MIND MAPS IN CLINICAL CHEMISTRY Part I

Simmi Kharb

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100

(Part I)

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Mind Maps in Clinical Chemistry (Part I)

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PREFACE

This book treats clinical chemistry as an interdisciplinary subject to teach the importance of lab both for students in basic science as well as clinical medicine.

The approach to clinical chemistry in real clinical situations requires knowledge, experience and an integrated and clinically relevant model. I have attempted to bring this integrated model together in the book.

The book has been written in a lucid manner and is packed with practical approach of lab tests targeting undergraduate and also 1st postgraduate students of various streams of medicine. The reader should gain the knowledge and understanding of the value, limitations and interpretation of lab tests in modern medicine.

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No potential conflict of interest is declared by the author. It is also declared the complete work is an individual effort by the author and there was no financial/ administrative/academic support availed from any individual/institution/ organization.

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Section I Introduction

CHAPTER 1

Collection and Processing of Specimens

Learning objectives:

- 1. Describe the method of sample collection.
- 2. Differentiate the factors affecting lab results of the patient.
- 3. Explain about sample processing.
- 4. Recognize and analyse the causes of errors in the lab.
- 5. Define POCT (Point of Care Testing) and its applications.

Collection of Sample

While blood, serum, plasma, urine, feces, saliva, sweat, amniotic, cerebrospinal, pericardial, peritoneal, pleural and synovial fluids are the biological specimens, they are analyzed in clinical chemistry laboratories.

Steps - 1. Preanalytical testing – Request

– Preparation of patient

– Preparation for collecting sample

2. Sample collection

Lab Test Request

The process of clinical laboratory investigation starts with a clinician making a request.

Test request form includes patient's demographics: patient's name, age, sex date of admission date on which request for lab test is made ward/clinic/address clinical diagnosis tests requested physician's identity.

Test request information is conveyed through written or computer order entry.

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Patient

• Correct interpretation of lab results can only be performed after careful consideration of individual patient factors (Table 1.1).

Table 1.1: Patient factors	affecting inter	rpretation of la	ab results
----------------------------	-----------------	------------------	------------

Age Sex Stress Body temperature Previous intake of food or liquid Drug therapy Race, individual variables

In general, patients scheduled for sampling should refrain from strenuous physical activity, alcohol, drugs, dietary change and should have usual time and amount of sleep (Table 1.2).

Facto	or	Examples	Reasoning
1.	<i>Between individual o</i> Age Sex	differences urea, alkaline phosphatase uric acid gonadal steroids HDL-C	Rise with age Higher in males Different between sexes Higher in premenopausal women
	Race	Creatine kinase	Higher in Africans than Caucasians
2.	Within individual var Circadian rhythm* Iron	<i>riations</i> Cortisol	Highest between 7-9 am Lowest between 11 pm to 4 a m Rise in stress Lost in Cushing's syndrome Higher in morning Reversed in night workers Monthly variation in female Low concentration just before or during menses
* 3.	Travel across several time zones affects normal circadian rhythm. Also, during prolonged flight, fluid and sodium retention occurs. <i>Others</i>		
	Pregnancy Posture	Thyroxine Proteins	Thyroxine binding globulin elevate from supine to upright position
	Exercise Nutritional status:	Creatine kinase	elevated
	High meat or protei	n: Urea, urate,	Rises

Table 1.2: Patient factors affecting lab reports

Contd...

Collection and Processing of Specimens

Contd...

serotonin-rich diet. bananas, pine apple	·,	raised serotonin
tomato recent food intake: FF, glucose, lipid		increased
fasting	Glucose	Fall
time	Bilirubin Cortisol	Rise after 48 hrs of fasting Circadian rhythm
Alcohol	Lactic acid Triglyceride	Elevated Elevated Elevated
Smoking	GGT Carboxyhemoglobin Cortisol Catecholamine Protein, AST	Elevated High levels High levels Decrease Excretion increased
Immobilization	Ca, Na, K, PO₄, SO₄	Falsely increased
Tourniquet	Lactate, calcium, proteins triglycerides	
Stress	Hormone, Lactate, FFA	Hormone secretion affected Elevated

Few Important Points

How Often a Test should be Ordered?

- i. Over investigation may be harmful, causing unnecessary discomfort or inconvenience to patient.
- ii. Frequency of sampling should be carefully decided, e.g. plasma protein concentration are unlikely to change significantly in less than a week, plasma urea will not change significantly during first 12 hours of oliguria.
- iii. Numerically significant changes sometimes do not alter treatment or course of disease, e.g. plasma transaminases.
- iv. Plasma potassium concentration may alter after diuretics and indicate need to investigate or change treatment.

Urgency

An urgent lab request is indicated when that investigation will alter the clinical management of patient.

Are the Differences Significant?

Biochemical results obtained on specimens taken sequentially from a single individual are frequently numerically different; consider the possible sources of variation:

i. Pre-analytical variation

Lab Hazards: Biological Hazards

Learning objectives:

- 1. Recognise the different lab hazards.
- 2. Illustrate Labelling identification system.

To operate a clinical laboratory safely, it is essential to prevent the exposure of laboratory workers to

infectious agents (Hepatitis B virus, HIV) by:

- i. accidental puncture with needles
- ii. spraying of these materials by syringe or spilling on benchtop or floor
- iii. centrifuge accidents
- iv. cuts or scratches from contaminated vessels (Fig 2.1)
- It is essential that specimens should be handled using universal precautions such as:
- 1. Handle all specimens with care by using barriers protection (glove, gown, lab coats, face shield, eye protection)
- 2. Never mouth pipette or blow out pipettes that contain potentially infectious materials.
- 3. Dispose all sharps appropriately.
- 4. Hepatitis B vaccination should be offered to all employees at risk of potential exposure (technician, phlebotomist, etc.) (Fig. 2.1).



Fig. 2.1: Lab hazards

Nine classes of hazardous materials (UN classification)

- 1. Explosives
- 3. Flammable liquids
- Oxidizer materials
 Radioactive materials
- 9. Miscellaneous materials.

- Compressed gases
 Flammable solids
- 6. Toxic materials
- 8. Corrosive materials



Lab Hazards: Biological Hazards

Hazard symbols and Labelling

Hazard symbols are recognizable symbols to warn about hazardous materials or locations. They may appear with different colors, backgrounds, border and supplemental information in order to signify the hazard (Fig 2.2, Fig 2.3)







Fig. 2.3: Labeling identification system

Safety in the Laboratory

One must always be aware that chemicals used in the laboratory are potentially toxic, irritating or inflammable. Such chemicals are a hazard, however, only when they are mishandled or improperly disposed off.

Proper disposal of all waste chemicals, sharp objects, and infectious agents is essentially not only to maintain safe laboratory working condition, but also to protect the general public and local environment.

Questions:

- 1. What are biological lab hazards?
- 2. Classify hazardous materials?
- 3. What are hazard symbols and labelling?
- 4. Elaborate the various safety measures taken in laboratory?
- 5. Explain Labeling identification system.

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Safety in the Laboratory

Learning objectives:

- 1. Evaluate the aspects of safe operations of a Clinical Chemistry lab.
- 2. Explain the guidelines for Lab safety.

A clinical chemistry laboratory should have formal safety program.

Aspects of Safe Operations of a Clinical Chemistry Lab:

- Formal safety program
- Mandated plans: Chemical hygiene plans

Blood-borne pathogen plans

• Identification of lab hazards:

biological chemical electrical fire

• OSHA, CDC approved hazard

• Communication standards



Fig. 3.1: Lab safety network material

Guidelines for Lab Safety

- 1. Each new employee should get general lab safety material, undergo orientation program.
- 2. Each employee should have knowledge of location of available evacuation routes, firefighting equipments and their operation.
- 3. Employee should undergo continuing education programs on lab safety.

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4. Supervision of lab safety measures in terms of:

- proper labeling, handling and disposal of chemicals in terms of hazards
- fire extinguisher
- -hoods
- earthing of electrical equipment
- proper handling and disposal of patient specimens.
- 5. Inspection: Periodic and scheduled safety inspections should be the routine.
- 6. Accreditation of lab with Health Care Organization.
- 7. Safe and scientific waste disposal and management.

Questions:

- 1. What are the aspects of Safe Operations of a Clinical Chemistry Lab?
- 2. Write the guidelines for lab safety.

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Biochemical Tests in Clinical Medicine

Learning objectives:

- 1. Discuss the purpose of biochemical tests.
- 2. Illustrate the outline of Lab workflow.

The purpose and function of laboratorians are to provide biochemical information to assist clinicians (Fig. 4.1) in:

1. diagnosis

- 2. management
- 3. prognosis
- 4. detection and screening
- 5. monitoring follow-up of disease
- 6. teaching, research and development.

For results to be useful for any of these purposes, they must be free of error.





Lab Test Request

Most clinicians use lab tests primarily on the basis of their own clinical expertise and interpret results intuitively, and their results are used on the basis of outcome measure. In selecting a test, it is essential to consider what type of information is required and whether the test would provide it or not.

A clinical chemistry laboratory performs a large number of biochemical analytes on body fluids which can give answers to specific clinical questions about an individual patient. Such analyses are requested by clinicians in blood and urine samples or treatment.

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The entire process from a request for analysis to receipt of a result involves several steps and can take many hours. Also, quality assurance for analyte is performed to ensure that results thus produced are analytically and clinically valid. Also timeliness, promptness or turnaround time of a test report is equally important in patient care.

The usual procedure by which a clinician obtains a medically useful result is an extremely complex chain of events (Fig. 1.1). This chain involves: clinicians, nurses, porter, technical staff, clinical biochemists or lab physician. Errors can occur at every link in the chain.

Samples to be analyzed must be collected under appropriate conditions and the analytical methods selected must be reliable. Also, the possible contribution of any analytical or biological variation should be considered.

Outline of Lab Workflow

Steps involved in generation of lab results (Fig. 1.4) towards a test result must be considered. The laboratory personnel must ensure that data are accurate and precise and the clinician should appreciate how useful the test is, the context in which it is used. Also, clinical staff should avail the opportunity to consult their lab colleagues about applications of lab tests in management of their patients. **Ouestions:**

- 1. What is the purpose and functions of lab tests?
- 2. Discuss Lab Test Request.

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Section II Metabolic Disorders

Bone Metabolism: Calcium, Phosphate and Magnesium

Learning objectives:

- 1. Discuss the normal metabolism of Calcium, Phosphorus and Magnesium in body.
- 2. Describe the metabolic disorders associated with Calcium, Phosphorus and Magnesium.
- 3. Demonstrate the markers of Bone Turnover.
- 4. Compare different disorders of mineralization of bone.

Normal Calcium Homeostasis

Calcium is the most abundant mineral in the human body. Bones and teeth contain 99 percent of calcium. An average human body contains 1 kg (24.95 mol) of calcium (Fig 5.1). Calcium is present in three main compartments:

- Skeleton 99 percent
- Soft tissue
- Extracellular fluid (ecf) 1 percent

Calcium is physiologically classified as either intracellular or extracellular. The skeleton is major reservoir for providing both extracellular and intracellular pools.

Intracellular calcium	Physiology of calcium	
	Muscle contraction	
	Hormonal secretion	
	Glycogen metabolism	
	Cell division	
Extracellular calcium	Source for maintenance of intracellular calcium	
	for bone mineralization	
	Coagulation cascade	
	Maintaining plasma membrane potential	
Functions of calcium		
Structural	Bone	
Suddulul	Teeth	
	Controls membrane potential	

	Controls memorane potential
Neuromuscular	Neuromuscular excitability
	Neurotransmitter release
Enzymatic Signaling	Coagulation cascade (as coenzyme)
	Intracellular second messenger

Total calcium in extracellular fluid is only 22.5 mmol (10 mg/dl) of which 9 mmol (4.1 mg/dL) is in plasma.

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Calcium in Plasma

Calcium exists in three physiochemical states in plasma:

50 percentfree or ionized40 percentbound to plasma proteins: 80 percent with albumin, 20 percent with globulin10 percentcomplexed with small anions.

Calcium Concentration

In normal adults, range of plasma concentration is 2.2 to 2.6 mmol/L (8.8 to 10.4 mg/dL). The concentration of free calcium ions, mean value being 1.2 mmol/L (4 to 8 mg/dL), is subject to tight hormonal control (Fig. 5.2). A decrease in serum free calcium concentration causes increased neuromuscular excitability and tetany.

Calcium Intake and Absorption

Calcium Intake

Average dietary calcium intake should be 0.6 to 0.8 g/d in adults. Less than half of it is absorbed. (Fig. 5.2)



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Metabolism: Phosphate and Magnesium

Calcium Absorption

Increased during period of rapid growth in -	
--	--

children pregnancy lactation

Decreased with advancing age

Site

Most calcium absorbed in proximal small intestine by active transport in upper part and by simple diffusion in lower part.

-

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Favor	Decrease
pH Acidic pH Dietary factors:	Alkaline pH
High protein-diet (esp. lysine, arginine) sugar and organic acid	Oxalate, phytate fibers
citric acid	Excess PO ₄ and Mg

Calcium Homeostasis

Key Target Organs of Control

Intestine Parathyroid glands Kidneys

35

Carbohydrates

Learning objectives:

- 1. Describe the role of different enzymes and hormones involved in carbohydrate metabolism.
- 2. Analyse the mechanism of blood glucose homeostasis.
- 3. Discuss Inborn errors of metabolism.
- 4. Describe disorders of Carbohydrates metabolism in detail.
- 5. Differentiate between Type I and Type II Diabetes Mellitus.
- 6. Explain the metabolic complications of Diabetes.

Carbohydrates are widely distributed in plants and animals performing multiple functions (Table6.1).

Table 6.1: Functions of carbohydrates

- 1. Structural
- 2. Source of energy
- 3. Storage
- Constituent of: DNA and RNA (deoxyribose, ribose sugars) Proteoglycan Glycosaminoglycan Glycoproteins Cell membranes
 Storad as glycoprot
- 5. Stored as glycogen

Glucose is a major fuel of tissues and cells. The body depends on glucose for energy. Body closely regulates blood glucose to maintain an adequate supply of glucose for cells. Diseases associated with carbohydrates include diabetes mellitus, galactosemia, glycogen storage diseases, and lactose intolerance. This chapter discusses carbohydrate metabolism and its abnormalities.

Metabolism: Carbohydrates

Through the process of digestion and absorption, carbohydrates in diets following metabolism provide glucose — primary source of energy. (Figs 6.1 to 6.3 and Table 6.1).

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Fig. 6.2: Glucose in action

REGULATION OF BLOOD GLUCOSE

Main hormones regulating blood glucose:

Insulin Glucagon

(Fig 6.3, Fig 6.4, Table 6.2)



Fig. 6.3: Actions of insulin and glucagon

Table 6.2: Hormones affecting carbohydrate, lipid metabolism and protein metabolism

Enz	zymes		Fed state	Fasting	Insulin	Glucagon	Other activators/ inhibitions
1	1. glycogen s	synthase	+	-	(+)	()	G-6-P
11.	1. Hexokinase 2. Glucokinase 3. PFK-1 4. Pyruvate k 5. PDH	e se sinase	+ + +	-	(+) (+) (+) (+) (+)	(-) (-) (-) (+)	AMP, F-6-P, F2,6-BIS P/ CITRATE, ATP F1,6 BIS P/ ATP, ALANINE ADD:ADP,NAD,PYRUVAT, CoA/ATP, NADH, ACETYL
Ш	GLUCONEOGEN	NESIS	T	-	(-)		CoA
	2. PEP carbo	oxykinase	-	+	-	+	Acetyl CoA/ADP (-)
	3. F-1-6, bisp 4. G-6-Pase PPP	bhosphatase	-	+ +	-	+ +	-/F 1, 6 bis PO ₄ , AMP, F 2, 6 bis PO ₄
IV	1. G-6-PD 2. 6-	DeH	+		+		
V	LIPID METABOI LIPOGENESIS	ISM		-	+ +		-
	1. Acetyl Co	A carboxylase	+	-	+		
VI	2. FA syntha LIPOLYSIS	se	+	-	+		
VII		Synthesis			(-)		
	TROTEIN	Breakdown			(-)		

Net effect: Insulin: Plasma glucose and NEFA fall Glucagon: Plasma glucose rise

Lipids and Lipoproteins

Learning objectives:

- 1. Define the role of Fatty Acids in lipid formation and their classification.
- 2. Illustrate different groups of Lipoproteins.
- 3. Discuss about disorders of Lipid metabolism.

Lipids play an important role in almost all aspects of biological life (Table 7.1).

Table 7.1: Functions of lipid

Structural component in cell Structural and functional component in biomembranes Provides insulation Serves as hormone or hormone precursors Aids in digestion Involved in metabolic and hormonal pathway Source of energy

Knowledge of lipid disorders is important since they are common in clinical practice and have a role in atherosclerosis.

NEFA (Non-esterified FA)

They are liberated from adipose tissue by action of lipase, transported to liver and muscle, bound to albumin, NEFA are important source of energy in body.

Essential Fatty Acid

Such FA which can not be synthesized in the body and must be supplied in diet.

e.g. Linoleic acid (C18 : Δ9,12) (Table 7.2).

		Table 7.2: Major FA in plasma	
Carbon	Saturated	Unsaturated	Source
C16	Palmitic acid	Palmitoleic Acid	Plant
	(C16:0)	(C16 Δ ⁹)	
C18	Stearic acid	Linoleic Acid (C18 : Δ ^{9,12})	Animal/Plant oil
	(C18 : 0)	Linoleic Acid (C18 : $\Delta^{9,12,15}$)	Plant
		Arachidonic Acid (C20 : $\Delta^{5,8,16,14}$)	-
		Eicosapentamoic Acid (C20)	Fish oil

Table 7 Oc Maion EA in places



Lipids: Classification

Based on Chemical Structure

Fatty Acids

Short chain FA	(C_{2-4})
Medium FA	$(C_{6,10})$
Long chain FA	(C_{10})
Eicosanoids	(C_{20}^{12-26})

Glycerols

TA G DAG MAG Phosphoglycerides

Sphingosine Derivatives

Sphingomyelin Glycosphingolipids

Sterol Derivatives

Cholesterol Vitamin D Steroid hormones

Isoprenes

Vitamin A Vitamin E Vitamin K

PPAR: Peroxisome Proliferator- Activator (Table 7.3)

 Table 7.3: PPAR: Peroxisome proliferator - activator receptors

Family of nuclear receptors Activated by FA Implicated in insulin resistance, dyslipidemia Types : α PPAR γ PPAR Drugs targets for different PPAR α (+) by fibrates γ (+) by thiazolidenedione e.g. Pioglitazone Rosiglitazone Simmi Kharb

TAG (Triacylglycerol): Also called as triglycerides (TG)

Storage form of fat

Transported from intestine to liver and adipose tissue as lipoproteins Contain both saturated and unsaturated FA.

 Cholesterol: Salient Features

 Present in all cells and body fluids

 Precursor of steroid hormones and bile acids

 Absorbed from intestine and also synthesized endogenously by liver mainly

 Rate-limiting step of its synthesis : HMGCoA reductase is controlled by :

 feedback inhibition by

 cholesterol

 therapeutic agents - statins

 2/3rd cholesterol in plasma exists as cholesterol ester

 Excreted in bile as such or after metabolism to bile acids

 If excess amount of cholesterol is excreted in bile, it results in gallstone formation.

Phospholipids

Complex lipids Similar to TG containing a phosphate group and N-base in place of one FA residue.

Lipoproteins

Lipoproteins are transport form of lipid and contain lipid in association with proteins. Lipoprotein particle consists of non-polar core of TG and CE surrounded by polar groups of phospholipids, proteins and free cholesterol (Table 7.4, 7.5).

Particle	Property	Electrophoretic mobility	Source
Chylomicron (CM)	Largest Least dense	Origin	Intentine
VLDL IDL LDL	Formed from TG Intermediate form Principal carrier of cholesterol	Pre -β broad β β	Liver Catabolism of VLDL Catabolism of VLDL via IDL
HDL	Nascent HDL is disc- shaped which is converted to HDL, and HDL	α	Liver, intestine

rable 7.4: Main groups of lipoprotein	lable	7 .4: Mair	n groups	ot lip	oproteins
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D`Uga U`DfchY]bg

Learning objectives:

- 1. Define different categories of plasma proteins.
- 2. Discuss functions of all plasma proteins.
- 3. Explain albumin in detail.
- 4. Describe proteinuria and its causes.

More than hundred different proteins are present in blood known as *Plasma Proteins*. Examination of proteins in plasma can provide information reflecting disease states in many different organ systems. Different categories of plasma proteins can be:

Acute phase reaction proteins Carrier proteins Fibrinogen Coagulation factor Complement Immunoglobulins Enzymes Enzyme inhibitors Transport proteins.

Functions of proteins Example Alpha-1 AT Acute phase reaction Haptoglobin Ceruloplasmin CRP All proteins AFP Buffering Oncofetal C4, C3 Albumin Complement Renin Enzymes Coagulation factors Complement Immunity Immunoglobulin Coagulation Clotting factors Fibrinogen

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Enyme inhibitors	Alpha-1 AT Antiplasmin Antithrombin III
Transport proteins	Albumin Thyroxine binding protein Apoproteins Transferrin Erythropoietin

Hormones*

* Other protein hormones circulating in blood are not designated as plasma proteins. Even ferritin is not a plasma protein.

Table 8.1: Proteins in other body fluids			
Fluid	Condition		
CSF	↑ in infection		
	Tumor		
	Hemorrhage		
	Demyelinating diseases		
Amniotic fluid	AFP		
	Acetylcholinesterase		
	Fetal Hb		
Saliva	Secretory IgA		
Feces	α ₁ AT		
Pleural fluid and ascitic fluid	↑ in infection		
	Malignancy		

Plasma Proteins

Plasma contains water, electrolyte, metabolites, nutrients, proteins and hormones.

Salient Features of Plasma Proteins

1. Proteins in plasma can be simple, conjugated (glycoprotein, lipoproteins).

2. Concentration of protein in plasma determine distribution of fluid between blood and tissues.

3. Plasma proteins exert osmotic pressure.

4. Most plasma proteins are synthesized in liver.

5. Most plasma proteins are glycoproteins, and removal of terminal sialic acid residues from them shorten their half-life (Table 8.2, 8.3).

Increase	Decrease	
↑ Synthesis:	↓ Synthesis:	
Paraproteinemia	Malabsorption	
↓ Blood volume:	Chronic liver disease	
Hemoconcentration	Immunodeficiency	
Dehydration	↑ Blood volume:	
	Overhydration	
	Increased permeability:	
	Septicemia	
	Hypoxia	
↑ Loss/catabolism:		
Catabolic state		
Protein losing states:		
Enteropathy		
Nephrotic syndrome		
Exfoliative disorder of skin, e.g. pemphigus		
Extensive burns		
Hemorrhage		

Table 8.2:	Total	plasma	protein	concentration
------------	-------	--------	---------	---------------

Prealbumin	
albumm	
α1-globulin	α₁-antitrypsin
α ₂ -globulin	Haptoglobin
	α2-macroglobulin
	Ceruloplasmin
β-globulin	Transferrin
	LDL
	C3
γ-globulin	IgG, IgA, IgM, IgD, IgE

Table 8.3: Principal plasma proteins

Table 0.4. Other plasma proteins	Table 8.4:	Other	plasma	proteins
----------------------------------	------------	-------	--------	----------

Plasma proteins	Functions	↑	\downarrow
α1 acid glycoprotein	Glycoprotein group of protein: control bioavailability of drugs downregulation of immune response	Acute phase response by glucocorticoides (GC)	by estrogen nephrotic syndrome
α1 ΑΤ	Serpin (serine protease inhibitor) inhibit leukocyte elastase prevent elastic recoil in bronchial tree	Acute phase response estrogens	Genetic deficiency: emphysema Hepatic damage
Ceruloplasmin	α2 globulin, contains 95% of total serum copper regulates ionic state of iron (Fe2+ \rightarrow Fe3+)	Acute phase estrogen	Wilson's disease
CRP	Activator of classical complement	Acute phase response	—
Haptoglobin	Binds Hb irreversibly	Acute phase response protein- losing syndrome GC, androgens	genetic deficiency estrogen hemolytic disease hepatocellular disease
α ₂ macroglobulin	Plasma proteinase inhibitor inhibits kinin, complement, coagulation, fibronolytic pathways	Estrogen nephrotic syndrome	genetic deficiency pancreatitis prostate CA
β2 microglobulin	It is light or β -chain of HLA on cell surface	Renal failure neoplasm inflammation	<u> </u>
Retinol binding protein	Binds all trans-retinol prevents retinol from being filtered by glomeruli	Chronic renal disease Diabetic nephropathy	Liver disease protein - malnutrition acquired immunodeficiency

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Nucleic Acid

Learning objectives:

- 1. Explain metabolism of purines and its clinical importance.
- 2. Describe metabolic disorders of Purine Catabolism.
- 3. Discuss Diagnostic application of Nucleic Acid.

Purine and urate metabolism

Abnormalities of purine metabolism commonly found in clinical practice, include gout, hyperuricemia, Lesch Nyhan's syndrome, adenosine deaminase deficiency.

Purine Metabolism

Humans catabolize purines to uric acid.

Uric acid is end-product of purine degradation in humans. Since humans lack uricase (that converts uric acid to water-soluble allantoin), their uric acids are higher.

Purine synthesis and breakdown occurs in all tissues, urate is produced only in tissues containing xanthine oxidase, i.e. liver and small intestine (Table 9.1).

Table 9.1: Factors affecting urate production

Dietary intake of purine Rate of purine biosynthesis, degradation and salvage Renal function Age, sex Alcohol intake

Four steps of renal handling of urate (Fig. 9.1)

- 1. Glomerular filtration
- 2. Reabsorption in PCT (proximal convoluted tubule)
- 3. Secretion into distal portion of PCT
- 4. Reabsorption in DCT (distal convoluted tubule)
- 5. 75 percent of uric acid is excreted in urine and rest is eliminated through intestine.

Properties of Uric Acid (UA)

- Weak acid, pKa of 5.75 and 10.3
- Exists predominantly as ionized form: urate

Nucleic Acid

- 98 percent exists as monosodium urate at pH 7.4 UA is poorly soluble in plasma and urate is ionized •
- •
- Ionization of UA decreases as pH falls and becomes less soluble. •



Fig. 9.2: Total body urate pool and causes of hyperuricemia

Hyperuricemia

Defined as a plasma/serum urate concentration greater than 7 mg/dL.

Causes of Hyperuricemia

Causes: According to underlying physiology:

- 1. Increased synthesis of purines
- 2. Increased intake of purines
- 3. Increased breakdown (turnover)
- 4. Increased rate of urate formation
- 5. Decreased rate of excretion (Table 9.2, Fig. 9.2).

Cau	se			Reason	
1			<i>c</i>		
Ι.	Increa	ased formation of UA			
	a.			de Nevreit DDDDC*	
		i.	Purine synthesis	de Novo:↑ PRPPS* Salvage:↓ HGFRT*	
		ii.	Inherited metabolic disease (IMD) GSDI	Insulin/glucagon ↑ ATP degradation Lactic acidemia block uric acid excretion Metabolism of G-6-P through PPP,↑R-5-PPurine synthesis More G-6-P available diverted to HMP shunt: ↑ R-5-P Purine	
			F1P Aldolase deficiency	aldolase deficiency (both mechanisms)	
	b.	Seco i. ii.	ndary increase Increased dietary intake of purines increased nucleic acid turnover <i>Cause</i> trauma surgery Malignancy, starvation, Psoriasis cytotoxic drugs	Purines oxidized to urate Purines oxidized to urate	
		iii.	Altered ATP metabolism causes:		
			Alcohol, tissue hypoxia	Hypoxia and $\downarrow ATP$ synthesis, causing lacticacidosis which blocks UA excretion, alcohol \downarrow excretion of UA	

Table 9.2: Causes of hyperuricemia

* HGPRT deficiency: ↓activity of salvage pathway causing decreased purine utilization and ↑uric acid synthesis (Fig 9.3) ** PRPPS: ↑PRPPS result in increased purine synthesis and increased uric acid synthesis

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Inherited Metabolic Diseases

Learning objectives:

- 1. Enlist and describe all Inherited Metabolic Disorders with Clinical Laboratory Assessment.
- 2. Discuss Autosomal Recessive Inherited Metabolic Disorders.
- 3. Explain Metabolic Disorders caused as a result of mutation.

Inherited Metabolic Disorders IMD

Inborn metabolic disorders are caused by genetically determined abnormalities that lead to a block in one of many interrelated biochemical pathways.

The block frequently leads to accumulation of substrate and secondary metabolites or to deficiencies of downstream products (Table10.1).

Features

- 1. IMD are categorized by type of metabolic pathways that are impaired, such as disorders of carbohydrates, fats or amino acids.
- These disorders may involve pathways of specific cellular organelles, including lysosomes, mitochondria, peroxisomes.

When to Suspect an IMD?

When there are unusual, unexplained clinical features or abnormal lab findings in infancy or childhood, the possibility of an IMD should be considered. Also, history of consanguineous marriage or more than one infant in family affected by same abnormality.

Cause of presentation can be due to (i) direct or enzyme abnormality and (ii) can be demonstrated indirectly.

Disorders of Intermediary Metabolism

It occurs as a result of three basic mechanisms:

1. Enzyme deficiency with defective substrate conversion (Table10.2).

2. *Membrane transport defect* resulting in failure of absorption or excessive excretion of a compound (Table10.3).

3. Defects in receptors involved in mediating metabolism.

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Biochemical Basis of Resulting Disease (Fig. 10.1)

- 1. Accumulation of a substrate to toxic levels $(\uparrow A)$
- 2. Deficiency (due to lack of production) or excessive loss of desired compound $(\downarrow B)$
- 3. Conversion of accumulated compound to altered/toxic metabolite (\uparrow C)



Inherited metabolic diseases are the result of gene mutations causing production of an abnormal protein or preventing synthesis of a protein (Table 10.1-10.5).

Table 10.1: Inherited metabolic diseases

α, antitrypsin deficiency
Cystic fibrosis
Classic galactosemia
Familial hypercholesterolemia
Glycogen storage disease
Hereditary fructose intolerance
Lesch-Nyhan syndrome
Liver: (disorders of conjugation and excretion of bile:) Gilbert, Crigler-Najjar, Dubin Johnson, Rotor syndrome
Hemochromatosis:
Lysosomal storage disease
Maple syrup urine disease
Phenylketonuria
Porphyrias
Renal glycosuria
Steroid 21-hydroxylase deficiency
Tyrosinemia type 1
Vitamin D-dependent and resistant rickets
Wilson's disease

Table 10.2: IMD								
	Diseases	Inheritance	Defect	Clinical Features	Diagnostic approach/ detection			
1.	α_1 -antitrypsin	Homozygosity for Z allele	Single amino acid	Liver or lung disease	Phenotyping screening of			

Contd...
Inherited Metabolic Diseases

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	Diseases	Inheritance	Defect	Clinical Features	Diagnostic approach/ detection
		(PiZZ)	Substitution	Emphysema and risk increased	affected individual's
		Heterozygotes (PiMZ)		In smokers Liver: Neonatal Hepatitis Cirrhosis Lung disease	members antenatal screening using fetal DNA from Chorionic Villous
2.	Cystic fibrosis	Familial	Impaired Cl ⁻ Transport Due to CFTR Gene defect (cystic fibrosis transmembrane Conductance receptor) involved in chloride trans- port, deletion of single codon: common:	affected children develop recurrent respiratory infections irreversible lung disease pancreatic insufficiency leading to malabsorption Intestinal obstruction in neonates infants:	α1 ATlevelshigh sweatsodiumhighplasmaimmunoreacti-ve trypsinmoleculargenetic analysisof CFTR gene
3.	Classical Galactosemia	Autosomal recessive	∆ F 508 Galactose-1- phosphate Uridyl trans- ference absent (GALT)	failure to thrive vomiting hepatospleno- megaly	plasma galactose ↑ urine galactose positive GALT deficien- cy in RBCs & chorionic villi
		Adults	cataract	Jaundice cataract, Impaired renal function	
4.	Familial Hypercholes- terolemia	Autosomal dominant	defect in uptake and catabolism of LDL	cholesterol deposition in skin, tendon, arteries	high serum HDL, total cholesterol
5.	Glycogen Storge Disease Type I		Glucose-6- phosphatase deficiency	fasting hypoglycemia accumulation of glycogen in liver and hepato- megaly	liver biopsy for G-6-Pase enzyme deficiency lact- acidosis common hyperlipidemia hyperuricemia

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Oral Manifestations of Inherited Disorders

Learning objectives:

1. Describe oral manifestation of all Metabolic Disorders.

WHypophosphatemic Vitamin D Resistant Rickets

X-linked AD.

Clinical Features

- Hypophosphatemia •
- Rickets or osteomalacia
- Resistant to usual doses of vitamin D.

Causes of Hypophosphatemia

- Defective reabsorption and increased excretion of phosphate by renal tubules
- Rickets secondary to biochemical abnormality. ٠

Oral Manifestations

Gingival and periapical abscess without concurrent evidence of caries or tooth fracture.

Systemic Manifestation

- ٠ Rickets
- Osteomalacia.

Laboratory Investigations

•	Serum Calcium	n
---	---------------	---

- ALP n/↑ Ţ
- Serum Phosphate.

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Pseudohypoparathyroidism (PHP) and Pseudopseudo-hypoparathyroidism (PPHP)

PHP Hypocalcemia PPHP Normocalcemia X-linked AD

Causes: Lack of end-organ receptor for PTH.

Oral Manifestation

- Enamel covered with pits
- Pulp stones near pulp horns
- Retarded root development with large root canals.

Systemic Manifestation

PHP

- Short stature
- Obesity
- Mental retardation.

PPHP

- Tall
- Less obese.

Common Features

- Short metacarpals
- Calcification in subcutaneous tissues of scalp and extremities.

Laboratory Investigations

- S. Ca low
- S. PO_{4} high.

Fabry Syndrome

X-linked AR α-galactosidase deficiency.

Oral Manifestations

Angiokeratoma of lips (lower lip).

Systemic Manifestations

- Angiokeratoma of skin
- Pain in hand and feet.

Clinical Features

- Pain in extremities
- High blood pressure
- Cardiomegaly
- Albuminuria.

Laboratory Findings

- Proteinuria
- Anemia
- Uremia
- Urine-birefringent lipid inclusion.

Lesch-Nyhan Syndrome

- X-linked AR
- HGPRTase deficiency
- Hyperuricemia
- Choreoathetosis
- Mental retardation
- Self-mutilation.

Facies

- Distorted due to chewing of lips
- Multiple scars on ears, face, head due to self-inflicted trauma.

Oral Manifestation

Self-chewing of lips.

Systemic Manifestations

- Mental retardation
- Amputation due to chewing of distal phalanges.
- Choreoathetosis
- Quadriparesis.

Laboratory Investigations

Urine: Uric acid raised.

MPS VIII

AR

- β-glucuronidase absent
- Accumulation of acid mucopolysaccharides.

Heme, Iron and Porphyria

Learning objectives:

- 1. Explain the synthesis of Porphyrin and describe Porphyria.
- 2. Discuss Iron in detail.
- 3. Enumerate all abnormal derivatives of Heme.

Porphyrin

A cyclic compound with four pyrrole rings connected by methenyl bridges. The arrangement of four nitrogen atoms in the center of porphyrin ring enables porphyrins to chelate various metal ions, e.g.:

Iron chelate Magnesium Magnesium porphyrin—heme

um : Magnesium porphyrin—chlorophyll

Metal-free porphyrins have no biological function in humans and protoporphyrin that contains iron is HEME.

Hemoproteins

Proteins that contain heme are hemoproteins (Table 12.1).

Examples:

- Hemoglobin (Hb)
- Myoglobin (Mb)
- Cytochrome C (Cyto C)
- Cyt P₄₅₀
- Catalase
- Tryptophan pyrrolase.

Table 12.1: Hemoproteins

Proteins	Function
Hb Mb	Transport of oxygen in blood Storage of oxygen in muscle
Cytochromes:	
Cyt C	Electron transport chain
Cyt P ₄₅₀	detoxification of xenobiotics (hydroxylation)

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Enzymes:	
Catalase Tryptophan pyrrolase	Uses $H_2 O_2$ as electron donor and acceptor to form water and oxygen (degrades $H_2 O_2$) Cleaves indole ring with incorporation of oxygen to form N-formylkynurenine
(oxygenase)	(Tryptophan catabolism)

Heme

Heme is synthesized from porphyrin and iron and is type III porphyrin belonging to series IX. (Fig. 12.1, Table 12.2)



Fig. 12.1: Heme formation and breakdown

Table 12.2: Fact-file—heme

1. Synthesis 85% here synthesized in erythroid cells \rightarrow Here for
Post: Heme produced in liver , out P450 enzyme
Nest. Theme produced in liver \rightarrow cyt 1 450 enzyme
2. Breakdown
Under physiological condition, $1-2 \times 10^8$ RBCs destroyed/hour
70 kg adult turns ~ 6 g Hb/day
IgHb yields 35 mg bilirubin.

Heme, Iron and Porphyria

Heme synthesis begins with succinyl CoA and glycine and ends with insertion of Fe^{2+} into molecule of protophyrin using eight enzymes (four mitochondrial and four cytosolic). Each step produces a progressively less water-soluble molecule until, with protophyrin and heme which are insoluble in water.

Thus, excess intermediates early in the pathway tend to appear in urine, while intermediates late in the pathway (particularly protoporphyrin) are found in blood, bile and feces and not in urine.

Porphyria are rare group of disorders of heme synthesis resulting from deficiency of one of the enzymes of this pathway (Fig.12.2).



Porphyrin Synthesis (Fig. 12.3)

- Types of Porphyria
 - Inherited
 - Acquired.
- Classification of Porphyria
 - Hepatic
 - Erythropoietic
- Types of Porphyria
 - Acute
 - Acute intermittent porphyrias (AIP)
 (HCP) Hereditary coproporphyria
- hepatic
- (VP) Variegate hepatic porphyria
- Chronic
 - Cutaneous hepatic porphyria (CHP)
 - Congenital erythropoietic porphyrias (EP) ≻ erythropoietic
 - Erythropoietic protoporphyria (EPP)

Nutrition

Learning objectives:

- 1. Discuss the causes, classification and signs of Malnutrition.
- 2. Illustrate Nutraceuticals.
- 3. Describe Nutritional Anemias.
- 4. Explain Vitamins, functions and deficiency symptoms.

For normal growth and development and maintenance of health, adequate intake of nutrients is essential (Table 13.1)

Table 13.1: Essential nutrients

Water Carbohydrates Proteins (amino acids) Fats Fat soluble : A, D, E, K Vitamins: Water soluble : B, C Minerals: Na, K, Ca, M g, P, Cl Trace elements: Cu, Fe, Zn, Cr, Mn, Se, I, F, Mo

Malnutrition is suboptimal nutrition arising from inadequate or unbalanced intake, bioavailability of nutrients which leads to biochemical and metabolic consequences (Table 13.2).

In malnutrition, deficiency of energy, protein, vitamin and minerals can occur. Two forms of protein energy malnutrition are marasmus and kwashiorkor (Table 13.3).

	Marasmus	Kwashiorkor
Cause	Inadequate intake of protein and calories	Inadequate intake of proteins after trauma or infection
Muscle fat	Loss of sub- cutaneous tissue	Muscle and subcutaneous tissue preserved
Weight S. albumin	Loss of weight S.albumin normal	Weight loss, edema S. albumin low (a state of PEM, where adaptation has failed).

In malnutrition, patient shows features of deficiency of energy, protein, vitamins and mineral.

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	Causes	Lab investigations
1.	Fat malabsorption	Fecal fat
	·	Breath Test (14C glycocholate)
		B ₁₂ absorption test
		Pancreatic enzymes in stool :
		trypsin, chymotrypsin, elastase
		microscopic examination for fat droplets
2.	Protein malabsorption	Serum protein
		 α – 1 anti-trypsin in feces
		α -anti-trypsin clearance by intestine
3.	Celiac disease	Visualization technique
		antigliadin (AGA) Ab assay in serum
		anti- <i>endomysium</i> (AEA) Ab in serum
		antireticulin (ARA) Ab in serum
4.	Carbohydrate malabsorption	D-Xylose absorption test
		Breath H ₂ after lactose administration
5.	Vitamin malabsorption	B ₁₂ malabsorption, correction by pancreatic
		enzyme administration
		Lab investigation of megaloblastic anemia
		Vitamin A and D absorption test
5.	Mineral malabsorption	59Fe absorption

Malnutrition: Causes

Table 13.2: Classification: Malnutrition

Ι.	On	the basis	of lesion
1. 2.	Gas Sma a.	stric: all intestine: Liver	Deficiency of intrinsic factor causing defective absorption by vitamin B ₁₂ . Luminal Cirrhosis of liver Extrahepatic biliary obstruction causing defective bile secretion
	b.	Pancreas	Pancreatitis CA pancreas Zollinger-Ellison Syndrome
	C.	Brushborder i. Lesion	r defect of mucosa: Celiac disease Gluten-induced enteropathy Tropical sprue Infiltration by tumor Sarcoidosis Radiation Drug-induced Infection Parasite

Contd...

<i>II.</i> 1.	ii. Inborn o On the basis o Fat malabsorptio	errors: Amino acid transport defect Glucose transport defect Abetalipoproteinemia of nutrient on
		Steatorrhea Hepatobiliary disease Pancreatic disorder Brushborder lesion
2.	Carbohydrate m	alabsorption Brushborder lesions Enzymatic defect: Disaccharidase deficiency (maltase, sucrase, lactase)
3.	Protein malabso Protein losing e	orption enteropathy: Tropical sprue Colitis Crohn's disease Infantile allergy Amino, acid, transporter, defect
4.	Malabsorption of Water-soluble v Fat-soluble vitar	r vitamin itamin: B (pernicious anemia: IF deficiency) nin: In fat malabsorption
5.	Malabsorption o	f minerals
	Iron:	Parasite infestation Phytates, oxalates

Table 13.3: Signs associated with malnutrition

Organ	Signs	Deficiency
Face Skin	Diffuse depigmentation Purpura Hyperpigmentation Hyperkeratosis	Riboflavin Vitamin K Cobalamin, folic acid Retinol, EFA Ascorbic acid, niacin
Eyes Lips	Petechial hemorrhage Poor dark adaptation, Bitot's spots Angular stomatitis, cheilosis	Retinol
Tongue	Scarlet tongue Glossitis	Riboflavin or niacin Riboflavin Riboflavin Niacin riboflavin folic acid
	Atrophic filiform papillae	cobalamin, iron Niacin, folate.
Teeth Gums Nails CVS Nervous system	Mottled enamel, caries Pale Koilonychia, pallor Cardiomegaly, wet beri-beri Neuropathy, sensory and motor loss, dry beri-beri	riboflavin, iron, cobalamin Fluoride Ascorbic acid Niacin Thiamin Thiamin

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Malignancy

Learning objectives:

- 1. Describe Endocrine Syndromes.
- 2. Illustrate Biochemical Changes in Cancer.
- 3. Discuss MEN and differentiate between MEN I and MEN IIa.

Malignancy

Term *paraneoplastic syndrome* includes all the systemic manifestations of cancer not directly related to presence of primary tumor, whether or not they are due to a hormone termed as *Ectopic hormone* (Table 14.1).

Most of these endocrine syndromes occur with tumors of non-endocrine tissue which have embryonic origin from neural crest cells. However, non-APUD tumors do occur.

	Syndrome	Tumor	Hormone
1.	Cushing's syndrome	Small cell CA bronchus Carcinoid tumors	ACTH
2.	Hypercalcemia of malignancy*	Non small cell CA lung Renal adeno CA	PTHRP
3. 4.	Hyponatremia (SIADH) Hypoglycemia	Mesenchymal tumors (non β cell tumors) Small cell cancer	Vasopressin Insulin-like growth factors (IGEs)
5.	Gynecomastia	Lung testicular cancer Hepatic tumor Carcinoid	hCG
6.	Ectopic acromegaly	Small cell lung CA	GHRH GH
7.	Polycythemia	Pancreatic islet tumors Uterine fibromyomata Cerebellar hemangioblastoma	IGF - I Erythropoietin

Table 14.1: Endocrine syndromes

* Hypercalcemia is common in hematological malignancies, particularly myeloma due to release of osteoclast-activating cytokines (IL-1, TNPβ) by tumors.

Metabolic Effects of Tumors

Neoplastic cells differentiated tissues sometimes synthesize compounds that are not normally produced from that tissue. These substances may alter the metabolism and may produce clinical effects and hormone syndromes. Also, these substances may be biologically inactive and serve as *tumor markers*.

Also, neoplasias are associated with rare syndromes with endocrine or neurotransmitter properties showing common tumors, cytological characteristics, e.g. in *APUDomas* staining technique show ability for *Amine Precursor Uptake and Decarboxylation* (Table 14.2, 14.3).

Certain tumors secrete physiologically active amines, while others secrete peptide hormones (e.g. pituitary, parathyroid and C-cells of thyroid).

Biochemical Changes in Cancer

Metabolic changes in cancer are not always due to aberrant hormone secretion, but may be due to some other effect of tumor or as a consequence of treatment.

- 1. *Serum: High*: Calcium, uric acid, lactate, globulin, potassium, phosphate *Low*: Fasting glucose, albumin, magnesium
- 2. *Anemia:* Common, could be due to hemorrhage, hemolysis, malnutrition or bone marrow infiltration by tumor cells.
- 3. *Hypercoagulable* state resulting in thromboembolism.
- 4. *Cancer cachexia*: A syndrome of weakness and generalized wasting. Causes can be deficient food intake, intestinal obstruction or anorexia of malignancy, malabsorption, increased demands and consumption of nutrients by tumor, release of cachectin (TNFα). The condition is rarely reversible unless the underlying tumor can be treated successfully.

Site	Enterochromaffin cells of gut: cells of APUD series
	90% in appendix and ileocecal region
	Others: Gut. gallbladder, pancreatic duct, bronchi
	Low grade malignancy
Property	
-1 - 9	Baraly metastasize
	CIT: pausa vomiting diarrhaa colia
	Configuraceulary Hushing, diameta, conc
Clinical features	Cardiovascular. Ilusning, hypotension
	Respiratory: bronchospasm
	Pellagra
	Manifestation of secretion of other hormones
Others	: Vasoactive amines: serotonin mainly
	Histamine
Madiatara	. Kinin Hormones
Mediators	ACTH
	5 HIAA in urine
	Plasma 5 HTP, histamine, peptide normone
Lah diagnosis	
Lub. diagnosis	•

Table 14.2: Carcinoid tumor

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Origin	Tumor
GIT Pancreas CNS	Carcinoid Islet cell CA Ganglioneuroblastoma Neuroblastoma
Thyroid Skin Adrenal medulla Lung	Medullary thyroidal CA Melanoma Pheochromocytoma Small cell CA Carcinoid tumor

Table 14.3: Origin of APUD tumors

Argentaffin cells:

Round and stain with silver salts Derived from embryonic gut Present in ileum, appendix in abundance so, present in pancreas, stomach, rectum

Multiple Endocrine Neoplasia (MEN)

MEN are familial disorders with autosomal dominant inheritance, where tumor hyperplasia occurs in two or more endocrine glands (Table 14.4).

MEN I	MEN IIa
Parathyroid Pancreas Pituitary (anterior) Thyroid (follicular cell) Adrenal cortex	<i>Thyroid (medullary cell CA)</i> Adrenal medulla (pheochromocytoma) Parathyroid CA MEN II b Thyroid (medullary cell CA) Adrenal medulla (pheochromocytoma) Mucosal neuroma may be associated with Marfanoid, Hirschsprung disease

Table 14.4: Pancreatic tumors

Pancreatic islet tumors	Hormone produced
Zollinger-Ellison syndrome Peptic ulcer gastrinoma Insulinoma - Hypoglycemia Glucagonoma - Hyperglycemia VIPoma - Watery diarrhea, hypokalemia Somatostatinoma - diarrhea, steatorrhea, gallstones DM Carcinoid syndrome - diarrhea, hepatomegaly	Gastrin Insulin Glucagon VIP Somatostatin Serotonin, PG Serotonin Histamine Kinin ACTH

Questions:

- 1) What are the metabolic effects of tumors?
- 2) Discuss the biochemical changes in cancer?
- 3) What is Carcinoid tumor?
- 4) Explain Mutiple Endocrine Neoplasia (MEN) in detail.
- 5) Name some endocrine syndromes and hormones associated with it.

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Toxicology

Learning objectives:

- 1. Enlist Toxic agents and discuss its features.
- 2. Describe Forensic Toxicology
- 3. Illustrate common methods for analysis of different drugs.
- 4. Explain Toxicology disciplines.

Toxicology includes analysis of drugs, heavy metals and other chemical agents in body fluids and tissues for three main purposes:

- 1. Diagnosis and management in drug-overdose (Table 15.1, 15.6)
- 2. Therapeutic monitoring of drug (TDM) (Table 15.2-15.4)
- 3. Screening for the presence of drugs of abuse

Table 15.1: Reasons for high serum drug concentrations

Patient noncompliance Improper dosage Poor bioavailability of preparation Malabsorption Drug interaction Liver disease Kidney disease Altered protein binding Genetic factors affecting metabolism

Table 15.2: Need for monitoring of drug therapy

1. Patient taking more than one drug has increased probability of drug interaction and toxicity

- 2. To follow patient compliance
- 3. Indicated in drug groups which show individual variation or are toxic above therapeutic range like:

Antiepileptics Theophylline Tricyclic antidepressants Lithium carbonate Aminoglycosides

	Drug	Therapeutic range (toxic level)
1. 2. 3.	Carbomazapine Digoxin Cyclosporine	4–12 μg/ml (>15.0 μg/ml) 0.5–2 ng/ml (> 2.5 mg/ml) 12 hrs after dose 100–400 ng/ml (renal transplant) 24 hrs after dose 100–200 ng/ml (> 400 ng/ml)
4. 5. 6.	Phenytoin Phenobarbitone Theophylline	10—20 µg/ml (> 20 µg/ml) 15—40 µg/ml (> 35 µg/ml) 8—20 µa/ml (>20 µa/ml)

Table 15.3: Drugs requiring TDM

Table 15.4: Features of toxic agents

Agent		Properties	Clinical features	Analysis/Measurement
1. a.	Alcohol Ethyl alcohol	Principal pharmaco- logic action : CNS depression Legal intoxication : 80–100 mg/dl >400 mg/dl : death	disorientation or mild euphoria stupor coma	blood alcohol breath alcohol saliva alcohol urine alcohol*
b.	Methyl alcohol	Used as solvent in a number of commercial product consumed as illicit liquor	severe metabolic acidosis peripheral circulatory failure blindness causes optic neuro- pathy and blindness death	serum formate
c.	Isopropanol	Used as rubbing alcohol has twice the CNS depressant action as ethanol not as toxic as	similar to ethanol	Urine isopropanol levels Urine acetone
2. a.	Analgesics Acetaminophen (paracetamol)	methanol used in treatment of mild pain or fever	nausea, vomiting, abdominal discomfort <i>over dosage</i> causes hepatic, nephrotoxicity liver toxicity (which can be predicted after 4 hrs post ingestion	Reference internal : Serum 10–30 μg/ml Toxic level : >200 μg/ml Immunoassay (EMIT) for acetaminophen
b.	Acetyl salicylic Acid (Aspirin)	Analgesic Antipyretic	<i>Therapeutic</i> <100 µg/ml <i>Toxic</i> >100 GI intolerance	S.salicylate U.salicylate

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		Anti-inflammatory	impaired hemostasis, deafness, headache, vertigo, tinnitus, nausea, vomiting, hyperventilation	(photometric GC HPLC)
3.	Barbiturates			
		Low therapeutic index	Coma hypothermia	S.barbiturate level
	D ///	High abuse potential Suppress CNS and neuronal activity sedative and hypnotic	hypotension cardiorespiratory arrest	(immunoassay)
	Benzodiazepin	es CNC democrate		
4.		anxiolytic sedative hypnotic muscle relaxant anticonvulsant	drowsiness slurred speech ataxia	S. benzodiazepine U. benzodiazepine (HPLC immunoassay)
		"date-rane" nill	coma	
		uale-rape pill		
5.	Cannabinoids:	Principal cannabinoid i	s 🖞 -	
		Insight drug psychoactive effects : euphoria Inhaled in smoke t½ THC - day in casual user and 3-5 d. in chronic users	drug of abuse in infrequent users : Impairment of intell- ectual performance	THC +ve in urine for 2-5 d after use immunoassay cut off value of 20 ng/ml THC
6	Cocaine			
0.	Golanie	CNS stimulant Euphoria	mydriasis tachycardia hypertension hyperthermia agitation seizure coma	Urinary benzoylecgonine and ecgonine methyl ester (Immunoassay GC, HPLC)
7	Lyseraic acid	diethylamide (ISD)		
1.	Lyseigie deid	Hallucinogenic	mydriasis tachycardia salivation lacrimation vomiting panic attack	Urine LSD immunoassay
8	Amnhetamines			
	,, <i>p</i>	Used to treat obesity CNS stimulant	Overdose : dizziness tremor hypertension cardiac arrhythmia convulsion coma	Urine Immunoassay GC/MS
0	Oninida/Orist			
9.	Opioias/Opiate	25	addian	
		analgesic	seuation	Ininunoassay
		sedative	euprioria	

Contd...

Contd...

Section III Endocrines

Endocrine Hypothalamus

Learning objectives: 1. Examine the role of Hypothalamus in body

The brain is also one of the most important endocrinal glands.

Hypothalamus

Hypothalamus lies at the base of the brain and contains specialized nerve cells (nuclei) that synthesize hormones to regulate hormone secretion from the pituitary. These hormones are transported along the axon of the nerve terminal to be finally released into portal blood system.

Hypothalamus is composed of three regions: Rostral or supraoptic hypothalamus Middle or tuberal hypothalamus

Caudal or mammary hypothalamus

Biorhythm

In most endocrine systems, rhythmic secretion of hormones occurs which may vary over minutes to hours, days, weeks, or even longer periods.

Circadian or Diurnal Rhythm

When rhythm occurs with a time interval of approximately 24 hrs, they are termed as *circadian* or *diurnal*. They are usually regulated by one or more internal "clocks" synchronized by factors such as dark/light cycle and sleep.

Ultradian Rhythm

They are the biorhythms that occur more frequently than once a day.

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* Infradian Rhythm

They occur over time periods longer than 24 hours, e.g. menstrual cycle. Endocrine rhythms involve pulsatile and circadian release of pituitary hormones, e.g. LH (every 90 min) ACTH (peak at 8 am).

Questions:

- 1. Write the functions of Hypothalamus.
- 2. What is Biorhythm? Write its types.

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Pituitary Gland

Learning objectives:

- 1. Describe Hypothalamic Pituitary axis.
- 2. Enlist and explain all Pituitary hormones.
- 3. Discuss all disorders related to Pituitary gland.

Pituitary Gland

Pituitary consists of three lobes—anterior lobe, or adenohypophysis (primary glandular tissue), posterior lobe, or neurohypophysis and intermediate lobe. Anterior pituitary grows from primary oral cavity (Rathke's pouch) and consists of glandular tissue; posterior pituitary is neural in origin (Table 17.1).

Table 17.1: Pituitary hormones

Adenohypophysis :	GH
	Prolactin (PRL)
	Thyroid stimulating hormone (TSH)
	Follicle stimulating hormone (FSH)
	Luteinizing hormone (LH)
	Adrenocorticotropic hormone (ACTH) and β-Lipotropin (LPH)
Neurohypophysis ho	ormones:
	ADH (Antidiuretic Hormone)
	Oxytocin

	Flow sheet of	trophic hormo	ones and targe	t gland hormo	nes	
Hypothalamic hormone	GnRH	TRH	SS	GHRH	CRH	AVP
			(GHRH)			ADH
Pituitary hormone	FSH, LH	TSH	-	GH	ACTH	-
Target gland hormone	Estrogen	T3, T4	-	-	Corticosteroid	S
	Progesterone					
	Testosterone					

* Combined Test (Triple Bolus Test) of Anterior Pituitary Function

Procedure

In a overnight fasting patient, take basal blood sample. Analyze for glucose, cortisol (or ACTH), FSH, LH, TSH, fT4, GH. Give 200 µg TRH, 100 µg GnRH, 1.5 U/kg body weight soluble insulin. Take blood samples at various interval and Table 17.2 describes assessment of pituitary function.

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Pituitary Gland

		A	nalysis		
Time (min)	Glucose	Cortisol	TSH	GH	FSH, LH
0				\checkmark	
15	\checkmark	-	-	-	-
20	-	-	\checkmark	-	\checkmark
30	\checkmark	\checkmark	-	\checkmark	-
45	\checkmark	-	-	-	-
60	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
90	\checkmark	\checkmark	-	\checkmark	-
120	\checkmark	\checkmark	-	\checkmark	-
Response	<2.2	> 200	> 5 mU/L	>20	> 1.5 times,
		mmol/L		nmol/L	>5 times

Table 17.2: Assessment of pituitary function

In 1. 2. M	dications Detection of hormonal c a. before and after trea b. as a result of pituita Recognition of hormone ethods	leficiency tment of pituitary tumors ry surgery or irradiation. producing tumors
G	and/Organ	Test
a.	Before surgery Adrenal	Serum cortisol Cosyntropin stimulation test Estradiol in females
	Gonads	Testosterone in males
Thyroid b. <i>After surge</i> Adrenal Gonads Thyroid	Thyroid After surgery	TSH
	Adrenal Gonads Thyroid	Cosyntropin stimulation test Sex hormones TSH

Hypothalmic Pituitary Axis

Hypothalamus synthesize hormones to regulate hormone secretion from the pituitary (Table 17.3-17.6)

Table 17.3:	Test for	hypothal	amic	target	gland	/organ	axis
-------------	----------	----------	------	--------	-------	--------	------

Hypothalamic-Pituitary-Adrenal axis
Normal morning cortisol
Cosyntropin stimulation test
Hypothalamic-Pituitary-Thyroid axis
Serum free thyroxine TSH
Hypothalamic-Pituitary-Gonadal axis
Serum gonadotropin (LH, FSH)
Sex steroids (estradiol/testosterone)

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Table 17.4: Problems in evaluation of hypothalamic pituitary axis

Condition	Reason
Obesity	GH dynamics impaired insulin induced hypoglycemia
DM (Diabeters Mellitus)	GHRH, arginine, levodopa test fail to provoke GH secretion Diabetics have normal or elevated GH levels which do not further rise in response to hypoglycemia, arginine
CRF (Chronic Renal Failure)	Due to prolongation of their half-life, GH, PRL, LH, FSH, TSH and free cortisol levels are elevated
Starvation	Dexamethasone suppression of cortisol impaired With fasting and malnutrition, GH secretion increases
Depression	PRL and TSH dynamics are normal Dexamethasone suppression altered

Table 17.5: Endocrine tests of hypothalamic pituitary function

Cosyntropin test (ACTH stimulation) Insulin hypoglycemia test (IHT) Metyrapone test GHRH - arginine infusion test Glucose GH suppression test TRH test GnRH test Clomiphene test CRH test

Table 17.6: Causes of hypothalamic and pituitary dysfunction

Invasion	Craniopharvngioma
111/43/011	Primary central nervous system tumor
	Epidermoid and dermoid tumors
	Pituitary adenoma
Infarction	Postpartum hemorrhage
	Spontaneous hemorrhage
Infiltration	Sarcoidosis
Innitiation	Hemochromatosis
	Histiocytosis X
Injury	Hoad trauma

Contd...

Adrenals



Fig. 18.1: Adrenal cortex and medulla

Learning objectives:

- 1. Explain Pituitary Adrenal axis.
- 2. Describe all hormones secreting from Adrenals.
- 3. Illustrate Cushing's Syndrome.
- 4. Discuss all endocrinal disorders associated with Adrenal gland.

Adrenals lie just above kidneys and can be divided into cortex and medulla on the basis of anatomical and functional grounds.

Cortex secretes glucocorticoids (GC) mineralocorticoids (MC) and sex steroid hormones which are synthesized from cholesterol obtained from both HDL and LDL in plasma. Medulla secretes, catecholamines, mainly epinephrine.



Corticosterol binding globulin or transcortin CBG

90% CBG bound 10% free CBG ↑ pregnancy estrogen treatment ↓ hypoproteinemia (Nephrotic syndrome)

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Adrenal Cortex Hormones (Fig 18.1, 18.2)

Glucocorticoids Mineralocorticoids Sex hormones

Adrenal Medulla Hormones

Epinephrine Norepinephrine

Cortisol: Characteristics

Show diurnal variation

Circadian rhythm with peak secretion in early morning and declining with lowest level at midnight.

Sampling at 8 to 9 am and 11 pm to detect loss of diurnal variation.

Stresses such as fever, trauma, exercise, anxiety cause increased secretion of CRH (Table 18.3-18.6).

Caution: Synthetic glucocorticoid prednisolone cross-reacts with cortisol in immunoassay.

Diurnal Rhythm of GC = Biological Clock.

Biological clock resides in suprachiasmatic area of bran synchronized by exogenous influences of light. Related to sleeping waking cycle.

Levels are highest at start of working day and 8 am sample cortisol is normal but, 10 pm cortisol falling to lowest with onset of sleep.

	Table 18.1: Diagno	stic test for causes of	f Cushing's syndrome	
	Pituitary macroadenoma	Pituitary microadenoma	Ectopic ACTH or CRH	Adrenal tumor
ACTH Response to high dose dexamethasone	↑ ↑↑ < 10	n - ↑ 95	↑/↑↑↑ <10	↓ <10
Response CRH to	> 90	> 90	< 10	< 10

 Table 18.2: Tests of pituitary-adrenal axis

ACTH stimulation test IHT CRH test Metyrapone test

Table 18.3: Adrenal hypofunction

Cause	S	
	Glucocorticoid trea Autoimmune	Itment
	Infection (TB, viral)	
Tests		
	Plasma cortisol :	Low
	Synacthen test :	Response absent or blunt

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Table 16.4. Adrenal hyperfunction	
Causes: Cushing's Syndrome ACTH	
Corticosteroid or ACTH treatment	
Pituitary hypersecretion of ACTH (Cushing's disease)	
Tests: Adrenal adenoma	
Adrenal carcinoma	
Ectopic ACTH secreting tumors carcinoid, carcinoma bronchus	
24 hrs U. Cortisol excretion increased	
Dexamethasone suppression test: failure to suppress ACTH release	
IHT: glucose intolerance	
Loss of diurnal variation of cortisol secretion	

Cushing's syndrome (Fig 18.4-18.6)



Fig. 18.4: Cushing's Syndrome



Fig. 18.5: Causes of Cushing's syndrome

Thyroid

Learning objectives:

- 1. Explain about synthesis of Thyroid hormones.
- 2. Discuss utility of measuring free T4 and T3.

Hormones secreted	Cells
Thyroxine (T4)	Follicular cell
Tri-iodothyronine (T3)	Follicular cell
Calcitonin	C-cells

While T4 is 10 times more in concentration, than T3, T3 is 3-4 times more potent than T4.



Fig. 19.1: Synthesis of thyroid hormones

Biologically active hormone T3,
85% T3 in plasma formed by deiodination of T4
rT3 arise from monodeiodination of T4 and is biologically inactive 70% of plasma T4 bound to TBG
80% of plasma T3 bound to TBG
Rest bound to transthyretin and albumin
Only 0.05% T4 are free
0.2% T3 are free



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Thyroid

Lab investigations p TSH p T3, T4 Thyroid antibody Serum thyroglobulin Thyroid enzyme USE OF THYROID TESTS TT3 is reliable measure of hyperthyroidism, but is no value in hypothyroidism.
Normal TSH rules out primary thyroid dysfunction

Utility of measuring free T4 & T3 (fT4, fT3): Free T3, T4 concentration are independent of changes in concentration and affinity of thyroid hormones finding proteins and provide reliable measure to diagnose thyroid disorders.

Condition	Reason
Assay interference	Endogenous heterophilic Ab
	Observed in thyrotoxicosis
Pregnancy	Ist trimester – weak thyrotroplic effect of placental hCG
	(present in high concentrations)
(TBG)	\uparrow [TBG] during pregnancy results in \uparrow plasma (TT4) and
	(TT3)
	Transient postpartum thyroid dysfunction.
Secondary thyroid disorders:	
Central hypothyroidism	[ISH] normal [FI3], [FI4] low ISH bloactivity reduced
Thyroid tumor	↑ [F13], [F14]
(TSH secreting tumor)	hyperthyroidism ↑ [TSH]
Endorgan resistance	↑ P T ₃ , T ₄
Non thuraidal illnass (NTI)	n or ↑ [TSH]
	Sick-Euthyroid syndrome low [T ₃]
	 Alteration in hypothalamus – pituitary thyroid axis (-)
	(–) TSH release by ↑ dopamine, cytokine, cortisol,
	somatostatin
	 Change in TBG and affinity characteristics.
	 Impaired uptake of thyroid hormone in peripheral tissues
	\downarrow Production of T3 in peripheral tissues.
In NIT, TSH < 0-1 m U/L and increase	Change in T3 ®
due to recovery	
Drug intake	
G.C. dopamine	
Li, amiodarone, iodide	↓ ISH
	↓ Inyroid normone secretion
Estrogen, tamoxifen, raloxifene clofibrate	Induce nypertnyroldism
Androgen, GC, anabolic steroids	↓ IBG
Phenytoin carbamazepine barbiturates	() nepatic metabolism

Synthesis



Secondary

(pituitary hypothalamic)

Screening Tests for Thyroid Disease

Congenital hypothyroidism

- TSH in capillary blood
 - T4

Questions:

- 1. Write the mechanism of synthesis of thyroid hormones.
- 2. Describe hyper and hypothyroidism.
- 3. What are screening tests for thyroid disease?

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Section IV Pathophysiology

Cardiac Function

Learning objectives:

- 1. Discuss Cardiac biomarkers.
- 2. Explain markers in Cardiac failure.
- 3. Enumerate Cardiovascular risk factors.

Cardiac Marker is a clinical laboratory test useful in detection of acute myocardial infarction (AMI) or minor myocardial injury.

Cardiac Biomarkers (Table 20.1, 20.2)

Creatine kinase (CK) Lactate dehydrogenase (LDH) Myoglobin Troponin

		СК	CK-2	LDH-1	Myoglobin	Troponin
1.	Hours until marker increases above upper reference limit	3–8	3–8	8–12	1–3	3–8
2. 3.	Hours until peak concentration Days until return	10–24	10–24	72–144	6–9	24–48(1st peak) 72–100 (2nd peak)
	to within reference interval	3–4	2–3	8–14	1	4–10

Table 20.1: Cardiac biomarkers

Table 20.2: Prediction of reperfusion status

Test	Utility
CK-2	Rate of appearance of CK-2 in association with reperfusion occurs 90 minutes after thrombolysis
Troponin Myoglobin	Useful in detecting reinfarction in postinfarct angina

Contd...

Collection and Processing of Specimens

Contd...

Myoglobin	to	total	CK	ratio	>	5	implies reperfusion
							(specificity of > 96%)
							(sensitivity of 75%)
							best indicator for prediction

Ischemia-Modified Albumin (IMA)

It is an early and sensitive marker of cardiac ischemia. N-terminal of albumin gets altered in myocardial infarction and it no longer can bind to metals such as Cu, Co, Ni. This is termed as *ischemia-modified albumin (IMA)* and can be detected by reduction in albumin's ability to bind cobalt. IMA is promising marker for early detection and has greater sensitivity than ECG and troponin. However, its precise role in patient management remains to be established.

Details of apolipoproteins and lipid profile can be referred in concerned section. *Marker of deep vein thrombosis: D-dimers*

D-dimers are released during conversion of fibrinogen to fibrin (during thrombus formation). Presence of raised values of D-dimer in plasma is diagnostic of presence of a thrombus.

Cardiovascular risk factors (Table 20.3)

Table 20.3:	Cardiovascular	risk factors
-------------	----------------	--------------

Classic risk factors: i. Abnormal levels of lipids:
ii. Cholesterol Triglyceride HDL-C (low) Others: Hypertension Smoking Diabetes mellitus Obesity Family history
Recent Biochemical risk factors: Homocysteine C-reactive protein (hs-CRP) Lipoprotein (a) Fibrinogen IMA

Markers of Cardiac Failure

Cardiac failure is a clinical condition associated with signs and symptoms of left or right ventricular dysfunction.

Natriuretic Peptides (Table 20.4)

Three natriuretic peptides are:

- 1. Atrial natriuretic peptide (ANP)
- 2. Brain natriuretic peptide (BNP)
- 3. C-type natriuretic peptide (CNP)

Table 20.4: Natriuretic peptides

	ANP	BNP	CNP
Site of production	atria	brain cardiac ventricles	brain kidney endothelial cells B-type
Binding to receptors	A-type C-type	C-type natriuresis	C-type vasodilator
Function	reduce ecf volume	reduce ecf volume prognostic marker	local tissue action no proven value
Utility	diagnostic marker of cardiac failure	in cardiac failure marker of both right and left ventricular dysfunctions	as a cardiac hormone
Analyte	Assay		Reference range
CRP Homocysteine Fibrinogen	Immunoassay GC-MS, HPLC Colorimetric		6.8-820 μg/dl 4–12 μmol/L 200–400 mg/dL

Tests useful in diagnosis and management of hypertension (Table 20.5)

Table 20.5: Clinical biochemistry tests useful in diagnosis and management of hypertension

Analyte	To rule out
Glucose Urea Creatinine Urine protein Potassium Aldosterone:renin ratio Calcium Phosphate PTH IGF-1 OGT Catecholamine metabolites (HMMA)	Diabetes mellitus Kidney disease Kidney disease Primary hyperaldosteronism monitoring treatment Primary hyperaldosteronism monitoring treatment Primary hyperparathyroidism Primary hyperparathyroidism GH excess: acromegaly GH excess: acromegaly Pheochromocytoma
Urine cortisol	Cushing's syndrome

Questions:

- 1. What are cardiac biomarkers?
- 2. Define Ischemia Modified Albumin (IMA).
- 3. Discuss Natriuretic Peptides.
- 4. Write the name of tests useful in diagnosis and management of hypertension.

Cardiac Function

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Liver Functions

Learning objectives:

- 1. Illustrate different functions of liver.
- 2. Discuss Bilirubin metabolism and laboratory tests of Bilirubin.
- 3. Describe Jaundice and Cirrhosis in detail.
- 4. Explain different tests done in liver disease.

Liver

Functions of Liver

Liver is the 'metabolic factory' of the body. It has essential metabolic, synthetic and excretory functions (Table21.1-21.3).

Table 21.1: Normal liver function

Metabolic Carbohydrate metabolism Lipid and lipoprotein metabolism Protein metabolism
Protein synthesis:
Most plasma proteins: (except Ig, RhF, complement) Blood coagulation factors: II, V, VII, IX, XI Primary bile acids Lipoprotein Urea Bilirubin glucuronide Excretory
Detoxification of:
Druas
Toxic metabolic wastes (ammonia, bilirubin)

Table 21.2: Half-life of plasma proteins

Plasma protein	t1/2
Albumin Factor VII Transthyretin Transferrin	20 d 4–6 hrs 1–2 d 6 d

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a. b. c.	Inactivation of steroids: Cholesterol Steroid hormones Inactivation and metabolism of drugs, toxins Urea synthesis
d.	Excretion Cholesterol Bile acids Conjugated steroid hormones (with glucuronate/sulfate) Drugs Toxins

Bilirubin metabolism (Fig 21.1)



Laboratory Tests of Bilirubin (Fig 21.4-21.7)

Total bilirubin Direct bilirubin or conjugated Indirect bilirubin or unconjugated (total minus direct).

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Albumin

Prothrombin time

Table 21.4: Location of	hepatocellular enzymes
Site	Enzyme
Cytoplasmic	LDH
	AST
	ALT
Mitochondrial	mt AST
	Glutamate dehydrogenase (GDH)
Canalicular surface of hepatocyte	ALP
* also found in minutes	GGI^
also found in microsomes	
Table 21.5: Localization of liver of	lamage with the help of enzymes
1. Serial enzyme determination:	ALT
, , , , , , , , , , , , , , , , , , , ,	LDH
2. Isoenzyme determination:	СК
Estimation of more than one enzyme:	ALT
	AST
Table 21 6: Storage (denot) function of liver
Site of storage of:	
Iron (700 mg iron)	
Glycogen	
Amino acids	
Lipids (TAG)	
Vitamins	
Investigating a liver disease:	
Bilirubin excretory function	
Hepatocellular damage:	
ALT/AST	
GGI	

Table 21.7: Tests for assessment of cell damage		
Acute cell damage	Very high ALT	
Cirrhosis	Slightly raised ALT	
Severe liver disease (terminal)	Fall in enzyme activity	

Extent of cell damage and rate of release of enzyme from damaged cells and their clearance from plasma determine the plasma levels of enzymes.

CHAPTER 22

Renal Functions

Learning objectives:

- 1. Explain Renal functions and Renal function tests.
- 2. Describe Renal failure.
- 3. Illustrate Urine osmolarity and its importance clinically.
- 4. Discuss Acid-base balance and disorders associated with it.

Kidneys

Kidneys are paired organ system lying in lumbar region, each having about 1 million nephrons. (Table 22.1, 22.2)

Table 22.1: Major functions of kidney

Excretion: excretion of end products of metabolism Regulation of ecf: regulation of extracellular fluid (ecf) volume and composition and acid-base status Endocrine function: synthesis of hormones namely, renin, erythropoietin, calcitriol

Glomerular Fluid (GF)

It is an ultrafiltrate of plasma and its composition is similar to plasma except that proteins are absent. (Table 22.3, 22.4)

Glomerular Filtration Rate (GFR)

Normal GFR is 120 mL/min approximately and is equivalent to volume of 170 L/24 h. *GFR depends on:*

- rate of blood flow
- balance between hydrostatic and oncotic forces in afferent arterioles and glomerular filter (tubular fluid).

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Renal Functions

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Table 22.2: Functions of kidney

Formation of urine Regulatory function: acid-base balance water-electrolyte balance Excretion of end products of protein metabolism Endocrine function: Vitamin D metabolism Renin release Erythropoietin production PG and TX production Body protein homeostasis

Table 22.3: Glomerular permeability: Salient features

Glomerulus is a size-, charge- and shape-dependent filter Glomerular basement membrane has strong negative charge: for negatively charged molecules, size cut off is 18 nm. Proteins of molecular weight lower than albumin (66.3 kD) filterable. Damage to negative charge results in leakage of albumin (molecular radii 3.6 nm) through basement membrane.

Table 22.4: Renal function tests

1.	Glomer	ular function:
	а.	GFR:
		Exogenous substance:
		Inulin
		Cr – EDTA
		Endogenous substance:
		Urea
		Creatinine
		β macroglobulin
		Retinol-binding protein
		α1 microglobulin
		Cystatin C
	b.	Glomerular permeability:
		Urine protein
2.	Tubular	function:
		Tubular proteinuria
		Osmolality
		Specific gravity
		Concentration and dilution tests
		Tubular secretory mass measurement by diodone/PAH

Clearance

It is ml of plasma cleared off a particular substance by both the kidneys per minute. (Table 22.5-22.6) *Properties of ideal substance for clearance:*

1. It should be neither secreted nor reabsorbed by the kidney.

2. It should not be affected by rate of urine flow.

^{3.} Its levels in blood should remain constant.

^{4.} Its clearance should be equivalent to GFR.

Urea cle	earance	Creatini	ine clearance
1.	Its value is 3/5th of GFR	1.	Values are nearly equal to GFR
2.	Plasma values of urea are not	2.	lts plasma values remain
	constant throughout the day		constant over 24 hrs
3.	Urea is both secreted and	3.	Creatinine is neither secreted nor
	reabsorbed by kidney		reabsorbed by kidney
4.	It is affected by rate of urine flow	4.	4. It does not depend on rate of urine flow

Table 22.5: Compar	ison of urea	and creatinine	clearance
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	Table	22.6 :	Plasma	urea/Creatinine	ratio
--	-------	---------------	--------	-----------------	-------

Inc	creased	Decreased
Hig	gh protein intake	Low protein intake in diet
Hy	percatabolic state	Severe liver disease
De	ehydration	Dialysis
GI	bleeding	

Overflow Proteinuria

Abnormal amounts of low molecular weight proteins appearing in plasma and urine.

Table 22 7. Princi	inal proteins	that annear	in urino
Table 22.7. FILLE	ipai proteiris	that appear	in unne

Protein	Disease
Amylase	Acute pancreatitis
Bence Jones	Multiple myeloma
Hemoglobin	Hemolysis (intravascular)
Lysozyme	Myeloid Leukemia
Myoglobin	Crush injury to muscle

Microalbuminuria

More correctly termed as *minimal albuminuria*. It is mildly increased excretion (200 to 300 mg/L) of albumin in urine.

It appears to be a predictor of future development of clinical renal disease in patients with DM or hypertension.

Guidelines for investigating microalbuminuria

- 1. Measure albumin/creatinine, if > 30 mg/d, do albumin excretion rate (AER) in 24 hours collection.
- 2. AER between 30 to 300 mg/24h is microalbuminuria.
- 3. Further monitor AER, blood pressure, baseline GFR on every follow-up.

The incidence of microalbuminuria may be reduced by optimal control of glycemia, blood pressure.

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Pregnancy

Learning objectives:

- 1. Enumerate all substances that can pass and cannot pass through placenta.
- 2. Describe monitoring during pregnancy.
- 3. Explain characteristics and features of Amniotic fluid.

Transport Across Placenta

- 1. Passive transport
 - i. Limited passive transport:

FFA

Unconjugated steroids

Steroid sulfates

ii. Passive transport:

 O_2 CO_2 Na Cl Urea Ethanol Lipid soluble molecules up to 5000 Da 2. Active transport

Glucose

Calcium

Many amino acids

3. Receptor mediated endocytosis Insulin LDL Maternal IgG

Substances not Transported Across Placenta

Maternal IgM Thyroid hormones Most proteins Maternal and fetal RBCs

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MONITORING DURING PREGNANCY (Table 23.1-23.4)

Table 23.1: Lab evaluation during pregnancy

1st Trimester	2nd Trimester
Hb	15–21 weeks
ABO, Rh (D)	Maternal serum αAFP
Urine:	24–24 weeks:
Protein	Hb
Culture	Diabetes detection/screening
Toxoplasma Ab (if indicated)	Urine protein
Syphilis Ab	
HIV Ab	

Table 23.2: Metabolic changes during pregnancy

Decreased	Increased
Urea	Cortisol
Albumin	Copper
Total protein	Thyroxine
Glucose tolerance	HDL - C
LDL – C	ALP

Table 23.3: Hormonal changes during pregnancy

	Hormone	Source
1.	hCG	Corpus luteum
2.	Estrogen	Corpus luteum
		Placenta
		Fetal Adrenal
3.	Human placental lactogen	Placenta
4.	Placental ALP	Placenta

Table	23.4:	Aminocentesis:	Biochemistry
abic	20.4.	/	Dioononiony

Parameter	Diagnostic value
Lecithin/Sphingomyelin ratio (L/S)	Fetal lung maturity
Phosphatidylglycerol	Fetal lung maturity
Creatinine	> 2 mg/dl - Fetus is mature
Bilirubin	Reserved for monitoring blood group immunized cases
Blood acid-base and electrolyte level	Feto-placental well-being
Hormones:	Feto-placental well-being
Estriol	Feto-placental well-being
hCG	Feto-placental well-being
hPL	Feto-placental well-being
AFP	Diagnosis of neural tube defects, Down's syndrome
Chorionic villus sampling and analysis of	Screening of inherited disorders
fetal chromosome and DNA	

PG

PGE_

 $PGF_{2\alpha}^{\tilde{}}$

Amniotic Fluid: Characteristics

Origin *:

Placenta Fetal kidney Skin membrane Lung Intestine

* relative contribution of each source depends on stage of fetal development

Biochemistry

- i. before keratinization of fetal skin: it can result as a transudation from fetal surface
- ii. after keratinization of fetal skin: fetal urine makes a significant centribution.

Amniotic Fluid: Features

Isotonic (early pregnancy) to hypotonic (term, 255 m Osm/kg of water) Nitrogenous products: Urea Creatinine

Uric acid

Proteins:

Source : fetal (skin, urinary, GIT and respiratory tract) : maternal (by transudation)

Hormones:

PeptideSteroidACTHEstradiolFSHEstriolLHEstronehCGHPLPRLOxytocinRelaxinThyrotropinThyroxineThyroxine

Monitoring in Gestational Diabetes*

Maternal blood glucose OGT HbA_{IC} Urine albumin Serum creatinine *for further details, see section on diabetes.

Section V Oral Cavity

CHAPTER 24

The Oral Cavity—A Diagnostic Window to the Body

Learning objectives:

1. Discuss saliva as a diagnostic tool.

Saliva is the protective fluid of the oral cavity with its vast supply of microbe killers, saliva combats invading pathogens such as HIV and a host of bacteria associated with oral and systemic diseases. Antibodies directed against pathogens such as polio and cold viruses, are formed in saliva. Large salivary glycoproteins called mucins, appear to have antiviral properties as well.

Oral fluid is also a mirror of the body, containing many compounds that are indicator of health, disease status of a person. Also, like blood and urine, composition of oral fluid may be altered in the presence of disease. Saliva may be collected in a much less invasive fashion than blood or urine, and at times preferred over blood for analyzing analytes (Table 24.1).

|--|

Analyte in saliva	Use
Alcohol	For alcohol screening at roadside emergency department—test cards are available
Free cortisol	Practical, convenient and accurate
Drug abuse testing	For therapeutic drug monitoring, detecting illicit drug use
Estrogen	Useful in diagnosis of and treatment of infertile women with anovulatory cycle during
	in vitro fertilization, monitoring hormone replacement therapy * and closely reflect
	free fraction of hormone
Progesterone	To investigate luteal defects in infertile female and reflect free unbound fraction
Protein	Screening IgA in infantile hypogammaglobulinemia and BMG in Sjogren's syndrome
Steroid hormones	Useful in frequent sampling
Testosterone	Indicator of androgen status

*requires sensitive assay for accurate measurement.

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Other Uses of Saliva Analysis

- 1. Diagnostic marker for early detection of cancer related protein in breast cancer.
- 2. Gene therapy using salivary glands offers hope in type I DM, GH deficiency and hypoparathyroidism.
- 3. In future, Oral fluid chips will be available for disease point-of-care diagnostic platform.
- 4. Nanotechnology based salivary biosensor for ultrasensitive salivary diagnostic analytes.

Diagnostic Molecular Targets in Saliva

Salivary transcriptome consists of ~ 3000 mRNA that can be used for disease diagnostics. Although, salivary proteome is still several years away, the complete normal salivary transcriptome has been reported.

As a biomarker, RNA (in saliva) is as robust and as informative as any other analyte. Highly diagnostic RNA signatures have been identified for head and neck cancer and few major human systemic diseases. Latest target for candidates for salivary diagnostic are cardiovascular disease, cancer (lung, prostate, ovarian and colon), Alzheimer's disease, osteoporosis, cerebrovascular diseases, nephritis, septicemia, chronic respiratory diseases, chronic liver disease and pneumonitis.

Questions:

- 1. How is saliva used as diagnostic tool?
- 2. Explain diagnostic Molecular Targets in saliva.
- 3. What are the uses of saliva analysis?

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