetic and impaired glucose tolerance
	b	**Fasting plasma glucose low**
		Drug-induced hypoglycemia
		ACE inhibitors
		Oral hypoglycemic agents
		Insulin
		Ethanol
		Salicylates (late in overdose)
		Pentamidine (early in therapy)
		Combinations of the above
	c	**Factitious-fasting glucose normal or low**
II.	**Anatomic lesion present**	
	Insulinoma	
	Extrapancreatic neoplasms	
	Adrenocortical insufficiency	
	Hypopituitarism	
	Acute liver failure	

- ➢ **ORAL GLUCOSE TOLERANCE TEST**
  - ✓ In this test a patient is asked to have about ten hrs. fast and given 75 g. glucose in drinking water.
  - ✓ Just before administration of glucose, a blood sample is taken.
  - ✓ After glucose, blood sample are withdrawn at 30 min, 60 min and 120 min. in normal patients the glucose levels decline after 60 min and by 120 min return to normal (140 mg/dl).
  - ✓ In diabetic patients this decline is not seen.
- ➢ **SERUM INSULIN:**

- ✓ In order to differentiate Type I and Type II diabetes, blood samples may be analysed for serum insulin.
- ✓ Type I diabetic patients have lower insulin levels as compared to normal.
- ✓ Type II diabetic patients may have higher insulin levels.
- ✓ **This test is carried out by radioimmunoassay.**
- ✓ **Normal insulin levels: 30-60 µU/ml.**

➢ **C-PEPTIDE:**
- ✓ **This is another test done by radioimmunoassay.**
- ✓ This confirms whether the patients is type- I or not.
- ✓ However, this test is not rountinely used.

➢ **GLYCOSYLATED HAEMOGLOBIN:**
- ✓ Glucose binds to a part of the haemoglobin molecule to form a small glycated fraction.
- ✓ Normally about 5% of haemoglobin is glycated, but this amount is dependent on the average blood glucose concentration over the lifespan of the red cells (about 120 days).
- ✓ The major component of the glycated fraction is referred to as HbA_{1c}.
- ✓ Measurement of HbA_{1c} is well established as an indicator of chronic glycaemic control in patients with diabetes.
- ✓ Several methods exist for its determination and until standardization is achieved, clinicians should be aware that the ranges indicating good or poor glycaemic control can vary between different assays and laboratories.

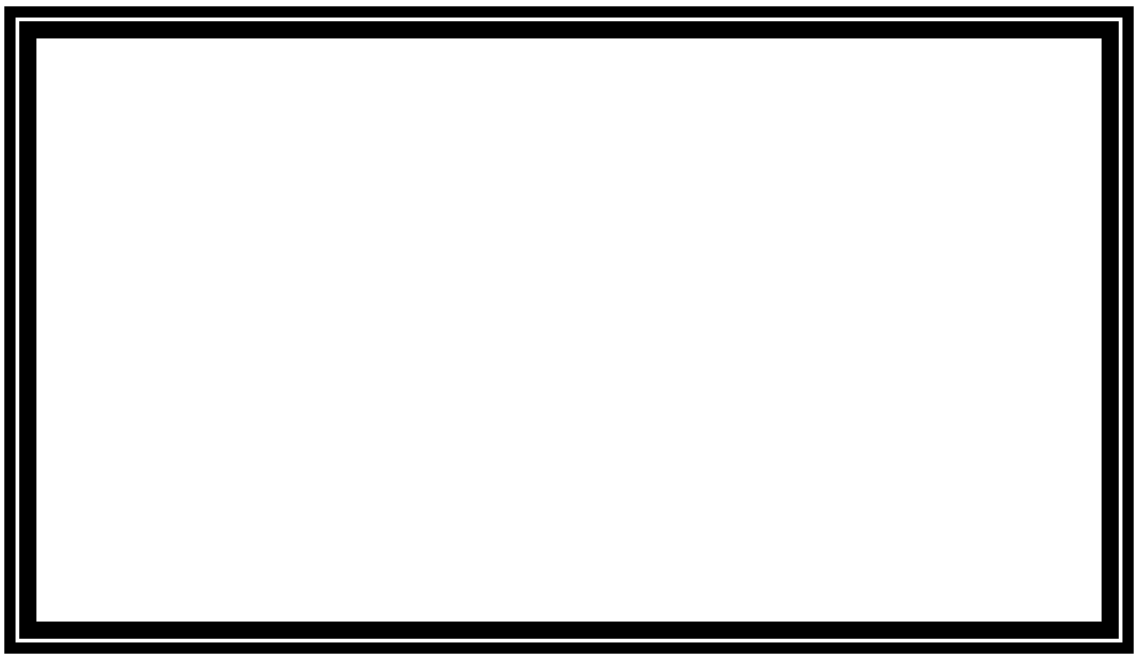
SERUM PROTEINS

➢ **TOTAL PROTEIN**
- ✓ **Normal Range :6.0 to 8.0 g/dL**
- ✓ **SI units = 60 to 80 g/L,**
- ✓ **CF = 10**
- ✓ Serum proteins are separated by serum protein electrophoresis into prealbumin, albumin, and globulin fractions.

- **PREALBUMIN**
  - ✓ **Normal Range : 0.15 to 0.36 g/dL**
  - ✓ **SI units = 1.5 to 3.6 g/L,**
  - ✓ **CF = 10**
  - ✓ Prealbumin makes up a small percentage of total protein (<1%) and is not widely used for clinical management.
  - ✓ Prealbumin contains retinol-binding protein, which plays a role in the transport and metabolism of vitamin A.
  - ✓ Prealbumin is exquisitely sensitive to nutritional intake and has a short half-life in the circulation.
  - ✓ Measurements of prealbumin, therefore, have clinical utility as a marker for nutritional status.

- **ALBUMIN**
  - ✓ **Normal Range: 4.0 to 6.0 g/dL**
  - ✓ **SI units = 40 to 60 g/L,**
  - ✓ **CF = 10**
  - ✓ Albumin is by far the most abundant serum protein.

- ✓ Albumin is synthesized in the liver and accounts for up to 65% of total protein.
- ✓ **Albumin has three major functions:**
  (a) Controlling oncotic pressure in the plasma,
  (b) Transporting amino acids synthesized in the liver to other tissues,
  (c) Transporting poorly soluble organic and inorganic ligands.
- ✓ Albumin accounts for 80% of the oncotic pressure of the plasma.
- ✓ Capillary hemodynamics is controlled by **four major forces**, including
  a. Intravascular oncotic pressure,
  b. Interstitial oncotic pressure,
  c. Capillary hydrostatic pressure, and
  d. Interstitial hydrostatic pressure.
- ✓ Intravascular oncotic pressure and interstitial hydrostatic pressure are the forces holding fluid in the intravascular space, while capillary hydrostatic pressure and interstitial oncotic pressure force fluid into tissue spaces.
- ✓ Normally intravascular oncotic pressure overrides capillary hydrostatic pressure having a net hemodynamic flow into the vasculature.
- ✓ These forces may be disrupted causing local edema, ascites, or anasarca.
- ✓ Malnutrition, malignancy, severe trauma, or burns cause a net catabolic state, decreasing serum albumin and oncotic pressure.
- ✓ In hepatic cirrhosis, there is decreased synthesis of albumin and increased portal capillary pressure resulting in ascites.
- ✓ In severe sepsis, toxin-mediated increases in capillary permeability allow intravascular albumin to escape into the interstitial tissues, accounting for increases in interstitial oncotic pressure.
- ✓ Nephrotic syndrome and protein-losing enteropathies cause increased losses of serum albumin resulting in anasarca.
- ✓ CHF alters pulmonary capillary hydrostatic pressure, resulting in pulmonary edema.
- ✓ Dehydration and hemodilution may increase or decrease serum albumin concentrations respectively.
- ✓ Albumin acts as a carrier protein for organic and inorganic molecules, which may bind ionically or covalently.
- ✓ Several common medications, which are highly insoluble in serum, bind over 90% to albumin, including phenytoin, salicylates, first generation sulfonylureas, valproic acid, warfarin, and certain sulfonamides.
- ✓ Since free drug is thought to be the active portion, changes in serum albumin concentrations may have a large influence on drug distribution and pharmacologic effect.

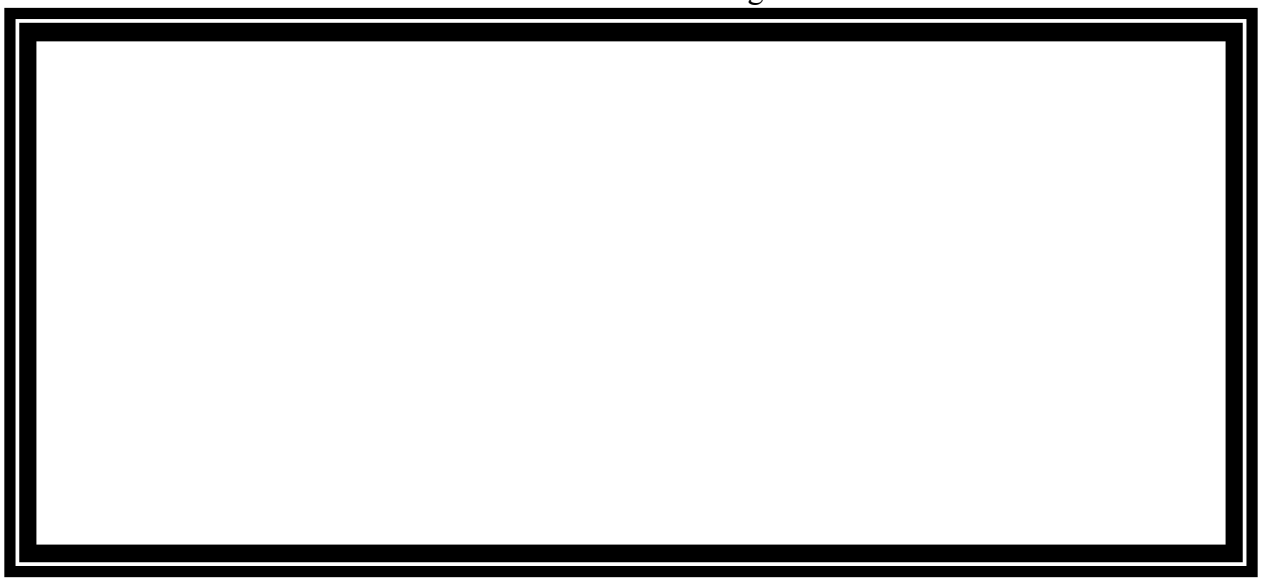


- **GLOBULIN**
  - ✓ Normal Range: 2.0 to 4.0 g/dL
  - ✓ SI units = 20 to 40 g/L,
  - ✓ CF = 10
  - ✓ The globulin fraction comprises one third of total protein and is composed of **four major components including α-1, α-2, β, and γ.**
  - ✓ Important proteins located in the α-1 fraction are α-1 antitrypsin, which is a scavenger enzyme for lysosomal proteases, and α-1 acid glycoprotein (AAG).
  - ✓ Young patients with homozygous α-1 antitrypsin deficiency develop severe pulmonary emphysema due to protein lysis by elastase.
  - ✓ AAG is an acute-phase reactant that acts as a carrier protein for poorly soluble medications.
  - ✓ **AAG is increased** transiently in a variety of clinical conditions, including burns, chronic pain, enzyme induction, rheumatoid arthritis, morbid obesity, MI, malignancy, surgery, or trauma.
  - ✓ Several common medications bind to AAG, including amitriptyline, chlorpromazine, dipyridamole, disopyramide, erythromycin, imipramine, lidocaine, meperidine, methadone, nortriptyline, propranolol, and quinidine.
  - ✓ The transient elevations in AAG levels during the previously mentioned conditions may cause important changes in the binding and pharmacologic effect of these medications.
  - ✓ The α-2 portion consists primarily of α-2-macroglobulin, haptoglobin, and ceruloplasmin.
  - ✓ **α-2 Macroglobulin is another major protease inhibitor; haptoglobin is a carrier protein for hemoglobin; and ceruloplasmin is a copper-binding protein.**
  - ✓ The β portion is composed of low-density lipoprotein (LDL), transferrin, C_3, and fibrinogen.

- ✓ LDL is the major transport protein for cholesterol to tissues; transferrin transports ferric iron stores to bone marrow for erythropoiesis; C_3 is a major component of the complement system; and fibrinogen is a coagulation precursor for fibrin.
- ✓ The gamma globulin portion is composed of antibody immunoglobulins IgA, IgE, IgG, and IgM.
  - IgA is responsible for surface immunity;
  - IgE binds to mast cells and is responsible for hypersensitivity reactions;
  - IgM is responsible for initial humoral immunity;
  - IgG for sustained humoral immunity.
- ✓ The primary disorder associated with hypergammaglobulinemia is multiple myeloma.

HAEMATOLOGICAL DATA

- **COMPLETE BLOOD COUNT WITH DIFFERENTIAL**
  - ✓ The complete blood count provides information about the erythrocytes, leukocytes, and platelets.
  - ✓ The number of parameters provided with a CBC depends on the type of machine used for the analysis.
  - ✓ Any other desired tests may be ordered separately.
  - ✓ In the normal adult, blood cells are predominantly made in the bone marrow of the sternum, skull, ribs, vertebrae, pelvis, and the proximal ends of the long bones (humerus and femur).
  - ✓ The pathways of hematopoiesis from the pluripotential stem cell and the relationship between the different cell lines are shown in Figure.



- **ERYTHROCYTES**
  - ✓ **Normal Range: Men = 4.3 to 5.9 × 10^6/mm^3 (4.3 to 5.9 × 10^{12}/L);**
    Women = 3.5 to 5.0 × 10^6/mm^3 (3.5 to 5.0 × 10^{12}/L);
  - ✓ **CF = 1**
  - ✓ The main functions of erythrocytes, or red blood cells (RBC), are to carry oxygen from the lungs to the tissues and transport carbon dioxide back to the lungs.

- ✓ Anemia occurs when the hemoglobin, hematocrit, and/or erythrocyte count are below the normal range.
- ✓ This can be a result of impaired erythrocyte production, increased erythrocyte destruction, blood loss, or increased plasma volume.
- ✓ **The extent of anemia is generally described by the hemoglobin or hematocrit values.**
- ✓ **The RBC indices may be used to further characterize the anemia by cell morphology or color.**
- ✓ **Normal-sized RBC is called normocytes, small ones are microcytes, and large RBC is macrocytes.**
- ✓ If there is abnormal variation in size, the patient is said to have anisocytosis, which is a feature of most anemias.
- ✓ Those with **normal amounts of hemoglobin** are said to be **normochromic**;
- ✓ Those with **decreased, hypochromic**; and
- ✓ Those with **increased hemoglobin, hyperchromic**.
- ✓ Abnormally shaped cells are poikilocytes.
- ✓ Polycythemia means "many blood cells" but usually refers to an increased RBC mass and/or an elevated hematocrit value.
- ✓ Red cell production is regulated by tissue oxygenation.
- ✓ Tissues receive inadequate oxygen if there is an insufficient supply in inspired air, impaired oxygen transport from the alveoli into the blood stream, hypoventilation, inadequate hemoglobin to carry oxygen, decreased arterial oxygen saturation, abnormal blood flow, or a failure of hemoglobin to release bound oxygen at tissue sites.
- ✓ This can occur in diseases such as anemia, in cardiac or pulmonary disease, or with decreased oxygen tension in the air, such as at high altitudes. Smokers tend to have a stimulation of erythrocyte production.
- ✓ Hypoxia or decreased oxygenation stimulates the production of erythropoietin, with most being produced by the kidneys.
- ✓ A small amount of erythropoietin is produced by the liver.
- ✓ Erythropoietin stimulates erythroid differentiation and survival.
- ✓ Erythropoietin increases in most anemias, but its production and effects may be impaired in those associated with chronic diseases.
- ✓ If tissue oxygen concentrations are perceived as inadequate, erythrocyte production continues, regardless of the erythrocyte count or hemoglobin concentration, resulting in a secondary or reactive polycythemia.
- ✓ The life span of erythrocytes in circulation is 120 days.
- ✓ They are removed by the RES.
- ✓ Normally, most RBC destruction occurs in the spleen, liver, and bone marrow by phagocytosis by macrophages.
- ✓ With an abnormally large spleen, there is increased destruction of normal cells.

- ✓ The spleen may be enlarged in conditions such as liver disease, CHF, leukemias, lymphomas, or protozoal infections.
- ✓ There can be accelerated destruction of erythrocytes by a normal spleen when they contain abnormal hemoglobin or have abnormal membranes or enzymes.
- ✓ Increased destruction can also occur with abnormal physical, chemical, microbiologic, or immunologic conditions.
- ✓ **Hemolysis** refers to the disruption of the mature erythrocyte membrane and release of hemoglobin before the end of the usual life span.
- ✓ It can take place in the spleen (or other RES organs) or vasculature.
- ✓ This accelerated destruction of cells can occur in response to physical trauma or massive exertion, severe burns, infections such as malaria, mycoplasmal pneumonia, or mononucleosis, or toxic insults such as *Clostridium* infections or brown recluse spider bites.
- ✓ Hemolysis can also occur with drugs and chemicals, such as arsine gas, lead, or copper salts.
- ✓ With oxidizing drugs, such as nitrates, methemoglobin can be formed and lead to severe cases of erythrocyte destruction.
- ✓ Destruction of erythrocytes may be mediated by antibodies.
- ✓ Various types of antibody-mediated hemolysis are associated with drugs.
- ✓ **Penicillins and cephalosporins** can tightly bind to erythrocyte membranes and stimulate production of IgG antibodies and hemolysis.
- ✓ **Cephalosporins** can also change erythrocyte membranes leading to nonspecific adsorption of proteins.
- ✓ **Methyldopa** can directly induce a positive antiglobulin reaction and hemolysis.
- ✓ In the immune complex type of drug-induced hemolytic anemia, the drug loosely combines with the RBC membrane to form a neoantigen that then binds an antibody.
- ✓ Complement is attracted and cell lysis occurs.
- ✓ Only a small amount of drug is needed for this to occur.
- ✓ The reaction can be abrupt and severe and may be accompanied by renal failure.
- ✓ In the past, the RBC was considered to be an "innocent bystander" on which the drug-antibody complex settled, but now it is thought to be an essential component in promulgating this reaction.
- ✓ This has been reported with quinidine, quinine, p-aminosalicylic acid, phenacetin, rifampin, antihistamines, chlorpromazine, sulfonylureas, sulfonamides, and insecticides.
- ✓ Patients with chronic diseases, such as infections, renal or liver disease, various endocrine disorders, rheumatoid arthritis, or neoplasms, often have anemia.
- ✓ Aplastic anemia involves a pancytopenia or a depression of erythrocytes, neutrophils, and platelets.
- ✓ About 11% to 20% of cases can be attributed to drug or chemical exposure, and about 2% to 9% to infectious hepatitis.

- ✓ It can occur secondary to infections; thymoma; ionizing radiation; pregnancy; drugs such as chloramphenicol, cimetidine, gold salts, indomethacin, ibuprofen, sulfonamides, thioamides, anticonvulsants, or antineoplastic drugs; or chemicals such as benzene, mercury, or DDT.
- ✓ About 70% of aplastic anemia cases are primary or idiopathic, where there is no known predisposing cause.
- ✓ Patients with aplastic anemia may later develop acute leukemia, paroxysmal nocturnal hemoglobinuria, or myelodysplastic syndrome.
- ✓ Polycythemia vera is a myeloproliferative syndrome in which there is a spontaneous increase in erythrocytes.
- ✓ The predominant picture is one of erythrocyte proliferation, but other elements of the blood are also hyperactive.
- ✓ It most commonly presents in middle age.
- ✓ Thrombosis and hemorrhage are common complications.

- **HEMOGLOBIN**
  - ✓ **Normal Range: Men = 13.6 to 17.2 g/dL (8.45 to 10.65 mmol/L or 136 to 172 g/L);**
    Women = 12.0 to 15.0 g/dL (7.45 to 9.30 mmol/L or 120 to 150 g/L);
  - ✓ **CF = 0.6206 for mmol/L and 10 for g/L**
  - ✓ Hemoglobin (Hb), the primary component of erythrocytes, transports oxygen and carbon dioxide.
  - ✓ Hemoglobinopathies occur when genes code for abnormal amino acid sequences.
  - ✓ The most common abnormal hemoglobin is sickle hemoglobin.
  - ✓ Thalassemias are characterized by decreased synthesis of globin chains.
  - ✓ The preferred assay for hemoglobin is the cyanmethemoglobin method.
  - ✓ Errors in venipuncture technique can lead to hemoconcentration, which results in falsely elevated values for hemoglobin and cell counts.
  - ✓ The difference in the normal range between men and women is thought to result mainly from androgen stimulation of erythropoiesis in the marrow.
  - ✓ Estrogen may slightly suppress erythrocyte production.
  - ✓ Menstrual blood loss is also a contributing factor.
  - ✓ In older men, the hemoglobin tends to fall.
  - ✓ This occurs to a lesser extent in women, who may even have a slight increase in the value.
  - ✓ As a result, there is a <1 g per dL (0.62 mmol/L) sex difference in hemoglobin in older individuals.
  - ✓ There is a diurnal variation of approximately 8% to 9% in hemoglobin concentrations, with the highest value in the morning and the lowest in the evening.
  - ✓ Hemoglobin values are approximately 0.5 to 0.6 g per dL (0.31 to 0.37 mmol/L) lower in blacks than in whites.
  - ✓ Some attribute this to a higher incidence of iron deficiency anemia in blacks.
- **HEMATOCRIT**
  - ✓ **Normal Range: Men = 39% to 49% (0.39 to 0.49);**
    Women = 33% to 43% (0.33 to 0.43);
  - ✓ **CF = 0.01**

- ✓ The hematocrit (Hct) is the ratio of the volume of erythrocytes to that of whole blood or the packed erythrocyte volume.
- ✓ It increases when more fluid is lost than erythrocytes and volume depletion occurs, as is seen in patients with vomiting, diarrhea, burns, prolonged fever, or those taking diuretics.
- ✓ An inappropriate polycythemia occurs with renal cancer, hepatomas, pheochromocytomas, or adrenal cortical neoplasms where there is increased erythropoietin and increased hematocrit.
- ✓ The hematocrit is unreliable for patient assessment immediately after blood loss or transfusion.

- **RETICULOCYTES**
  - ✓ **Normal Range: 10,000 to 75,000 mm^{-3} ($10–75 \times 10^9$/L);**
  - ✓ **CF = 0.001;**
  - ✓ Reticulocytes are immature erythrocytes.
  - ✓ Generally, the absolute reticulocyte count is more useful than the percentage of erythrocytes.
  - ✓ Reticulocytes provide an estimate of erythrocyte production; however, as the hematocrit drops, increasingly immature reticulocytes are released into the blood.
  - ✓ To accurately estimate erythrocyte production in response to anemia, a correction factor must be used to account for this longer maturation time and avoid overestimating the erythropoietic response.
  - ✓ The reticulocyte production index (RPI) can be calculated by:
  - ✓ 
  - ✓ In general, an RPI >2 represents an adequate response to anemia and an RPI <2 indicates an inadequate increase in RBC production.
  - ✓ The reticulocytes are most markedly increased in patients with hemolysis or acute blood loss and also increase when iron or vitamin B_{12} is administered to a deficient patient.
  - ✓ If the reticulocyte count is normal, but the hemoglobin low, there is an inadequate response to anemia, such as what may be seen in iron deficiency.
  - ✓ If the reticulocyte count is increased, but the hemoglobin is normal, there is probably some destruction or loss of erythrocytes occurring, and the body is appropriately compensating for the loss.
- **ERYTHROCYTE INDICES**
  - ✓ The size and hemoglobin content of erythrocytes can be quantified by the erythrocyte indices.
  - ✓ The **MEAN CORPUSCULAR VOLUME (MCV)** is the average volume of erythrocytes.
  - ✓ It can be measured by machines or calculated by the formula **MCV = Hct/RBC**.
  - ✓ **The normal range is 76 to 100 μm^3 or 76 to 100 femtoliters (fL)** in SI units (a femtoliter is 10^{-15} L).
  - ✓ The MCV is decreased in microcytic anemia and increased in macrocytic anemia.
  - ✓ Young erythrocytes and reticulocytes are larger than mature cells, so when there is rapid erythrocyte production, the MCV will be increased.
  - ✓ This type of macrocytosis can be observed in compensated hemolytic conditions or when a patient is recovering from acute blood loss.

- ✓ **Megaloblastic** changes can occur when DNA production is impaired but RNA production is normal.
- ✓ This causes nuclear maturation to lag behind cytoplasmic maturation.
- ✓ This change occurs in all cells, but is most dramatic and can be most easily diagnosed in erythrocyte precursors.
- ✓ It is distinguished by the presence of oval macrocytes and hypersegmented neutrophils.
- ✓ The most common causes of megaloblastosis are deficiencies of vitamin B_{12} or folic acid, which are required for DNA synthesis.
- ✓ **Drugs that interfere with DNA synthesis** by blocking folate metabolism (e.g., methotrexate or trimethoprim), interfering with vitamin B_{12} absorption (e.g., colchicine, metformin, neomycin, or cholestyramine), inhibiting purine synthesis (e.g., 6-mercaptopurine) or pyrimidine synthesis (e.g., cytarabine), or alkylating agents (e.g., cyclophosphamide) may also **cause megaloblastosis**.
- ✓ It may also result from drugs that **decrease folate absorption** such as oral contraceptives, sulfasalazine, phenytoin, phenobarbital, and primidone.
- ✓ Megaloblastic anemias can be seen with inherited disorders of DNA synthesis such as Lesch-Nyhan syndrome.
- ✓ Excessive alcohol intake is associated with macrocytosis due to poor nutrition, impaired folic acid absorption and metabolism, and direct effects on the bone marrow.
- ✓ **Macrocytic anemia** can also be associated with hypothyroidism, liver disease, multiple myeloma, myelodysplastic syndromes, and aplastic anemia.
- ✓ A **microcytic anemia** is associated with iron deficiency, thalassemias, sideroblastic anemia, and sometimes chronic diseases.
- ✓ The **MEAN CORPUSCULAR HEMOGLOBIN (MCH)** is the weight of the hemoglobin in the average RBC.
- ✓ It is calculated by **MCH = Hb/RBC**.
- ✓ **The normal range is 27 to 33.**
- ✓ In microcytic anemia it is decreased, and increased in macrocytic anemia.
- ✓ Hypochromic cells are associated with iron deficiency anemia, thalassemias, sideroblastic anemia, and sometimes anemia of chronic disease.
- ✓ The **MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION (MCHC)** is the average concentration of hemoglobin in a given volume of packed erythrocytes and is described by MCHC = Hb/Hct.
- ✓ **The normal range is 33 to 37 g per dL or 330 to 370 g per L in SI units (CF = 10).**
- ✓ In microcytic anemia it is decreased. In macrocytic anemia it may be normal or decreased. In hypochromic anemias, both the MCH and MCHC are decreased.
- ✓ The **RED CELL DISTRIBUTION WIDTH (RDW)** quantifies the extent of variation in the size of erythrocytes.
- ✓ **The reference value is 11.5 to 14.5.**
- ✓ **It may be calculated by RDW = (standard deviation of RBC size) per MCV.**

INDICES	CALCULATED FORMULA	NORMAL VALUE	INCREASED IN	DECREASED IN
Mean corpuscular volume (MCV)	MCV= Hct/Ercs	87 ± 5 μm^3 / cell	Macrocytic anaemia	Microcytic anaemia
Mean corpuscular haemoglobin (MCH)	MCH=Hb/Ercs	29 ± 2 pg	Macrocytic anaemia	Microcytic anaemia, Hypochromic anaemia
Mean corpuscular haemoglobin concentration (MCHC)	MCHC=Hb/Hct	34 ± 2 g/dl	Macrocytic anaemia	Microcytic anaemia
Red cell distribution width (RCDW)	RCDW= std. deviation of erythrocyte size / MCV	11.5 to 14.5		

- **ERYTHROCYTE SEDIMENTATION RATE**
  - ✓ **Normal Range: Men = 0 to 20 mm/h;**
    Females = 0 to 30 mm/h, Westergren technique
  - ✓ **The erythrocyte sedimentation rate (ESR) is the rate of fall from the top of a column of erythrocytes in anticoagulated blood over a given period.**
  - ✓ It is directly proportional to the weight of the cell aggregates, and is inversely proportional to the surface area.
  - ✓ Microcytes settle slower than macrocytes.
  - ✓ **The ESR generally increases in anemia and decreases if there are abnormal or irregularly shaped erythrocytes.**
  - ✓ **The ESR gradually increases with age and moderately increases during pregnancy.**
  - ✓ The ESR is used mainly as an indicator of active inflammatory diseases (e.g., rheumatoid arthritis), chronic infection (e.g., tuberculosis, osteomyelitis, hepatitis, bacterial endocarditis), collagen disease, or neoplastic disease (e.g., multiple myeloma) and may be used to monitor the disease course.
  - ✓ It may have some prognostic value in sickle cell disease, stroke, prostate cancer, and coronary artery disease.
  - ✓ It is particularly useful in the diagnosis and monitoring of temporal arteritis and polymyalgia rheumatica.
  - ✓ **The Westergren technique is widely used as the standard for determining ESR.**
  - ✓ **Alternatives are the Wintrobe method and the Zeta Sedimentation Ratio.**
- **LEUKOCYTES**
  - ✓ **Normal Range: 3,200 to 9,800 mm^3 (3.2 to 9.8 × 10^9/L);**
  - ✓ **CF = 0.001**
  - ✓ Laboratories commonly report **six types of leukocytes or white blood cells (WBC)** found in the peripheral blood: Neutrophils, Bands, Lymphocytes, Monocytes, Eosinophils, and Basophils.

- ✓ Less mature or abnormal forms may be observed in certain disease states.
- ✓ The differential white count indicates the percentage of the total leukocyte count that is accounted for by each type (addition of the differential should total 100%).
- ✓ The leukocyte and differential counts can change within minutes to hours of stimulation.
- ✓ **Cigarette smokers have a higher average leukocyte count.**
- ✓ It is about 30% higher in heavy smokers, who inhale, with an increase in neutrophils, lymphocytes, and monocytes.
- ✓ In leukocytosis, the total WBC count is increased above the normal range.
- ✓ Exercise can lead to a leukocytosis with an increase in neutrophils due to shifting of cells and lymphocyte drainage into blood.
- ✓ **The leukocyte count and/or the differential count may be abnormal in patients with sepsis.**
- ✓ However, this is not always the case and normal or low values would not rule out an infection.
- ✓ If nucleated RBC are present, they may be read as leukocytes.
- ✓ Leukemias are malignant diseases characterized by abnormal leukocytes, which may be greatly increased in number (although they may also be decreased).
- ✓ A massive increase in leukocytes as a systemic response to various conditions (e.g., tuberculosis, severe burns, eclampsia, hemolysis, hemorrhage) is called a leukemoid reaction because the hematologic picture strongly resembles that seen in chronic leukemia. Different WBC lines may predominate depending on the etiology.

➢ **GRANULOCYTES**

- ✓ Granulocytes are leukocytes with granules in their cytoplasm.
- ✓ They develop from the same precursor cell as monocytes in the bone marrow.
- ✓ Their synthesis is stimulated by the hormone colony-stimulating factor for granulocytes (G-CSF) and granulocytes-monocytes (GM-CSF).
- ✓ Unlike erythrocytes, granulocytes retain their nuclei.
- ✓ There are three main types of granulocytes: **neutrophils (including bands), eosinophils, and basophils.**

➢ **NEUTROPHILS**

- ✓ **Normal Range: 1,800 to 7,000 mm^3 (1.8 to 7.0 × 10^9/L);**
- ✓ **CF = 0.001**
- ✓ In normal adults, about 56% of leukocytes are neutrophils, also called polymorphonuclear leukocytes (PMN), polys, segmented neutrophilic granulocytes, or segs.
- ✓ **The lower limit of the normal range is 1,800 mm^3 (1.8 × 10^9/L) for white adults and 1,100 mm^3 (1.1 × 10^9/L) for blacks.**
- ✓ There is some diurnal variation in neutrophils, with the highest values in the afternoon and lowest in the morning.
- ✓ The nuclei of neutrophils have two to five lobes connected by thin filaments.
- ✓ Their cytoplasm is packed with enzyme-containing granules that react with acidic and basic stains.
- ✓ Bands or stabs are the immature form of neutrophils.
- ✓ They have thicker strands connecting their nuclear lobes or U-shaped nuclei that look such as curved bands.
- ✓ Band neutrophils normally average 3% of leukocytes.

- ✓ **A "shift to the left" means there is an increase in the number of bands and immature neutrophils in the blood.**
- ✓ The term is derived from a time when the differential was reported on a grid that listed the immature forms on the left and the mature neutrophils on the right.
- ✓ Neutrophils remain in the "maturation and storage pool" in the marrow for about 6 to 7 days.
- ✓ Neutrophils usually spend less than a day in circulating blood.
- ✓ Their primary site of activity is in tissues.
- ✓ When tissue is damaged or foreign material enters the body, substances are released that stimulate neutrophils to move to that area. This is called **chemotaxis.**
- ✓ **CHEMOTAXIS** can be abnormal in some diseases such as Hodgkin's disease, cirrhosis, rheumatoid arthritis, and diabetes mellitus.
- ✓ The neutrophils then phagocytize and destroy microorganisms and other materials at the site enzymatically.
- ✓ The neutrophils must attach to the particles before they can engulf them.
- ✓ This attachment is enhanced by the presence of antibodies or complement coating the surface of the particles.
- ✓ It is decreased by exposure to alcohol, aspirin, prednisone, or nonsteroidal antiinflammatory drugs.
- ✓ This action of neutrophils is important in host defense against infection, but when enzymes are released outside the cell, it may also play a part in causing tissue damage to the host in other diseases.
- ✓ Neutrophils are stored in the bone marrow and in the marginal granulocyte pool along the vessel walls or in capillary beds.
- ✓ In **response to stress**, they can be released from these sites into the circulating pool, resulting in a neutrophilia.
- ✓ In an **acute infection**, the neutrophils leave the circulation and migrate into the tissues.
- ✓ Production of neutrophils will also increase, in which case, more immature forms will be seen.
- ✓ If supply cannot keep up with demand, a neutropenia may occur.
- ✓ A toxic suppression of the bone marrow may also be involved in this process.
- ✓ An increase in neutrophils is associated with some infections (especially bacterial), various inflammatory diseases (e.g., rheumatoid arthritis, vasculitis), tissue destruction or necrosis (e.g., as in trauma, surgery, MI, or burns), metabolic disorders (e.g., uremia, diabetic ketoacidosis, gout, hemorrhage, hemolysis), and solid tumors.
- ✓ Endogenous or exogenous adrenal corticosteroids cause lymphocytes and eosinophils to disappear from circulation within 4 to 8 hours, with circulating granulocytes increasing due to release from the marrow storage pool.
- ✓ Prolonged use of corticosteroids can lead to chronic neutrophilia by decreasing the rate at which neutrophils leave circulation.
- ✓ Epinephrine can cause granulocytosis within minutes and probably is the mediator of neutrophilic leukocytosis associated with physiologic stimuli such as exercise, emotional stress, or exposure to extreme temperatures.
- ✓ Other drugs that can stimulate neutrophilia include lithium, histamine, heparin, digitalis, and many toxins, venoms, and heavy metals (e.g., lead, mercury).

- ✓ Neutropenia is a result of impaired production, increased removal from blood, or altered distribution of neutrophils.
- ✓ It occurs when the absolute neutrophil count is below the normal range and is associated with certain bacterial (e.g., typhoid, tularemia, brucellosis), viral (e.g., measles, rubella), and protozoal (e.g., malaria) infections, or an overwhelming infection of any kind.
- ✓ This can occur when demand exceeds supply and neutrophils leave circulation and migrate to tissues faster than they can be replaced by the bone marrow.
- ✓ It can be caused by drugs interfering with DNA synthesis (e.g., lamivudine, zidovudine, phenothiazines, anticonvulsants, antibiotics, sulfonamides), idiosyncratic drug reactions (e.g., chloramphenicol, gold salts, antithyroid drugs, indomethacin, quinidine), or treatment with cytotoxic drugs or ionizing radiation.
- ✓ There can be increased destruction of neutrophils through immunologic mechanisms in patients receiving drugs such as aminopyrine, phenylbutazone, or sulfapyridine.
- ✓ Neutropenia is also seen with hypersplenism due to liver or storage diseases, some collagen-vascular diseases (e.g., lupus erythematosus), and folic acid or vitamin B_{12} deficiency.
- ✓ A more severe form of neutropenia is agranulocytosis, in which the granulocytes suddenly disappear.
- ✓ Often other blood elements are also affected.
- ✓ Agranulocytosis can occur as a complication of drug therapy (e.g., clozapine and ticlopidine).

➢ **EOSINOPHILS**

- ✓ **Normal Range: 0 to 500 mm^{-3} (0 to 0.5 × 10^9/L);**
- ✓ **CF = 0.001**
- ✓ Eosinophils are structurally similar to neutrophils but their cytoplasm contains larger round or oval granules that contain enzymes and have a strong affinity for acid (red) stains.
- ✓ Their nuclei usually contain two connected segments.
- ✓ Eosinophils normally average 3% of leukocytes.
- ✓ The count is higher in individuals with allergic conditions.
- ✓ Eosinophils are capable of phagocytosis but are not bactericidal.
- ✓ They modulate activities associated with immunologically mediated inflammation and can destroy some helminth parasites.
- ✓ Eosinophils are increased in allergic diseases (e.g., asthma, hay fever), parasitic infections (e.g., trichinosis), infectious diseases (e.g., scarlet fever, human immunodeficiency virus infection), certain skin disorders (e.g., atopic dermatitis, eczema, pemphigus), neoplastic diseases, collagen vascular diseases, adrenal cortical hypofunction, ulcerative colitis, and "hypereosinophilic" syndrome.
- ✓ Eosinophilia may also be associated with drug use (e.g., pilocarpine, digitalis, sulfonamides).
- ✓ Eosinophils are decreased during acute stress or other conditions with increased epinephrine secretion or elevated levels of adrenal corticosteroids, and in acute inflammatory states.

➢ **BASOPHILS**

- ✓ **Normal Range: 0 to 200 mm^3 (0 to 0.2 × 10^9/L);**

- ✓ **CF = 0.001**
- ✓ Basophils look similar to neutrophils except that their nuclei are less segmented and their cytoplasmic granules are larger and have a strong affinity for basic (blue) stains.
- ✓ They average about 0.5% of total leukocytes.
- ✓ They show diurnal variation, with levels highest during the night and lowest in the morning.
- ✓ Tissue mast cells have some characteristics and functions similar to basophils.
- ✓ Both basophils and mast cells bind immunoglobulin E on their cell membranes.
- ✓ They react with antigens and cause release of histamine, slow-reacting substance of anaphylaxis, and other substances from the basophil granules, producing immediate hypersensitivity reactions.
- ✓ Basophils may be increased in allergic reactions, myeloproliferative disorders, chronic hemolytic anemia, hypothyroidism, and following splenectomy.
- ✓ They may be decreased with chronic corticosteroid therapy, acute infection or stress, or in patients with hyperthyroidism.

➢ **LYMPHOCYTES**

- ✓ Normal Range: 1,000 to 4,800 mm^3 (1.0 to 4.8 × 10^9/L)
- ✓ CF = 0.001
- ✓ Lymphocytes are mononuclear cells without cytoplasmic granules.
- ✓ They average 34% of leukocytes in adults.
- ✓ They may form plasma cells which are not normally present in blood.
- ✓ Plasma cells may be found in patients with neoplasms (e.g., multiple myeloma), viral or chronic infections, allergic states, and other conditions with increased gamma-globulin concentrations.
- ✓ Lymphocytes and plasma cells are important for the immune defenses of the body.
- ✓ Normally, the majority of circulating lymphocytes are T cells, which are responsible for cell-mediated immunity including delayed hypersensitivity, graft rejection, graft-versus-host reactions, defense against intracellular organisms, and defense against neoplasms.
- ✓ They have a life span of months to years.
- ✓ They are named for the thymus gland, where they differentiate.
- ✓ Natural killer (NK) cells share a precursor with T cells and develop in the bone marrow.
- ✓ They target virus-infected cells and participate in antibody-dependent cell lysis.
- ✓ B-lymphocytes (B cells) account for 10% to 20% of circulating lymphocytes and are responsible for humoral immunity.
- ✓ In humans, the bursal equivalent is thought to be in fetal liver and bone marrow, with further differentiation occurring in secondary lymphoid organs.
- ✓ These organs, important for postnatal lymphocyte production, include the spleen, lymph nodes, and intestine.
- ✓ B-cells have a life span of days and can differentiate into antibody-producing plasma cells.
- ✓ There are also “null” or unmarked (non-T, non-B) lymphocytes that cannot be classified.

- ✓ Although lymphocytes can be found in circulation, they mainly concentrate in the lymph nodes, spleen, mucosa of alimentary and respiratory tracts, bone marrow, liver, skin, and chronically inflamed tissue.
- ✓ Changes in the proportion of lymphocytes in the total leukocyte count usually reflect changes in numbers of granulocytes.
- ✓ An absolute or relative increase in lymphocytes occurs with some viral or other infections (e.g., tuberculosis, infectious mononucleosis, cytomegalovirus, pertussis, toxoplasmosis, hepatitis, mumps, chickenpox), thyrotoxicosis, Addison disease, inflammatory bowel disease, vasculitis, and hypersensitivity reactions to drugs (e.g., phenytoin, paraaminosalicylic acid).
- ✓ When the number of lymphocytes is decreased abnormally (lymphocytopenia) or function is impaired, the patient suffers from immunodeficiency.
- ✓ This can be an inherited disorder or may be associated with immunodeficiency syndromes (e.g., acquired immune deficiency syndrome [AIDS]).
- ✓ Lymphocytopenia may occur with diseases such as CHF, renal failure, miliary tuberculosis, myasthenia gravis, systemic lupus erythematosus, or with defects of lymphatic drainage.
- ✓ Lymphocytopenia can also occur after irradiation or administration of antineoplastic drugs, or with high concentrations of adrenocortical hormones.
- ✓ Lymphocyte dysfunction may be observed with chronic lymphocytic leukemia, multiple myeloma, Hodgkin disease, sarcoidosis, leprosy, malnutrition, or terminal malignancy.

➢ **MONOCYTES**

- ✓ Normal Range: 0 to 800 mm^3 (0 to 0.8 × 10^9/L];
- ✓ CF = 0.001
- ✓ Monocytes are the largest cells in normal blood with a diameter two to three times that of erythrocytes.
- ✓ They have a single nucleus that is partly lobulated and may appear round, oval, or horseshoe shaped.
- ✓ Their cytoplasm contains fine granules.
- ✓ Monocytes average 4% of leukocytes.
- ✓ After circulating briefly, they enter the tissues and transform into the larger macrophages, and remain there for several months.
- ✓ Macrophages are capable of motility, phagocytosis, killing microorganisms and malignant cells, and interactions with the immune system.
- ✓ They synthesize and secrete many biologically active molecules.
- ✓ They have important functions in host defense and control of hematopoiesis.
- ✓ They remove old or defective blood cells in the marrow and inhaled particles in the lungs.
- ✓ Monocytes are increased in some infectious diseases (e.g., mycotic, rickettsial, protozoal, viral infections; tuberculosis, subacute bacterial endocarditis), leukemias, lymphomas, sarcoidosis, inflammatory bowel disease, and connective tissue disorders.
- ✓ The circulating monocytes and tissue macrophages together compose the mononuclear phagocyte or RES.

➢ **PLATELETS**

- ✓ **Normal Range: 130 to 400 × 10^3/mm^3 (130 to 400 × 10^9/L)**

- ✓ **CF = 1**
- ✓ Platelets maintain the integrity of blood vessels and play a key role in hemostasis. The precursors of platelets are megakaryocytes.
- ✓ Their proliferation, differentiation, and maturation are controlled by megakaryocyte colony-stimulating factor (Meg-CSF) and thrombopoietin.
- ✓ Normally, about two thirds of platelets are in circulation and one third in the spleen.
- ✓ However, when the spleen is enlarged up to 80% to 90% may be sequestered there.
- ✓ In patients without a spleen, all are in circulation.
- ✓ Platelets circulate for about 8 to 11 days.
- ✓ Platelets are removed from circulation by the mononuclear phagocytic system.
- ✓ Antibodies may also destroy platelets.
- ✓ They may be directed against the platelets, or the platelets may be "innocent bystanders" that are destroyed when an immune complex attaches to them.
- ✓ Immune destruction of platelets may occur with exposure to drugs such as platelet glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban), carbamazepine, quinine, quinidine, gold salts, sulfonamides, or heparin.
- ✓ Thrombocytopenia, a reduced number of circulating platelets, can occur as a congenital or acquired disorder.
- ✓ It may result from decreased production, abnormal distribution or dilution, or increased destruction of platelets.
- ✓ These may be associated with factors such as malignancies, immune processes, infections, exposure to drugs or chemicals, or an enlarged spleen, and may be combined with abnormalities of other blood elements such as in aplastic anemia.
- ✓ Thrombocytosis, an increased number of circulating platelets, can be part of a reactive process (e.g., infections, chronic inflammation, severe trauma) or a myeloproliferative disorder.
- ✓ Half of patients with an otherwise unexplained increase in platelets are found to have a malignancy.
- ✓ Platelets are activated at times of vascular injury by exposure to substances such as collagen and thrombin.
- ✓ They adhere to exposed surfaces and aggregate in the presence of calcium.
- ✓ They release adenosine diphosphate (ADP) that promotes further aggregation.
- ✓ When platelets are activated, glycoprotein IIb/IIIa receptors on their membranes undergo conformational changes that allow binding of fibrinogen and von Willebrand factor.
- ✓ This leads to cross-linkage of platelets and formation of a platelet plug.
- ✓ Aggregation is also stimulated by thromboxane A_2 from platelets and inhibited by prostacyclin (prostaglandin I_2) from vascular endothelium.
- ✓ Both are products of arachidonic acid metabolism mediated by cyclooxygenase.
- ✓ Platelets also release various substances that activate or allow progression of the clotting cascade.
- ✓ These actions lead to the formation of thrombi. Overall platelet function may be assessed by the bleeding time.
- ✓ Various in vitro techniques using activator substances may also be used to assess platelet aggregation.
- ✓ Platelet contraction within thrombi is responsible for clot retraction.

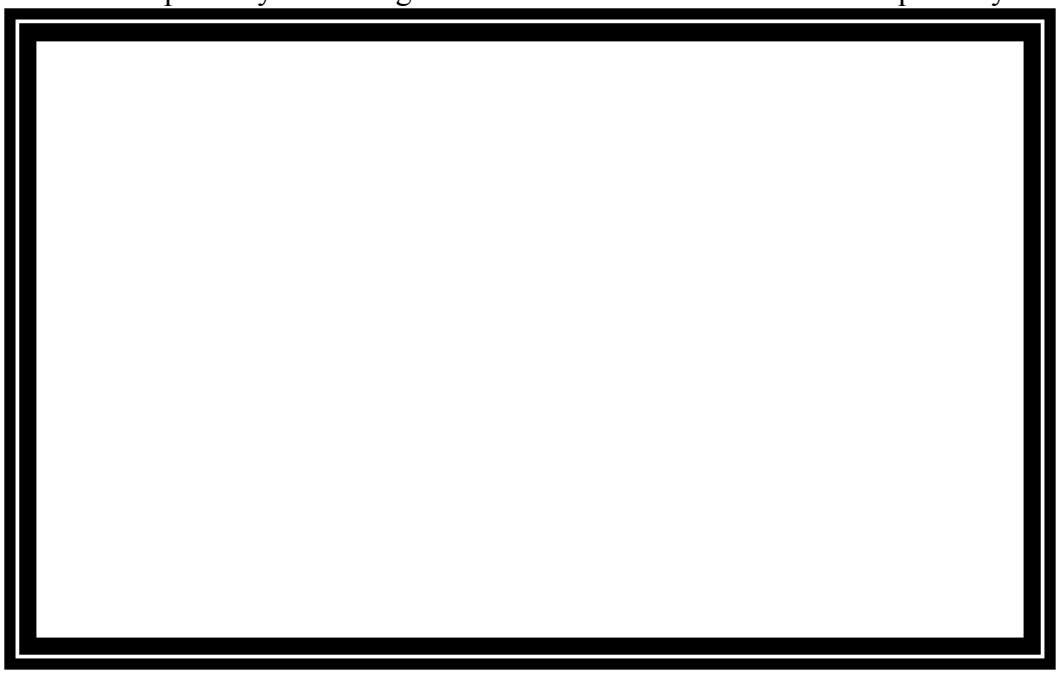
- ✓ **If the platelet count is 20 to 50 × 10^3/mm^3 (20 to 50 × 10^9/L), the patient is at a high risk for minor spontaneous bleeding and bleeding after surgery, and if it is less than 20 × 10^3/mm^3 (20 × 10^9/L), the patient is at risk for more serious bleeding.**
- ✓ Platelet function is impaired in various diseases such as uremia, myeloproliferative or lymphoproliferative disorders, myeloma, systemic lupus erythematosus, chronic immunologic thrombocytopenic purpura, or disseminated intravascular coagulation.
- ✓ Numerous drugs can also interfere with platelet function. Most affect the arachidonic pathway shown in Figure.
- ✓ **Aspirin** irreversibly acetylates platelet cyclooxygenase, thus inhibiting aggregation for the life of the platelet by decreasing formation of thromboxane A_2.
- ✓ This effect is observed for up to 10 days following ingestion of aspirin.
- ✓ Most other nonsteroidal antiinflammatory drugs will also affect platelet cyclooxygenase, but it is a reversible effect observed only while the drug is present.
- ✓ **Other drugs** inhibit platelet effects by activating adenylate cyclase (e.g., prostaglandins) or inhibiting phosphodiesterase (e.g., dipyridamole), both of which result in increased cyclic adenosine monophosphate (CAMP).
- ✓ Ticlopidine and clopidogrel are drugs that inhibit ADP-induced platelet aggregation. Abciximab, a monoclonal antibody, is a platelet glycoprotein IIb/IIIa receptor antagonist.
- ✓ Examples of additional drugs that may inhibit aggregation include dextran, antimicrobial agents (e.g., penicillins, cephalosporins), psychotropics (e.g., imipramine, chlorpromazine), clofibrate, and beta-adrenergic blocking agents (e.g., propranolol).
- ✓ Synthesis of platelets is inhibited by flucytosine, interferons, thiazide diuretics, chloramphenicol, and numerous antineoplastic agents Ethanol can inhibit the synthesis and function of platelets.

HAEMATOLOGICAL DATA: TYPICAL NORMAL ADULT REFERENCE VAULES	
Haemoglobin	Males: 13.0-18.0 g/dL Females: 11.5-16.5 g/dL
Red blood cell count (RBC)	Male: 4.5-5.9 × 10^{12}/L Female: 3.8-5.2 × 10^{12}/L
Reticulate count	50-100 × 10^{9}/L
Packed cell volume (PCV)	Male: 0.40-0.52 Female: 0.37-0.47
Mean cell volume (MCV)	83-101 fL
Mean cell haemoglobin (MCH)	27-34 pg
Mean cell haemoglobin concentration (MCHC)	31.5-34.5 g/dL
White cell count (WBC)	4.0-11.0 × 10^{9}/L
Different white cell count: Neutrophils (30-75%) Lymphocytes (5-15%) Monocytes (2-10%) Basophils (<1%) Eosinophils (1-6%)	 2.0-7.0 × 10^{9}/L 1.5-4.0 × 10^{9}/L 0.2-0.8 × 10^{9}/L <0.1 × 10^{9}/L 0.04-0.4 × 10^{9}/L
Platelets	150-450 × 10^{9}/L
Erythrocyte sedimentation rate (ESR)	< 10 mm/h
Serum iron	13-32 µmol/L
Transferrin	1.2-2.0 µmol/L
Ferritin	Male: 21-300 µg/L Female: 15-150 µg/L
Total iron binding capacity (TIBC)	47-70 µmol/L
Serum B_{12}	170-700 ng/L
Red cell folate	160-600 µg/L
Iron	11-29 µmol/L
Transferring	1.7-3.4 g/L

COAGULATION TESTS

- **CLOTTING CASCADE**
  - ✓ The clotting cascade involves the progressive activation of clotting factors, with the end result of a stable fibrin clot.
  - ✓ Platelets and other substances help or accelerate this process. A simplified diagram of the traditional clotting cascade is shown in Figure.
  - ✓ The process is actually much more complex, with additional clotting factor interactions not shown.
  - ✓ The clotting factors are identified by Roman numerals, although they also have other names.
  - ✓ Each factor must be activated before it can in turn activate other factors in the cascade.
  - ✓ The active forms of most factors are serine proteases, except V and VIII that act as cofactors.
  - ✓ Factors II, VII, IX, and X require vitamin K for their synthesis.
  - ✓ The main source of phospholipid is platelets.

- ✓ Ionized calcium is required for some of the steps to proceed.
- ✓ The intrinsic pathway is initiated by contact activation, for example, by exposure to damaged vascular endothelium.
- ✓ The extrinsic pathway is stimulated by factors released from damaged tissue.
- ✓ The two pathways come together at factor X to form the common pathway.



- ✓ Different tests are used to assess the body's ability to form a clot, by evaluating the function of different parts of the clotting cascade.
- ✓ They can also be used to monitor anticoagulant drug therapy.
- ✓ For most coagulation tests, the blood is centrifuged to remove platelets.
- ✓ Citrate is added to bind calcium and thus prevent the cascade from progressing.
- ✓ Patients with defective or deficient clotting factors can experience bleeding.
- ✓ This may be a congenital disorder such as hemophilia, where there is a deficiency of factor VIII or IX, an acquired disorder such as the impaired factor synthesis seen in liver disease, vitamin K deficiency, or an effect of drugs.

- **ACTIVATED PARTIAL THROMBOPLASTIN TIME (aPTT)**
  - ✓ **Normal Range: 25 to 38 seconds.**
  - ✓ The activated partial thromboplastin time (aPTT) is used to assess the integrity of the intrinsic and common coagulation pathways.
  - ✓ It is performed by adding a contact activating agent (e.g., kaolin, ellagic acid, silica, or celite), phospholipid, and calcium to citrated plasma, then measuring the time required for a clot to form.
  - ✓ It will be prolonged if there is a deficiency of factor XII, XI, IX, VIII, X, V, II, fibrinogen, prekallikrein, high molecular weight kininogen, or if an inhibitor of one of those is present.
  - ✓ A mixing study can be used to distinguish between a factor deficiency and presence of a factor inhibitor (e.g., lupus anticoagulant) in patients with a prolonged aPTT.
  - ✓ Patient and normal plasma are mixed together. If the aPTT corrects, there is a factor deficiency.
  - ✓ If the aPTT remains abnormal, a factor inhibitor is present.

- ✓ The aPTT is not affected by abnormal factor VII or XIII.
- ✓ The aPTT usually is prolonged when the plasma concentration of the clotting factors is less than 15% to 30% of normal.
- ✓ It is sometimes abnormal in those with liver failure, since many clotting factors are synthesized in the liver.
- ✓ It may be shortened in an active coagulopathy.
- ✓ It is the most common test used to monitor unfractionated heparin therapy, and can be prolonged in the presence of thrombolytic drugs or coumarin derivatives.

➢ **PROTHROMBIN TIME**

- ✓ **Normal Range:11 to 16 seconds**
- ✓ The prothrombin time (PT) is used to evaluate the extrinsic and common pathways.
- ✓ Tissue thromboplastin (e.g., brain, lung, or placenta extract or recombinant human tissue factor with phospholipid) and calcium are added to citrated plasma, and the time to clot formation is measured.
- ✓ The PT is prolonged if there is a deficiency of factor VII, X, V, or II, or fibrinogen, (concentrations <10% of normal), or the presence of an inhibitor to one of those factors.
- ✓ It is not affected by abnormal factor VIII, IX, XI, or XII. For standardization of test results, the PT is expressed as the International Normalized Ratio (INR).
- ✓ This is calculated by the formula INR = PT ratio, where the PT ratio is the ratio of the patient's PT to mean normal PT, and ISI is the International Sensitivity Index, which relates an individual batch of thromboplastin to the World Health Organization international reference preparation.
- ✓ The PT is prolonged in liver disease, in patients with a vitamin K deficiency, and in disseminated intravascular coagulation.
- ✓ It is used to monitor coumarin (e.g., warfarin) treatment, but may be prolonged by the presence of heparin or a thrombolytic drug.

➢ **ANTIFACTOR Xa ACTIVITY ASSAY**

- ✓ **Normal Range : 0.6 to 1.0 IU/mL**
- ✓ Antifactor Xa activity can be used to gauge the concentration of heparin or danaparoid present in plasma.
- ✓ The chromogenic antifactor Xa assay method is preferred for monitoring low molecular weight heparin.
- ✓ The patient's citrated plasma is mixed with excess antithrombin, then a known amount of factor Xa.
- ✓ After a substrate is added, residual factor Xa is measured.
- ✓ For most patients, it is not necessary to monitor low molecular weight heparin with laboratory tests.
- ✓ It is, however, useful in pediatric and pregnant patients, very obese or underweight patients, or those with renal dysfunction or malignancy.
- ✓ It may also be monitored in those at high risk for thromboembolism or bleeding.
- ✓ Antifactor Xa activity should be checked at peak concentrations of the low-molecular-weight heparin, 4 hours after a subcutaneous injection.
- ✓ The desired range is 0.6 to 1.0 IU per mL if dosed every 12 hours and 1.0 to 2.0 IU per mL for once a day administration.

➢ **THROMBIN TIME**

- ✓ **Normal Range: 12 to 18 seconds**

- ✓ The thrombin time (TT) is used to assess the body's ability to convert fibrinogen to fibrin.
- ✓ Thrombin is added to citrated plasma, and the time for clotting is measured.
- ✓ The thrombin time is prolonged if there is a deficiency or abnormality of fibrinogen, or if heparin, hirudin, or fibrin degradation products are present.
- ✓ It can also be increased in patients with uremia, high concentrations of monoclonal immunoglobulins (e.g., myeloma or macroglobulinemia), or antithrombin antibodies.
- ✓ It may also be used in monitoring thrombolytic therapy (e.g., streptokinase or urokinase).

➢ **BLEEDING TIME**

- ✓ **Normal Range: 120 to 480 seconds**
- ✓ The bleeding time may be used as a screening test to assess platelet function, although it is imprecise.
- ✓ It may be useful in evaluating a patient with a history of increased bleeding but does not appear to predict risk for perioperative bleeding.
- ✓ It is performed by making a uniform incision on the arm while a blood pressure cuff on the upper arm is inflated to maintain a constant pressure of 40 mm Hg.
- ✓ Blood that bead up is removed every 30 seconds by filter paper with care taken not to touch the wound and disturb platelet plugs.
- ✓ The blood is removed to prevent fibrin from forming and stopping the bleeding.
- ✓ The endpoint of the test is when there is no longer a spot on the filter paper after blotting.
- ✓ The test is prolonged when there is platelet dysfunction, when the number of platelets is less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$), or when a platelet-inhibiting drug, such as aspirin, is present.
- ✓ It also is prolonged in patients with uremia or von Willebrand disease.
- ✓ If the bleeding time is shorter than expected, many young, active platelets may be present.

➢ **D-DIMER**

- ✓ **Normal Range: <0.5 µg/mL (<0.5 mg/L);**
- ✓ **CF = 1**
- ✓ D-dimer fragments are produced when crossed-linked fibrin is lysed by plasmin.
- ✓ Their presence provides evidence of a physiologic response to venous thrombosis.
- ✓ The various D-dimer assays all use monoclonal antibodies but they vary in their sensitivity and specificity.
- ✓ For example, the enzyme-linked immunosorbent assay (ELISA) and automated latex immunoassay have high sensitivity (96% to 99%) and low specificity (~40%) for detecting venous thrombosis.
- ✓ This means that most patients with pulmonary embolism or deep vein thrombosis will have elevated D-dimer concentrations, but so will many patients with other disorders (e.g., malignancy, infections, MI, heart failure, or recent surgery).
- ✓ D-dimer values also increase with age and pregnancy.
- ✓ A normal D-dimer concentration can be used to rule out a thromboembolic disorder in patients with low clinical probability of pulmonary embolism or deep vein thrombosis.

- ✓ The test is more useful in outpatients than those who are hospitalized since the latter are more likely to have one or more of the other conditions that can increase D-dimer values.
- ✓ An elevated D-dimer test is also an important component in establishing a diagnosis of disseminated intravascular coagulation (DIC), also called **consumption coagulopathy.**
- ✓ Other typical laboratory findings in DIC include decreased platelets and fibrinogen, prolonged PT and aPPT, and increased fibrin degradation products.

ELECTROLYTES

- ➢ **SODIUM (Na)**
  - ✓ Sodium is the major cat ion of the extracellular fluid.
  - ✓ Sodium along with chloride (Cl), potassium (K), and water is important in the regulation of osmotic pressure and water balance between intracellular and extracellular fluids.
  - ✓ **Normal values are 135-147 mEq/L or mmol /L.**
  - ✓ The sodium concentration is defined as the ratio of sodium to water, not the absolute amounts of either.
  - ✓ **Laboratory tests for sodium are used mainly to detect disturbances in water balance and body osmolality.**
  - ✓ The kidneys are the major organs of sodium and water balance.
  - ✓ An **Increase** in sodium concentration (hypernatremia) may indicate impaired sodium excretion or dehydration.
  - ✓ A **Decrease** in sodium concentration (hyponatremia) may reflect overhydration, abnormal sodium loss, or decreased sodium intake.
  - ✓ Patients with kidney, heart, or pulmonary disease may have difficulty with sodium and water balance.
  - ✓ In adults, changes in sodium concentrations most often reflect changes in water balance, not salt imbalances.
  - ✓ Therefore, sodium concentrat ion is often used as an indicator of fluid status, rather than salt imbalance.
  - ✓ **Control of sodium by the body is accomplished mainly through the hormones aldosterone and antidiuretic hormone (ADH).**
    - ADH is released from the pituitary gland in response to signals from the hypothalamus.
    - ADH's presence in the distal tubules and collecting ducts of the kidney causes them to become more permeable to the reabsorption of water; therefore, concentrating urine.
    - Aldosterone affects the distal tubular reabsorption of sodium as opposed to water.
    - Aldosterone is released from the adrenal cortex in response to low sodium, high potassium, low blood volume, and angiotensin II.
    - Aldosterone causes the spilling of potassium from the distal tubules into the urine in exchange for sodium reabsorption.
  - ✓ **HYPONATREMIA** is usually related to total body **depletion of sodium**—as in mineralocorticoid deficiencies, sodium-wasting renal disease, replacement of fluid loss with nonsaline solutions, gastrointestinal (GI) losses, renal losses, or loss of sodium through the skin—or to dilution of serum sodium—as in cirrhosis, CHF,

nephrosis, renal failure, excess water intake, or syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

- ✓ **HYPERNATREMIA** usually results from a loss of free water or hypotonic fluid or through excessive sodium intake.
- ✓ Free water loss is most often associated with diabetes insipidus, but fluid loss can be via the GI tract, renal, skin, or respiratory systems.
- ✓ Excess sodium intake can occur through the administrat ion of hypertonic intravenous (IV) solutions, mineralocorticoid excess, excessive sodium ingestion, or after administration of drugs high in sodium content (e.g. ticarcillin, sodium bicarbonat).

➢ **POTASSIUM (K)**

- ✓ Potassium is the most abundant intracel lular cation (intracellular fluid potassium averages 141 mEq/L).
- ✓ Approximately 3500 mEq of potassium is contained in the body of a 70-kg adult.
- ✓ Only 10% of the body's potassium is extracellular.
- ✓ **Normal values are 3.5-5.0 mEq/L or mmol/L.**
- ✓ The serum potassium concentration is not an adequate measure of the total body potassium because most of the body's potassium is intracellular. Fortunately, the clinical signs and symptoms of potassium deficiency—malaise, confusion, dizziness, electrocardiogram (ECG) changes, muscle weakness, and pain—correlate well with serum concentrations.
- ✓ The serum potassium concentration is buffered by the body and may be "normal" despite total body potassium loss.
- ✓ Potassium depletion causes a shift of intracellular potassium to the extracellular fluid to maintain potassium concentrations.
- ✓ There is approximately a 100 mEq total body potassium deficit when the serum potassium concentration decreases by 0.3 mEq/L.
- ✓ This may result in misinterpretation of serum potassium concentrations as they relate to total body potassium.
- ✓ The role or function of potassium is in the maintenance of proper electrical conduct ion in cardiac and skeletal muscles (muscle and nerve excitability), it exerts an influence on the body's water balance (intracellular volume) and plays a role in acid-base equilibrium.
- ✓ Potassium is regulated by:
  a. Kidneys (renal function)
  b. Aldosterone
  c. Arterial pH
  d. Insulin
  e. Potassium intake
  f. Sodium delivery to distal tubules
- ✓ **Hypokalemia**
- ✓ The kidneys are responsible for approximately 90% of the daily potassium loss. Other losses occur mainly through the GI system.
- ✓ Even in states of no potassium intake, the kidneys still excrete up to 20 mEq of potassium daily.
- ✓ Therefore, prolonged periods of potassium deprivation can result in **Hypokalemia**.

- ✓ Hypokalemia can also result from potassium loss through vomiting or diarrhea, nasogastricsuction, laxative abuse, and by diuretic use (mannitol, thiazides, or loop diuretics).
- ✓ Excessive mineralocorticoid activity and glucosuria can also result in hypokalemia.
- ✓ Potassium can be shifted into cells with alkalemia and after administration of glucose and insulin.
- ✓ **HYPERKALEMIA** most commonly results from decreased renal elimination, excessive intake, or from cellular breakdown (tissue damage, hemolysis, burns, infections).
- ✓ Metabolic acidosis may also result in a shift of potassium extracellularly as hydrogen ions move into cells and are exchanged for potassium and sodium ions.

➢ **CHLORIDE (Cl)**

- ✓ Chloride is the major anion of the extracellular fluid and is important in the maintenance of acid-base balance.
- ✓ Alterations in the serum chloride concentration are rarely a primary indicator of major medical problems.
- ✓ Chloride itself is not of primary diagnostic significance.
- ✓ It is usually measured to confirm the serum sodium concentration.
- ✓ **The normal value for Cl is 95-105 mEq/L or mmol/L.**
- ✓ **Hypochloremia** is a decreased chloride concentration, and it is often accompanied by metabolic alkalosis or acidosis caused by organic or other acids.
- ✓ Other causes include chronic renal failure, adrenal insufficiency, fasting, prolonged diarrhea, severe vomiting, and diuretic therapy.
- ✓ **Hyperchloremia** is an increased chloride concentration that may indicate hyperchloremic metabolic acidosis.
- ✓ Hyperchloremia in the absence of metabolic acidosis is unusual because chloride retention is often accompanied by sodium and water retention.
- ✓ Other causes include acute renal failure, dehydration, and excess chloride administration.

➢ **BICARBONATE /CARBON DIOXIDE (CO_2) CONTENT**

- ✓ The carbon dioxide (CO_2) content represents the sum of the bicarbonate concentration and the concentration of CO_2 dissolved in the serum.
- ✓ The CO_2 system is the most important buffering system to maintain pH within physiological limits.
- ✓ Most disturbances of acid-base balance can be considered in terms of this system.
- ✓ **Normal values are 22-28 mEq/L or mmol /L.**
- ✓ Clinically, the serum concentration is measured because acid-base balance can be inferred if the patient has normal pulmonary function.
- ✓ **Hypobicarbonatemia** is usually caused by metabolic acidosis, renal failure, hyperventilation, severe diarrhea, drainage of intestinal fluid, and by drugs such as acetazolamide.
- ✓ Toxicity caused by salicylates, methanol , and ethylene glycolcan also decrease the level .
- ✓ **Hyperbicarbonatemia** is usually caused by alkalosis, hypoventilation, pulmonary disease, persistent vomiting, excess intake with poor renal function, and diuretics.

MINERALS

- **CALCIUM (Ca)**
  - ✓ Calcium plays an important role in nerve impulse transmission, muscle contraction, pancreatic insulin release, hydrogen ion release from the stomach, as a cofactor for some enzyme reactions and blood coagulation, and most important bone and tooth structural integrity.
  - ✓ **Normal total calcium values are 8.8-10.3 mg/dL or 2.20-2.56 mmol /L.**
  - ✓ The total calcium content of normal adults is 20-25 g/kg of fat - free tissue, and about 44% of this calcium is in the body skeleton.
  - ✓ Approximately 1% of skeletal calcium is freely exchangeable with that of the extracellular fluid.
  - ✓ The reservoir of calcium in bones maintains the concentration of calcium in the plasma constant.
  - ✓ About 40% of the calcium in the extracellular fluid is bound to plasma proteins (especially albumin), 5%-15% is complexed with phosphate and citrate, and 45%-55% is in the unbound, ionized form.
  - ✓ Most laboratories measure the total calcium concentration; however, it is the free, ionized calcium that is important physiologically.
  - ✓ Ionized calcium levels may be obtained from the laboratory.
  - ✓ Clinically, the most important determinant of ionized calcium is the amount of serum protein (albumin) available for binding.
  - ✓ The normal serum calcium range is for a serum albumin of 4 g/dL.
  - ✓ A good approximation is that for every 1 g/dL decrease in albumin, 0.8 g/dL should be added to the calcium laboratory result.
  - ✓ Doing this corrects the total plasma concentration to reflect the additional amount of free (active) calcium.
  - ✓ **Hypocalcemia** usually implies a deficiency in either the product ion or response to parathyroid hormone (PTH) or vitamin D.
  - ✓ PTH abnormalities include hypoparathyroidism, pseudo-hypoparathyroidism, or hypomagnesemia.
  - ✓ Vitamin D abnormalities can be caused by decreased nutritional intake, decreased absorption of vitamin D, a decrease in production, or an increase in metabolism.
  - ✓ **Administation of loop diuretics causing diuresis can also decrease serum calcium.**
  - ✓ **Hypercalcemia** is an increased calcium concent ration, and it is usually associated with malignancy or metastatic diseases.
  - ✓ Other causes include hyperparathyroidism, Paget disease, milk-alkali syndrome, granulomatous disorders, thiazide diuretics, excessive calcium intake, or vitamin D intoxication.
- **PHOSPHATE (PO_4)**
  - ✓ Phosphate is a major intracellular anion and is the source of phosphate for adenosine triphosphate (ATP) and phospholipid synthesis.
  - ✓ Serum calcium and PO_4 are influenced by many of the same factors. It is useful to consider calcium and PO_4 together when interpreting lab results.
  - ✓ **Normal PO_4 values are 2.5-5.0 mg/dL or 0.80-1.60 mmol /L.**
  - ✓ Hyperphosphatemia and hypophosphatemia can occur.

- ✓ The extracellular fluid concentration of phosphate is influenced by PTH, intestinal absorption, renal function, nutrition, and bone metabolism.
- ✓ **Hyperphosphatemia** is usually caused by renal insufficiency, although increased vitamin D or phosphate intake, hypoparathyroidism, and hyperthyroidism are also causes.
- ✓ **Hypophosphatemia** can occur in malnutrition, especially when anabolism is induced, after administration of aluminum-containing antacids or calcium acetate, in chronic alcoholics, and in septic patients.
- ✓ Hyperparathyroidism and insufficient vitamin D intake can also induce hypophosphatemia.

➢ **MAGNESIUM (MG)**

- ✓ Magnesium is the second most abundant intracellular and extracellular cation.
- ✓ It is an activator of numerous enzyme systems that control carbohydrate, fat and electrolyte metabolism, protein synthesis, nerve conduct ion, muscular contractility, as well as membrane transport and integrity.
- ✓ **Normal values are 1.6-2.4 mEq/L or 0.8-1.20 mmol /L.**
- ✓ Hypomagnesemia and hypermagnesemia can occur.
- ✓ **Hypomagnesemia** is found more often than hypermagnesemia.
- ✓ Depletion of magnesium usually results from excessive loss from the GI tract or the kidneys.
- ✓ Depletion can occur from either poor intestinal absorption or excessive GI fluid loss.
- ✓ Signs and symptoms include weakness, muscle fasciculations with tremor, tetany, and increased reflexes.
- ✓ Decreased intracardiac magnesium may manifest as an increased QT interval with an increased risk of arrhythmia.
- ✓ **Hypermagnesemia** is most commonly caused by increased magnesium intake in the set ting of renal insufficiency.
- ✓ Other causes include excess magnesium intake, hepatitis, and Addison disease.
- ✓ Signs and symptoms of hypermagnesemia include bradycardia, flushing, sweating, nausea and vomiting, decreased calcium level, decreased deep- tendon reflexes, flaccid paralysis, increased pulse rate and QRS intervals, respiratory distress, and asystole.